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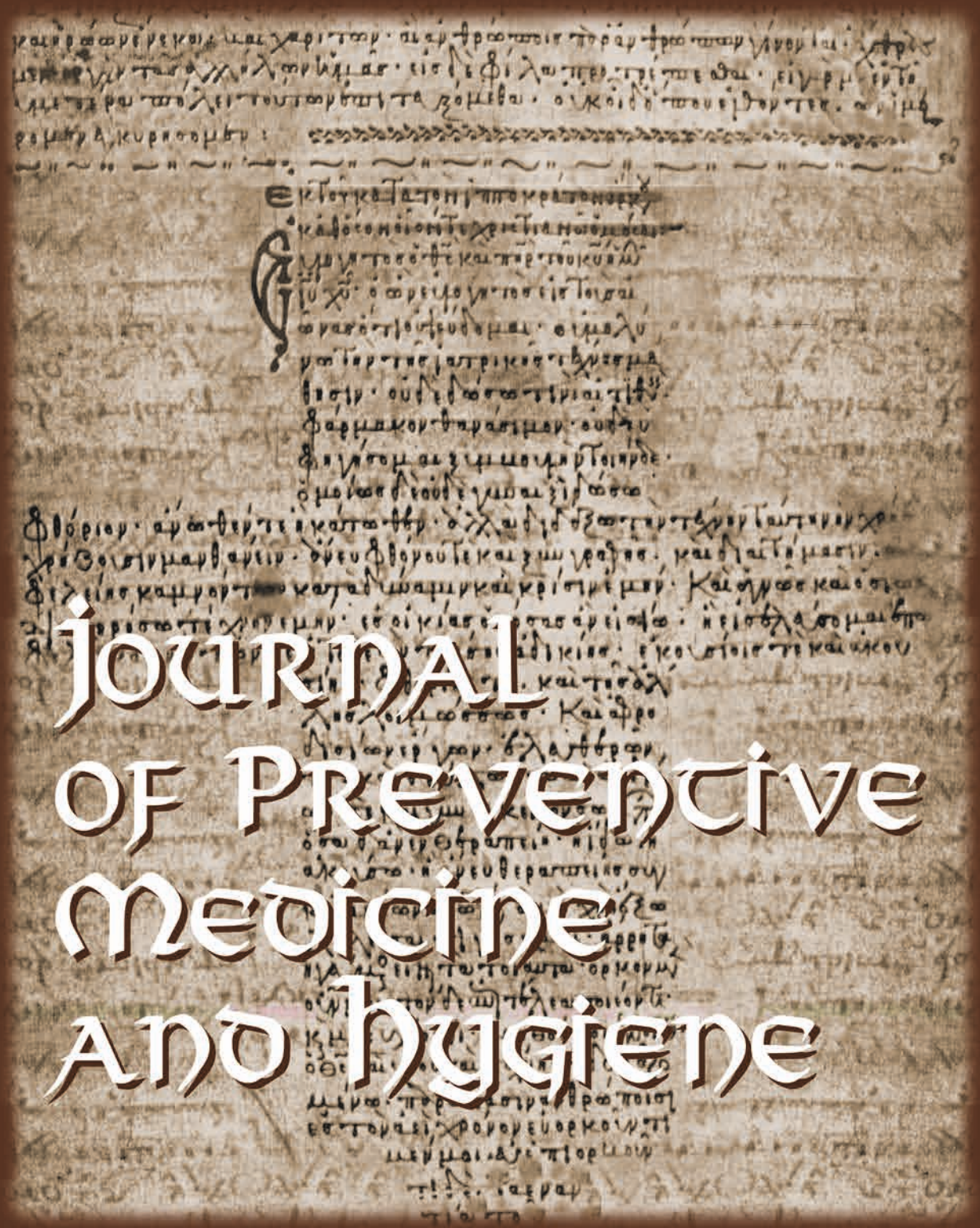

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HEALTH PROMOTION

Implementing surveillance in territorial healthcare facilities: a proposal from ASST Nord Milano (Italy)

BARBARA MANGIACAVALLI[1], VITO MARGHERITA[1], LUIGI PETRELLA[1], GIANMARCO TROIANO[1], TOMMASO RUSSO[1]
[1] ASST Nord Milano, Cusano Milanino (MI), Italy

Keywords

Inspection • Italy • Management • Healthcare • Pilot Study

Sir,
The SARS-CoV-2 pandemic increased pressure on the world's healthcare systems, threatening their stability and, at the same time, confirmed the importance of primary health care to guarantee effective care for patients who suffer from complex and chronic diseases. Through funding provided by the European Union to enhance the health care system in Italy the so called "Community Houses" (*Case di Comunità*) were opened and represent new organisational models of Primary Health Care [1].
Community Houses (CHs) are new entities in the Italian Healthcare System, envisaged to provide proximity care to citizens. CHs are part of the Italian National Recovery and Resilience Plan [2]. Mandatory requirements for Community houses include: the presence of a Single Access Point (PUA), home care services, and integration with General Practitioners (GPs) and Pediatricians (PLS). Recommended but not mandatory services include those related to mental health, addictions, neuropsychiatry and sports medicine, as well as screening programs and vaccinations [3].
The word "inspection" is used in several settings and denotes "critical appraisal involving examination, measurement, testing, gauging, and comparison of materials or items. An inspection determines if the material or item is in proper quantity and condition, and if it conforms to the applicable or specified requirements" [4].
Inspections are used in healthcare to promote improvements in the quality of care, promoting changes in organisational structures or processes, in healthcare provider behaviour and thereby in patient outcomes [5].
In this context, territorial healthcare facilities represent a particularly complex setting, characterized by organizational heterogeneity, ongoing structural reorganization, and the coexistence of multiple clinical and non-clinical activities. Unlike hospital settings, standardized inspection models for territorial healthcare are still limited. Therefore, the development and application of a structured inspection tool specifically designed for territorial facilities may support clinical governance, promote adherence to hygienic and organizational standards, and foster continuous quality improvement. This study aims to describe and evaluate a structured inspection Model applied to Community Houses and other territorial healthcare facilities, and to explore its role as a tool for identifying critical issues and supporting system-level improvement actions.
In "Azienda Socio-Sanitaria Territoriale (ASST - Socio-Sanitary Territorial Authority) Nord Milano" there is a specific unit called Territorial Medical Management Unit (*Direzione Medica Territoriale*) created to guarantee the clinical governance, to plan and manage the territorial health services, to supervise hygienic and organizational conditions of territorial facilities.
On February-April 2025, a multidisciplinary staff composed of personnel working for the Territorial Medical Management Unit, and working for the Infection Prevention Service (the so called "SPIO"), carried out inspections in the healthcare facilities (except for hospitals) across the ASST Nord Milano territory, to verify multiple hygienic and organizational issues.
For these inspections the staff used a form created ad hoc for territorial facilities and created by the collaboration of several units of ASST Nord Milano (Tab. I).
The questions were divided into the following macro-categories:

1. Workers;
2. Signage;
3. Space organization;
4. Warehouse, materials and drug management;
5. Environmental hygiene;
6. Medical and urban waste;
7. Fire emergency;
8. Crash cart;
9. Decontamination, washing and sterilization processes;
10. Healthcare-associated infections (HAIs) and Pandemic Influenza Plan (PanFlu);
11. General organization.

During the inspections facilities' general conditions were observed, in particular the environmental conditions, the microclimate, the presence of bulky waste for disposal and the correct application of the internal procedures and the hygienic-sanitary conditions.
The inspection process was designed not only as a control activity but also as a formative audit aimed at promoting awareness and shared responsibility

among healthcare professionals. For this reason, nurse coordinators were asked to complete the inspection form in advance. This approach was intended to encourage the early identification and resolution of critical issues and to frame the inspection as a collaborative quality improvement process rather than a punitive assessment. For any items the answers could be*: good, improvable, not applicable*.

The inspections were performed between 14 February and 18 April 2025 (12 days of inspections) in territorial facilities placed in the ASST Nord Milano (specifically formed by the following cities: Bresso, Cormano, Cinisello Balsamo, Cologno Monzese, Cusano Milanino, Sesto S. Giovanni). Specifically the community houses have been analyzed and included also nursing clinic; blood collection center; vaccination center; outpatient clinics; doctor-on-call clinic (the so called "guardia medica"); single point of access (the so called "PUA"); family counseling clinic (the so called "consultorio familiare"); centers for mental health assistance and neuropsychiatry; centers for addictions.

In the examined time span we reported the following results:

1. Workers
   The section includes two questions regarding staff identification through identification cards, clothing, garments and personal protective equipment (PPE). The average positive result for all facilities was over 95%.
2. Signage
   The section includes two questions regarding information to patients through signage and indications in the facilities. The average positive result for all facilities was 62%. The signage in Community Houses and Psychosocial Centers sometimes was not totally correct, clear and visible at the entrance and on all floors (especially because of several renovations works in these facilities).
3. Space organization
   The section includes eight questions regarding the destination and organization of spaces, in particular the separation of deposits for dirty and clean material, the waste room, toilets reserved for staff and patients and workers' dining room. The average positive result for all facilities was 75%: this result was particularly influenced by the lack of workers' dining room or refrigerators for storing workers' meals.
4. Warehouse, materials and drug management
   The section includes eight questions regarding supplies of materials and drugs, the presence and condition of dedicated cabinets and refrigerators. The average positive result for all facilities was 88%. The question regarding the presence and condition of cabinets or shelves had highest number of responses "improvable".
5. Environmental hygiene
   The section includes six questions regarding the rooms and furnishing conditions, lighting, air changes, temperature and cleaning conditions. The average positive result for all facilities was 66%. The most critical questions were related to the conditions of the rooms and furnishings, followed by the poor order in work spaces (with a following difficulty in daily cleaning). Another issue regarded the high temperatures (especially in the summer months) reported in some facilities due to technical problems.
6. Medical and urban waste
   The section includes twelve questions regarding the management of medical waste, hazardous waste, infectious waste and urban waste. The average positive result for all facilities was 88%. The questions regarding the presence of the sign on the doors of temporary waste storage facilities and the one on separate waste collection had highest number of responses "improvable".
7. Fire emergency
   The section includes seven questions regarding the management of fire emergencies. The average positive result for all facilities was 79%. The questions regarding the dissemination of the emergency and evacuation plan, the one related to the presence of no smoking signs, and the one on the storage of flammable products had highest number of responses "improvable".
8. Crash cart
   The section includes eleven questions regarding the management of aspects related to the territorial clinical emergency. The average positive result for all facilities was 91%. The questions regarding the quality of crash carts, the one on the signage relating to the crash carts and the one on the knowledge of the methods of reporting events had highest number of responses "improvable".
9. Decontamination, washing and sterilization processes
   The section includes two questions regarding the decontamination, washing and sterilization phases and the average positive result for all facilities was 100%.
10. Healthcare-associated infections (HAIs) and Pandemic Influenza Plan (PanFlu)
    The section includes two questions regarding the prevention of healthcare-associated infections (HAI) and the pandemic influenza plan (PANFLU) and the average positive result for all facilities was 89%. In some waiting rooms a lack of hand sanitizer gel was reported and some sinks didn't have soap and paper towels.
11. General organization
    The section includes two questions regarding the forms for reporting adverse events and the ease of finding documentation on JDOC (internal platform for storing procedures and documents). The average positive result for all facilities was 81%.

After the inspections, the coordinators received inspections' reports with the identified critical issues and the suggested improvement actions.

Among the critical issues identified during the inspections, some have been considered "urgent" and required an immediate intervention.

A task force involving several units (technical service,

Tab. I. Form used during inspections.

Workers
Are internal and external workers identifiable by an identification badge?
Are workers' clothing, garments and PPE suitable and correctly worn?
Signage
Are the signage correct, clear and visible at the entrance and on all floors?
Is there appropriate signage to inform patients about the hours of services and access to the facilities?
Space organization
Are there dedicated spaces for storing clean material?
Are there dedicated spaces for storing dirty material?
Are there dedicated spaces or cabinets for storing materials, equipment and instruments?
Is medical waste stored in a suitable location?
Are there toilets for staff, separate from those for users?
Are there disabled-friendly toilets?
Is there a dining room for workers? If so, is it kept clean and tidy?
Is there a refrigerator used exclusively for food? Is it marked "for food"?
Warehouse, materials and drug management
Are there cabinets/shelves dedicated to drug/material supplies and in good condition?
Are there clean uniforms and gowns and PPE (gloves/masks, *etc.*) in stock available for staff?
Is the cleaned material well kept and tidy?
Is the dirty material orderly stored?
Are there expired drugs or devices?
Is the medicine refrigerator in good condition?
Is there a temperature detection system in the refrigerator with daily recording?
Is there the anti-spill kit and is the related procedure known to the operators?
Environmental hygiene
Are the premises and furnishings in good condition?
Is there an adequate lighting in all rooms and outdoor spaces?
Are air changes ensured in all confined spaces (waiting rooms, clinics, corridors, *etc.*)?
Is the environmental temperature controlled and maintained at adequate values: in winter 19-22°C; in summer 24-26°C?
Are spaces in good general hygiene conditions?
Are countertops, surfaces, and furnishings neat and clear enough to allow for daily cleaning?
Medical and urban waste
Are the containers for hazardous infectious medical waste for sharps and needles (yellow rigid plastic containers) used properly? Check that there are no drugs in vials, syringe caps, cotton wool, *etc.*
Are the sharps containers, filled to no more than 3/4 of their volume and hermetically sealed, placed inside the appropriate cardboard containers with the bag for infectious waste (yellow) inside, for disposal?
Are containers for hazardous infectious medical waste (white and yellow cardboard container with a special yellow bag inside) used correctly? Check for the absence of non-infectious urban waste, such as glasses, cotton, urine containers, diapers.
Are cardboard containers closed when they reach no more than 2/3 of their volume and no more than approximately 5 kg in weight (value refers to 60 L containers)?
Are potentially infectious medical waste containers intact and free of spills/tears?
Do closed cardboard containers show: company name, structure and closing date?
Are closed cardboard containers transported directly to the temporary storage facility, without intermediate steps? Make sure they are not left unattended in the aisles until the operators in charge pass by.
Is the temporary storage room for hazardous infectious medical waste marked with a sign on the door and warning signs? Is it accessible only to operators and locked? Is it used exclusively for this purpose?
Is the documentation (register and 4 copies of the completed form with the weight) archived and kept for the time required by law?
Is the collection of solid urban waste carried out correctly? Are there containers for separate waste collection? Are they disposed of correctly?
Is municipal waste properly stored before disposal (e.g. in bins awaiting collection day)?
Are there unused/discarded medical devices, furniture and materials waiting to be disposed of?
Fire emergency
Is the smoking ban respected? Are there signs indicating the smoking area and the prohibition in all identified internal and external points?
Are flammable products properly stored and protected?
Are the emergency routes and exits well identified, signalled and perfectly clear of materials/obstacles and openable?
Are emergency signs present and clearly visible?

▶

Tab. I *(follows).*

Are the REI doors held open with systems that allow automatic closing in the event of fire/Are the REI doors working? Check that there are no blocks such as wedges under the doors to keep them open.
Are fire extinguishers easily visible and usable?
Has the emergency and evacuation plan been printed and available to all staff? Have meetings been organised to disseminate the plan? Has a list of operators been prepared with the date of participation in the meeting and signature?
Crash cart
Is there a crash cart?
Is the crash cart neat, clean and well organized?
Is the crash cart sealed, updated and accessible?
Are there in the crash cart all the medicines and supplies required by the internal procedure?
Are the expiration dates of the drugs and crash cart supplies periodically checked?
Is the AED charged and functioning?
Are there signs indicating the location of the crash cart and the AED, visible and updated on all floors of the building?
Is there the "crash cart and defibrillator station" sign, and well visible on the door?
Are the following checked periodically: the integrity and expiry of the plates; the pressure of the 02 cylinders?
Are the crash cart and AED used by different services/units? Is there coordination for their control?
Does the staff know and can find the forms for reporting emergency/urgent events?
Decontamination, washing and sterilization processes
Verify the correct management of the decontamination and sterilization process phases
Are the attachments for decontamination and sterilization completed?
Healthcare-associated infections (HAIs) and Pandemic Influenza Plan (PanFlu)
Are there indications for proper hand hygiene near the sinks?
Are there soap and paper towels near the sinks?
Is there hydroalcoholic gel and possibly a column at the assistance points and waiting rooms?
Regarding the prevention of legionellosis, are the flushing forms kept by the nursing staff and correctly filled out by the operators in charge?
Have the PAN-FLU plan and the Health Directorate's recommendations for the prevention of respiratory syndromes regarding the use of masks and hand hygiene been disseminated to all operators?
Are masks available for operators to wear according to the recommendations of the health management?
Are checks carried out to ensure that patients and their companions wear masks in case of respiratory symptoms, according to the recommendations of the health management?
General organization
Does the staff know and is able to find the forms for reporting adverse events/non-compliance?
Are operators able to find documentation on the intranet and on JDOC (the electronic data warehouse storing procedures and documentation)?

clinical engineering, communication, risk management, infection prevention service, nursing management unit, territorial medical management unit, *etc.*) was activated to ensure the implementation of these actions within certain deadlines. Each unit received a complete list of interventions to be carried out in the territorial structures and the deadline to complete the interventions.

Overall, the inspection results highlighted a heterogeneous level of compliance across different domains. Higher levels of compliance were observed in areas related to staff identification, emergency equipment management, and decontamination processes, while lower scores were mainly related to signage, environmental hygiene, and space organization. These critical areas were often associated with structural constraints, ongoing renovation activities, or organizational factors rather than with a lack of procedural knowledge. Several issues were considered easily correctable through targeted organizational interventions.

The findings of this study suggest that structured inspections in territorial healthcare facilities can effectively identify organizational and hygienic criticalities and the lower compliance observed in areas such as signage, environmental hygiene, and space organization reflects the intrinsic complexity of Community Houses, where multiple services coexist and structural adaptations are often ongoing. These results underline the need for inspection models specifically tailored to territorial settings, rather than directly derived from hospital-based frameworks.

Beyond the identification of critical issues, the inspection process described in this study contributed to the activation of concrete improvement actions. The classification of findings according to urgency allowed the prioritization of interventions and led to the activation of a multidisciplinary task force involving technical, clinical, and managerial units. This structured follow-up transformed the inspection from a descriptive assessment into an operational tool for system improvement, supporting decision-making processes and the implementation of corrective actions within defined timelines.

From a governance perspective, this experience highlights the potential role of territorial inspections as a

strategic tool to support clinical governance and quality improvement in primary care settings. The proposed inspection Model is adaptable and may be replicated in other territorial healthcare systems undergoing similar organizational transformations. By fostering collaboration among professionals and promoting a shared culture of quality and safety, inspections may contribute to strengthening the resilience and effectiveness of territorial healthcare services.

This preliminary study demonstrates that a structured and participatory inspection Model can support the identification of organizational and hygienic critical issues in territorial healthcare facilities. When integrated into a broader governance framework, inspections may act as a catalyst for targeted improvement actions and interdepartmental collaboration. Although further studies are needed to evaluate long-term outcomes, this approach represents a feasible and replicable strategy to promote continuous quality improvement in primary and community-based healthcare settings.

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Conflict of Interest Statement

No one to declare.

Authors' Contribution

VM, GT: contributed to the study conception and design. VM, LP: coordinated the inspection activities and data acquisition. LP, GT: contributed to data analysis and interpretation. GT: drafted the manuscript. BM, TR: supervised the study and revised the manuscript.

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Correspondence: Gianmarco Troiano, ASST Nord Milano, Via Ginestra 1, Cusano Milanino, Milano. E-mail: gianmarco-89@hotmail.it; gianmarco.troiano@asst-nordmilano.it; dirmedica.territoriale@asst-nordmilano.it

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HEALTH PROMOTION

Trends in Adolescent Mental Wellbeing in an Italian sample from 2004 to 2022 (HBSC Study): Gender, Age, and Socioeconomic Difference

ANTONELLA MISERENDINO[1], CLAUDIA MARIA TROMBETTA[1,2,3], DARIO LIPARI[1], BIANCA MARIA BOCCI[1], ELENA FRONGILLO[1], ANDREA PAMMOLLI[2,4], RITA SIMI[2,4], GIACOMO LAZZERI[1,2,3,4]
[1] Post Graduate School of Public Health, University of Siena, Siena, Italy; [2] Department of Molecular and Developmental Medicine, University of Siena, Siena, Italy; [3] Interuniversity Research Centre on Influenza and Other Transmissible Infections (CIRI-IT), Genoa, Italy; [4] Research Center on Health Prevention and Promotion (CREPS), University of Siena, Siena, Italy

Keywords

Adolescence • Mental health • Mental wellbeing • Socioeconomic status, HBSC

Summary

Introduction. *There is an increasing discussion about the decline in adolescent mental well-being over time, but existing literature provides limited data on this trend.*
The aim of our study is to examine how the mental health of Tuscan adolescents aged 11-13 and 15 years may have changed over the years. Additionally, we seek to investigate the influence of factors such as gender, age, and socioeconomic status on these changes.
Method. *We analyzed data representative of the Tuscan region, collected from 18,439 adolescents through six rounds of the Health Behaviour in School-aged Children (HBSC) surveys conducted in 2004, 2006, 2010, 2014, 2018, and 2022. Hierarchical regression models were used to assess regional trends in adolescents' mental well-being, considering life satisfaction, psychological and somatic symptoms, and to evaluate how age, gender, and socioeconomic status might moderate these trends.*
Results. *In all survey years (except 2004), girls consistently reported higher levels of psychological and somatic complaints and lower life satisfaction compared to boys. Trend analysis from 2004 to 2022 showed a steady decline in all measured areas: life satisfaction, psychological complaints, and somatic complaints. Generally, older adolescents reported lower life satisfaction and higher levels of psychological and somatic symptoms.*
Conclusion. *Our findings indicate that the gender gap in mental well-being appears to be widening over time, whereas differences related to age and socioeconomic status have remained relatively stable. It is therefore crucial to pay increased attention, especially considering the potential impacts of the COVID-19 pandemic on adolescent mental health.*

Introduction

Adolescence is a unique developmental phase that marks the transition from childhood to adulthood. It is characterized by significant changes not only in physical development but also in psychological, relational, and social aspects. In recent years, there has been an increased focus on understanding the factors, particularly social ones, that influence health outcomes and contribute to health inequalities within populations [1]. Adolescent mental well-being is considered a public health priority at both the global and national levels [2], as more than half of adult mental health issues emerge during childhood and adolescence [3]. Previous research study has defined adolescent mental health as a multifaceted concept, including both mental health problems and subjective well-being [3].
In recent years, adolescents report lower levels of well-being and more mental health problems compared to their peers from one or two decades ago [4].
Evidence suggests a decline in the mental well-being of children and adolescents in developed countries, particularly among older girls [2, 4]. Numerous studies have identified increasing trends in mental health issues, especially internalizing problems, among adolescents across various countries over time [5, 6]. Several factors contribute to this increase. Lifestyle and health-related elements, including sleep patterns, physical activity, and sedentary behavior, play a significant role. School-related stress and the pervasive influence of the digital age also have an impact. Additionally, inter-parental conflict, social adversity, and the complex, bidirectional relationship between mental health and activity levels are recognized as important contributors [7].
Studies have consistently reported gender, age, and socioeconomic differences in the trends of adolescents' mental well-being [2, 4]. Analyses of temporal trends indicate that, in comparison to boys, girls are increasingly likely to report emotional problems [5], internalizing problems [4], lower life satisfaction, and more multiple health complaints [2]. Additionally, a notable decline in mental well-being has been observed from the onset to the conclusion of adolescence across several cohorts [2]. This decline in well-being, along with rising internalizing problems over time, is particularly pronounced among older adolescent girls [4]. Self-assessments of health

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among adolescents have shown a steady deterioration with age, with girls experiencing a more significant decline than boys [2, 6]. Socioeconomic inequalities play a significant role in influencing adolescents' mental health [8]. Adolescents from socially disadvantaged backgrounds report higher rates of poor subjective health, lower life satisfaction, and a greater burden of multiple health symptoms compared to their peers from more affluent families [8]. These individuals also experience reduced quality of life and well-being [9]. Previous literature indicates that social inequalities in adolescent mental health have intensified over time [9].

According to a recent UNICEF estimate, based on a Global Burden of Disease study, about 16.1% of Italian adolescents (age range 10-18) had a mental health disorder (17.2% girls and 16.6% boys) in 2019 which was below the European average (16.3%) [10]. In recent years, certain risky behaviors among Italian adolescents, such as alcohol use, smoking, binge drinking, and a sedentary lifestyle, have remained stable or slightly decreasing but continue to be prevalent and concerning according to the most recent data. Specifically, 17% of Italian 15-year-olds reported binge drunk at least once in the previous month; 14% of 15-year-old boys and 20% of 15-year-old girls have smoked at least one cigarette in their lifetime; 21% of 13- and 15-year-olds do not engage in sufficient physical activity. [11]. Additionally, there has been a steady increase in the number of children and adolescents receiving psychiatric care. According to the Ministry of Health, over 100,000 minors were under the care of child neuropsychiatry services in 2021. The international HBSC (Health Behaviour in School-aged Children) Report 2022 on adolescents across Europe shows that Italians are below the European average in terms of their mental well-being, particularly girls [12].

As such, it is important to provide an overview of the situation at the baseline before these policies are implemented.

Between 2004 and 2022, the mental well-being of Italian adolescents progressively worsened, as reflected by a decline in life satisfaction – from an average of 7.4 in 2004 to 7.0 in 2022 among 11 – to 15-year-olds. This period also saw an increase in psychological symptoms such as irritability, nervousness, and difficulty sleeping, as well as a rise in somatic complaints including headaches, stomachaches, and dizziness. While these trends were observed in the Tuscan sample of the HBSC study, they also mirror patterns identified at the national level [13]. This survey analyzes changes in adolescents' mental well-being, measured through life satisfaction, psychological symptoms, and somatic symptoms, and evaluates whether gender, age, and socio-economic gaps in these trends have increased in the Tuscany Region between 2004 and 2022 through data from the six HBSC surveys carried out in Tuscany.

Material and Methods

HBSC international survey collects data every four years on health behaviors, social environments, and sociodemographic characteristics in adolescents aged 11 to 15 using a standardized research protocol [13, 14]. The Italian HBSC survey is organized under the base of the "Surveillance system for risk behaviours in 11-15-year-olds". Data collection involved the recruitment of a two-stage stratified sample of classes and grade levels that represent the economic, and public-private distribution of schools in Italy [13, 14].

Classes were the primary sampling unit and 88.7% (5,669) of the total sampled classes (6,388) consented to participate. Adolescents completed anonymous questionnaires in classroom setting. This study included 18,439 students (97.3% of response rate at the individual level) aged 11, 13 and 15 years old from six Tuscany HBSC surveys (2004, 2006, 2010, 2014, 2018 and 2022). Regionally representative samples of 11, 13 and 15-year-olds were included in each wave: 2004 (N = 3,614; 49.5% girls), 2006 (N = 3,405; 51.2% girls), 2010 (N = 3,291; 48.3% girls), 2014 (N = 2,511; 52.4% girls), 2018 (N = 3,087; 49.8% girls) and 2022 (N = 2,531; 48.0% girls), respectively (Tab. I). Before data collection, students' parents received an information note describing the survey's purpose. Families could deny participation by filling in and returning the note to the teachers in each class involved. The study was conducted according to the guidelines of the Declaration of Helsinki.

The participants were assured of the anonymity and confidentiality of their responses. In 2022, the Italian HBSC study protocol and questionnaire were formally approved by the Ethics Committee of the Italian National Institute of Health (Ref. PROT- PRE876/17, 20 November 2017). Ethical approvals have been granted for the previous surveys as well.

Instruments

Psychological and Somatic Symptoms

The HBSC Symptom Checklist is a non-clinical tool used to assess two types of health symptoms: psychological symptoms (such as feeling down, irritability, nervousness, and sleep problems) and somatic symptoms (like headaches, stomach aches, back pain, and dizziness). Participants were asked to report how often they experienced these symptoms over the past six months. Response options included: "about every day," "more than once a week," "about every week," "about every month," and "rarely or never." This instrument has proven to be reliable and valid. In our sample, both subscales showed acceptable reliability, with Cronbach's alpha values of 0.70 for psychological symptoms and 0.77 for somatic symptoms. The items were scored in reverse where necessary. For each subscale, a mean score from 0 to 4 was calculated, with higher scores indicating more frequent symptoms.

Life Satisfaction

Life satisfaction was measured using the Cantril ladder,

where participants rated their happiness with life on a scale from 0 (worst possible life) to 10 (best possible life). For this study, the scale was treated as a continuous variable.

Gender and Age

Participants were asked to specify whether they are a boy or a girl and to provide their date of birth (month and year).

Socioeconomic Status

Socioeconomic status was assessed using the Family Affluence Scale (FAS), a 4-item measure developed by the HBSC network. FAS gauges material wealth within the family by asking about possessions like the number of cars and computers, whether they have their own bedroom, and how many family holidays they took in the past year. The scores are summed, ranging from 0 (lowest affluence) to 9 (highest affluence), and this score was used in further analyses.

Statistical Analysis

To assess how mental wellbeing indicators have changed from 2004 to 2022, we calculated the average scores for each survey year, both for the entire sample and separately for boys and girls. To analyze trends in adolescent mental wellbeing, we performed multiple regression analyses, using 2004 as the baseline year, with other survey years included as dummy variables (these are called Null models).

Next, we repeated these analyses while controlling gender, age, and family affluence (this is referred to as Model 1). To see if the trends differed between girls and boys, we added an interaction term between survey year and gender in the Model (Model 2). Then, we examined whether differences based on age and socioeconomic status changed over time by including interaction terms between survey year and age (Model 3), and between survey year and family affluence (Model 4). Finally, we tested whether the trends were more pronounced for older adolescent girls by running a Model with a three-way interaction among survey year, gender, and age (Model 5). To check for linear trends over time, we also conducted separate linear regressions with time treated as a continuous variable. All analyses were performed using SPSS version 24.0. We considered results statistically significant if the *p*-value was less than 0.05.

Results

Table I shows the characteristics of the sample. The average age of participants was 13.52 (SD = 1.67) (mean age range from 13.21 in 2022 to 13.80 in 2018). About half of the participants (49.8%) were girls, with yearly percentages ranging from 48.0% in 2022 to 52.4% in 2014. Across most survey years (except 2004 for psychological and somatic symptoms), girls reported significantly higher levels of psychological and somatic symptoms and lower levels of life satisfaction (Tab. II). Overall, mean scores for psychological symptoms were lower than those for somatic symptoms.

Changes over time were recorded for all three wellbeing indicators, but each followed a different trajectory. Life satisfaction was significantly lower in 2014 (B = -0.018; ns) and 2022 (B = -0.443; $p < 0.001$) compared to 2004, but it returned to levels similar to 2004 in 2006 (B = 0.071; ns), 2010 (B = 0.016; *ns*) and increased significantly in 2018 (B = 0.132; $p < 0.004$). Psychological symptoms were significantly lower in all survey years after 2004, with the largest difference being observed in 2010 (B = -1.665; $p < 0.001$) and 2014 (B = -1.653; $p < 0.001$). Similarly, somatic complaints were significantly lower in all waves, with the greatest difference in 2006 (B = -1.013; $p < 0.001$) (Tab. III, Model 1). Linear trend analyses from 2004 to 2022 showed a linear decrease in adolescent across all mental wellbeing measures: life satisfaction (B = -0.05; $p < 0.001$), psychological complaints (B = -0.217; $p < 0.001$) and somatic complaints (B = -0.075; $p < 0.001$).

Compared to boys, girls reported significantly lower life satisfaction (B = -0.372; $p < 0.001$), and higher levels of psychological (B = 0.353; $p < 0.001$) and somatic symptoms (B = 0.237; $p < 0.001$) throughout the study period. However, changes in the gender gap over time were not consistent across the mental wellbeing indicators. For example, the gap between in life satisfaction between boys and girls was only significantly smaller in 2022 compared to 2004. In contrast, the differences in

Tab. I. Sample characteristics (N = 18,439).

	2004	2006	2010	2014	2018	2022	Total
Participants per survey	3,614	3,405	3,291	2,511	3,087	2,531	18,439
Gender							
Boys (%)	50.5	48.8	51.7	47.6	50.2	52.0	50.2
Girls (%)	49.5	51.2	48.3	52.4	49.8	48.0	49.8
Mean age (SD)[a]	13.51 (1.66)	13.54 (1.66)	13.31 (1.64)	13.75 (1.68)	13.80 (1.64)	13.21 (1.69)	13.52 (1.67)
Mean family affluence (SD)[b]	5.15 (1.75)	5.33 (1.74)	5.97 (1.71)	5.20 (1.73)	5.38 (1.74)	5.10 (1.67)	5.37 (1.75)
Mental health and wellbeing							
Mean life satisfaction (SD)[c]	7.39 (2.02)	7.49 (1.99)	7.57 (1.89)	7.35 (1.89)	7.51 (1.78)	7.03 (1.95)	7.41 (1.93)
Mean psychological symptoms (SD)[d]	2.64 (0.54)	1.02 (0.85)	0.97 (0.82)	1.01 (0.87)	1.10 (0.90)	1.22 (1.02)	1.37 (1.05)
Mean somatic symptoms (SD)[d]	2.49 (0.95)	1.48 (0.96)	1.49 (0.97)	1.54 (1.06)	1.69 (1.06)	1.94 (1.10)	1.78 (1.08)

FAS: Family Affluence Scale. [a] Range age 10.58-16.50; [b] Range FAS scale 0-9; [c] Range scale 0-10; [d] Range 0-4.

Tab. II. Marginal estimated means for life satisfaction and health symptoms by gender (N = 18,439).

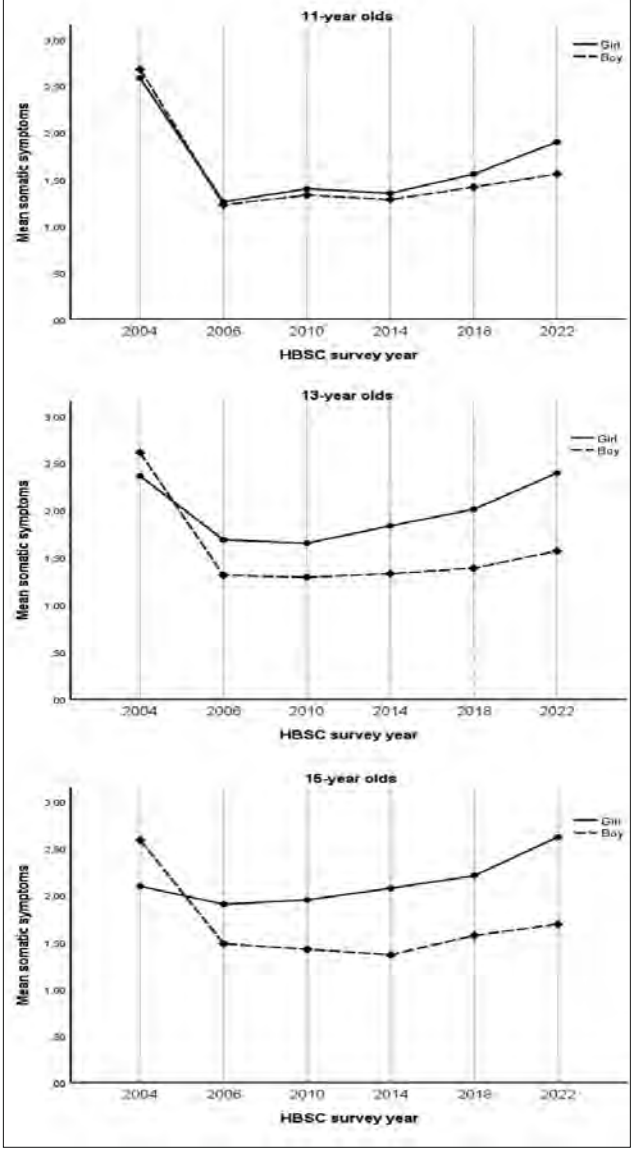
	2004	2006	2010	2014	2018	2022
	Mean (95% CI)[a]	Mean (95% CI)[a]	Mean (95% CI)[a]	Mean (95% CI)[a]	Mean (95% CI)[a]	Mean (95% CI)[a]
Boys						
Mean life satisfaction[b]	7.58 (7.49-7.66)	7.70 (7.61-7.78)	7.62 (7.53-7.70)	7.61 (7.51-7.71)	7.72 (7.63-7.81)	7.34 (7.24-7.44)
Mean psychological symptoms[c]	2.68 (2.64-2.71)	0.84 (0.81-0.88)	0.82 (0.79-0.86)	0.77 (0.73-0.81)	0.91 (0.87-0.94)	0.89 (0.85-0.93)
Mean somatic symptoms[c]	2.63 (2.58-2.67)	1.33 (1.029-1.38)	1.35 (1.30-1.39)	1.32 (1.26-1.37)	1.45 (1.40-1.50)	1.61 (1.56-1.67)
Girls						
Mean life satisfaction[b]	7.30 (7.21-7.39)	7.32 (7.23-7.41)	7.29 (7.20-7.39)	7.23 (7.13-7.34)	7.42 (7.32-7.52)	6.65 (6.54-6.76)
Mean psychological symptoms[c]	2.61 (2.57-2.65)	1.18 (1.14-1.22)	1.13 (1.09-1.18)	1.21 (1.17-1.26)	1.26 (1.22-1.31)	1.62 (1.57-1.67)
Mean somatic symptoms[c]	2.34 (2.30-2.39)	1.61 (1.56-1.66)	1.66 (1.61-1.71)	1.71 (1.65-1.76)	1.89 (1.84-1.94)	2.33 (2.27-2.39)

[a]Adjusted by age and family affluence; [b]range scale 0-10; [c]range 0-4

psychological symptoms between boys and girls were significantly larger in all survey years compared to 2004 and the same pattern was observed for somatic symptoms. Three-way interaction analyses were run (survey year × gender ×age; not shown in Table III) showing that increases in psychological complaints were stronger for older adolescent girls across survey years: 2006 (B = 0.06; < 0.001), 2010 (B = 0.08; < 0.001), 2014 (B = 0.12; $p < 0.001$), 2018 (B = 0.10; $p < 0.001$) and 2022 (B = 0.19; $p < 0.001$) (Fig. 2). A similar pattern was observed for somatic symptoms: 2006 (B = 0.10; < 0.001), 2010 (B = 0.12; $p < 0.001$), 2014 (B = 0.15; $p < 0.001$), 2018 (B = 0.12; $p < 0.001$) and 2022 (B = 0.15; $p < 0.001$), as well as for life satisfaction, which decreased more for older adolescents: 2006 (B = -0.14; < 0.001), 2010 (B = -0.10; $p = 0.01$), 2014 (B = -0.17; $p < 0.001$), 2018 (B = -0.11; $p = 0.01$) and 2022 (B = -0.11; $p = 0.02$) (Figs. 1, 3).

Overall, with increasing age, adolescents in Tuscany reported lower life satisfaction (B = -0.195; $p < 0.001$, Tab. II, Model 1) and higher psychological (B = 0.044; $p < 0.001$) and somatic symptoms (B = 0.064; $p < 0.001$). Over time, the differences between younger and older adolescents increased for psychological and somatic symptoms (Tab. III, Model 3). In contrast, the age gap for life satisfaction remained mostly stable, except in 2006, when it decreased slightly (B = -0.06; $p = 0.026$).Higher family affluence was associated with greater life satisfaction (B = 0.112; $p < 0.001$). The link between family affluence and psychological symptoms was found only in 2014 compared to 2004 (B = 0.025; $p = 0.039$), while for somatic symptoms in all survey years except for 2014. Regarding life satisfaction, the differences related to family affluence decreased only in 2022 compared to 2004 (B = -0.061; $p = 0.033$).

Fig. 1. Trends over time in somatic symptoms by gender and age.



Discussion

This study investigated trends in three key indicators

Tab. III. Time trends in life satisfaction, psychological and somatic symptoms: interaction effects with gender, age and family affluence (N = 18,439).

Main effects		Life satisfaction			Psychological symptoms			Somatic symptoms		
		B	SE	*p*-value	B	SE	*p*-value	B	SE	*p*-value
Null models	2006 (ref. 2004)	0.10	0.05	0.03	-1.625	0.02	< 0.001	-1.01	0.02	< 0.001
	2010 (ref. 2004)	0.176	0.05	< 0.001	-1.674	0.02	< 0.001	-0.996	0.02	< 0.001
	2014 (ref. 2004)	-0.045	0.05	0.375	-1.628	0.02	< 0.001	-0.948	0.03	0.120
	2018 (ref. 2004)	0.123	0.05	0.01	-1.545	0.02	< 0.001	-0.797	0.03	< 0.001
	2022 (ref. 2004)	-0.357	0.05	< 0.001	-1.421	0.02	< 0.001	-0.55	0.03	< 0.001
Model 1	2006 (ref. 2004)	0.071	0.05	0.11	-1.63	0.02	< 0.001	-1.013	0.02	< 0.001
	2010 (ref. 2004)	0.016	0.05	0.73	-1.665	0.02	< 0.001	-0.98	0.02	< 0.001
	2014 (ref. 2004)	-0.018	0.05	0.71	-1.653	0.02	< 0.001	-0.974	0.03	< 0.001
	2018 (ref. 2004)	0.132	0.05	0.004	-1.56	0.02	< 0.001	-0.815	0.02	< 0.001
	2022 (ref. 2004)	-0.443	0.05	< 0.001	-1.393	0.02	< 0.001	-0.515	0.03	< 0.001
	Gender (ref. boys)	-0.372	0.03	< 0.001	0.353	0.01	< 0.001	0.237	0.01	< 0.001
	Age (continuous)	-0.195	0.008	< 0.001	0.044	0.004	< 0.001	0.064	0.004	< 0.001
	FAS (continuous)	0.112	0.008	< 0.001	0.005	0.003	0.15	0.001	0.004	0.795
Interaction effects										
Model 2	2006×gender	-0.118	0.09	0.19	0.413	0.04	< 0.001	0.567	0.05	< 0.001
	2010×gender	-0.056	0.09	0.53	0.379	0.04	< 0.001	0.592	0.05	< 0.001
	2014×gender	-0.133	0.10	0.18	0.533	0.04	< 0.001	0.691	0.05	< 0.001
	2018×gender	-0.071	0.09	0.44	0.453	0.04	< 0.001	0.750	0.05	< 0.001
	2022×gender	-0.385	0.10	< 0.001	0.775	0.042	< 0.001	0.976	0.05	< 0.001
Model 3	2006×age	-0.06	0.03	0.026	0.045	0.01	< 0.001	0.176	0.01	< 0.001
	2010×age	-0.001	0.03	0.96	0.047	0.01	< 0.001	0.141	0.01	< 0.001
	2014×age	0.014	0.03	0.642	0.072	0.01	< 0.001	0.172	0.02	< 0.001
	2018×age	-0.002	0.03	0.952	0.070	0.01	< 0.001	0.167	0.02	< 0.001
	2022×age	-0.008	0.03	0.78	0.102	0.01	< 0.001	0.163	0.02	< 0.001
Model 4	2006×FAS	-0.011	0.03	0.67	-0.007	0.01	0.52	-0.053	0.01	< 0.001
	2010×FAS	-0.046	0.03	0.08	0.014	0.01	0.21	-0.047	0.01	0.001
	2014×FAS	-0.054	0.03	0.06	0.025	0.01	0.039	-0.027	0.01	0.07
	2018×FAS	-0.038	0.03	0.154	0.002	0.01	0.88	-0.044	0.01	0.001
	2022×FAS	-0.061	0.03	0.033	0.015	0.01	0.21	-0.050	0.02	0.001

FAS: Family Affluence Scale; Models 2, 3 and 4 are controlled for main effects of survey year, gender, age, and family affluence, respectively.

of adolescent mental wellbeing using regionally representative cross-sectional data from the Tuscany Region (2004, 2006, 2010, 2014, 2018 and 2022). Moreover, it also explored whether gender, age, and family affluence may have influenced these trends. The main finding shows that adolescent mental wellbeing in Tuscany evolved between 2004 and 2022 across all three indicators, with each indicator exhibiting a distinct pattern of change over time.

Throughout the entire period analyzed, adolescent mental wellbeing showed a linear decline, specifically in life satisfaction, psychological complaints, and somatic complaints. Compared to 2004, life satisfaction was significantly lower in 2014 and 2022, though it rebounded to levels similar to 2004 in 2006, 2010, and notably in 2018. Compared to 2004, psychological symptoms were significantly lower in all subsequent years, with the largest decline observed in 2010 and 2014. Similarly, somatic complaints decreased significantly in all survey years, with the most substantial difference seen in 2006. Adolescent wellbeing is a growing public health concern worldwide. Since the early 21st century, a decline in adolescent emotional wellbeing, such as lower life satisfaction, increased emotional symptoms, and more psychosomatic health complaints, has been observed in high-income countries such as Denmark, Sweden, Iceland, the UK, and the United States [15-17]. A study examining in adolescent wellbeing trends over time (2005-2009-2013-2017) in the Netherlands, a country where young people have consistently reported one

Fig. 2. Trends over time in psychological symptoms by gender and age.

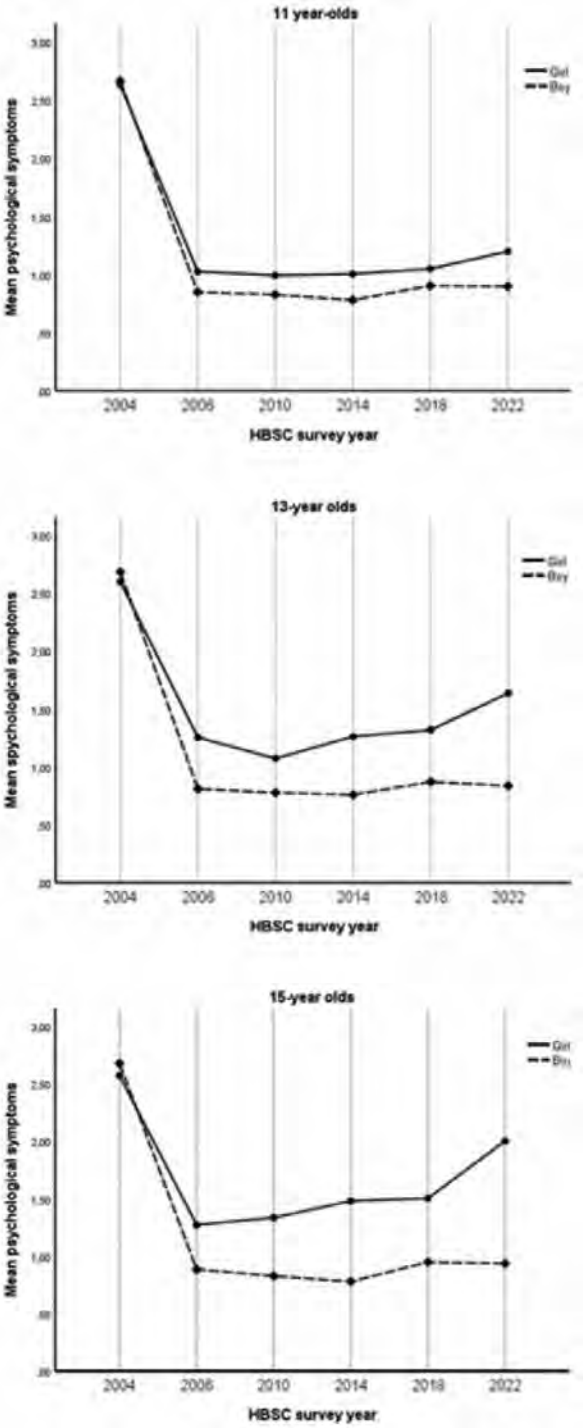
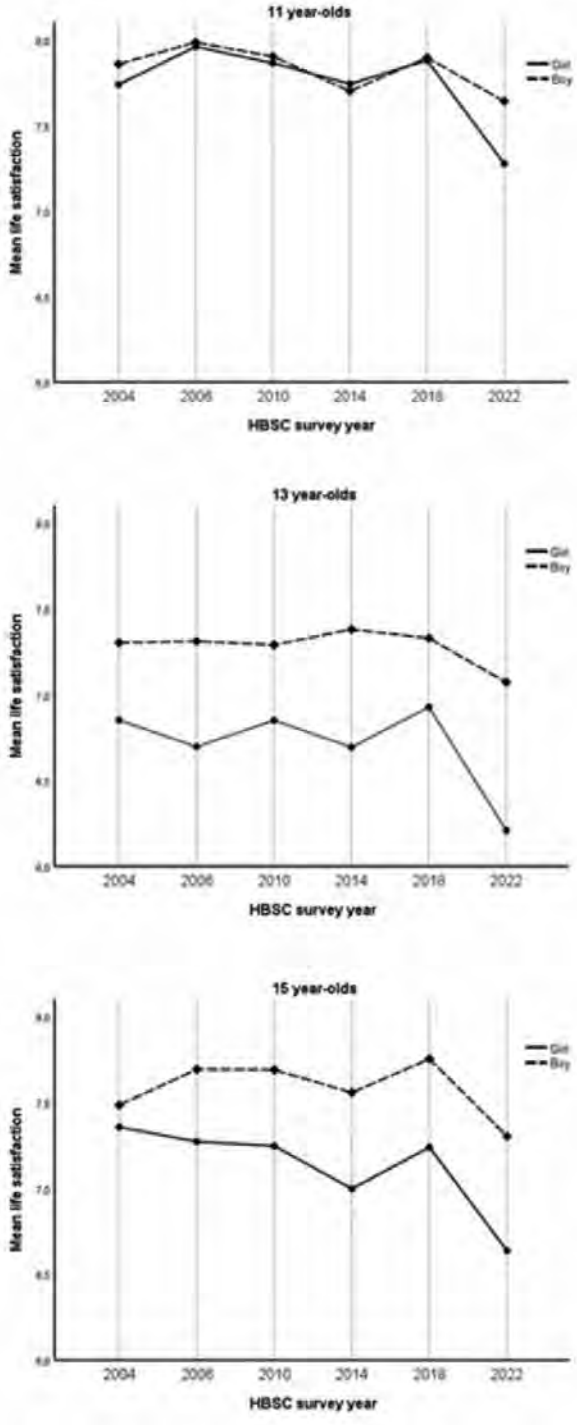


Fig. 3. Trends over time in life satisfaction by gender and age.



of the highest levels of wellbeing in Europe, found a slight decline in mental wellbeing among adolescents between 2009 and 2013 [18]. While time trends in adolescent mental wellbeing in the Czech Republic between 2002 and 2018 did not provide evidence for substantial temporal changes in mental wellbeing among adolescents. Specifically, there was a consistent increase in the prevalence of psychological symptoms from 2002 onwards, while life satisfaction declined until 2014, followed by an increase from 2014 to 2018. Regarding somatic complaints, these rose until 2010, after which a subsequent improvement was observed [19]. The 2022 HBSC Tuscany report highlights how diverging trends in psychological complaints, somatic complaints, and life satisfaction reinforce the idea that adolescent mental wellbeing is not a unidimensional construct. These different components of mental wellbeing can follow distinct trajectories and may have varying

susceptibilities. Life satisfaction, reflecting global cognitive evaluations of one's life, can be seen as a broad indicator of subjective wellbeing, therefore influenced by wider life experiences and relationships. In contrast, psychosomatic complaints may reflect immediate stress symptoms, which, when more severe, can impair daily functioning and may be linked to internalizing disorders. Additionally, emotional components of wellbeing, such as psychological complaints, tend to fluctuate more than life satisfaction, which is generally considered a more stable aspect [19]. These findings underscore the importance of viewing mental wellbeing as a multidimensional construct and highlight the need for a deeper understanding of the associations between risk factors and different aspects of mental wellbeing. To address this, the Governmental Council for Mental Health has been established, with one of its goals being to monitor and promote the mental wellbeing of young people.

The low levels of life satisfaction observed in this study in 2022 may be attributed to the negative effects of the COVID-19 pandemic on adolescents lives, as also reported in other studies [20, 21].

A large survey in Oslo revealed a marked decline in the proportion of adolescents reporting high life satisfaction during COVID-19 school closures compared with pre-pandemic levels. Specifically, rates dropped from approximately 88-92% before the pandemic to around 62-71% during periods of restriction, varying by gender, indicating a substantial decrease in subjective well-being associated with pandemic conditions [22]. Similarly, another study comparing adolescents before and during the pandemic found lower life satisfaction during the pandemic, alongside reduced physical activity, both factors well-established as correlates of overall well-being [23]. During the pandemic, a decline in life satisfaction of adolescents was noted, accompanied by an increase in depressive symptoms, increased distress, subjective well-being, reduced optimism, and increased sadness. Prior to the pandemic, no significant differences in life satisfaction were found among younger adolescents across European countries, with Polish adolescents reporting the highest levels of life satisfaction in relation to overall family climate, alongside Norwegian adolescents [20, 21, 24-29].

Our data highlights that, compared to boys, girls consistently reported significantly lower life satisfaction, along with more psychological and somatic symptoms throughout the study period. However, the gender gap over time was not consistent across the mental wellbeing indicators. For instance, the gap in life satisfaction between boys and girls was significantly smaller only in 2022 compared to 2004. In contrast, the gender differences in psychological symptoms were significantly larger over time in all years when compared to 2004. A similar trend was observed for somatic symptoms. This finding aligns with previous research indicating that girls are more likely to report poorer mental well-being outcomes and supports evidence [19, 29] showing rising trends in emotional problems [30] or psychological and somatic symptoms [6] among girls only. The widening gender gap over time may be attributed to factors such as exposure to societal gender role expectations and the distinct roles assigned to women and men, alongside gender-specific stressors. Additionally, considerable evidence suggests that girls are expected to exhibit greater emotional sensitivity [31], face more restrictive gender roles and body dissatisfaction [32, 33] and are more likely to experience and communicate health symptoms [34], or experience higher school performance pressure [35] but potential underlying mechanisms for such trends are yet to be examined. This study investigates cross-national time trends in adolescent mental well-being (psychosomatic health complaints and life satisfaction, all of which may contribute to the gender disparities in mental well-being observed among adolescents in the Tuscany Region and in other countries such as the Czech Republic [19]. Notably, the smaller gap in life satisfaction between boys and girls reported in 2022 only compared to 2004 may be associated with the impact of the COVID-19 pandemic, which affected both genders. These findings are consistent with other studies reporting a decline in adolescents life satisfaction during the lockdown [36-40]. While some studies suggested that girls, including adults, were more negatively affected than boys [41], others report the opposite [42].

Our results indicate that the increase in psychological complaints has been more pronounced among older adolescent girls in 2006, 2010, 2014, 2018, and 2022. A similar trend was observed for somatic symptoms and life satisfaction during these years. Overall, as adolescents aged, those in Tuscany reported lower levels of life satisfaction and higher levels of psychological and somatic symptoms. However, the differences between younger and older adolescents have increased over time only for psychological and somatic symptoms. In contrast, the age gap in life satisfaction remained stable throughout the study period, except in 2006, when the age difference in life satisfaction decreased. These findings partially align with a study [19], which found that older adolescents were more likely to report poor mental wellbeing, and this age gap has increased over time, although not for all outcomes. Specifically, the differences between younger and older adolescents have increased over time only for psychological symptoms. For life satisfaction and somatic symptoms, the age gap remained stable throughout the study period, except in 2006, when the age gap increased for life satisfaction. Moreover, the increase in psychological complaints had been most pronounced among older adolescent girls, as also highlighted by a review [4] evaluates evidence on whether the population prevalence of child and adolescent mental health problems has changed. The primary focus of the review is on epidemiological cross-cohort comparisons identified by a systematic search of the literature (using the Web of Knowledge database evaluating whether the population prevalence of child and adolescent mental health problems has changed. This body of evidence suggests that this trend is not something to be considered as a national

phenomenon [19] but warrants greater attention. A comprehensive understanding of trends in child and adolescent psychopathology is essential for shaping public health priorities and assessing progress in addressing the burden of childhood psychiatric disorders. However, findings from various studies are not always consistent. For instance, in Norway, an increasing trend in health complaints among adolescents from 1994 to 2014 was observed, particularly among older adolescent girls [6]. In Sweden, an increase in psychological complaints over time (1985 to 2005) was noted in older adolescents (boys and girls), while no significant change was seen in the youngest groups (11-year olds) [43]. Considering these mixed results, there is a clear need for a more comprehensive study that includes multiple countries over a longer time frame and uses a consistent set of mental health and wellbeing outcomes for boys, girls, adolescents of different age groups, and socioeconomic backgrounds [19]life satisfaction.

This study found a positive association between higher family affluence and higher levels of life satisfaction. The relationship between family affluence and psychological symptoms was observed only in 2014 compared to 2004, while associations with somatic symptoms were found in all years except 2014. For life satisfaction, the differences decreased by 2022 compared to 2004. Family affluence plays a crucial role in adolescent well-being and is a potential source of health inequalities. A cross-national comparative analysis conducted among adolescents aged 11 to 15 years in 45 countries during 2017-2018 found a positive association between life satisfaction scores and high family support across all 45 countries [44]. In the majority of countries, living with both parents and having higher levels of family affluence positively influenced adolescent life satisfaction, both directly and indirectly, through family support. These findings highlight that the path system of relationships, which exist between family support, family structure, and family affluence controlling for gender and age, are a key factor in predicting the level of adolescent life satisfaction. In fact, socioeconomic status is a significant determinant of adolescent well-being. Cross-national evidence from the HBSC study shows that adolescents from less affluent families report significantly lower life satisfaction than their more affluent peers [45].

High life satisfaction is important for the overall quality of adolescents' life and for their mental health in general. As such, promoting high life satisfaction for all adolescents, while addressing their health needs based on age and gender, should be a major priority in public health and social policy. Additionally, prevention and intervention programs aimed at improving adolescent well-being could be enhanced by incorporating strategies that help parents recognize and understand the significance of family support in fostering their child's emotional development, happiness, and life satisfaction.

A key strength of the present study is investigating representative samples of adolescents using identical study protocols across a 16-year period. Nonetheless, this inherently fosters the limitation that data collected across time is cross-sectional and self-reported and no causality can be inferred. The measures used were restricted to those available in the HBSC study since 2002, therefore providing a relatively limited perspective on adolescent mental health. Further research should include a broader range of mental health outcome measures and other potential drivers of mental health trends, such as changes in the school or family environment, or social media use, which are required to better understand this complex issue. Nonetheless, the present study provides essential and up-to-date information about changing mental health trends in early adolescence.

Conclusion

These findings indicate that the rise in psychological health issues should be viewed as a public health concern. It is positive that life satisfaction did not decline further and even showed some improvement. To better identify factors influencing adolescent mental wellbeing, ongoing longitudinal research and monitoring of health trends are essential. Additionally, our results emphasize the importance of sustained efforts in primary prevention and promoting adolescent wellbeing, taking into account age and gender differences, as well as initiatives to improve mental health awareness.

Acknowledgments

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Ethics approval

This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethical Board of the National Institute of Health (General protocol: PRE-876/17) on 10 November 2017.

Consent to participate

Informed consent was obtained from all subjects involved in this study.

Conflicts of interest statement

The authors have explicitly stated that they have no known financial interests or personal affiliations with third parties that could potentially impact the outcome of this study.

Availability of data and material

Data presented in this study are available in accordance with the 2022 Italian HBSC data access policy. Requests should be directed to the Italy Principal Investigator, Prof. Giacomo Lazzeri: giacomo.lazzeri@unisi.it.

Authors contributions

GL: Conceptualization, Methodology, Resources, Data Curation, Supervision, Project Administration and Funding Acquisition; AP: Formal Analysis; AM, DL, RS, GL: Investigation; AM, CMT, GL: Writing-original draft, Writing-review and Editing; AM, CMT, DL, AP, RS, GL: Visualization.

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Correspondence: Claudia Maria Trombetta,Via Aldo Moro 2, 53100 Siena, Italy. E-mail: trombetta@unisi.it

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HEALTH CARE MANAGEMENT

Developing health research impact assessment in Italy: the case of the Piedmont Region

GUIDO RESANI[1], GUGLIELMO PACILEO[2,3], ERICA PICASSO[1,2,3], ANTONIO MACONI[3,4], MARTA BETTI[3,4], ANNALISA ROVETA[3,4], VALERIA DOMENICA TOZZI[5], FRANCESCA UGO[3,4], GLORIA SPATARI[2,3,6], ANNA ODONE[1]
[1] Department of Public Health, Experimental and Forensic Medicine, University of Pavia, Pavia, Italy; [2] Local Health Authority of Alessandria, Alessandria, Italy; [3] DAIRI (Department of Integrative Activities for Research and Innovation); [4] SS. Antonio e Biagio e Cesare Arrigo University Hospital of Alessandria, Alessandria, Italy; [5] SDA Bocconi School of Management, University of Milan, Italy; [6] Department of Health Sciences (DISSAL), University of Genoa, Genoa, Italy

Keywords

Research Impact Assessment • Health Research Evaluation • Healthcare System Research • Healthcare System Management

Summary

Background. *Research Impact Assessment (RIA) is complex and still in the process of being defined. The most appropriate RIA framework should be selected and adapted according to the context and the specific purpose.*
The real challenge is experimenting with RIA and sharing the findings with the scientific community.
Italy has a National Health System in which the Regions are granted with significant legislative authority in the healthcare sector.
The Piedmont Region has a healthcare system based on 12 Local Health Authorities (LHA) and six autonomous public hospitals.
The Piedmont Region has entrusted DAIRI (Department of Integrative Activities for Research and Innovation), an interinstitutional department of the Alessandria LHA and Alessandria Hospital, with the task of monitoring regional health research.

Aims. *This study aims to identify an RIA framework that can be applied to health research organisations in Alessandria Province and subsequently at the regional level.*
We aim to disseminate the results of these evaluations to contribute to the advancement of RIA within the scientific community and initiate a continuous RIA process.
Methods. *We approached the study in two phases. First, a literature review to identify a range of frameworks suitable for our context; second, a focus group to determine the most appropriate framework from this pool.*
Findings, discussion and conclusion. *Since adopting an existing framework requires tailoring it to the specific needs of the research organisation, we decided to select the framework proposed by Banzi et al. (2011) and adapt it to the context in which DAIRI operates.*

Background

The need to optimize the results of research investments is increasingly pressing. Hence, there is a growing interest in developing and applying processes for measuring the impact of research [1].
This work aims to identify a framework to conduct a research impact assessment (RIA) to be applied to health research organizations in the Italian Piedmont Region.
Frameworks are valuable in RIA to collecting, organising, and analysing data, providing methodological guidance, and offering the possibility to compare the impact of research across different disciplines, institutions, and countries [1].
RIA employs mixed methods and multiple data sources to examine the research process to maximise its societal and economic impacts, such as intellectual property, spin-out companies, health outcomes, public understanding and acceptance, policy-making, sustainable development, social cohesion, gender equity, cultural enrichment, and other benefits [1]. Frameworks utilising associated measures are also helpful in informing impact categories.
The term "research impact" refers to any output of research activities that can be considered a "positive return" for the scientific community, health systems, patients, and society in general [2, 3]. It also refers to any identifiable benefit to or positive influence on the economy, culture, public policy or services, health, environment, quality of life, or academia [4].
The York Research Impact Statement describes research impact as "…when the knowledge generated by our research contributes to, benefits and influences society, culture, our environment and the economy" [5].
For the ARC (Australian Research Council), Research Impact is the contribution that research makes to the economy, society, environment, or culture beyond the contribution to academic research [6].
Organization for Economic Co-operation and Development's (OECD) Development Assistance Committee's (DAC) definition of impact: "Positive and negative, primary and secondary long-term effects produced by a development intervention, directly or indirectly, intended or unintended" [7].
UK Research and Innovation (UKRI) defined the impact as "an effect on, change or benefit to the economy, society, culture, public policy or services, health, the environment or quality of life, beyond academia" [8].
US National Science Foundation (NSF) defines broader

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impacts as the potential to benefit society and contribute to achieving specific, desired societal outcomes [9].

RIA practice is still in its creation and definition phase; therefore, there are no internationally validated and approved standards and procedures despite the development and dissemination of several RIA methodological frameworks worldwide [1].

Nevertheless, significant work has been done on Research Assessment: The Declaration on Research Assessment (DORA) recognises the need to improve how scholarly research outputs are evaluated. DORA is a worldwide initiative covering all scholarly disciplines and all critical stakeholders, including funders, publishers, professional societies, institutions, and researchers [10].

Five experts have proposed ten principles for measuring research performance to support researchers and managers: the Leiden Manifesto for Research Metrics [11].

The impact of research is complex to analyse; it is not linear, often difficult to predict, involves different processes, individuals, and organisations, and can be observed in the short, medium, and long term [1, 3, 4, 12]. Generally, RIA is ex post, while it is also essential to have an ex ante evaluation [2, 4].

In RIA, there is a widespread tendency to "count what can be easily measured" rather than measuring what "matters" in terms of more significant and lasting changes [3, 13].

Traditional academic indexes of research productivity assessment (such as the number of articles produced, journal impact factors, citations, research funding, and estimation measures) are widely used but primarily measure the dissemination of research findings rather than their impact [4].

These measurements hardly allow us to fully evaluate the results of the research [14] and are not sufficient to fully determine its value, as they say little about the advantages it brings to the system in which it is applied [3]. Therefore, there is a growing interest in RIA on the systems that constitute the world in which we live beyond the individual academic world [1].

There is no consensus on systematic approaches to conducting RIA [1, 2, 4], but there is growing consensus about the need for principles/guidelines [1] and on using mixed methods and multiple data sources; no RIA tool has proven superior, and we do not know enough about the influence of health research on broad systems such as health policy and practice [3].

Conducting RIA takes a considerable amount of time and resources, and attributing specific contributions to the impact of research, transaction costs, and administrative burdens associated with collecting and analysing data is challenging. Collecting standard metrics is of significant value but can be time-consuming, resource-intensive, and challenging; two characteristics are fundamental in the development of standard metrics: burden and value. It is also essential to take into account the credibility of frameworks, which can have a significant impact on their effectiveness [2-4, 12, 15-18].

We have identified many experiences worldwide that have institutionalised the RIA process through various methodologies [1]. We anticipate increasing interest in it.

The Research Excellence Framework (REF) is the system for assessing the excellence of research in UK higher education providers. Its objectives are to provide accountability for public investment in research and produce evidence of the benefits of this investment; to provide benchmarking information and establish reputational yardsticks for use in the higher education sector and for public information; and to inform the selective allocation of funding for research [19].

Australia's national research assessment is ERA (Excellence in Research for Australia), administered by the ARC. It identifies and promotes excellence in research in Australia's higher education institutions through comparisons with international benchmarks. ERA aims to promote excellence, inform decisions, demonstrate quality, and enable comparisons. No ERA evaluation round will not be conducted in 2023 because the ARC will develop a plan to transition ERA to a modern, data-driven approach [20].

In the Netherlands, VSNU (Association of Universities in the Netherlands), KNAW (Royal Netherlands Academy of Arts and Sciences), and NWO (Netherlands Organisation for Scientific Research) are responsible for the quality of research at their institutions. As part of their quality assurance cycle, all academic research in the Netherlands is evaluated every six years. The executive board of the relevant university, the board of NWO, or the board of KNAW commissions the research assessment and determines which research units will be evaluated each year. To coordinate the assessment, all research organisations associated with VSNU, KNAW, and NWO use the Strategy Evaluation Protocol (SEP). The main goal of a SEP evaluation is to assess a research unit in light of its aims and strategy [21].

In the United States, the NSF funds scientists and engineers in charge to conduct research that advances discovery and innovation.

The NSF funds scientists and engineers to perform research aimed at advancing discovery and innovation. The agency also expects the work of researchers to have broader impacts: the potential to benefit society and contribute to achieving specific, desired societal outcomes [22].

As the range of RIA methods expands, it is crucial to select the most appropriate method for the various contexts (and purposes) in which RIA must be conducted [12]. Numerous frameworks for RIA and several reviews in the literature help elucidate its advantages and limitations. However, we have found few examples of RIA practice published in scientific journals (perhaps because many look at RIA as "an administrative duty rather than a research activity" [2]). Thus, the primary challenge for research organisations is to practically adapt and experiment with RIA approaches within their context and to share their findings with the scientific community [1-3, 12, 15].

The Italian and Piedmont Region context

Italy has a National Health System (NHS) established in 1978. In 1992 and 1993, the government approved the first reform of the NHS (Legislative Decrees 502/1992 and 517/1993), devolving healthcare powers to the Regions, along with a parallel delegation of managerial autonomy to public hospitals and Local Health Authorities (LHA). In 2001, with the amendment to Title V of the Italian Constitution, the Regions were further entrusted with the legislative power in the health field [23].

The Piedmont Region is the second-largest region in Italy, located in north-west of the Country. The health system within the region is based on 12 LHAs, which aim to protect and promote public health in their respective areas, as well as six autonomous public hospitals.

National Institutes for Scientific Research (IRCCS) conduct research activities in the biomedical field and the organisation and management of health services. They also provide high-specialty hospitalisation and care services or carry out other activities characterised by excellence. The Ministry of Health is responsible for the supervision and control of IRCCS; Regions are responsible for the legislative and regulatory functions related to the assistance and research activities carried out by the Institutes. The establishment of new IRCCS must align with the health planning of the Region (and with European regulations regarding research organisations). The entity seeking recognition as an IRCCS submits an application to the Region, which then reviews and, if appropriate, forwards the application to the Ministry of Health. The Minister of Health appoints an evaluation commission and submits the documentation to the State-Regions Conference for approval. Following an agreement with the President of the relevant Region, the Minister of Health approves the request by decree [24].

In our case, the Piedmont Region, through the Regional Council of 18 May 2021 No. 10-3222, mandated the Alessandria LHA and Alessandria Hospital to establish the IRCCS for environmental diseases and mesothelioma and assigned DAIRI the task of leading the process. DAIRI is an interinstitutional department of the Alessandria LHA and Alessandria Hospital.

In March 2022, a resolution by the Piedmont Region identified DAIRI as the coordinating and supporting infrastructure for the regional "governance" of clinical and biomedical research, ensuring organisational homogeneity and proper functioning of these activities through the promotion and integration of research and innovation programmes of the Regional Health Authorities (RHAs).

In order to promote research and innovation as a condition for excellence in the Italian National Health Service, it was necessary to establish an integrated and coordinated "research system," at the level of the Piedmont Region, aimed at ensuring organisational homogeneity and proper functioning of research activities by fostering a higher level of governance, integration, collaboration, and coordination among the RHAs.

Methods

We pursued the study objective in two steps. First, we carried out a literature review to identify a pool of frameworks suitable for the needs of our context. The inclusion criteria were restricted to reviews published in English between 2012 and 2022 to ensure access to synthesized, high-level evidence of pre-validated models. Primary studies were excluded unless cited by the selected reviews as foundational. Furthermore, grey literature was intentionally excluded to prioritize peer-reviewed methodological rigor, ensuring that the starting point for regional governance was based on internationally recognized standards.Secondly, we used a focus group (composed of the DAIRI board) to identify the most appropriate one to use among this pool of frameworks.

The literature review took place in June-July 2022 by searching for the terms: "research impact", "research impact assessment", "research impact evaluation", "health research impact", "health research impact assessment", "health research impact evaluation" using the PubMed and Embase biomedical research archives, as well as search engines such as Google.

We selected the literature published between 2012 and 2022 to obtain the most recent data.

We considered only reviews published in English, analysing titles and abstracts.

To identify an RIA framework to be applied to our context, we chose the reviews that selected and described the most used and widespread RIA frameworks.

The reviews that have turned out to be more exhaustive in this regard are one systematic review [4] and three narrative reviews [3, 12, 15] that have been read in full text and analysed.

We evaluated the citations reported, and we have selected one review [2], one guideline for conducting RIA processes [1], three RIA frameworks [14, 25, 26], as well as four publications on organizational experiences of the impact of research and its evaluation [16, 17, 27, 28].

The authors of two reviews [2, 4] describe a pool of existing RIA frameworks and propose their framework.

To achieve our purpose, we selected the frameworks proposed by two reviews [2, 4] and the three frameworks identified by the systematic review [4] as more [14, 25, 26] (Tab. I).

Consequently, we shared the literature analysis results with the focus group.

Findings

Adam et al. [1] proposed a guideline for RIA applicable to all research disciplines articulated in ten points that suggest: 1) analyse the context, 2) reflect continuously on your purposes, 3) identify stakeholders and their needs, 4) engage with stakeholders early on in the process, 5) choose conceptual frameworks critically and use when appropriate, 6) use mixed methods and multi-data sources, 7) select indicators and metrics

Tab. I. Table of Frameworks Comparison.

Framework	Description	Categories of Impact Assessment
Assessing the impact of healthcare research: A systematic review of methodological frameworks	Analyses 24 research impact evaluation frameworks, obtaining a framework based on 5 categories with related subcategories; The 5 categories describe the impact of the research and are grouped by timeline (Short, Medium and Long Term Impact)	1. Primary research-related impact 2. Influence on policy-making 3. Health & health systems impact 4. Health-related & social impact 5. Broader economic impacts
Conceptual frameworks and empirical approaches used to assess the impact of health research: an overview of reviews	Adaptation of the CAHS Framework through a review of reviews. It includes five categories of research impact and offers a series of indicators for each domain. Results are obtained using bibliometric analysis, surveys, audits, document review, case studies, panel evaluation, and impact of the research in question on management decisions	1. Advancing Knowledge 2. Capacity Building 3. Informing policies and product development 4. Health and health sector benefits 5. Economic and social benefits
Research Impact Framework	Developed in the UK from the union of 12 works, the Framework is applied by researchers as a guide for semi-structured interviews aimed at identifying the impact of their research. It is built around four impact categories, within each of which further subcategories are identified	1. Research-related impact 2. Policy impact 3. Service impact 4. Societal impact
The Health Service Research Impact Framework	Framework developed in Australia, which derives from the union of three frameworks. It provides a system for monitoring research, the nature and level of impact of research to ensure that health service policies and programs are based on rigorous evidence. The results are obtained by analysing data, administrative databases, bibliometric data plus, possibly, surveys of individuals or groups relevant to the evaluation. It has 4 categories of impact assessment.	5. Research – related Impact: *"Advancing knowledge"* 6. Policy impact: *"Informing decision making"* 7. Service Impact: *"Improving health and health systems"* 8. Societal Impact: *"Creating broad social and economic benefit"*
Framework Canadian Academy of Health Sciences (CAHS)	Built by a group of international experts, approved by 28 Canadian bodies and refined with public consultation. It allows a careful evaluation of the context and consideration of the impacts in five categories, for each category a set of metrics and measures is offered. The CAHS can be used to track impacts within any of the four "pillars" of health research (basic biomedical, applied clinical, health services and systems, and population health or within domains that cross these pillars) and at various levels (individual, institutional, regional, national or international).	1. Advancing Knowledge 2. Capacity Building 3. Informing Decision Making 4. Health Impacts 5. Broad Economic and Social Impacts

responsibly, 8) anticipate and address ethical issues and conflict of interest, 9) communicate results through multiple channels, 10) share your learning with the RIA community. The guidelines help anyone who wishes to perform RIA in any scientific field at any level of assessment. Rivera et al. [4] reviewed and analysed twenty-four RIA frameworks [14, 25, 26, 29-39] and then propose their framework that identifies five categories of research impact subdivided into sub-categories: primary research-related impact, influence on policy-making, health and health systems impact, health-related and societal impact, and broader economic impact. We found a description of these frameworks and a table with a category/sub-category of impact. This table gives an immediate and intuitive picture of the completeness of each framework regarding the topics covered. The framework proposed five impact categories in a timeline (short, medium, and long-term impact); this allows us to consider the elements and metrics for a prospective impact assessment in the design phase of a study. The authors also state that literature supports collecting other forms of impact besides academic indicators. The impact of research on complex systems is more challenging to measure. It takes time for the impact of research to occur, and different processes, individuals, and organizations are involved. It is also essential to have an ex-ante assessment of the impact of research with early stakeholder involvement and well-designed dissemination. No evaluation tool is the best, and the most appropriate for a given study will depend on the needs of stakeholders.

The proposed framework allows researchers to select its components and create a tool to facilitate the study's optimal design and maximise its impact. Using a multidimensional approach is helpful. Among the frameworks analysed, we selected those able to address a more significant number of impact categories/sub-categories, *i.e.*, Research Impact Framework [14], Health Services Research Impact Framework [25], and Framework proposed by the Canadian Academy of Health Sciences (CAHS) [26].

In the narrative review of Milat et al. [3], authors extrapolated from the literature thirty-one primary studies and one systematic review and described the three most representative frameworks [2, 14, 29]. Among these, we selected and analysed for our work the Research Impact Framework [14] and the framework proposed by Banzi et al. [2], as well as a work describing the implementation of the CAHS framework in a Canadian research organization [17].

The authors of this review point out that using mixed methods to assess impacts is crucial. Governments point out that research quality metrics are insufficient to determine its value because they say little about the benefits it brings in the real world. RIA should regularly involve end-users of research in addition to researchers. Research often takes a long time to reveal its impact, and there is a low propensity to publish RIA results in scientific journals.

The revision of Greenhalgh et al. [12], starting from the analysis of revisions and publications, selected six RIA tools and proceeded with a description of them; among these, there are also the Research Impact Framework [14] and the CAHS Framework [26] used for the development of our work. Authors state that narrative accounts are needed when exploring less directly attributable aspects of the research-impact link and that short-term RIA is simpler than long-term RIA. They argue that in RIA, it is essential always to find the compromise between quality and completeness and, in addition to developing impact assessment methods, also to put them into practice.

The revision of Kamenetzky et al. [15] argues that many RIA frameworks and tools exist. Still, how organizations practice this activity is unknown and unshared. It aims to describe the experiences of research organizations in putting RIA activities into practice by combining the analysis of published RIA examples [16, 27, 28, 40, 41] with interviews with RIA professionals. They state that theoretical and conceptual RIA models abound, and the research organization's challenge is to adapt and experiment with practical RIA approaches in their context. This review guides research organizations preparing to run RIA: 1) get set up, 2) work together, and 3) recognize benefits. Among references for this review, we selected and analysed two articles [16, 27] and a guideline for the RIA [1] because they are relevant to our work.

In the revision of Banzi et al. [2], the authors included twenty-two publications from four systematic reviews and fourteen primary studies and also gave a qualitative description of ten popular RIA frameworks, including the Research Impact Framework [14]. They developed a framework derived from the CAHS framework with five impact categories: Advancing knowledge, Capacity Building, Informing Policies and Product Development, Health and Health Sector Benefits, and Economic and Social Benefits. They proposed each category's indicators, data collection methodologies, and application levels. It indicated which existing evaluation models support the specific impact category and the advantages and disadvantages for each. The authors state that RIA is evolving and focuses on 1) theoretical frameworks and models to assess research impact concerning multidimensional and integrated categories, 2) methodological approaches to the evaluation exercise, and 3) the development of valid and reliable indicators and metrics. They also state that a shared and complete framework is not available and that multidimensional frameworks seem adequate. Planning RIA and carrying it out simultaneously with developing research programs is helpful.

The Research Impact Framework by Kuruvilla et al. [14] was born from the union of twelve works and consisted of a guide to carry out semi-structured interviews to be submitted to researchers to help them assess the impacts of their research [3, 12]. It identifies four impact categories with sub-categories: 1) Research-related impacts, 2) Policy impacts, 3) Service impacts (health and intersectoral), and 4) Societal impacts.

The Health Service Research Impact Framework by Buykx et al. [25] comes from the union of three frameworks, including the Research Impact Framework [14]. They identify four impact categories with sub-categories: Advancing knowledge, informing decision-making, improving health and health systems, and creating broad social and economic benefits. They worked through mixed methodologies. They described the audience involved in the specific categories. They divided the impact evidence into active dissemination, *i.e.,* the efforts made by researchers to disseminate research to the target audience, and uptake, *i.e.,* how much the target audience has received and actively uses the research results. Authors say that data requiring qualitative and quantitative assessments are more challenging to measure than others.

The framework proposed by the Canadian Academy of Health Sciences (CAHS) [26] is an adaptation of the Payback Framework [29], which takes a more remarkable account of the various nonlinear influences involved in health research systems [12]. It comes from an international group of experts, endorsed by twenty-eight Canadian stakeholder bodies, and refined through public consultation [12]. This framework divides the impact of research into five categories: advancing knowledge, capacity building, informing decision-making, health impacts, and broad economic and social impacts. Each category has sub-categories, metrics, and measurement methods. Users are encouraged to tap into it flexibly to suit their needs [12] best. It is a complete framework that, in addition to providing impact categories, also provides indications on what data to analyse and how to collect this data.

Searles et al.'s RIA approach [27] proposes a framework that, in addition to the impact of the research, allows for evaluating and predicting the translation of the research, which is considered a prerequisite for having an impact.

The RIA approach of Rubio et al. [16] describes the development of a methodology to [1] generate potential metrics, [2] define and operationalize the most promising metrics, and [3] assess the feasibility of collecting data for the metrics. We find six categories for fifteen metrics: Clinical Research Processes, Careers, Services, Economic Return, Collaboration, and Products. This project represents the verification of the feasibility of the three metrics of the first category. It turned out that all those who are interested must clearly define metrics; it is helpful to test metrics on a few institutions; data collection takes a long time: some are easy to collect, while others are difficult; context variables are crucial; wanting to manage too many metrics can make the work impossible; when developing metrics, it is critical to

consider the burden and value of them, focusing on high-value metrics whose collection represents a low burden; it is essential to work dynamically using a formative assessment methodology; collecting data across multiple institutions is difficult.
Alberta Innovates Health Solutions has developed and applied a framework based on the CAHS framework [17]. The authors say the process has taken much time and resources. Data acquisition and reporting are challenging, and developing common, shareable, and applicable data standards throughout the research cycle is helpful. In addition to traditional scientific indicators, it is beneficial to include measures of greater interest to the broader community of stakeholders while challenging: the benefits to society are difficult to measure directly. Many think that the CAHS Model proved helpful; it is flexible enough to be customized to the needs of an organization, offers a practical guide to carry out RIA, and can be applied at multiple levels. The framework appropriately assesses the impacts on the entire spectrum of health research. Implementing the impact framework has changed how the AIHS monitors and evaluates its investments in research.

Meeting with the focus group

We shared the literature review results with the DAIRI experts (focus group). We provided them with the elements to decide whether to adopt an existing evaluation framework or create an ad hoc one. Considering that adopting an existing framework requires adapting it to the needs of the research organization, we agreed to choose the Banzi et al. Framework [2] and to proceed by shaping it to the reality in which DAIRI operates for an RIA on research organizations in the province of Alessandria.

Discussion

It is increasingly important to evaluate the impact of health research. However, it is not simple to link research to its impact because the factors that characterize it are multiple and interconnected, and research results can emerge slowly and be absorbed gradually [2, 4].
Short-term impacts are more easily attributed; long-term effects are more complex and sometimes impossible to grasp [12]; so, especially for those, the possibility of *ex-ante* evaluation is essential.
It is necessary to plan for conducting RIA, and it is suggested that policymakers have an early involvement in the research project, together with a good dissemination strategy. Interactions between stakeholders and researchers from the early stages of the research process are essential [4].
RIA should also involve end-users and users/organizations engaged in the research and network analysis. It should assess multidimensional impacts using mixed methodologies. Therefore, in addition to bibliometric and econometric methods, for example, interviews with researchers and intermediate/end users of research, peer evaluations, case studies, surveys, analysis of documents, databases, and others [1, 3].
Considering that no RIA tool has proven superior, the most appropriate framework for a study should be chosen based on the context and the specific purpose [1, 4]. Beyond its intrinsic adaptability, the selection of the Banzi et al. framework over alternatives like CAHS or RIF was driven by its superior operational balance. While the CAHS framework provides an exhaustive list of metrics, its implementation in a regional system like Piedmont one is likely to impose a prohibitive administrative burden. Conversely, while the Research Impact Framework (RIF) is excellent for qualitative narratives, it lacks the structured indicators necessary for institutional benchmarking. The Banzi framework was selected because it bridges this gap: it provides five clear impact categories with specific indicators and data collection methodologies already mapped, offering a 'turnkey' structure that minimizes transaction costs while maintaining multidimensional depth.
It is crucial to use selected categories for each specific field and to choose a time frame appropriate to the research type and the impact size; it should also be as flexible and adaptable as possible [2].
We can say that choosing a framework with multidimensional and integrated categories is crucial to carrying out an RIA and developing valid, reliable, and practical methodological approaches, indicators, and metrics.
For a multidimensional RIA, it is necessary to find the right balance between completeness and feasibility [3]. This balance implies considering many stakeholders and identifying the proper impact categories for each field. Using mixed methods of survey and adapting the frameworks according to the evaluation is crucial. Finally, it is requested to identify the right metrics, also considering the specific organisations' possibilities (it is helpful to test the metrics on a small sample) [16].
Many RIA frameworks are from the literature, but few publications describe their application. This fact is negatively affecting RIA development.

Conclusion

This work aimed to support DAIRI in identifying and selecting an RIA Framework for research organizations in the Alessandria Province and Piedmont Region. At the regional level, the Health Directorate set up a working group with the regional health organizations' research representatives. The aim was to share with them both the RIA literature review and the results of the first RIA activity carried out by DAIRI in Alessandria Province to apply the framework at the regional level in the future.
For several reasons, the RIA at the regional level requires an incremental approach. It allows a progressive adaptation of the selected framework to the organizations' needs. It also gives time to find the resources and involve the stakeholders. It helps to select the optimal metrics for the evaluation's best cost/benefit ratio.
We aim to disseminate the results of these evaluations to

contribute to the growth of the RIA process within the scientific community and to establish a continuous RIA process at the regional level.
A critical first step in realizing the goal of promoting research and innovation within the Regional Health Services has been the mapping of the research activities of Piedmont's Hospitals and LHAs, carried out through a survey conducted by all eighteen Piedmont's Hospitals and LHAs (Twelve Local Health Authorities, three Public Hospitals, three university hospital authorities), which collected research organization, research results (publications, clinical trials, funding, and collaborations), research infrastructure and research training.
The mapping revealed the need to centralize and coordinate the organizational aspects of research, which is also being addressed through the creation and operation of working groups dedicated to the development of research areas deemed priorities for the Regional Health Services, the implementation of a shared training system on health research, networking to increase the system's ability to attract funding, a biobanking network and the role of research administrators.
Our research was helpful to DAIRI in building the mapping of regional health research activities for the year 2022. The detailed results of this mapping will be the subject of subsequent dissemination activities.

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Conflicts of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' contributions

GR: performed the literature review, was one of the two main contributors in writing the manuscript, and presented the findings to the focus group; GP: performed the literature review, was one of the two main contributors in writing the manuscript and gave the results to the Focus group; EP: performed the literature review; AM: took part in the focus group as responsible of DAIRI; MB: contributed to developing the conclusions of the paper; AR: took part in the focus group as affiliated to DAIRI; VDT: contributed to developing the conclusions of the paper; FU: took part in the focus group as affiliated to DAIRI; GS: revised and edited the paper; AO: contributed to developing the conclusions.

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Correspondence: Gloria Spatari. Clinical Governance, Quality, Research Unit (Local Health Authority of Alessandria - ASL AL), Via Venezia 6, 15121 Alessandria (AL). E-mail: drgloriaspatari@gmail.com

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HEALTH PROMOTION

The digital tether: a SA-SV based survey on smartphone addiction among young adults in Southern Italy

ROBERTO VENUTO[1,2], CATERINA ELISABETTA RIZZO[2,3], GIOVANNI GENOVESE[2,3], GIUSEPPE TRIMARCHI[4], GIUSEPPE LA SPADA[3], RAFFAELE SQUERI[3], VINCENZA LA FAUCI[3], CRISTINA GENOVESE[3]
[1] Department of Chemical, Biological, Pharmaceutical and Environmental Sciences, University of Messina, Messina, Italy; [2] Department of Prevention, Local Health Authority of Messina, Messina, Italy; [3] Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, Messina, Italy; [4] SIR, University of Messina, Messina, Italy

Keywords

Smartphone addiction • Smartphone problematic use • Young adults • SAS-SV • Digital behavior

Summary

Introduction. *In the post-pandemic era, smartphone usage has surged globally, particularly among young adults. While these devices offer convenience and connectivity, their excessive use has raised concerns about behavioral addiction and psychological well-being. This study investigates the prevalence of problematic smartphone use among young adults in Southern Italy, focusing on usage patterns and socio-demographic correlations.*
Methods. *A cross-sectional survey was conducted between March and June 2025 using an anonymous online questionnaire. The instrument combined ad hoc questions on lifestyle and digital habits with the validated Smartphone Addiction Scale-Short Version (SAS-SV). Participants aged 18-40 were recruited primarily from Sicily and Calabria via university and community networks. Data were analyzed using non-parametric statistical tests and chi-square analysis.*
Results. *The final sample included 451 respondents (average age: 22.42 years), predominantly Italian and non-working students. The SAS-SV identified smartphone addiction in 21.3% of participants, with no significant gender differences. Most users engaged with smartphones for leisure, social media, and entertainment. Significant associations were found between SAS scores and variables such as region, education level, and income. Notably, higher scores correlated with emotional reliance on smartphones and difficulty disengaging from use.*
Conclusion. *Problematic smartphone use affects over one-fifth of young adults in Southern Italy, driven more by app features than screen time alone. These findings underscore the need for targeted public health strategies, including early screening and behavioral interventions, to address digital dependency and promote healthier technology habits in this demographic.*

Introduction

Global smartphone use has surged in recent years, reflecting a growing dependence on these devices across all age groups [1, 2]. This trend is driven by their user-friendly interfaces, portability, and immediate access to a vast array of applications catering to diverse daily needs [3]. Projections indicate a continued worldwide increase of 1.7 billion users between 2025 and 2029, with the total number expected to reach a record 6.2 billion. This pattern is mirrored in Italy, where the number of users is forecasted to grow by 5.9 million to a total of 53.5 million by 2029, establishing smartphones as an integral part of modern life [4, 5].
Similarly, in Italy, smartphone users will grow steadily by 5.9 million users (+ 12.39%) between 2025 and 2029. The number of smartphone users is predicted to reach 53.5 million in 2029, marking a new record after 15 years of growth [6]. However, while smartphones offer many benefits, excessive use has been associated with a range of negative clinical, psychological, and social impacts [7]. Excessive smartphone use has been linked to mental health issues, such as elevated anxiety, depression, and emotional distress, according to several studies [8, 9]. Overuse of screens can disrupt good social relationships, which can result in feelings of social isolation, loneliness, and poor communication skills, particularly in younger people [10]. The addictive aspect of smartphone use has also been brought to light in recent years by research, with some findings indicating that excessive use is akin to behavioral addictions in that it reinforces compulsive behaviors that worsen psychological and social issues [11].
The WHO has focused on the possible health implications due to the excessive use of smartphones, and some researchers have suggested a possible new form of behavioral addiction [12].
Currently, there is no unanimous consensus on the definition of smartphone addiction (SA), and there are differing viewpoints regarding the nature of this behavior [13]. According to some authors, it is misleading to categorize excessive smartphone use as an addiction, as addiction is traditionally defined as a disorder with severe and long-lasting effects on physical and psychological health [14]. Although behaviors may resemble addictions in terms of excessive use, problems with control, and unfavorable outcomes, they are not always addictions [15]. Therefore, a recent review of the literature proposed the definition of "problematic

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use" referring to the behaviors regarding technological devices [16].

As a result, "problematic use of smartphones" (PSUD) is becoming a more common term to describe a persistent inability to regulate the addictive behavior that causes discomfort or functional damage [17]. The global spread of smartphones has raised concerns about their negative effects related to problematic use, especially in the younger population [18]. The use of smartphones and other digital devices for a variety of purposes, such as gambling, online gaming, and sexual activity, is on the rise [19]. These activities can all result in several behavioral issues [20]. In addition to causing psychological pain. Excessive participation in these activities can occasionally even lead to the emergence of other types of addiction, including an addiction to gambling or the internet [21]. This change in emphasis from substance-based addiction to behavior-based addiction calls into question long-held beliefs about dependency and poses significant issues regarding the definition and management of different types of addiction in the digital age [22].

Furthermore, behavioral addiction does not exhibit the outward manifestations of substance addiction. Behaviorally addicted people, according to others, exhibit specific signs and will experience the same outcomes as those who are addicted to drugs and alcohol and engage in other compulsive behaviors [19]. While the phenomenon of problematic smartphone use is globally recognized, there remains a paucity of research focused specifically on young adults in Italy, particularly in the southern regions. This study, therefore, aims to define the prevalence of this phenomenon in this specific demographic and to evaluate its association with socio-demographic variables, habits, and lifestyles, thereby providing crucial data for region-specific public health initiatives.

Excessive smartphone engagement is marked by varied terminology, including 'smartphone addiction' (SA), 'excessive use,' and 'problematic smartphone use' (PSU). While SA is a commonly used term, its classification as a true behavioral addiction remains debated, as some argue it lacks the severe, long-lasting effects of clinically defined addictions. 'Excessive use' is a descriptive term that may not necessarily imply negative consequences. Consequently, this paper will primarily adopt the term 'problematic smartphone use,' defined as a persistent inability to regulate usage, leading to significant discomfort or functional impairment. We will, however, use the term 'smartphone addiction' when referencing validated instruments like the Smartphone Addiction Scale (SAS) and in line with the existing literature for comparative purposes.

Given the rising prevalence of smartphone use and the associated risks, there is a need to quantify this phenomenon in specific contexts. While international data exists, there is a gap in the literature regarding young adults in Southern Italy. Therefore, the primary objective of this study is to determine the prevalence of smartphone addiction in a sample of young adults from Southern Italy. The secondary objectives are: 1) to identify the primary activities for which smartphones are used, 2) to explore the association between smartphone addiction and various socio-demographic and behavioral variables (*e.g.* gender, lifestyle habits), and 3) to profile the characteristics of individuals identified as having a smartphone addiction.

Material and Methods

The study follows a cross-sectional descriptive design. The study was conducted between March and June 2025 through the administration of an anonymous questionnaire elaborated partly *ad hoc* and partly by proposing the Smartphone addiction scale (SAS) [23] and the short version of the Smartphone addiction scale (SAS-SV) [24].

The *ad hoc* elaborated part contained questions regarding socio-economic factors, habits, and lifestyles, such as physical activity (yes/no), regular consumption of alcohol and coffee (yes/no), with particular attention to the type of use of the IT platforms and social networks and to the time spent daily on them. The *ad hoc* section of the questionnaire was developed by the research team based on a review of relevant literature on digital habits and lifestyle factors associated with problematic technology use. The questions were designed to gather data on socioeconomic factors, lifestyle habits (physical activity, substance use), and specific patterns of social media engagement. Prior to its distribution, the questionnaire was pilot-tested on a small sample of 20 university students to assess its clarity, comprehensibility, and time for completion. Feedback from the pilot phase was used to refine the wording of several questions to ensure they were unambiguous.

The SAS is a scale for smartphone addiction consisting of 6 factors (daily-life disturbance, positive anticipation, withdrawal, cyberspace-oriented relationship, overuse, and tolerance) and 33 items with a six-point Likert scale (1: ''strongly disagree'' and 6: ''strongly agree'') based on self-reporting. It is important to keep in mind that the cut-off score for the 33-item SAS varies across studies, reflecting different populations and methodologies. Therefore, we did not use this scale to define smartphone addiction: we investigated the presence of problematic use in our cohort mainly using a short version of the smartphone addiction scale (SAS-SV) [24], validated in adolescents and young adults [25], consisting of 10 items with a six-point Likert scale.

The questionnaire was distributed online through social networks and messaging apps (especially WhatsApp) and based on multiple-choice questions.

Study Population

Assuming an expected prevalence of smartphone addiction of 20%, the sample size was calculated using the standard formula for estimating a proportion in a large population:

$$n = \frac{Z^2 \cdot P \cdot (1-P)}{d^2}$$

where Z = 1.96 for a 95% confidence level, P is the expected prevalence (assumed at 20%, or 0.20), and d is the margin of error (5%, or 0.05). The calculation was performed using the software G*Power 3.1. %. Considering a target population of approximately 1,750,000 university students in Italy, the minimum required sample size was determined to be 247 participants. The target population consisted of young adults aged 18-40 residing in Italy, with recruitment efforts primarily focused on the southern regions, in particular Sicily and Calabria, through university and community networks.

Recruitment Method and Eligible Criteria

An anonymous questionnaire was administered to participants of both sexes, aged 18 to 40, who could understand Italian in order to provide informed consent and complete the survey. The questionnaire was delivered using the Computer-Assisted Web Interviewing (CAWI) method, allowing participants to self-complete it online. The questionnaire link was distributed via email and social networks to approximately 800 potential participants. A total of 465 responses were received (response rate: 58%). After excluding 14 incomplete questionnaires (where more than 10% of questions were unanswered), the final sample consisted of 451 participants.

All participants were informed about the confidentiality measures in place, and written informed consent was obtained in compliance with Italian privacy laws. The interviews were conducted in settings that ensured adequate privacy.

Data Analysis

Prior to analysis, the distribution of continuous variables, including the SAS and SAS-SV scores, was assessed for normality using the Shapiro-Wilk test. As the data did not follow a normal distribution, non-parametric tests were used for group comparisons where appropriate (Mann-Whitney U test for two groups, Kruskal-Wallis for more than two groups). The chi-square test was used for comparisons between categorical variables. Descriptive statistics are reported as means and standard deviations or medians and interquartile ranges, as appropriate. Where applicable, proportions are presented together with their 95% confidence intervals (CI) to provide a more precise estimate of the observed prevalence and associations.

The present analysis was exploratory and primarily bivariate in nature, allowing the identification of statistically significant associations between smartphone addiction scores and socio-demographic data (sex, professional profile, working sector, *etc.*), without modeling independent predictors.

All statistical analyses were performed using R software (rel. 4.2.0).

Results

Demographic, Socio-Economic, and Behavioral Factors

The questionnaire was filled in by 451 participants with an average age of 22.42 years (DS 3,97): 170 (38%) were males and 281 (62%) were females. Almost all the participants (n = 442, 98%) were Italian.

Most of them were single (n = 431,96%), non-working students (n = 413,92%) with an average income less than € 30.000 annually (n = 388,86%).

About three-quarters of them (n = 343,76%) engaged in physical activity, a similar percentage (n = 333,74%) habitually drank coffee, whereas only 17% (n = 76) regularly drank alcohol, and 27% (n = 123) were smokers.

Demographic, socio-economic, and behavioral factors are shown in Table I.

Almost half of the subjects (n = 219, 49%) declared to be quite satisfied with the interpersonal relationships of their life, 144 of them (32%) very satisfied, 45 (10%) a little, 16 (4%) not much, and 27 (6%) extremely.

Regarding the use of smartphones while driving, women replied 48% never *vs.* men 22%.

The activities for which smartphones were used are shown in Table II, and the time spent (in hours) on each social network and activity is shown in Table III.

As regards the habit of publishing stories on Instagram, Facebook and WhatsApp, and if yes, why, about a quarter of the sample (n = 106, 24%) replied never, the majority (n = 275, 61%) declared to do it because they liked to show what they do. The motivations reported by the remaining part are very variable, from the desire to emulate others (3%) to the need to fight boredom (0,9%).

Smartphone Addiction Scale (SAS)

According to the results of the SAS administration, the average score was 86.94 ± 22.71, although the mean score in the female sample was higher (87.61 ± 22.74).

We used SAS to investigate the presence of statistical associations between smartphone use and other variables (see Table III for all *p*-values). The gender was associated with a more rational use of smartphones in males; besides, men used smartphones for gaming more than women, and had more difficulty concentrating or problems related to sleeping. However, they used more video gaming and had a higher use while driving; on the other hand, women were more aware of the problematic use. In addition, students had an overuse of smartphones, and they had them in mind even when they were not using them.

The item-by-item analysis of the SAS, detailed in Table IV, revealed several statistically significant associations between socio-demographic variables and specific smartphone use behaviors. Specifically, respondents from the Sicilian region showed a significant association with items related to feeling calm and cozy while using a smartphone and having more fun with it compared to other activities ($p < 0.05$). Regarding educational level, undergraduate interviewees were more likely to report feeling pleasant or excited and confident while using their device ($p < 0.01$). Finally, income level was associated with specific items: those with higher incomes were more likely to have their

Tab. I. Distribution of demographic and socio-economic factors.

N		All (n = 451; 100%)		Male (n = 170; 38%)		Female (n = 281; 62%)	
		%	N	%	N	%	
Nationality	**Italian**	442	98	163	96	279	99
	Other	9	2	7	4	2	1
Marital status	**not married**	431	96	160	94	271	96
	married	20	4	10	6	10	4
Work	**No**	413	92	146	86	267	95
	Yes	38	8	24	14	14	5
Income	**< 25.000**	192	43	75	44	117	42
	25.000-30.000	196	43	67	39	129	46
	> 30.000	63	14	28	16	35	12
Cohabitation	**No**	27	6	10	6	17	6
	with family	310	69	115	68	195	69
	with others	114	25	45	26	69	25
Physical activity	**No**	108	24	27	16	81	29
	Yes	343	76	143	84	200	71
Coffee consumption	**No**	118	26	43	25	75	27
	Yes	333	74	127	75	206	73
Alcohol consumption	**No**	375	83	129	76	246	88
	Yes	76	17	41	24	35	12
Smoke	**No**	328	73	110	65	218	78
	Yes	123	27	60	35	63	22
Electronic cigarette	**No**	423	94	151	89	272	97
	Yes	28	6	19	11	9	3

Tab. II. Answers to the question "For which activity do you use your smartphone?" (data in percentages).

Category	Female (% / N)	Male (% / N)	Total
Text messaging	62.9% (61)	37.1% (36)	97
Phone calls	61.3% (57)	38.7% (36)	93
Studying	65.4% (51)	35.9% (28)	78
Games	48.8% (20)	53.7% (22)	41
Working	38.1% (8)	61.9% (13)	21
Entertainment	57.9% (33)	40.4% (23)	57
Web surfing	46.9% (15)	53.1% (17)	32
Social network	61.9% (52)	38.1% (32)	84
Photo and video	63.5% (54)	36.5% (31)	85
Reading	61.9% (26)	38.1% (16)	42
Useful apps	59.7% (37)	40.3% (25)	62
Shopping	60.0% (30)	40.0% (20)	50
Others	63.6% (7)	36.4% (4)	11

smartphone in mind even when not using it and to not give it up despite negative effects on their daily life ($p < 0.05$).

We also evaluated the association between higher scores and the investigated variables, and we found a higher score in subjects with a higher use of smartphones, especially while driving, and the presence of symptoms such as difficulty concentrating and wrist pain ($p < 0.001$). Furthermore, they thought more of their smartphone even when they did not use it, and they felt that relationships with digital friends are much more intimate than relationships with their real-life friends ($p < 0.001$).

Short version of Smartphone Addiction Scale (SAS-SV)

The answers relating to the SAS-SV are shown in Table V. According to the results of the SAS-SV administration, the average score was 26.4 ± 1.72.

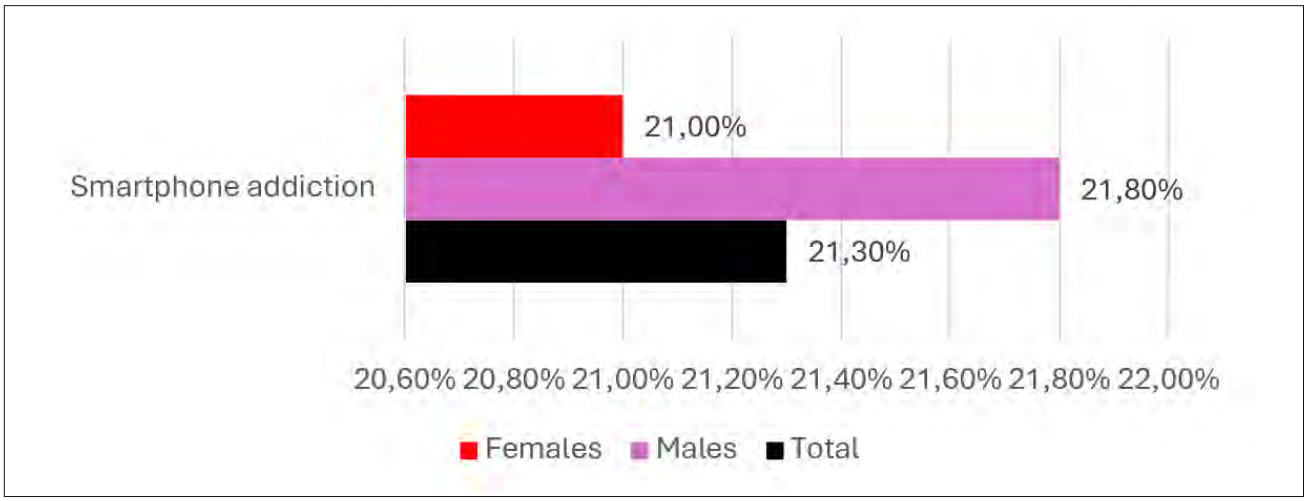
A cut-off score of 31 for males and 33 for females for smartphone dependency was established, as suggested in the literature [24].

Using the SAS-SV cut-offs, the overall prevalence of smartphone addiction was 21.3% (95% CI: 17.6-25.4), with comparable proportions observed among males (21.8%; 95% CI: 15.9-28.8) and females (21.0%; 95% CI: 16.5-26.2) (Fig. 1).

Tab. III. Time spent by our sample using specific apps or devices.

Apps	Never		1-2 hours/day		2-4 hours /day		4-6 hours /day		Always	
	N	%	N	%	N	%	N	%	N	%
WhatsApp	0	0	121	30,6	124	27,5	62	13,7	144	31,9
Instagram	44	9,8	138	30,6	132	29,3	71	15,7	66	14,6
Facebook	128	28,4	226	50,1	58	12,9	27	6,0	12	2,7
Twitter	435	96,5	12	2,7	2	0,4	2	0,4	0	0,0
Messenger	361	80,7	75	16,6	6	1,3	4	0,9	2	0,4
Skype	433	96,0	12	2,7	2	0,4	2	0,4	4	0,4
Tinder	446	98,9	2	0,4	1	0,2	2	0,4	0	0,0
Messaging app	361	80,0	69	15,3	13	2,9	4	0,9	4	0,9
Wikipedia	153	33,9	221	49,0	55	12,2	13	2,9	9	2,0
Youtube	93	20,6	237	52,5	80	17,7	24	5,3	17	3,8
Netflix	189	41,9	155	34,4	75	16,6	23	5,1	9	2,0
Spotify	201	44,6	127	28,2	67	14,9	36	8,0	20	4,4
App for Music	218	48,3	145	32,2	53	11,8	22	4,9	13	2,9
App for Game	278	61,6	130	28,8	28	6,2	12	2,7	3	0,7
Other	350	77,6	82	18,2	14	3,1	4	0,9	1	0,2
Devices	**Never**		**1-2 hours /day**		**2-4 hours /day**		**4-6 hours /day**		**Always**	
	N	%	N	%	N	%	N	%	N	%
Smartphone	0	0	53	11,8	124	27,5	100	22,2	174	38,3
PC	96	21,3	198	43,9	109	24,2	28	6,2	20	4,4
SmartTv	239	53,0	147	32,6	50	11,1	9	2,0	6	1,3
Tablet	361	80,0	68	15,1	13	2,9	4	0,9	5	1,1
Fixed console	373	82,7	59	13,1	15	3,3	2	0,4	2	0,4
Mobile console	424	94,0	19	4,2	7	1,6	1	0,2	0	0,0
E-reader	416	92,2	26	5,8	7	1,6	0	0,0	2	0,4

Fig. 1. Percentages of the sample with smartphone addiction using the SAS-SV score (M > 31, F > 33) by gender.



The subgroup of participants classified as addicted (n = 96) had a mean age of 22.1 years (SD 3.25). Their sociodemographic and lifestyle characteristics were largely comparable to those of the overall sample, with most being unmarried (96.9%), non-working students (90.6%), and with an annual income below € 30,000 (93.8%). Similarly, the prevalence of physical activity (74%), coffee consumption (71.9%), alcohol consumption (19.8%), and smoking (27.1%) mirrored the distributions observed in the total population (Tab. VI).

Discussion

This study considered the lifestyle and behavioral characteristics of the sample to assess the level of smartphone addiction, correlating it with the time spent online and in various apps. In our methodological

Tab. IV. SAS 33-items *p* value by gender, region of provenience, educational degree, and income (significant *p* values are reported in bold).

	SAS items	Gender	Region of provenience	Educational degree	Income
1	Missing planned work due to smartphones	0.291	0.190	0.597	0.269
2	Having a hard time concentrating in class, while doing assignments, or while working due to smartphone use	***0.002**	***0.067**	0.432	0.875
3	Experiencing lightheadedness or blurred vision due to excessive smartphone use	0.130	0.147	0.787	0.156
4	Feeling pain in the wrists or at the back of the neck while using a smartphone	0.22	0.196	0.199	0.649
5	Feeling tired and lacking adequate sleep due to excessive smartphone use	0.14	0.161	0.309	0.161
6	Feeling calm or cozy while using a smartphone	0.470	***0.003**	0.671	0.565
7	Feeling pleasant or excited while using a smartphone	***0.021**	***0.009**	***0.002**	0.799
8	Feeling confident while using a smartphone	0.706	***0.038**	***0.004**	0.694
9	Being able to get rid of stress with a smartphone	0.971	***0.017**	0.991	0.424
10	There is nothing more fun to do than using my smartphone	0.526	***0.001**	***0.001**	0.060
11	My life would be empty without my smartphone	0.354	0.485	0.750	0.488
12	Feeling most liberal while using a smartphone	0.282	***0.006**	0.051	0.389
13	Using a smartphone is the most fun thing to do	0.580	0.774	0.212	0.275
14	Won't be able to stand not having a smartphone	0.282	0.967	0.402	0.509
15	Feeling impatient and fretful when I am not holding my smartphone	0.108	0.301	0.744	0.788
16	Having my smartphone in my mind even when I am not using it	***0.038**	0.324	0.676	***0.001**
17	I will never give up using my smartphone even when my daily life is already greatly affected by it	0.993	0.660	0.939	***0.038**
18	Getting irritated when bothered while using my smartphone	0.253	0.078	0.783	0.630
19	Bringing my smartphone to the toilet even when I am in a hurry to get there	0.097	***0.043**	0.295	0.601
20	Feeling great meeting more people via smartphone use	0.079	***0.003**	***0.001**	0.961
21	Feeling that my relationships with my smartphone buddies are more intimate than my relationships with my real-life friends	0.897	***0.040**	0.130	0.460
22	Not being able to use my smartphone would be as painful as losing a friend	0.249	***0.037**	0.288	0.589
23	Feeling that my smartphone buddies understand better than my real-life friends	***0.012**	0.055	0.354	0.525
24	Constantly checking my smartphone so as not to miss conversations between other people on Twitter or Facebook	0.131	0.125	0.456	0.796
25	Checking SNS (Social Networking Service) sites like Twitter or Facebook right after waking up	0.592	***0.011**	0.132	0.791
26	Preferring talking with my smartphone buddies to hanging out with my real-life friends or with the other members of my family	0.079	***0.001**	***0.001**	0.061
27	Preferring searching from my smartphone to asking other people	0.875	0.060	0.767	0.705
28	My fully charged battery does not last for one whole day.	0.475	0.089	0.499	0.144
29	Using my smartphone longer than I had intended	0.480	0.064	0.886	0.794
30	Feeling the urge to use my smartphone again right after I stopped using it	0.267	***0.001**	***0.002**	0.715
31	Having tried time and again to shorten my smartphone use time, but failing all the time	***0.021**	0.050	0.465	0.165
32	Always thinking that I should shorten my smartphone use time	***0.002**	0.055	***0.010**	0.584
33	The people around me tell me that I use my smartphone too much	0.905	0.809	0.858	0.344

* Significative *p* value

approach, we utilized both the full Smartphone Addiction Scale (SAS) and its short version (SAS-SV), each serving a distinct purpose. The full 33-item SAS was employed as an exploratory tool to identify statistical associations between specific smartphone-related behaviors and sociodemographic variables, with the significant findings detailed in Table III. However, for the primary objective of classifying addiction and determining prevalence, we relied on the SAS-SV. This choice was deliberate, as the SAS-SV provides validated, gender-specific cut-off scores for young adults, offering a more robust and standardized method

Tab. V. Short version of the Smartphone addiction scale (SAS-SV).

	SAS-SV items		Strongly disagree		Disagree		Weakly disagree		Weakly agree		Agree		Strongly Agree	
			N	%	N	%	N	%	N	%	N	%	N	%
1	Missed planned work due to smartphone use	**Male**	51	11	36	8	42	9	28	6	7	2	6	1
		Female	73	16	48	11	91	20	53	12	12	3	4	1
2	Having a hard time concentrating in class, while doing assignments, or while working due to smartphone use	**Male**	43	10	23	5	31	7	46	10	16	4	11	2
		Female	45	10	50	11	84	19	76	17	21	5	5	1
3	Feeling pain in the wrists or at the back of the neck while using a smartphone	**Male**	67	15	33	7	37	8	28	6	3	1	2	0
		Female	94	21	30	7	84	19	53	12	13	3	7	2
4	Will not be able to stand not having a smartphone	**Male**	54	12	24	5	42	9	38	8	10	2	2	0
		Female	63	14	55	12	67	15	71	16	20	4	5	1
5	Feeling impatient and fretful when I am not holding my smartphone	**Male**	56	12	29	6%	55	12	22	5	3	1	5	1
		Female	76	17	45	10	86	19	58	13	12	3	3	1
6	Having my smartphone in mind even when I am not using it	**Male**	90	20	24	5	41	9	14	3	1	0	0	0
		Female	112	25	40	9	95	21	26	6	8	2	0	0
7	I will never give up using my smartphone, even when my daily life is already greatly affected by it	**Male**	49	11	28	6	44	10	36	8	9	2	4	1
		Female	76	17	44	10	79	18	59	13	17	4	6	1
8	Constantly checking my smartphone so as not to miss conversations between other people on Twitter or Facebook	**Male**	72	16	37	8	32	7	26	6	2	0	1	0
		Female	144	32	40	9	63	14	28	6	4	1	2	0
9	Using my smartphone longer than I had intended	**Male**	15	3	13	3	31	7	70	16	22	5	9	2
		Female	16	4	17	4	63	14	117	26	45	10	23	5
10	The people around me tell me that I use my smartphone too much	**Male**	62	14	22	5	41	9	31	7	9	2	5	1
		Female	93	21	38	8	81	18	46	10	16	4	7	2

* Percentages are calculated on the total of the sample.

for classification than the full SAS, for which cut-offs can vary significantly across studies.

Most of the sample used smartphones for media and basic communication. The degree to which people reported experiencing pleasure or excitement from using smartphones seems to be significantly influenced by the degree of education and the region of provenance. This may suggest that people's perceptions and enjoyment of smartphone interactions may be influenced by specific study settings or cultural/regional considerations [26]. Investigating how various factors, such as regional cultural variations, affect people's emotional reactions to smartphones can be worthwhile [27, 28].

Men and women may have different opinions on how their online friends comprehend them in comparison to their real-life friends. This implies that gender might influence how people establish and perceive relationships online, perhaps reflecting varying social behaviors or emotional commitments to virtual *vs.* face-to-face interactions [29-31]. Interestingly, the approaches that men and women use smartphones differ in a few significant ways: regarding web browsing, men are marginally more likely to use smartphones than women (17% M *vs.* 15% F); as concerns using smartphones for work, men are more likely than women (13% M *vs.* 8% F); finally, there is a slight but noticeable difference in the use of smartphones for gaming (22% men *vs.* 20% women).

Regarding smartphone use, according to the findings, all of the sample members use smartphones every day, implying that the majority of the sample population considers them to be an essential component of their everyday lives [32].

The survey also looked at using smartphones while driving and found some alarming trends: a startling 2% of respondents said they always used their smartphones while driving, while 23% said they used them infrequently [33]. According to SAS-SV score, 21.3% of our sample met criteria for smartphone addiction: a slightly higher result than of a study carried out in Switzerland in 2015 in which smartphone addiction occurred in 16.9% of young adults, revealing that this phenomenon was more prevalent in young adolescents (15-16 years) compared with young adults (19 years and older), in people reporting lower physical activity, and that alcohol and tobacco consumption were unrelated to smartphone addiction [34]. The prevalence of smartphone addiction in our sample, identified at 21.3%, warrants significant attention due to its potential clinical and functional implications. This finding suggests that more than one in five young adults in Southern Italy may be at an increased risk for negative mental health outcomes, such as elevated anxiety, depression, and sleep disturbances, which are consistently linked to problematic smartphone use. Furthermore, this level of prevalence could translate into tangible functional impairments, including difficulty concentrating in academic or work settings, a concern reported by our participants. In the socio-cultural context of Southern Italy, where strong interpersonal and family bonds are traditionally central, the risk of

Tab. VI. Sociodemographic and lifestyle characteristics of participants classified as addicted according to the SAS-SV.

N		All (n = 96; 100%)		Male (n = 37; 38,5%)		Female (n = 59; 61,5%)	
		%	N	%	N	%	
Marital status	**Not married**	93	96,9	34	91,9	59	100
	Married	3	3,1	3	8,1	0	0
Work	**No**	87	90,6	31	83,8	56	94,9
	Yes	9	9,4	6	16,2	3	5,1
Income	**< 25.000**	42	43,8	20	54	22	37,3
	25.000-30.000	48	50	14	37,8	34	57,6
	> 30.000	6	6,2	3	8,2	3	5,1
Cohabitation	**No**	8	8,3	3	8,2	5	8,5
	with family	72	75	28	75,7	44	74,6
	with others	16	16,7	6	16,1	10	16,9
Physical activity	**No**	25	26	5	13,5	20	33,9
	Yes	71	74	32	86,5	39	66,1
Coffee consumption	**No**	27	28,1	11	29,7	16	27,1
	Yes	69	71,9	26	70,3	43	72,9
Alcohol consumption	**No**	77	80,2	24	64,9	53	89,8
	Yes	19	19,8	13	35,1	6	10,1
Smoke	**No**	70	72,9	20	54	50	84,7
	Yes	26	27,1	17	46	9	15,3
Electronic cigarette	**No**	90	93,8	32	86,5	58	98,3
	Yes	6	6,2	5	13,5	1	1,7

developing cyberspace-oriented relationships at the expense of real-life interactions could have unique consequences, potentially exacerbating feelings of social isolation despite heightened digital connectivity. As our results showed, the sociodemographic and lifestyle characteristics of the addicted subgroup were broadly comparable to those of the overall sample. This lack of marked differences suggests that problematic smartphone use in our cohort cuts across typical demographic and behavioral profiles, rather than being confined to specific risk groups. Such a finding underlines the pervasiveness of this phenomenon among young adults and highlights the need for broad-based preventive strategies rather than interventions targeting only particular subpopulations.

Moreover, our findings indicate that patterns of smartphone use and vulnerability to problematic use differ according to sociodemographic characteristics. Similar studies have reported that while smartphone addiction may not be consistently associated with family income or parental education, variations in usage patterns and perceived dependence across gender and educational levels are frequently observed [24, 35, 36].

In this context, the present findings are consistent with and extend previous Italian research on problematic smartphone use across different population groups. In particular, the gender-related patterns in smartphone engagement and perceived dependence observed in our study align with those reported by Cali et al., who identified a higher prevalence of smartphone addiction among adolescents in Southern Italy, especially among females, suggesting that gender differences may emerge early and persist into young adulthood [37].

Similar results were reported by Caponnetto et al. during the COVID-19 lockdown in Italy, where younger individuals – especially females – exhibited higher levels of smartphone dependency, highlighting the role of contextual stressors and increased reliance on digital communication in amplifying problematic use [38].

Although conducted in a different population, the study by Vitale and Mea on Italian nurses provides additional comparative insight. Their findings demonstrated significant associations between smartphone addiction and lifestyle-related variables such as Body Mass Index, physical inactivity, and work experience, reinforcing the interpretation that problematic smartphone use is closely intertwined with broader health and behavioral patterns rather than being an isolated phenomenon [39].

Taken together, these studies support the interpretation that smartphone addiction represents a transversal public health issue in Italy, affecting adolescents, young adults, and working populations alike, and influenced by a complex interaction of individual, social, and contextual factors.

In our study, personal computers are the second most used devices (21.3% never use them). In particular, we did not find a specific computer addiction, keeping in mind that there are several forms of internet addiction and that diagnosing addictions is difficult [40-45].

A key implication of our findings is that the problematic behavior may be less about the smartphone as a device and more about the applications it hosts. The high reported usage of social media platforms like Instagram and messaging apps like WhatsApp points towards the underlying mechanisms of behavioral addiction. These platforms are engineered with features such as variable intermittent reinforcement (*e.g.* unpredictable

notifications, likes, and messages) and the constant opportunity for social validation, which are known to trigger compulsive checking and engagement. Therefore, the 'addiction' is likely to the social connection and validation these apps provide, with the smartphone simply being the ever-present vehicle for this reinforcement loop; in our sample, the reasons pushing to public stories or updates on Instagram, Facebook or WhatsApp are pleasure of sharing (61%), emulating the others (3%), need to public what they are doing because otherwise it is as if it never happened (2%), boredom (0.9%). Moreover, in our sample, the 7% considers it as something to do occasionally, only 4% shares only outstanding episodes of their own life or nothing personal, but it uses them as a political and cultural tool of propaganda.

Besides, most of our sample uses smartphones for longer than planned: despite prolonged use of the devices, no significant statistics were found regarding productivity ("I can't do a scheduled job due to using my smartphone") and physical symptoms (blurry vision, wrist, neck or back pain, sleep alteration) although in some cases it does affect the work sphere, the concentration, and the cognitive and social sphere and, as further highlighted in recent literature, found that the most common complaints were involving dry eyes, decreased vision, and cervical pain [46, 47]. Further reinforcing the severity of these clinical implications is a recent and large cohort study by Xiao et al., which analyzed the trajectories of habitual screen use in a cohort of 4,285 young Americans. The study highlighted a crucial point, perfectly in line with our hypothesis: it is not the total time spent in front of the screen that predicts negative outcomes for mental health, but rather the pattern of habitual use over time [48]. In addition to these serious psychological consequences, other research has also highlighted the implications for physical health. A cross-sectional study by Nagata et al. (2023), using data from the same cohort of adolescents, examined the association between screen usage time, physical activity (measured in steps), and Body Mass Index (BMI). The most notable finding was that, although low physical activity and high screen time were both associated with a greater risk of overweight and obesity, high physical activity was not able to fully compensate for the risks associated with high screen usage time [49].

Usage Patterns and Behaviors

The study's findings also illuminate the usage patterns and behaviors of young adults in Southern Italy. The primary functions of smartphones within this cohort are for leisure, social media, and entertainment. High levels of engagement were observed with popular applications; for instance, 73.2% of participants reported using WhatsApp for two or more hours daily, while 59.6% reported the same duration of use for Instagram. The motivation for this engagement appears to be rooted in social sharing, as a majority of the sample (61%) stated they post on social media because they enjoy displaying their activities.

An exploratory analysis utilizing the 33-item Smartphone Addiction Scale (SAS) indicated that high usage levels are associated with problematic behavioral patterns, with statistically significant correlations found within specific demographic cohorts. The student cohort, for example, demonstrated a heightened self-awareness of their extensive use, exhibiting a greater tendency to believe they should reduce their smartphone time compared to non-students ($p < 0.01$). Socioeconomic status emerged as another significant variable. Individuals with higher incomes reported a greater cognitive preoccupation with their devices, being more likely to have their smartphone in mind even when not actively using it ($p < 0.001$). This group also demonstrated more resistance to altering their habits, indicating they would not give up their smartphone even if it negatively affected their daily life ($p < 0.038$). Statistically significant gender-based differences were also identified. Males reported a higher incidence of concentration difficulties in academic or work settings due to smartphone use ($p < 0.002$). In contrast, females exhibited greater cognizance of their usage patterns, being more likely to contemplate reducing their screen time and to have made unsuccessful attempts to do so ($p < 0.002$ and $p < 0.021$, respectively).

Implications for prevention and public health

From a preventive perspective, our findings support the adoption of both individual- and system-level strategies to mitigate problematic smartphone use. At the individual level, simple behavioral interventions – such as disabling non-essential notifications, setting time limits for social media use, and creating "tech-free" times and spaces (*e.g.* during meals or before bedtime) – may help reduce compulsive checking behaviors. The use of control applications, such as Forest or similar digital well-being tools, may further support self-regulation by limiting access to the most time-consuming applications.

At the family and educational levels, establishing clear rules, promoting positive role modeling (particularly for younger users), and encouraging offline alternatives – including sports, reading, and creative hobbies – are crucial protective factors. Smartphones should be promoted as tools that serve functional purposes rather than dominant drivers of daily behavior. Importantly, the introduction of structured educational programs in middle and high schools focusing on the conscious use of technology, digital literacy, coding, and robotics may foster healthier relationships with digital devices. Such programs should be integrated into broader health education curricula and supported by partnerships between families, schools, healthcare providers, and public institutions to ensure a coordinated and sustainable approach.

From a regulatory perspective, international policy initiatives highlight growing concern regarding excessive smartphone and social media use among minors. Australia has recently introduced legislation restricting access to certain social media platforms – such

as TikTok, Instagram, and YouTube – for individuals under 16 years of age, while similar measures are under discussion or partial implementation in countries including Denmark and the United States [50].
In Italy, increasing attention has been directed toward restricting smartphone use in high schools, particularly during teaching hours [51]. These measures aim to reduce distractions, improve academic performance, and safeguard students' mental and physical health. Although our study focused on young adults, the observed prevalence of problematic smartphone use supports the rationale for such policies and underscores the importance of early preventive action before maladaptive usage patterns become consolidated.

Limitations of the study

Several limitations should be acknowledged. First, the age range of the participants represents a key limitation, as the sample consisted primarily of young adults; future research should extend to middle and high school students, who may be particularly vulnerable to developing problematic smartphone use. Second, the cross-sectional design precludes causal inference. Third, the reliance on self-reported data may have introduced recall and social desirability biases. Fourth, although pilot-tested, the ad hoc section of the questionnaire lacked formal psychometric validation. Fifth, the statistical approach was predominantly bivariate and exploratory. While suitable for identifying associations, it does not allow the identification of independent risk factors. Future studies should employ multivariate techniques, such as logistic regression, to better isolate predictors of smartphone addiction.
Finally, the recruitment strategy, based largely on online dissemination, may have resulted in selection bias and an overrepresentation of females, potentially limiting the generalizability of the findings.

Conclusion

The findings of this study indicate that smartphones have become central to the daily lives of young adults, primarily for leisure activities such as social media, gaming, and entertainment. This trend has been accentuated in the post-pandemic context, where social distancing and lockdown measures increased reliance on digital communication, fostering habitual and, in some cases, compulsive usage patterns [48]. While daily engagement with smartphones is widespread, it is important to distinguish between normalized, frequent use and behaviors that meet criteria for addiction, particularly when such use interferes with safety, well-being, or daily functioning.
Our analysis suggests that problematic smartphone use is closely tied to social media platforms, whose design features encourage continuous engagement and provide immediate social reinforcement [49, 52]. Compulsive use is not evenly distributed across the population; age, gender, education, and socioeconomic status appear to influence both the frequency of use and the potential for developing maladaptive behaviors [53]. These insights highlight that interventions should be sensitive to contextual and demographic factors rather than assuming uniform risk across all users.
The implications for prevention and management are clear. Universities and educational institutions should adopt broad-based digital literacy initiatives that teach mindful technology use and critical awareness of app design. Early screening and targeted counseling within mental health services can help identify at-risk individuals before problematic behaviors escalate [54-60]. Public health campaigns should emphasize the quality of digital engagement rather than mere screen time, encouraging the maintenance of real-life social connections alongside digital interaction [61-68].
In conclusion, problematic smartphone use affects a substantial proportion of young adults in Southern Italy and appears to be driven more by the design and functionality of social media applications than by screen time alone. These findings reinforce the need for early, coordinated prevention strategies that integrate behavioral interventions, educational programs, and policy measures.
Addressing smartphone addiction requires a multi-level approach involving individuals, families, schools, healthcare systems, and institutions. Promoting conscious and purposeful technology use – while preserving the benefits of digital innovation – represents a key public health challenge for the coming years.

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Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest Statement

The authors declare no conflict of interest.

Authors' contribution

RV, CER, VLF, CG: Conceptualization; GT, VLF: RV, CER, RS, VLF, CG: Methodology; GT, VLF, CG: Formal analysis; RV, CER, GLS, VLF, CG: Investigation; RV, CER, GG, CG: Resources; GT, VLF: Data Curation;

RV, CER, CG: Writing-original draft; RS, VLF, CG: Writing-review and editing; RS, VLF, CG: Supervision.

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Correspondence: Raffaele Squeri, Via Consolare Valeria 1, 98124 Messina, Italy. E-mail: squeri@unime.it

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Reviews

Assessing Health System preparedness for dog mediated rabies in South-East Asia Region

ISHA GARG[1], NAVYA VYAS[1], SRAJANA KOTEKAR[1], MINOSHKA TELES[1], NAJMIN SULTANA[1], SUDHEESH N[2], BASAVARAJ KATARAKI[3], ANOOP VELAYUDHAN[4]
[1] Department of Global Public Health Policy and Governance, Prasanna School of Public Health, Manipal Academy of Higher Education, Manipal, Karnataka, India; [2] Manipal Institute of Virology, Manipal Academy of Higher Education, Manipal, Karnataka, India; [3] Surveillance Medical Officer, World Health Organization, Bihar, India; [4] Indian Institute of Health Management Research, Jaipur, India

Keywords

Rabies • One Health • Health System Preparedness • Inter-sectoral coordination • Mass Dog Vaccination

Summary

Introduction. *Rabies is one of the major public health challenges in the South-East Asia Region (SEAR), which is home to diverse populations where close human-animal interactions are common, creating a conducive environment for the transmission of dog mediated rabies. The scoping review intended to assess the health system preparedness of WHO South-East Asia Region countries, for dog mediated rabies, focusing on prevention, detection, and control efforts.*
Methods. *The published literature was searched using PubMed, Embase, and Scopus databases, focusing on studies published from January 2013 to November 2023. The inclusion criteria encompass primary studies published in English between January 2013 and November 2023 focusing on health system preparedness for prevention, control, and elimination of dog-mediated rabies in SEAR.*
Results. *A total of 178 studies were reviewed. Over the years, significant improvements were seen among most SEAR countries, but countries like Myanmar and the Democratic People's Republic of Korea, have limited published evidence on health system preparedness for dog-mediated rabies. Most of the countries need to focus on various aspects like vaccine availability, inter-sectoral collaboration, robust rabies surveillance and reporting system for both humans and animals, strengthening of laboratory capacity and responsible dog ownership to be in alignment with the global goal of "Zero by 30" of ending dog mediated human rabies deaths by 2030.*
Conclusion. *Each SEAR country demonstrates distinctive strengths and challenges in the elimination of rabies. However, incorporation of inter-sectoral coordination and strengthening the rabies surveillance system by linking both animal and human contribute to the control efforts in South-East Asia countries.*

Introduction

Globally, rabies is estimated to cause 59,000 deaths per year in over 150 countries and causes economic burden in terms of lost lives, medical expenses, livelihood, and incidental expenses, altogether estimated to account for around US$ 8.6 billion per year [1]. Rabies is a zoonotic disease caused by the rabies virus, which spreads through two epidemiological cycles: an urban cycle and a sylvatic cycle [2]. The urban cycle maintains the infection in the dog population, while the sylvatic cycle sustains it within wildlife. According to the World Health Organisation (WHO), in 99% of human rabies cases, the rabies virus is transmitted to humans by dogs. Dog-mediated rabies is endemic in most South-East Asian countries, and therefore approximately 608 million people are at potential risk of rabies [3, 4]. The incidence of dog-mediated cases and the number of human deaths due to rabies both are higher in Asia as compared to other regions of the world [5, 6]. Rabies presents a persistent threat in South-East Asian countries despite being a vaccine- preventable disease and also having existing guidelines for its prevention and control. Asian and African countries contribute around 99% of human rabies deaths worldwide, among which a significant majority accounts for 60% of these deaths taking place in Asia [6].

According to recent studies, there are reportedly challenges which include close human-animal interactions, inadequate health system preparedness, poor inter-sectoral coordination, insufficient resources, absence of political will, ineffective surveillance system, stock shortage of vaccine, restricted access to modern rabies vaccines and complex interplay of epidemiological factors [7]. To effectively address these challenges, various public health strategies such as public awareness campaigns, vaccination programs, post-exposure prophylaxis (PEP), the mitigation of the risk of rabies transmission in humans, and a robust surveillance system for both humans and animals to gather evidence-based data, need to be incorporated [8, 9]. Essentially, a "Multi-sectoral One Health Approach" is now critical for rabies control by understanding the disease dynamics and its close interactions between humans, animals, and environmental elements [7]. Integration of the One Health approach into rabies

control strategies has proven to be cost-effective, where 2249 disability-adjusted life years (DALYs) were warded off during the program implementation period at the rate of 526 USD per DALY, exhibiting the intervention to be 'very cost-effective' by WHO definitions [10]. Therefore, this approach has also been endorsed by multilateral organizations namely WHO, the World Organization for Animal Health (WOAH), and the Food and Agriculture Organization of the United Nations (FAO), emphasizing the need for collaborative efforts to tackle zoonotic diseases [11]. In 2015, the world initiated action against rabies known as the 'Zero by 30' initiative, a global strategy to end dog mediated human rabies by 2030, with the collaboration of four organizations, including the WHO, FAO, WOAH, and the Global Alliance for Rabies Control (GARC). This global strategic plan highlights a country-centric, well-organized strategy to eliminate human death due to dog mediated rabies by 2023 [12]. The Association of South-East Asian Nations (ASEAN) also designated a cost-effective rabies control strategy, such as dog vaccination programme, supported by effective dog population management in the ASEAN Member States [4]. A robust health system plays a critical role in preventing and controlling infectious diseases by providing adequate support for early detection and prompt management of disease threats [13]. Health system preparedness for rabies control and prevention measures demands a critical evaluation of various aspects, including policies, practices, and infrastructure that are in place for the prevention and control of rabies within the healthcare and veterinary sectors. Health system preparedness is an essential component for the successful implementation of rabies control and prevention measures in both human health and animal health sectors. However, challenges persist across SEAR nations for consistent implementation of these components to control and prevent dog mediated rabies effectively. Therefore, the current scoping review intended to provide an in-depth overview of the health system preparedness of countries in the WHO South-East Asia Region (SEAR) for dog mediated rabies across the human and animal health sectors, focusing on the CDC (Centers for Disease Control and Prevention) framework of prevention, detection, and control [14].

Methods

The review methodology was developed based on the framework developed by Arksey and O'Malley and Levac et al., which includes the following stages [15].

1. Identifying the research question

For this review, the following research question was identified:
"What has been the overall health-system preparedness in rabies control and elimination in South-East Asia over the last decade?"

The JBI manual for Evidence Synthesis 2020 was used to develop the research question into PCC (Population, Concept, Context) format, where in this study context, the "Population" is the various stakeholders and components involved in rabies elimination efforts; this includes national government departments, healthcare professionals, veterinary agencies, local communities and animals at risk of rabies. The "Concept" is health system preparedness for rabies prevention, control and elimination and the "Context" is all countries under South-East Asia region as per WHO.

2. Identifying relevant studies

The published literature was systematically searched using journal databases, including PubMed, Embase, and Scopus. The search strategy was organized by main keywords in the research question and their synonyms, specifically "Health System", "Preparedness", Southeast Asia", "Rabies", and "Elimination". A combination of these keywords was utilized with the Boolean operators AND/OR. The search included grey literature on policy documents, animal bite management guidelines, and WHO publications available on the web. A manual search was conducted for the reference list of all articles included to confirm that all the relevant literature was included. Data was entered in Microsoft Excel 2019 for analysis.

3. Study selection

Inclusion criteria

The following was decided as the inclusion criteria:
1) studies focusing on health system preparedness for prevention, control, and elimination of dog-mediated rabies in SEAR countries, 2) written in English, and 3) primary research studies and grey literature resources from January 2013 to November 2023.

Exclusion criteria

Studies were excluded based on the following criteria:
1) Case reports that mainly focus on symptoms and treatment modalities for rabies, 2) studies focusing on the safety and efficacy of available Rabies vaccines, 3) systematic and scoping reviews, 4) perspective papers, book chapters, commentary and editorial papers, and conference papers.
All retrieved citations underwent three stages of the screening process: title, abstract, and full-text screening. Two researchers independently participated in reviewing all retrieved articles, and studies that complied with the predetermined inclusion and exclusion criteria were selected. The reviewers commenced with the blinded screening of the full texts once all the authors agreed on the selected studies.

4. Charting the data

Data were extracted from eligible articles as per the recommendations by Arksey and O'Malley [15]. The data were recorded by consolidating and understanding the data as per key themes. A data charting form was

developed to ensure relevant variables and themes were incorporated to answer the research question. Data were recorded from each article using MS Excel spreadsheets to ensure the comparability of extracted data among the articles.

5. Collating, summarising, and reporting the results

The findings of the review were summarized and reported according to the primary domains of the data extraction templates, and the findings were organized in such a way that addressed the review objectives. The results were reported based on the Preferred Reporting Item for Scoping Reviews (PRISMA-ScR) guidelines [16]. The result part is divided into three broad themes, including prevent, detect, and respond, as per the CDC framework [14]. In addition, each theme was elaborated under various categories such as Prevent: Pre-exposure prophylaxis and Post-exposure Prophylaxis vaccination, Rabies Awareness in the Community, Capacity Building, and Workforce Readiness, Inter-Sectoral Collaboration for Rabies Prevention and Control, Practise of One Health Approach; Detect: Reporting mechanisms for Rabies, Laboratory Diagnostic Capacity; Response: Dog Population Management and Mass Dog Vaccination, Dog Ownership.

Results

Characteristics of included studies

The PRISMA flow diagram summarizes the selection process (Fig. 1) for studies. Initially, 5,408 articles from different databases were identified. After removing 1,297 duplicates, 4,111 articles were included for the title and abstract screening. After these, 1,348 articles were excluded, as they were case reports, clinical trials, reviews or editorials, articles not published in the English

Fig. 1. PRISMA Diagram [16].

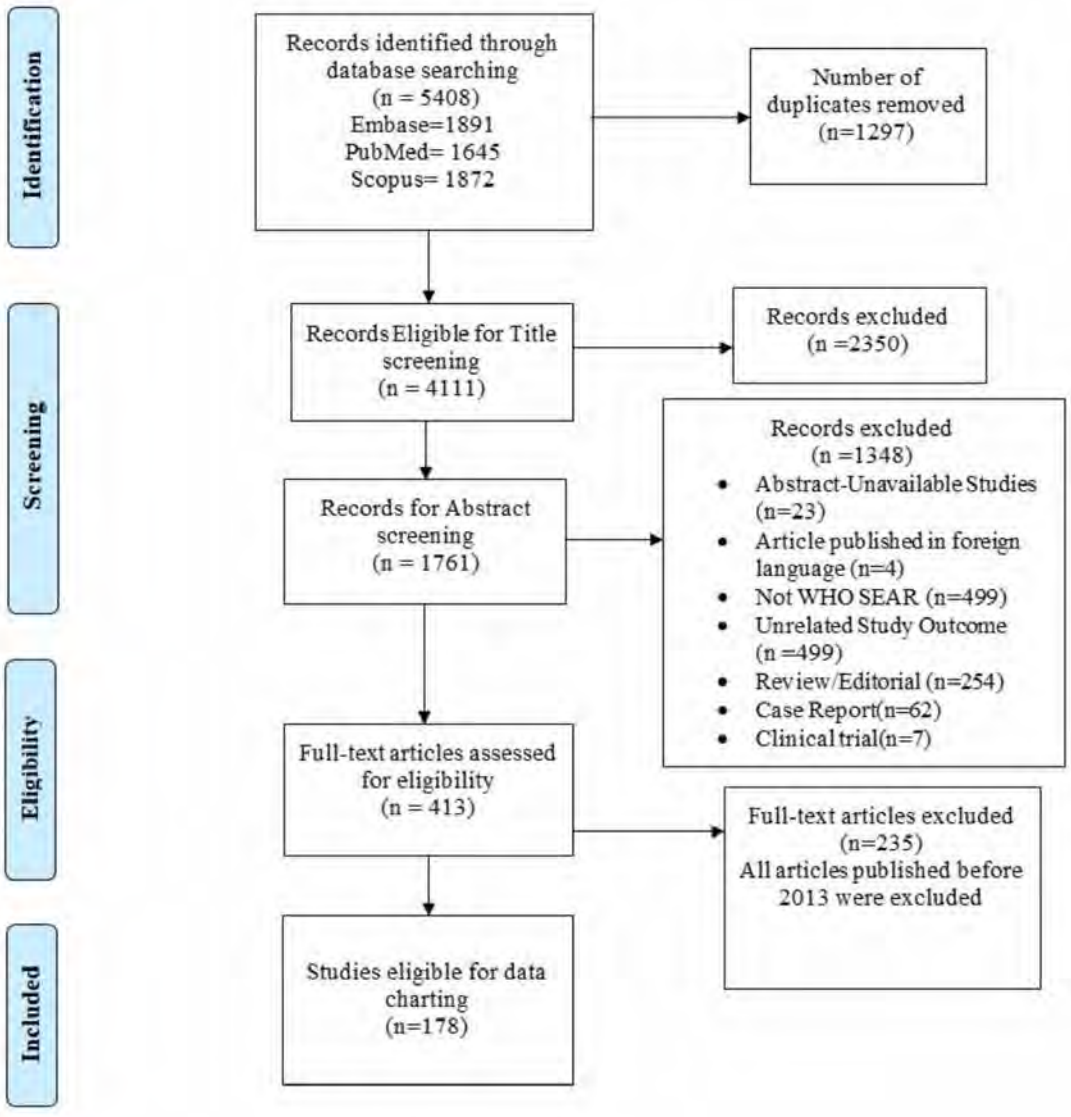
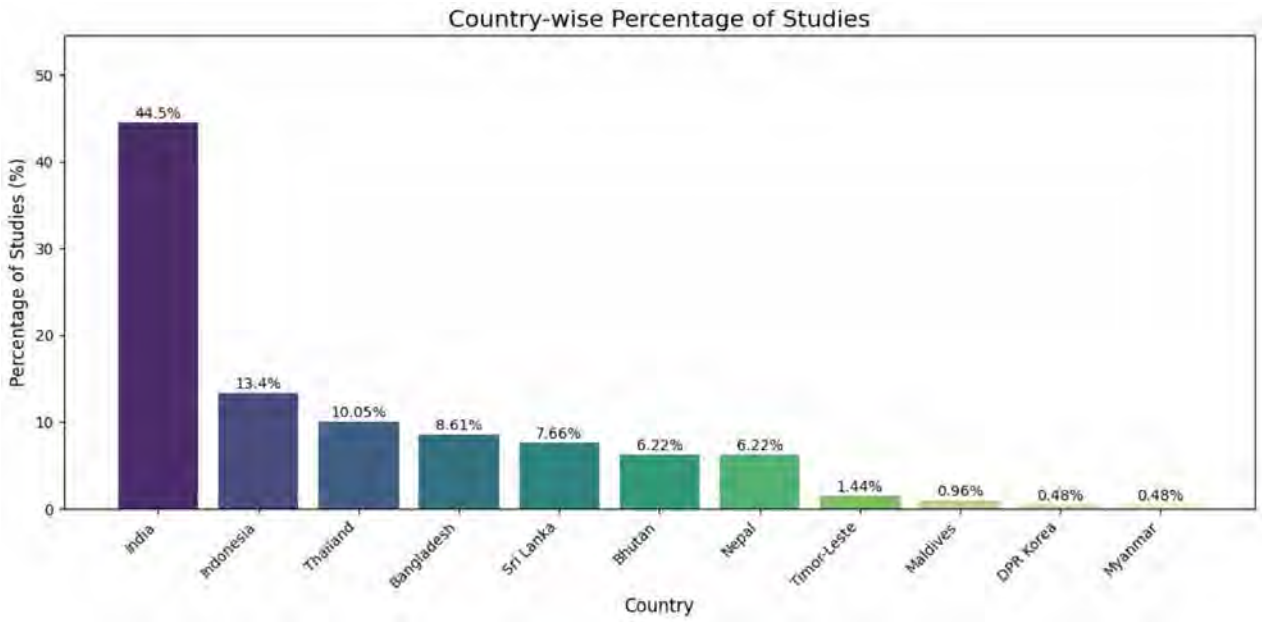


Fig. 2. Country-specific distribution of research based on published evidence in the South-East Asia Region.



language, studies not from SEAR countries, abstracts with unavailable studies, studies outcomes that did not match the objective of the review and articles published before 2013. The remaining 413 articles were included for review, with 178 studies meeting the eligibility criteria.

One of the significant findings from the review highlights the inadequate availability of data on the health system preparedness for dog mediated human rabies in rabies prevention, detection, and control efforts in SEAR countries like Myanmar and the Democratic People's Republic of Korea (DPRK Korea) During the review, we found that the highest number of publications related to rabies preparedness was from India, constituting 44.5% and the lowest number of publications was from Myanmar and the DPRK Korea, accounting for 0.48% of the total (Fig. 2). Relevant published articles were not identified from Timor Leste or the Maldives. Notably, the first human rabies cases were reported in the western part of the island of Timor Leste, which was rabies-free until May 2023 [17].

Publication-based trend analysis of rabies related studies conducted across SEAR countries from 2013 to 2023, highlights a regional disparity in rabies research (Figure 3). India consistently contributed to the highest number of studies with notable peaks in 2019 (24 studies), 2020 (11 studies) and 2022 (15 studies) demonstrating proactive research activity during these years. Other countries such as Bangladesh, Bhutan, Nepal, and Thailand, showed lower research activity, with minor fluctuations. Maldives, Myanmar, Sri Lanka, and Timor-Leste contributed minimally, generally ranging from 0 to 4 studies per year. Overall, the trend emphasizes the need for increased and systematic research in countries with low study output.

Prevent

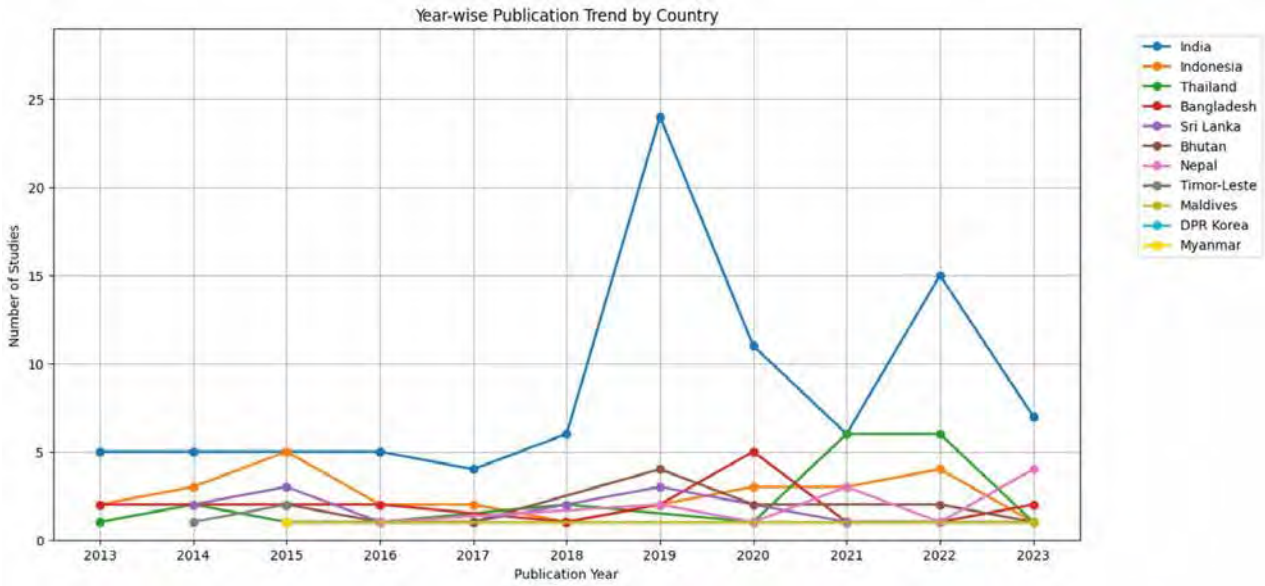
Pre-exposure prophylaxis (PrEP) and Post-exposure Prophylaxis (PEP) Vaccination

The findings identified that the implementation and adoption of PrEP and PEP vaccination programs have significant variations across South-East Asia. In Thailand, greater emphasis has been given to oral rabies vaccines (ORV) for dog and mass dog vaccination (MDV) over specific human vaccination programs [18]. The study's findings from Bangladesh, Bhutan, and Sri Lanka show that while rabies vaccines were available only at selected health facilities, often at a nominal or free of cost, availability of vaccine and distribution challenges often hinder accessibility, especially in rural areas [19]. A significant portion of Bangladesh's population (68.8%) relies on traditional healers to seek treatment after animal bites, including dog bites, causing low uptake of post-exposure prophylaxis [20, 21]. Evidence from India and Bhutan suggests that many people (56% and 78.2% of the participants) followed standard measures such as washing the bite wound with soap and water, followed by a dog bite [22-25]. In Nepal, basic wound care after a dog bite was most commonly practiced among upper-class people [26]. Obtaining pre- and post-exposure prophylaxis has been challenging for Indonesia due to inaccessible topographic areas, limited facilities, inadequate vaccine supply, lack of human resources, and the high cost of post-exposure treatment for humans [27-29].

Rabies awareness in the community

Studies from Thailand show that broadcasting plays a critical role in increasing awareness of rabies among the wider population, but there is a need to address

Fig. 3. Global Trends in Rabies Research Publications (2013-2023).



the importance of seeking medical intervention and adherence to the PEP regimen [30, 31]. In Bangladesh, studies indicate a lack of knowledge and belief in cultural myths and dogma among people, leading them to seek treatment from traditional healers [20, 21, 32, 33]. Over the years, people's level of awareness has changed. Still, there was a significant gap in knowledge about rabies prevention, treatment, and PEP regimens among populations, especially in rural populations of India [34-36]. In Bhutan, most of the participants (98%) had heard about rabies from different sources, but only a few followed post-exposure prophylaxis measures, revealing the need for mass education on rabies [25]. In Nepal, limited access to education, transportation, and medical facilities due to topographical challenges in hilly and Himalayan regions, impending rabies awareness campaigns, and control efforts [37-39]. The studies suggest community engagement, such as door-to-door mapping, GPS tracking, and the use of digital tools like SMS alerts, enhances public participation in rabies control efforts in Indonesia, but still, there are requirements for health education to increase public awareness about rabies, especially to the remote places where access to healthcare and vaccination services is limited [40-42]. In Sri Lanka, rabies prevention efforts have extensively prioritized community education with initiatives to incorporate rabies education into the school syllabus and empower the community through radio messages, educational videos, school campaigns, and print media, but studies suggest low participation of people in health education programs [9, 43].

Capacity Building and Workforce Readiness

The evidence suggests, in Thailand, over the years, there has been an emphasis on training the physicians, field staff, and volunteers to distribute of animal vaccine baits to the animal vaccination teams [44, 45, 18]. The findings from Bangladesh underscore the need for structured training modules for frontline health workers on rabies management [21]. Training programs were conducted in India for various community groups incorporating healthcare workers, village leaders, Primary Health Centre (PHC) staff, and auxiliary nurse midwives (ANMs); there was still a notable knowledge gap in various aspects of rabies control efforts, including understanding PEP regimens and management of animal bite injuries [46-48]. Bhutan's rabies control policy prioritized training on vaccine techniques and handling emergencies related to rabies exposure for the healthcare workers, which was reflected by the studies that indicate doctors and nurses are trained on PEP protocols and rabies vaccines are administered by trained staff for both the Expanded Program on Immunization (EPI) and rabies program [49, 19]. The rabies policy in Nepal stresses training for healthcare workers to equip them well to handle cases effectively; however, the evidence shows there are prerequisites for structured training for both healthcare workers and veterinarians in Nepal [50, 51]. The policy highlights training for animal health and health workers for mass dog vaccination campaigns, planning, analysing vaccination data, and PrEP/PEP administration in Indonesia and Sri Lanka [52, 53]. In Indonesia, training programs are conducted for various stakeholders from animal health sectors, including vaccinators, field teams to train in dog handling, laboratory staff, and veterinary staff received training in both dog vaccination and sampling [53, 54]. In Sri Lanka, doctors and nurses were trained in PEP protocols. Healthcare professionals also received training to utilize data platforms for monitoring and reporting rabies cases to assist in decision-making about PEP administration and tracking treatment outcomes [55, 19].

Inter-Sectoral Collaboration for Rabies Prevention and Control

The rabies control policies across SEAR countries emphasized collaboration and coordination among key stakeholders. In Thailand, local governments have collaborated with Non-Governmental Organizations (NGOs) and international partners, namely the United States Agency for International Development (USAID), to improve rabies control strategies [18]. Bangladesh also advocates for collaboration among various stakeholders, such as government agencies, NGOs, and community organizations [32, 56]. In India, mass vaccination campaigns, resource management, and community engagement were ensured through collaboration with Mission Rabies, local veterinary authorities, and other health departments [57, 58]. In Bhutan, there is a demand for improved coordination between human health and animal departments to enhance rabies control and prevention [59]. Similarly, the rabies control policies of Nepal, Indonesia, and Sri Lanka also emphasized the collaboration between the health sector, community organizations, livestock sector, and other relevant stakeholders to strengthen rabies control efforts [4, 51, 60]. Implementation of successful vaccine campaigns and capacity building was provided either through collaboration with local municipalities, NGOs, and community leaders or partnership with various international agencies such as World Animal Protection and other embedded agencies (*e.g.* FAO) in Nepal, Indonesia, and Sri Lanka [61-63].

Practice of the One Health approach

The One Health approach was observed to be an essential role in strengthening rabies surveillance by connecting animal bite surveillance with human rabies prevention and implementing mass dog vaccination to eliminate rabies [46, 37]. The rabies control policies of various countries reflect different levels of incorporation of the One Health approach. While most countries like Thailand, India, Bhutan, Sri Lanka, Myanmar, and the DPRK Korea have advocated a comprehensive one-health approach towards rabies prevention and control, others like Bangladesh, Nepal, and Indonesia have not explicitly mentioned it in their policies. While Thailand has limited evidence on the integration of the One Health approach in dog-mediated rabies control strategy, on the other side India has successfully demonstrated the feasibility and cost-effectiveness of a collaborative One Health approach for human rabies elimination at the state level by integrating public education, mass dog vaccination, and rabies surveillance [10]. The evidence from Bangladesh, Nepal, and Bhutan shows a need for a multi-dimensional approach that combining veterinary and medical capacity, which is more effective in rabies prevention for the respective countries [33, 64-67]. During emergency rabies response activities in Indonesia, the Rapid Response Team (RRT) involves animal and human health sectors, reflecting a One Health approach [28, 61]. The evidence from Sri Lanka highlighted that the execution of the rabies control program by incorporating the One Health approach will ensure efficient response and reporting of animal bite cases from the community through human and animal health officers by developing a digital tool that integrates public health data as well as animal health data [42].

DETECT

Reporting Mechanisms for Rabies

Effective reporting mechanisms are essential to control rabies across different SEAR countries. PEP human rabies cases in Thailand are reported to the National Database for treatment. Also, village health volunteers record dog vaccination coverage data and report it to community leaders, who, in turn, report it to the higher authority (the municipal, provincial, and national governments) [29, 30]. Studies from Bangladesh show limited evidence regarding reporting mechanisms in both the human health and animal health sectors for the detection of rabies. In India, there is the National Action Plan for Rabies Elimination (NAPRE). Complimenting this, periodic reporting is carried out at all levels through the Integrated Health Information Platform (IHIP), an online portal of the Integrated Disease Surveillance Program. Despite these efforts, disparities in reporting practices were seen in India, where rabid dog bite cases were reported even from higher socio-economic backgrounds [68]. While health facilities are provided with monitoring tools, PEP data are not consistently reported to the central level as there is a lack of a mandatory reporting system for rabies PEP in Bhutan [19]. Even in Nepal, underreporting of human rabies cases remains a significant challenge due to insufficient monitoring and coordinated approach despite having a national policy that mentions structured tools such as animal bite and rabies treatment forms to ensure timely reporting [45, 48, 69]. Reporting is mandatory for both human and animal rabies cases in Indonesia, reflected through the evidence, where once a case is reported to the public health authority, further coordinating with animal health officers for appropriate action [27, 42]. According to Sri Lanka's rabies control policies, every individual receiving PET (Post-Exposure Treatment) must be registered in the animal bite registry of the hospital, which is maintained by the rabies unit or OPD (Outpatient Department). Each rabies unit was required to send a summary of PET cases to the Public Health Veterinary Services (PHVS), denoted by the study, where trained nursing officers entered each bite incident at the hospital's rabies clinic. Also, reporting dog bite cases through apps has enhanced transparency for case reporting and vaccination monitoring [70, 61].

Surveillance System

Most SEAR nations have developed surveillance systems to control rabies that ensure early detection and prompt monitoring and detection of rabies cases across countries. In Thailand, the national rabies surveillance system, Thai Rabies Net (TRN) is utilized to evaluate the achievements of vaccination campaigns and monitor rabies outbreaks [18]. Setting up a

laboratory for rabies diagnosis and implementing an active surveillance system in Bangladesh to monitor emerging patterns and trends for both human and animal rabies cases [71]. The rabies control policy in India advocates a robust surveillance system for both human and animal rabies cases, yet animal bite cases are observed to be underreported, suggesting a need for strengthening surveillance systems to track rabies cases more effectively [58, 72, 73]. Bhutan's policy also mentioned a robust surveillance system for the human and animal sectors, but there is insufficient data on detailed surveillance systems [19]. The rabies control policy of Nepal has not explicitly mentioned the surveillance system, but the study indicates that the rabies surveillance systems in Nepal are improving [60]. In Indonesia, National surveillance for animals and humans produces data used as epidemiological indicators to report rabies cases to international databases like the WHO and WOAH. Integration of the existing surveillance system with a community-based surveillance approach is one of the approaches to strengthen the surveillance system in Indonesia [74, 75]. Sri Lanka mandates a strong surveillance system to monitor both human and animal rabies cases as per the rabies control policy, but there were insufficient data from the studies that shed light on its surveillance system pertaining to rabies control in both human and animal sectors [54].

Laboratory Diagnostic Capacity

In Thailand, laboratories are utilized for animal rabies and animal sample testing, commonly collected during surveillance [18]. India's rabies control policy highlights various algorithms for antemortem and post-mortem laboratory diagnosis for human rabies. For ante mortem cases, Reverse transcription polymerase chain reaction (RT-PCR), Rapid Fluorescent Foci Inhibition Test (RFFIT), and Fluorescent Antibody Virus Neutralization (FAVN) are employed. In the case of post-mortem, tests like Direct Fluorescent Antibody Test (DFAT) and Nucleic Acid Amplification Test (NAAT) are utilized [76, 77]. However, the existing evidence from India shows that biochemical profiles were used to assess treatment effectiveness for rabies Rapid Fluorescent Focus Inhibition Tests (RFFIT) are available at a WHO Collaborating Centre for Rabies Research [44, 78]. Advanced genome sequencing techniques confirm rabies infection for both human and animal cases [79]. Although laboratory capacity details were not explicitly mentioned, medical institutions were noted to have facilities for diagnosing both human and canine rabies [80, 81]. Despite all these, maintaining the cold chain has become a significant challenge during sample transportation [78]. ELISA is the most commonly used measure to identify rabies antibody levels in dog serum in Nepal [60]. Animal rabies cases are confirmed using the Fluorescent Antibody Test (FAT) at the Central Veterinary Laboratory (CVL), and human rabies cases are identified using indirect immune-enzymatic assays [82, 83]. Laboratory infrastructure is limited in Indonesia, which poses a challenge for rabies detection in both humans and animals [51]. However, the animal health sector conducts rabies testing for rabies-suspected dogs, and Direct Fluorescent Antibody Testing is used to test the brain samples of suspected rabid dogs at the Disease Investigation Center [84]. Other SEAR countries like Bangladesh, Bhutan, and Sri Lanka have inadequate existing evidence on the diagnostic capacity of rabies detection in both human and animal rabies cases.

Response

Dog Population Management and Mass Dog Vaccination

Dog population management and mass dog immunization are critical aspects of rabies control policies for most South-East Asian countries. Thailand focuses on vaccinating free-roaming dogs (FRD) that are hard to reach, stressing responsible dog ownership to reduce the number of stray dogs [85, 44]. The traditional approach of culling dogs in Bangladesh has been less practical for dog population management and has led to the transition to mass vaccination with ORV and CNVR [58, 34]. Even in India, FRD is a significant concern, and to tackle this challenge, various measures like animal birth control (ABC), garbage management, and seasonal planning for neutering campaigns to manage dog populations are indicated [86, 57, 49]. Rabies control is more structured in Bhutan by managing FRD by capturing, neutering, and vaccinating them through mass dog vaccination and the program [60]. Studies from Nepal emphasize the need for stray dog population management due to high reproductive rates [50]. In Indonesia, dog population management for rabies primarily revolves around the non-systematic culling of FRD [87, 88, 89]. Mass dog vaccination campaigns are operated through an app in Sri Lanka, and even dog population control strategies are focused on combination of dog vaccination and birth control measures [90].

Dog Ownership

Responsible dog ownership is an essential component in rabies control and prevention. Countries like India, Sri Lanka, Indonesia and the DPRK Korea have promoted responsible dog ownership in their policies for effective vaccination campaigns and management strategies. In India, evidence implies the need to emphasize responsible dog ownership in sterilization, registration, and vaccination of dogs, which is critical in managing the dog population and reducing FRD [86]. In Indonesia, the free roaming of owned dogs' complicate vaccine coverage, indicate the need to educate owners about routine vaccination and sterilization [88, 89]. In Sri Lanka, responsible dog ownership is emphasized by tailored rabies vaccine strategies [61, 63]. Prioritization of dog ownership is not well evident in Thailand, Nepal, Bhutan, and Bangladesh, emphasizes the need to promote responsible dog ownership among the population.

Discussion

The present review provides a comprehensive overview of health system preparedness for dog-mediated rabies across the WHO South-East Asia Region (SEAR). While several countries in the region have made notable progress, rabies continues to be endemic in most SEAR countries including Bangladesh, Bhutan, DPRK Korea, India, Indonesia, Myanmar, Nepal, Sri Lanka, and Thailand [91]. Although Myanmar and DPRK Korea possess national rabies policies, this review highlights a striking paucity of published evidence on operational health-system preparedness in these settings [92], suggesting institutional and surveillance gaps rather than true absence of disease burden.

While the original findings demonstrate considerable heterogeneity in rabies control strategies within SEAR, a broader synthesis reveals that progress is driven less by technical capacity alone and more by political will, governance strength, and sustainable financing. Global comparative analyses consistently show that countries with stronger governance structures, stable public financing, and legal frameworks for multisectoral coordination achieve higher levels of epidemic preparedness, independent of income status [93].

Within SEAR, Thailand exemplifies this pattern by sustaining strong political commitment, advanced surveillance infrastructure (Thai Rabies Net), and consistent mass dog vaccination (MDV) efforts [18, 31, 44]. Sri Lanka similarly demonstrates institutionalized reporting systems, workforce training, and integrated dog vaccination and birth-control strategies [9, 43, 90, 19]. In contrast, countries such as Nepal and Bangladesh continue to face fragmented governance, inconsistent funding, and weak intersectoral enforcement despite possessing technical guidelines and international support [20, 39, 60].

Beyond governance, the review highlights the influence of socioeconomic determinants and structural determinants. Rural residence, geographic isolation, poverty, limited health literacy, and reliance on traditional healers particularly evident in Bangladesh and parts of India continue to delay timely uptake of PEP [20, 22, 34, 35]. These findings highlight that structural inequities and weak primary healthcare systems significantly undermine rabies elimination despite the availability of effective vaccines. In various endemic regions, most notably in mountainous areas like Nepal and parts of India, topographical obstacles intensify rabies mortality. These geographical challenges create significant gaps in healthcare access, strain already limited personnel resources, and lead to frequent disruptions in the medical supply chain [39, 40].

Benchmarking SEAR against other regions further contextualizes performance. Latin American countries such as Mexico and Brazil achieved near-elimination of canine rabies through decades of strong municipal governance, compulsory MDV, surveillance and sustained domestic financing [94]. Conversely, many African and Asian countries continue to struggle with widespread stray dogs, fragmented veterinary public health systems, weak financing, and inconsistent vaccination coverage have allowed sustained transmission of the virus between animals and humans. Limited health-care resources and the high cost or poor availability of PEP further increase population vulnerability [95].

The collective evidence indicates that rabies elimination is fundamentally a governance and development challenge, not merely a biomedical one. Countries that embed rabies elimination within long-term national health financing frameworks, institutionalize One Health governance, and ensure predictable domestic funding demonstrate faster and more sustainable progress. This is evidenced by the stark contrast between the domestic-led success in Latin America and the fragmented, donor-dependent programs often seen in high-burden regions [94].

Within SEAR, strengths such as India's expanding One Health initiatives [10], Bhutan's structured training and community engagement [28, 19], and Sri Lanka's integrated reporting and surveillance [9, 43, 90] provide important foundations. However, persistent challenges uneven vaccine access, under-reporting of animal bites [22, 68], diagnostic capacity limitations [78], and workforce shortages [46-48] continue to impede uniform regional advancement.

Ultimately, the attainment of the 'Zero by 30' objective in SEAR countries is contingent upon a transition from localized interventions to systemic integration. This process demands the stabilization of national health budgets, improved horizontal coordination across sectors, and the rectification of geographical inequities in PEP and MDV distribution. Crucially, these efforts must be supported by the development of resilient surveillance frameworks and high-fidelity laboratory infrastructure to ensure data-driven policy implementation

Strengths and Limitations

This review provides a detailed representation of SEAR countries, where the sectors with deliberate progress in rabies control measures and the areas that need to be considered. The review's strengths include grey literature on policy documents and animal bite management guidelines of SEAR countries, which provides a comprehensive understanding of health system preparedness for dog-mediated rabies in the region. However, in the review, we identified studies from SEAR, which do not represent data for health system preparedness of dog-mediated rabies across the human and animal health sectors.

Conclusion

Each SEAR country demonstrates distinctive strengths and challenges in the elimination of rabies. This review underlines that while, over the years, all countries

under the South-East Asian Region (SEAR) have made progress in rabies prevention and control efforts, although certain aspects need to be focused on and strengthened. Strengthening inter-sectorial coordination by linking both animal and human data for rabies surveillance, expanding public education, improvising health infrastructure, and strengthening vaccine accessibility could contribute to the control efforts in South-East Asia countries and enhance the global goal "Zero by 30" of ending dog-mediated human rabies deaths by 2030.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Data Availability Statement

The data set used for the current study is available as supplementary material in the manuscript (Tab. S1).

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Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

Authors' Contributions

IG: formulating search strategy, search and screening articles, data extraction and analysis SUK: formulating search strategy, screening articles, data extraction, data analysis, and manuscript writing; MT: search and screening articles; NV: data analysis, third reviewer of conflict articles, guidance on methodology writing, and writing the manuscript; NS: searching and screening articles, data analysis, and writing the manuscript; AV: inputs on data analysis, writing, and reviewing of the manuscript; SN: inputs on data analysis, writing, and reviewing the manuscript; BK: inputs on data analysis, writing, and reviewing the manuscript.

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Correspondence: Navya Vyas, Associate Professor, Department of Global Public Health Policy and Governance, Prasanna School of Public Health, Manipal Academy of Higher Education, Manipal 576104, Karnataka, India. E-mail: navya.vyas@manipal.edu

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Tab. S1. Characteristics of Included Studies.

S.No	Author(s) (Year)	Country/Region	Study Design	Population	Sample Size	Key Findings	References
1	Mubashar et al. (2023)	Bhutan, India, Maldives, Nepal, Sri Lanka	Epidemiological Study	Dog bite victims	Not Specified	Regional rabies control requires mass dog vaccination, surveillance, and One Health collaboration.	[68]
2	Leelahapongsathon et al. (2023)	Thailand	Field Study	Free-roaming dogs	Not Specified	ORV integration improved vaccination of free-roaming dogs under a One Health framework.	[18]
3	Dhakal et al. (2023)	Nepal	Cross Sectional Study	Household heads	308	Integrated education, trained responders, strong healthcare systems, stakeholder collaboration, and mass dog vaccination are essential.	[96]
4	Fielding et al. (2023)	India	Mixed-Methods Study	Free-ranging dogs (FRD)	Not Specified	Standardized dog surveys improved assessment of sterilization coverage.	[97]
5	Lu et al. (2023)	Bangladesh	Retrospective Ecological Study	Cattle, buffalo, sheep, and goats	Not Specified	Higher education levels were associated with fewer livestock rabies cases.	[70]
6	Verma & Agarwal (2023)	India	Experimental Study Design	Preclinical medical students	Not Specified	Social media showed limited short-term impact on rabies awareness.	[98]
7	Shrestha et al. (2023)	Nepal	Retrospective Ecological Spatial Analysis	Data from VES and CVL	Not Specified	Spatial and seasonal rabies patterns support pulse vaccination in high-risk districts.	[81]
8	Karamoy et al. (2023)	Indonesia	Qualitative Study	Stakeholders from five sectors	Not Specified	Fragmented coordination and weak data systems hinder rabies prevention.	[87]
9	Giri (2023)	India	Cross Sectional Study	Animal bite cases	Not Specified	Strengthened community education is required despite high general awareness.	[99]
10	Balaraju et al. (2023)	India	Cross Sectional Study	MBBS Interns	Not Specified	Interns knew PrEP guidelines but lacked detailed PEP knowledge.	[100]
11	Cuddington & McAuliffe (2023)	India	Economic Modelling Study	Free-roaming dogs	Not Specified	Achieving >70% dog vaccination is essential for eliminating human rabies.	[101]
12	Tamanna et al. (2023)	Bangladesh	Cross Sectional Study	Patients given first dose of rabies IG	Not Specified	Delays in completing PEP were linked to poor knowledge and access barriers.	[102]
13	Rajpoot et al. (2023)	India	Cross Sectional Study	Visitors at Anti-Rabies Clinic	Not Specified	Incomplete disease knowledge persisted despite general awareness of rabies preventability.	[103]
14	Dhakal et al. (2023)	Nepal	Cross Sectional Study	Households	308	Survey findings guided targeted rabies prevention policies.	[37]
15	Laorujisawat et al. (2022)	Thailand	Cross Sectional Study	Primary school students	Not Specified	School-based rabies education improved preventive knowledge.	[104]
16	Subrata et al. (2022)	Indonesia	Mixed-Methods Study	Veterinarians, officers, leaders, dog owners, workers	Not Specified	Digital tools integrated with vaccination/ sterilization strengthened One Health rabies surveillance.	[40]
17	Saepudin et al. (2022)	Indonesia	Case-Control Study	Dog bite victims	Not Specified	Prevention depends on domestic animal vaccination, education, and surveillance.	[38]
18	More & Jadhav (2022)	India	Pre-experimental (pre-post test)	Caregivers in a hospital	100	Structured teaching significantly improved caregivers' knowledge of anti-rabies vaccination.	[105]

Tab. S1 *(follows).*

S.No	Author(s) (Year)	Country/Region	Study Design	Population	Sample Size	Key Findings	References
19	Rode (2022)	India	Pre-experimental (pre-post test)	Adults in Pune city	60	Health education improved community awareness of PEP following dog bites.	[106]
20	Kiratitana-olan et al. (2022)	Thailand	Qualitative Study	Permanent residents (urban, suburban, rural)	Not Specified	Multisectoral collaboration and community engagement sustained rabies-free status.	[29]
21	Chaudhari et al. (2022)	India	Descriptive and Evaluative study	Street dogs	Not Specified	Digital tools and CNVR improved dog population management and rabies vaccination outcomes.	[107]
22	Vanak et al. (2022)	India	Descriptive Observational Design	Dogs	Not Specified	Passive surveillance supports rabies monitoring, but revaccination gaps hinder elimination goals.	[108]
23	Manna et al. (2022)	India	Cross Sectional Study	Animal Bite Victims	Not Specified	PEP adherence linked to socio-economic status and awareness levels.	[24]
24	Aptriana et al. (2022)	Indonesia	Qualitative study	Relevant stakeholders	Not Specified	One Health coordination improved surveillance and vaccination despite resource constraints.	[27]
25	Bariya et al. (2022)	India	Interventional Study	Staff Nurse	Not Specified	CME programs improved nurses' awareness of rabies transmission, though protocol gaps remained.	[109]
26	Lhendup & Wangdi (2022)	Bhutan	Cross Sectional Study	Volunteer household members	55 households	Cultural beliefs and awareness gaps persist despite good rabies knowledge.	[25]
27	Jethani et al. (2022)	India	Retrospective cross-sectional study	Animal bite cases	Not Specified	Vaccine shortages forced patients to travel, underscoring prevention and supply-chain gaps.	[110]
28	Dua et al. (2022)	India	Retrospective record-based study	Animal bite cases	Not Specified	High animal-bite burden highlights need for expanded education and prophylaxis services.	[111]
29	Gibson et al. (2022)	India	Intervention study	Human and canine populations	Not Specified	Integrated surveillance, vaccination, and education supported rabies elimination in Goa.	[112]
30	Gongal et al. (2022)	India, Nepal, Sri Lanka, Thailand	Mixed-methods observational study	Health facilities and PEP providers	Not Specified	COVID-19 disrupted services, but PEP availability was largely maintained.	[113]
31	Lungten et al. (2022)	Bhutan	Interventional study	School Students	Not Specified	Short educational sessions significantly improved student rabies knowledge.	[114]
32	Evans et al. (2022)	India	Prospective observational study	Free-ranging dogs (FRD)	Not Specified	Annual campaigns achieved 70% coverage but required sustained implementation.	[115]
33	Nadal et al. (2022)	India	Mixed-method Study	Healer, Temple Caretaker	Not Specified	Engagement with faith healers is essential to address cultural barriers to rabies prevention.	[116]
34	Gill et al. (2022)	India	Dog Survey	Dog population	Not Specified	Inconsistent stray dog counts limit effective planning of control programs.	[117]
35	Sararat et al. (2022)	Thailand	Individual-based modeling study	Canine rabies cases	Not Specified	Modeling showed that increased vaccination and reduced dog populations are critical for rabies control.	[118]
36	Bharani (2022)	India	Cross Sectional Study	Individuals from rural community	Not Specified	Very low awareness of wound washing and vaccine availability in rural communities.	[119]
37	Kanankege et al. (2022)	Thailand	Retrospective study	Government and open-source data	Not Specified	Integrated One Health surveillance supported rabies control though reporting gaps persisted.	[30]

Tab. S1 *(follows).*

S.No	Author(s) (Year)	Country/Region	Study Design	Population	Sample Size	Key Findings	References
38	Royal et al. (2022)	India	Cost effectiveness analysis	Children	Not Specified	PrEP was highly cost-effective for high-risk children in rabies-endemic settings.	[120]
39	Khamduang et al. (2022)	Thailand	Cross Sectional Study	Village health volunteers	Not Specified	Trained village volunteers effectively supported animal rabies vaccination.	[121]
40	Silva et al. (2022)	Indonesia	Observational ecological study	Free-roaming dogs in rural/urban areas	Not Specified	Habitat-based tracking supported targeted dog vaccination strategies.	[122]
41	(Ross et al., 2022)	Bangladesh	Cross Sectional Study	Urban and peri-urban residents	Bangladesh	Improved PEP access and public awareness are key to rabies elimination by 2030	[123]
42	Tipsarp Kittisiam et al. (2021)	Thailand	Cross Sectional Study	Dogs	Not Specified	Network modeling identified high-risk dogs to guide targeted vaccination.	[124]
43	Rana et al. (2021)	Bangladesh	Cross Sectional Study	Community people, healthcare professionals, vets	Not Specified	Knowledge gaps and preference for dog culling hinder elimination efforts.	[21]
44	Mani et al. (2021)	India	Case Study	Asiatic wild dogs (*Cuon alpinus*)	Not Specified	Laboratory-confirmed rabies highlights need for mass vaccination of domestic dogs.	[78]
45	Pal et al. (2021)	Nepal	Retrospective Epidemiological Study	Various animal species	Not Specified	Long-term surveillance, mass vaccination, and One Health coordination are key to rabies control.	[63]
46	Fielding et al. (2021)	India	Model Analysis	Adult female free-roaming dogs	7,743	Understanding dog reproductive seasonality improves effectiveness of neutering and population management.	[125]
47	Saleem et al. (2021)	India	Record-based cross-sectional study	Dog bite victims	Not Specified	Strengthened surveillance, responsible ownership, and dog population control are essential.	[126]
48	Pal et al. (2021)	Nepal	Retrospective Study	Dog bite victims	Not Specified	Improved PEP use, surveillance, and One Health collaboration reduce rabies risk.	[36]
49	Taneja et al. (2021)	India	Retrospective Cross-Sectional study	Dog bite victims	Not Specified	Community awareness, vaccination, and data-driven dog population control enhance rabies prevention.	[127]
50	Rehman et al. (2021)	Indonesia	Cross sectional study	Respondents of different demographics	432	Major gaps in post-bite care-seeking behavior indicate urgent need for community education.	[39]
51	Premashthira et al. (2021)	Thailand	Cross Sectional Study	Dog owners	Not Specified	Public education should be prioritized over perception-based policy changes.	[128]
52	Sivagurunathan et al. (2021)	India	Cross Sectional Study	Residents	Not Specified	Primary care physicians play a key role in correcting community rabies misconceptions.	[129]
53	Weerapong Thanapongtharm et al. (2021)	Thailand	Retrospective analysis with spatial modeling	Animal rabies cases (dogs)	Not Specified	Implemented a national rabies control strategy involving mass dog vaccination, promotion of responsible dog ownership, strengthened surveillance and multisectoral collaboration under a One Health approach, contributing to improved rabies control.	[130]

Tab. S1 *(follows).*

S.No	Author(s) (Year)	Country/Region	Study Design	Population	Sample Size	Key Findings	References
54	Thanapongtharm et al. (2021)	Thailand	Dog surveys and spatial modelling	Owned and ownerless dogs	Not Specified	Surveillance systems and spatial planning supported effective dog vaccination strategies.	[131]
55	Chanachai et al. (2021)	Thailand	Field-based interventional study	Free-roaming dogs	Not Specified	ORV effectively reduced rabies risk among free-roaming dogs.	[43]
56	Warembourg et al. (2021)	Indonesia	Cross Sectional Study	Owned dogs	714	Targeting highly connected dogs improved vaccination efficiency.	[86]
57	Nale et al. (2021)	India	Observational Study	Vaccinated and owned dogs	Not Specified	Mass dog vaccination increased herd immunity through multisectoral collaboration.	[132]
58	Ubeyratne et al. (2021)	Sri Lanka	Cross Sectional Study	Residents in rural areas	Not Specified	Moderate PEP uptake but low education and vaccination hindered control efforts.	[133]
59	Christopher et al. (2021)	Indonesia	Cross Sectional Study	Community members in Songan Village	Not Specified	Community education and dog vaccination improved local rabies prevention.	[134]
60	Laorujisawat et al. (2021)	Thailand	Cross Sectional Study	Fourth-grade students	Not Specified	Protection-motivation based education improved rabies preventive behavior among school children.	[135]
61	Pal et al. (2021)	Nepal	Cross Sectional Study	Respondents from Nepal	5000	Preference for traditional healers and low vaccination knowledge increased rabies risk.	[64]
62	Rinchen et al. (2020)	Bhutan	Qualitative Risk Assessment	Dogs	Not Specified	Stronger coordinated public and expert engagement is required for rabies control.	[136]
63	Penjor et al. (2020)	Bhutan	Cross Sectional Study	Clinicians and human cases	Not Specified	Inconsistent PEP practices highlighted need for clinician training and coordination.	[48]
64	Rahaman et al. (2020)	Bangladesh	Cross Sectional Study	Local residents	Not Specified	Socio-economic barriers and myths reduced use of free rabies treatment services.	[137]
65	Zuhriyah et al. (2020)	Indonesia	Case Study	Outbreak affected population	>240,000	One Health–based PEP, mass dog vaccination, and workforce training are critical despite weak laboratory capacity.	[52]
66	Anandhan et al. (2020)	India	Cross-Sectional Study	Residents of Tamil Nadu	205	Public awareness, timely PEP, and dog vaccination are central to rabies prevention.	[138]
67	Gupta et al. (2020)	India	Cross-Sectional Study	University students	Not Specified	Student education improves awareness and supports community-level rabies prevention.	[139]
68	Marpaung & Monique (2020)	Indonesia	Qualitative study	Children in an endemic area	Not Specified	Rabies prevention in children relies on PEP access and targeted awareness programs.	[140]
69	Wallace et al. (2020)	Indonesia, India	Qualitative study	Dog populations globally	Not Specified	Parenteral vaccination remains primary; ORV, surveillance, and multisectoral collaboration strengthen One Health control.	[141]
70	Wani et al. (2020)	India	Cross Sectional Study	Patients with history of animal bite	Not Specified	Delayed PEP was associated with rural residence, low income, and referral barriers.	[142]
71	Alam et al. (2020)	Bangladesh	Cross Sectional Study	Dog-bite Victims	Not Specified	Low awareness and poor wound care increased exposure to rabies.	[143]
72	Rana et al. (2020)	Bangladesh	Retrospective cross-sectional study	Caregiver/relatives of deceased	Not Specified	Limited access to free vaccines and reliance on traditional healers led to fatal treatment delays.	[20]

Tab. S1 *(follows).*

S.No	Author(s) (Year)	Country/Region	Study Design	Population	Sample Size	Key Findings	References
73	Bashir et al. (2020)	India	Retrospective study	Dog bite victims	6172	Free ARV, surveillance and multisectoral coordination improved rabies control in high-risk areas.	[57]
74	Ghosh et al. (2020)	Bangladesh	Retrospective Study	Dog bite victims	Not Specified	Socio-cultural barriers and traditional healing limited PEP uptake, necessitating awareness and mass dog vaccination.	[66]
75	Gautam et al. (2020)	India	Cross Sectional Study	Institutional residents and stakeholders	Not Specified	Low vaccination coverage and weak community participation limited campus rabies control.	[144]
76	Gigante et al. (2020)	India	Cross Sectional Study	Rabies virus samples	Not Specified	Portable sequencing improved rabies surveillance capacity.	[145]
77	Belsare & Vanak (2020)	India	Agent-based modelling (ABM) simulation study	Free-roaming dog population	Not Specified	Underfunded CNVR programs limit rabies control without sustained One Health action.	[146]
78	Bonwitt et al. (2020)	Bangladesh	Observational field study	Free-roaming dogs	356	ORV combined with community engagement improved vaccination of free-roaming dogs.	[56]
79	Saleem et al. (2020)	India	Qualitative analysis	People living in Srinagar city	Not Specified	Low public preparedness increased vulnerability to dog bites.	[147]
80	Sabeena et al. (2020)	India	Intervention Study	Health Care Professionals	Not Specified	Mobile app improved guidance on rabies prevention and post-bite management.	[148]
81	Yurachai et al. (2020)	Thailand	Epidemiological study	Residents exposed to suspected rabid animals	Not Specified	Hospital-based electronic surveillance strengthened rabies monitoring and response.	[149]
82	Rimal et al. (2020)	Nepal	Cross Sectional Study	Vaccinated pet dogs	Not Specified	Training veterinary staff improved serological monitoring and vaccination effectiveness.	[82]
83	Larkins et al. (2020)	India	Cost-Effectiveness Case Study	Roaming dog and human population	Not Specified	Long-term sterilization and vaccination were cost-effective rabies control strategies.	[150]
84	Gibson et al. (2019)	India	Field-based comparative experimental study	Free-roaming dogs	Not Specified	Oral rabies vaccination effective for free-roaming dogs.	[151]
85	Gibson et al. (2019)	India	Field Survey	Dog population, vaccination staff	Not Specified	OBH vaccination reached more ownerless dogs than conventional methods.	[67]
86	Tiwari et al. (2019)	India	Cross-Sectional Study	Urban residents	204	Awareness gaps among low-SES groups; need targeted education and dog management.	[152]
87	Tiwari et al. (2019)	India	Observational Field Study	Free-roaming dogs	Not Specified	Tailored vaccination strategies and accurate dog population estimation are essential to achieve ≥70% coverage.	[153]
88	Tiwari et al. (2019)	India	Comparative observational study	Free Roaming Dog	Not Specified	Poor waste management undermined stray dog vaccination and birth-control programs.	[154]
89	Tiwari et al. (2019)	India	Cross Sectional Study	Free-ranging dogs (FRD)	Not Specified	Rapid online tools reliably estimated vaccination targets for FRDs.	[155]
90	Sreenivasan et al. (2019)	Bangladesh, Bhutan, India, Nepal, Sri Lanka	Cross-Sectional Study	Key informants from 23 countries	Not Specified	Large inter-country variation in PEP delivery; dog vaccination remains essential.	[156]

Tab. S1 *(follows).*

S.No	Author(s) (Year)	Country/Region	Study Design	Population	Sample Size	Key Findings	References
91	Li et al. (2019)	Bangladesh, Bhutan, Sri Lanka	Qualitative Study	Key informants from the public sector	Not Specified	One Health collaboration supported PEP delivery and animal vaccination.	[19]
92	Ojha (2019)	Nepal	Cross-Sectional Study	Street dogs	50	High antibody response in vaccinated dogs; highlighted need for surveillance and political commitment.	[60]
93	Brookes et al. (2019)	India	Observational Study	Farmers and householders	Not Specified	Informal information networks limit vaccination uptake, stressing need for formal surveillance systems.	[157]
94	Ashwath Narayana & Sudarshan (2019)	India	Record-based study	Human rabies cases and animal bite incidents	Not Specified	Improved PEP reduced cases but reporting and documentation gaps persisted.	[72]
95	Meunier et al. (2019)	India	Comparative observational field study	Free-roaming dogs	Not Specified	Systematic dog surveys are essential for planning vaccination campaigns.	[158]
96	Meunier et al. (2019)	India	Observational field study	Free-roaming dogs	Not Specified	>70% vaccination of free-roaming dogs achieved through coordinated One Health campaign.	[159]
97	Manoharan et al. (2019)	India	Quasi Experimental Study	Medical Students	Not Specified	Medical students lacked comprehensive training in rabies PEP protocols.	[160]
98	Narayana et al. (2019)	India	Mixed-Method Study	Stakeholders from govt. and private sectors	Not Specified	Gaps in PEP availability and coordination weakened rabies prevention efforts.	[161]
99	Sanjay et al. (2019)	India	Cross Sectional Study	General population	Not Specified	Low PrEP awareness necessitates public education campaigns.	[162]
100	Rinchen et al. (2019)	Bhutan	Cross Sectional Study	Cattle owners	562	High awareness but poor knowledge among cattle owners indicates need for stronger education.	[65]
101	Tiwari et al. (2019)	India	Cross Sectional Study	Rural residents of Maharashtra	127	Rural communities showed awareness but delays in treatment and poor ownership practices persisted.	[22]
102	Mani et al. (2019)	India	Descriptive Study	Officials from various sectors	Not Specified	Integrated medical-veterinary efforts maintained rabies-free status, requiring continued surveillance.	[71]
103	Penjor et al. (2019)	Bhutan	Cross Sectional Study	Dog-bite victims	Not Specified	Awareness and accessibility improved PEP adherence, though misconceptions caused delays.	[163]
104	Bharti et al. (2019)	India	Retrospective Study	Patients exposed to suspected rabid animals	Not Specified	Intradermal PEP with eRIG was effective and cost-saving.	[164]
105	Bharti (2019)	India	Retrospective Study	Animal bite patients	Not Specified	Wound infiltration with eRIG was effective and reduced costs.	[165]
106	Sánchez-Soriano et al. (2019)	Sri Lanka	Retrospective Study	Dogs Population	Not Specified	Coordinated vaccination campaigns achieved high dog coverage.	[166]
107	Srinivasan et al. (2019)	India	Mixed-method Study	General population	Not Specified	General awareness was high, but first-aid practices remained inadequate.	[167]

Tab. S1 *(follows).*

S.No	Author(s) (Year)	Country/Region	Study Design	Population	Sample Size	Key Findings	References
108	Ni et al. (2019)	Indonesia	Mixed method study	Dog and dog owners	Not Specified	Community-led veterinary and education programs reduced rabies risk but faced sustainability challenges.	[83]
109	Gill et al. (2019)	India	Prospective observational study	Canine and livestock populations	Not Specified	Community reporting improved rabies surveillance and dog management.	[168]
110	Amanatin et al. (2019)	Indonesia	Risk Assessment Study	Hunting dog	Not Specified	Vaccine shortages, cold-chain gaps, and limited workforce reduced dog vaccination coverage.	[26]
111	Hanumanthaiah et al. (2019)	India	Cross Sectional Study	Individuals attending anti-rabies clinics	Not Specified	ARCs require better training, supplies, and standardized reporting.	[169]
112	Kapoor et al. (2019)	India	Observational Cross-sectional study	Attendees of the anti rabies clinic	Not Specified	Knowledge of wound washing existed, but overall rabies prevention awareness was inadequate.	[170]
113	(Haradanhalli & D Hanumanthaiah, 2019)	India	Cross-sectional, multicentric survey study	Health system facilities and officials responsible for rabies biologicals logistics	India	The National Rabies Control Programme emphasizes training and monitoring, while gaps remain in vaccine distribution and cold chain management.	[171]
114	Hampson et al. (2019)	India	Modeling Study	Individuals exposed to potentially rabid animals	Not Specified	PEP is cost-effective, but mass dog vaccination remains essential for elimination.	[172]
115	Kanwal & Devgun (2018)	India	Cross-Sectional Study	Respondents	400	Significant gaps in ARV access and qualified care among dog bite victims.	[173]
116	Karmakar et al. (2018)	India	Cross Sectional Study	Dog bite victims	Not Specified	Proper wound care was common, but public awareness and street dog control need strengthening.	[174]
117	Behera (2018)	India	Cross Sectional Study	Veterinary staff	Not Specified	Veterinary staff showed poor rabies risk perception and low PrEP coverage, indicating training gaps.	[175]
118	Kasemsuwan et al. (2018)	Thailand	Field Study	Street dogs	Not Specified	ORV during mass campaigns offers a feasible solution to eliminate dog-mediated rabies.	[176]
119	Hiby & Tasker (2018)	Bangladesh, Indonesia	Qualitative Study	Stakeholders from Various sectors	Not Specified	Humane dog vaccination combined with capacity building improved rabies control outcomes.	[177]
120	Gibson et al. (2018)	India, Sri Lanka	Implementation study	Dogs population	Not Specified	Mobile apps enabled large-scale vaccination, education, and real-time monitoring.	[69]
121	Ramesh & Pruthvi S (2018)	India	Exploratory study	Dog/cat bite cases	69	Stray dogs caused most bites; incomplete PEP and weak diagnostics persisted.	[178]
122	Tiwari et al. (2018)	India	Cross Sectional Study	Nursing and non-nursing staff	54	Limited RIG availability and staff training gaps hindered effective PEP delivery.	[179]
123	Gautret et al. (2018)	Thailand, Sri Lanka	Observational study	Travelers exposed	Not Specified	Pre-travel rabies vaccination is critical for travelers to endemic regions.	[180]
124	Bharathy & Gunaseelan (2017)	India	Cross Sectional Study	Dog bite victims	Not Specified	Low pet vaccination persisted despite awareness, highlighting gaps between knowledge and practice.	[181]

Tab. S1 *(follows).*

S.No	Author(s) (Year)	Country/Region	Study Design	Population	Sample Size	Key Findings	References
125	Brookes et al. (2017)	India	Retrospective Study	Animal rabies cases	Not Specified	Integrated human-animal surveillance is needed for effective rabies control.	[182]
126	Tenzin et al. (2017)	Bhutan	Cross Sectional Study	Town residents	67	Outbreak response showed effective One Health coordination and high PEP uptake.	[183]
127	Silva et al. (2017)	Sri Lanka	Program Evaluation study	Animal Bites Cases	12,121	Digital platforms strengthened real-time rabies surveillance and response.	[53]
128	Holla et al. (2017)	India	Cross Sectional Study	Clinical faculty and postgraduates	Not Specified	Professional and public knowledge gaps limit effective rabies prevention.	[45]
129	Wera et al. (2017)	Indonesia	Cost-Effectiveness Modeling Study	Residents of Flores Island	Not Specified	Cost-effective rabies control relied primarily on sustained mass dog vaccination.	[28]
130	Arief et al. (2017)	Indonesia	Dog survey and Mapping	Owners of owned dogs	Not Specified	Vaccination coverage was high in owned dogs but low in free-roaming and juvenile dogs.	[88]
131	Auplish et al. (2017)	India	Cross Sectional Study	Students	226	Intersectoral school programs improved rabies awareness and bite prevention.	[184]
132	Kazi et al. (2016)	Bangladesh, India	Prospective Study	Cattle, Goats, dog	Not Specified	Low awareness and reliance on traditional healers increased rabies risk despite wound care.	[185]
133	Christiansen et al. (2016)	Thailand	Retrospective Study	Danish travelers	Not Specified	Increase in PEP/PrEP among travelers driven by travel volume, not awareness.	[54]
134	Ghosh et al. (2016)	Bangladesh	Cross Sectional Study	Households	3200	Traditional beliefs and low education hindered effective rabies prevention.	[33]
135	Fitzpatrick et al. (2016)	India	Mathematical modeling study	Dogs and human populations exposed	Not Specified	Mass dog vaccination and education reduced transmission and PEP demand.	[186]
136	Massei et al. (2016)	Nepal	Cross Sectional Study	Free-roaming owned dogs and owners	Not Specified	Low knowledge and dog vaccination rates highlight urgent education needs.	[47]
137	Dhaduk et al. (2016)	India	Cohort study	Animal bite victims	Not Specified	Intradermal vaccination was effective but surveillance gaps remained.	[187]
138	Wera et al. (2016)	Indonesia	Cost-Effectiveness Modeling Study	Dog population	Not Specified	Mass dog vaccination was more cost-effective than PEP alone.	[188]
139	Wera et al. (2016)	Indonesia	Cross Sectional Study	Dog owners	450	Dog-owner education and community participation improved vaccination coverage.	[61]
140	Kularatne et al. (2016)	Sri Lanka	Retrospective descriptive study	Animal exposure cases	19,661	Coordinated One Health strategies improved rabies prevention outcomes.	[89]
141	Rinzin et al. (2016)	Bhutan	Cross Sectional Study	Bhutanese households	Not Specified	CNVR programs achieved high coverage, but responsible ownership enforcement remains essential.	[189]
142	Mani et al. (2016)	India	Retrospective analysis	Patients with suspected human rabies	128	Inadequate PEP, shortages, and weak surveillance contributed to ongoing rabies risk.	[79]
143	Sharma et al. (2016)	India	Cross Sectional Study	Households	500	Urban slums showed awareness but poor wound care and low dog vaccination rates.	[190]

Tab. S1 *(follows).*

S.No	Author(s) (Year)	Country/Region	Study Design	Population	Sample Size	Key Findings	References
144	Shankaraiah et al. (2015)	India	Cross Sectional Study	Animal bite victims	Not Specified	Intradermal vaccination improved adherence compared to intramuscular schedules.	[191]
145	Wera et al. (2015)	Indonesia	Cross Sectional Study	Dog owners	Not Specified	Owner education and government leadership supported vaccination success.	[192]
146	Hampson et al. (2015)	Multiple SEA countries	Country Survey	Domestic dog population	Not Specified	Mass dog vaccination is more cost-effective than reliance on human PEP alone.	[193]
147	Craighead et al. (2015)	Sri Lanka	Survey	Street dog	Not Specified	Dog owners showed higher rabies awareness and reporting compared to the general public.	[194]
148	Tenzin et al. (2015)	Bangladesh	Prospective observational study	Free-roaming dogs	Not Specified	CNVR programs successfully integrated vaccination, population control, and community engagement.	[195]
149	Mustiana et al. (2015)	Indonesia	Cross Sectional Study	Dog-owning households and free-roaming dogs	Not Specified	High free-roaming dog populations required owner education and vaccination.	[196]
150	Tenzin et al. (2015)	Bhutan, India	Cross Sectional Study	Free-roaming dogs	Not Specified	CNVR achieved moderate coverage with strong intersectoral support.	[59]
151	Ward & Hernández-Jover (2015)	Indonesia, Timor Leste	Modeling Study	Rabies-free islands and regions	Not Specified	Monitoring dog transport reduced rabies introduction risk in rabies-free islands.	[197]
152	Gibson et al. (2015)	India	Field study	Free-roaming and owned dogs	Not Specified	Smartphone-based monitoring improved coordination of vaccination campaigns.	[198]
153	Kanda et al. (2015)	Sri Lanka	Interventional study	School children	Not Specified	School-based education strengthened community rabies awareness.	[199]
154	Samanta et al. (2015)	India	Prospective Observational Study	Children admitted in hospital	308	Timely PEP was common, but traditional wound care practices persisted.	[34]
155	Digna et al. (2015)	Indonesia	Mixed-methods cross-sectional study	Residents of 10 villages	Not Specified	Community education and mass dog vaccination were central to effective rabies prevention.	[73]
156	Häsler et al. (2014)	Sri Lanka	Case study	Dog and human populations	Not Specified	Vaccinating both owned and unowned dogs was most effective.	[42]
157	Morters et al. (2014)	Indonesia	Longitudinal study	Free-roaming dog populations	Not Specified	Sustained vaccination campaigns increased long-term canine immunity.	[50]
158	Karunanayake et al. (2014)	Sri Lanka	Retrospective Study	Human and animal rabies cases	Not Specified	Free PEP, surveillance, and dog vaccination underpinned rabies control.	[200]
159	Praveen & Kumar (2014)	India	Descriptive study	First-year medical students	90	Medical students showed poor knowledge of rabies PEP, indicating need for better training.	[201]
160	Sittichanbuncha et al. (2014)	Thailand	Retrospective study	Patients	372	PEP followed WHO guidelines; PrEP policies not clearly described.	[202]
161	Raju et al. (2014)	India	Prospective Interventional study	Residents of six villages	Not Specified	Integrated One Health intervention reduced animal bites and rabies risk.	[44]
162	Shridevi et al. (2014)	India	Cross-Sectional Study	Residents of the urban area	Not Specified	Low awareness of dog vaccination; IEC-based education found cost-effective.	[203]

Tab. S1 *(follows).*

S.No	Author(s) (Year)	Country/Region	Study Design	Population	Sample Size	Key Findings	References
163	Salve et al. (2014)	India	Observational Study	Patients treated at the ABM clinic	619	Intradermal PEP at primary care was cost-effective but challenged by adherence and vaccine wastage.	[204]
164	Morters et al. (2014)	Indonesia	Prospective Longitudinal Cohort Study	Owned Dogs and Owners	Not Specified	Sustained community-based vaccination and sterilization outperformed culling strategies.	[49]
165	Kashino et al. (2014)	Thailand	Cross Sectional Study	Japanese expatriates and travelers	Not Specified	Traveler PrEP awareness remained critically low.	[205]
166	Mahardika et al. (2014)	Indonesia	Molecular epidemiology study	Rabies-infected humans and dogs	Not Specified	Molecular surveillance enhanced understanding of rabies transmission and control.	[206]
167	Amaral et al. (2014)	Multiple SEA countries	Stratified Sight Survey	Roaming dog	Not Specified	Sight–resight surveys improved dog population estimates for rabies preparedness.	[207]
168	Jain & Jain (2014)	India	Cross Sectional Study	Local residents	Not Specified	Community awareness ensured ARV availability, but first-aid knowledge remained inadequate.	[208]
169	Joseph et al. (2013)	India	Cross Sectional Study	Animal bite victims	200	Low dog vaccination and poor public awareness delayed timely rabies treatment.	[209]
170	Patnaik (2013)	India	Cross-Sectional Study	Animal bite victims	100	Emphasized One Health collaboration, mass dog vaccination, and responsible ownership.	[210]
171	Sridhar et al. (2013)	India	Prospective observational study	Patients with dog bites and rabies complications	54	WHO-recommended PEP with RIG and vaccine was effectively implemented and monitored.	[77]
172	Reece et al. (2013)	India	Retrospective Analysis	Human residents and street dogs	Not Specified	Large-scale sterilization and vaccination effectively reduced rabies risk in urban settings.	[211]
173	Rumana et al. (2013)	Bangladesh	Cross Sectional Study	Adults from five villages	1,973	High awareness but low vaccination due to access barriers and traditional practices.	[212]
174	Belsare & Gompper (2013)	India	Primary Field-Based epidemiological study	Dog populations	Not Specified	Door-to-door and central-point vaccination effectively controlled rabies.	[80]
175	Sibunruang et al. (2013)	Thailand	Retrospective observational study	Travelers	Not Specified	Traveler education is essential in endemic rabies regions.	[213]
176	Putra et al. (2013)	Indonesia	Retrospective Study	Dog and human populations in Bali	Not Specified	Integrated One Health strategies improved rabies control in Bali.	[214]
177	Wera et al. (2013)	Indonesia	Cost-Effectiveness Modeling Study	Dog and human populations	Not Specified	Integrated mass dog vaccination, human prophylaxis, and education strengthened rabies control.	[215]
178	Hossain et al. (2013)	Bangladesh	Cross Sectional Study	Dog population	Not Specified	Accurate dog population counts were essential for rabies planning.	[216]

REVIEWS

The role of specific nutrients in preventing immune system and blood cell disorders: an umbrella review

ANDREA VECCHIETTI[1], PAOLO STRANO[1], GIUSEPPA MINUTOLO[2], VITTORIO GRIECO[3], GIORGIA CAPPUCCIO[3], GIUSEPPA GRANVILLANO[3], LAURA CONFALONIERI[4], GIOVANNI LEONARDO BRIGANTI[5], ELEONORA RASO[4], MARTINA CHIMIENTI[6,7], MARZIA PELLEGRINI[8], MICHELANGELO MERCOGLIANO[9], GLORIA SPATARI[10], CAMILLA LUGLI[11], TERESA URBANO[12], ANTONIO LORENZON[13,14]

[1] Department of Diagnostics and Public Health, Hygiene Section, University of Verona; [2] Food Hygiene, Nutritional Surveillance and Prevention, Department of Prevention, Provincial Healthcare Authority of Palermo; [3] Department of Medical and Surgical Sciences and Advanced Technologies "G.F. Ingrassia", University of Catania; [4] Department of Public Health, Experimental and Forensic Medicine, University of Pavia; [5] Department of Medical and Surgical Science, Alma Mater Studiorum, University of Bologna; [6] Department of Biomedicine and Prevention, "Tor Vergata" University of Rome; [7] Local health authority Rome 2; [8] Department of Translational Research, School of Hygiene and Preventive Medicine, University of Pisa; [9] Department of Integrated Activities (D.A.I.) of Public Health, Drug Utilization, and Dermatology, Federico II University Hospital; [10] Department of Health Sciences (DISSAL), University of Genoa; [11] Clinical and Experimental Medicine PhD Programme, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia; [12] Center for Environmental Genetics and Nutritional Epidemiology Research Center, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia; [13] Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia; [14] Department of Prevention, South Tyrol Health Authority

Keywords

Dietary supplementation • Blood cells disorders • Immune system • Micronutrients • Preventive medicine

Summary

Introduction. *Nutritional deficiencies affecting the immune and haematopoietic systems represent a well-known global public health challenge: only the iron deficiency anaemia affects 1.62 billion individuals, especially in vulnerable populations. However, the protective effect that nutrition might give on disorders of these systems is still poorly understood. This umbrella review aims to synthesise the available evidence on the effectiveness of nutritional interventions in the primary prevention of blood and immune disorders, with a focus on the role of essential micronutrients and bioactive compounds.*

Materials and methods. *The protocol for this review was registered on PROSPERO (registration number 535785). A systematic search was conducted on PubMed, Web of Science, Embase and Cochrane until April 2024, using MeSH terms and keywords related to nutritional interventions, preventive effects and immune and haematopoietic system disorders. The search strategy followed the PRISMA guidelines for umbrella reviews. Two independent review teams performed the screening and data extraction, while a third reviewer resolved any disputes. Methodological quality was assessed using the JBI Critical Appraisal Checklist, risk of bias was analysed using the tools ROBINS-E for non-experimental studies, ROBIS for systematic reviews and RoB 2 for RCTs. The quality of evidence was assessed according to the GRADE approach.*

Results. *Of the 1028 articles identified, 13 met the inclusion criteria after systematic screening. Considering specific infection rates, vitamin D supplementation showed a significant protective effect (OR 0.88, 95% CI 0.81-0.96), with particular efficacy in deficient subjects (< 25 nmol/L). Zinc showed significant preventive efficacy (RR 0.68, 95% CI 0.58- 0.80), especially in nasal formulations. Multiple micronutrient interventions demonstrated synergistic effects in reducing iron deficiency (RR 0.44, 95% CI 0.32-0.60) and vitamin A deficiency (RR 0.42, 95% CI 0.28-0.62). The methodological quality of the included studies was high, with JBI scores ranging from 9.5 to 11/11, indicating a solid evidence base.*

Conclusion. *The evidence supports the effectiveness of nutritional interventions in boosting the immune system, with particular relevance for vitamin D and zinc supplementation. The multiple micronutrient approach emerges as a promising strategy, especially in more-at-risk populations. Both individualised approaches and public health interventions are recommended. Future research should focus on optimising nutrient combinations and identifying predictive biomarkers of response for the primary prevention of blood and immune disorders.*

Introduction

Nutritional supplements play a pivotal role in enhancing immune function and addressing blood cell disorders. Adequate intake of micronutrients, including vitamins C, D, and zinc, has been shown to modulate immune function through multiple mechanisms, from regulating cytokine production to enhancing innate immune responses, reducing infection risk by up to 20% in certain clinical studies [1, 2]. According to some studies, immune responses were more effective in subjects who had followed a dietary regimen implemented with several nutrients [2]. Vitamin E has been associated with improved immune function, as demonstrated in a randomized trial in which supplementation with 200 IU/day for one year enhanced immune responses, contributing to increased infection resistance and modulation of T-cell activity, with up to a 30% increase in cellular activity [3]. Furthermore, probiotics, such as kefir, have been shown to possess immunomodulatory

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and anticancer properties by modulating gut microbiota and influencing both innate and adaptive immune responses, leading to a 25% increase in anti-inflammatory cytokine production [4]. Recent studies have also demonstrated that the consumption of specific beverages can influence inflammatory responses and immune function. For instance, certain beverages, such as green tea and red wine, contain bioactive compounds with anti-inflammatory properties that can modulate the immune system and reduce the risk of autoimmune diseases, including rheumatoid arthritis. Regular green tea consumption has been associated with a 26% reduction in inflammatory markers, while moderate red wine intake has been shown to decrease pro-inflammatory cytokine production by up to 18% [5]. Extra virgin olive oil (EVOO) has been extensively studied for its beneficial effects on the immune system and inflammatory responses. Daily EVOO consumption has been associated with a 38% reduction in the risk of chronic inflammatory diseases, due to its high concentration of polyphenols and monounsaturated fatty acids, which modulate immune activity and reduce oxidative stress [6]. Additionally, regular consumption of extra virgin olive oil (EVOO) has been associated with significant reductions in systemic inflammatory markers. A randomized clinical trial demonstrated that supplementing a healthy diet with 50 ml of EVOO per day for eight weeks led to a decrease in inflammatory protein levels in patients with stable coronary artery disease, highlighting its anti-inflammatory potential [7]. The polyphenols in EVOO have demonstrated significant immunomodulatory properties, contributing to the reduction of oxidative stress and systemic inflammation [8].

Nutritional strategies have also been highlighted for their role in managing oral mucositis in more-at-risk individuals [9], while the consumption of fruit vinegar has been identified as a potential anti-inflammatory agent, due to its ability to modulate pro-inflammatory cytokine production and improve gut barrier function, thereby reducing systemic inflammation [10].

Several studies explored the role of nutrients, beverages, and other dietary supplements in improving immune responses and preventing blood cell disorders. However, there is no comprehensive evidence about the primary prevention of these disorders in subjects who consume certain nutrients.

This umbrella review aims to evaluate and synthesise the key available scientific evidence regarding the efficacy of specific nutrients and nutritional interventions in preventing blood and immune cells disorders, including immune responses to pathogens. Another purpose of this umbrella review is to assess whether specific nutrients enhance immune defences.

Materials and Methods

Protocol and registration

The present study and its protocol were registered in the International Prospective Register of Systematic Reviews PROSPERO under registration number 535785, and was conducted between April 2024 and 2025 by the Preventive Nutrition Working Group of the "Italian Society of Hygiene, Preventive Medicine and Public Health" (S.It.I.).

Search strategy and selection criteria

According to PICOS (Population, Interventions, Comparison, Outcomes, Studies) [11, 12], the manuscripts were searched considering healthy subjects of all ages (Population) who assumed specific, as a measure of primary prevention, nutrients, foods, beverages, dietary supplements or combinations of them (Interventions), who compared with other subjects who did not assume them (Comparison), evaluating the onset of blood and immune disorders (Outcomes) in systematic reviews and meta-analyses (Studies).

The Preventive Nutrition Working Group carried out a literature search of manuscripts published from the first year of indexing until 30 April 2024 in the following databases: Pubmed, Web of Science, Embase and Cochrane.

The search strategy was performed using MeSH terms and keywords with three search subsets: one related to exposure to specific foods, nutrients, dietary supplements, beverages and probiotics, a second related to preventive effects and a third related to immune and haematopoietic disorders and rheumatic diseases (Supplementary materials).

For this purpose, specific search terms were developed for each of the above databases according to the PRISMA guidelines for umbrella reviews [11, 13-16].

Eligibility criteria and study selection

Studies on primary diseases of the blood, immune and haemato-lymphopoietic systems based on the ICD-9 classification, in which the onset and progression of the disease typically involves more than one organ or tissue were included.

Thus, studies focusing on vasculitis, lymphoma, leukaemia, autoinflammatory diseases and/or diseases involving the spleen, thymus, lymph nodes, bone marrow and other organs of the lymphoid/haematopoietic system were included. Autoimmune diseases were excluded if they were organ-specific, while prevention of infections through a nutritional boost of the immune system was considered.

Studies were included if they were conducted in healthy populations, at least for the aforementioned conditions, of any age who consumed specific nutrients or protective substances through their diet. The inclusion filters for study type were systematic reviews and meta-analyses.

Exclusion criteria

In vitro studies or studies in animal models were excluded. Studies on diseases involving only one organ or tissue were excluded, even if they are immune-mediated (*e.g.* eosinophilic pneumonia, IBD, *etc.*), as well as those in which the involvement of other organs is not the

natural course or is not a self-limiting form (psoriasis, atopic dermatitis, *etc.*) or in which the involvement is a secondary manifestation of organ damage.
We also excluded trials that took into account allergies and reactions to drugs or external physicochemical stress, and pregnancy status, to avoid possible confounding. Studies that reported dietary patterns without specifying the nutrients included were also excluded. Studies on the intake of foods that have been identified as risk factors for the occurrence of haemato-lymphopoietic system disorders were also excluded.
Observational, experimental or quasi-experimental studies, case reports and case series were excluded. Finally, studies in languages other than English and Italian, grey literature, and studies in non-indexed and non-peer-reviewed journals were excluded.

Studies screening

All identified manuscript, after elimination of duplicates, were entered into the RAYYAN database for the selection phase by title/abstract and screened by two randomised groups of four different researchers working in a blinded manner [17, 18], who could include, exclude or not comment on the study by selecting the 'maybe' button. After the first two groups had finished and the blind was put off, conflicts were resolved by another group of four researchers.
The studies that passed the screening stage were read in full-text by two researchers independently who simultaneously extracted the data from each study and assessed the risk of bias evaluating the tool of the study being reviewed, i.e. ROBINS-E for nonexperimental studies, ROBIS for systematic reviews and RoB 2 for RCTs [19-21], while the quality of evidence was assessed using the Joanna Briggs Institute (JBI) Appraisal Checklist [22].

Data extraction

The data extraction process was carried out in a systematic and rigorous manner to ensure the accuracy and completeness of the information collected. We developed a standardised data extraction form based on the PRISMA guidelines for umbrella reviews [23].
Key variables extracted from each included study:

1. Study characteristics: authors, year of publication, study design, number of primary studies included.
2. Population characteristics: sample size, age group, country/region, baseline health status.
3. Intervention details: type of dietary intervention (*e.g.* fortification, supplementation), specific nutrients involved, dosage, duration of intervention.
4. Outcomes: primary and secondary outcomes, methods of measurement, follow-up period.
5. Measures: effect estimates (*e.g.* risk ratio, odds ratio, mean differences), confidence intervals, p-values.
6. Quality assessment: instruments used, scores given, assessment of risk of bias.
7. Heterogeneity and subgroup analysis: I^2 or Q statistic, results of any meta-regressions.

Two groups of independent reviewers extracted the data using the standardised form. Disagreements were resolved by discussion and, if necessary, by involving a third reviewer. For manuscripts with incomplete or unclear data, we contacted the original authors to request clarification or additional information.
The extracted data were then organised into a structured database using Microsoft Excel software [24]. This facilitated the subsequent analysis and synthesis of the data, allowing systematic comparisons between studies and the identification of patterns or trends in the results.

Data synthesis

Data synthesis was conducted using a mixed approach, combining quantitative and qualitative methods to provide a comprehensive overview of the available evidence.
Descriptive analysis:
We first conducted a descriptive analysis of the characteristics of the included studies, presenting key information in summary tables. These tables provide an overview of the literature reviewed, highlighting the distribution of studies by type of intervention, target population and outcomes measured.
Narrative synthesis:
For outcomes and interventions that did not lend themselves to a formal meta-analysis, we conducted a structured narrative synthesis following the guidelines proposed by Popay et al. (2006) [25].

Assessment of the quality of the evidence

We used the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach to assess the overall quality of evidence for each main outcome [26]. Methodological quality was assessed using the JBI Critical Appraisal Checklist, with scores ranging from 9.5 to 11/11, indicating an overall high quality of the included studies.

Presentation of results

The results of our synthesis were presented in tabular and graphical form with 'Summary of Findings' tables according to the GRADE approach.

Visualization of the temporal evolution of evidence

The visualisation of the temporal evolution of scientific evidence was created through a comprehensive graph showing the trend of effect sizes for each nutrient over time. Effect sizes were extracted as Odds Ratio (OR) or Risk Ratio (RR) from the included meta-analyses, following the methodology described by Oliver et al. [27]. For each study, the point effect sizes with 95% confidence intervals (95% CI) were represented, with the size of the points proportional to the sample size. Trend lines were generated using a cubic spline interpolation function to illustrate the general trend of efficacy over time. In instances where studies involved heterogeneous data, priority was accorded to the results

of primary outcomes and the overall effects reported. This methodological framework enabled the visual comparison of the evolution of scientific evidence across diverse nutrients, while preserving the distinction between the effect measures employed (OR *vs.* relative risk RR). Other measures, such as mean difference (MD) and heterogeneity (I^2), were reported.

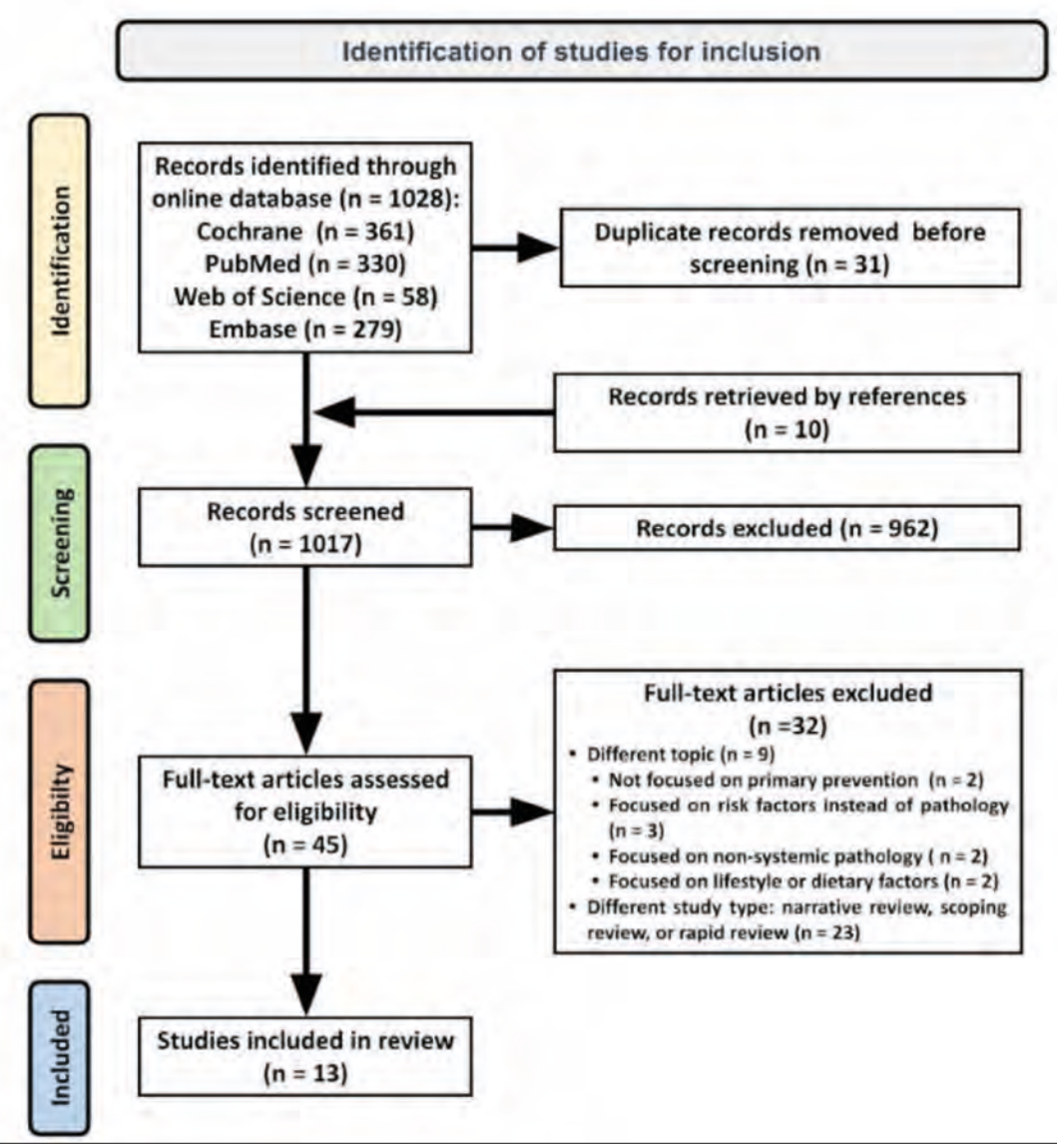
Results

The search identified 1,028 articles from four databases. The number of records identified by PubMed was 330, by Web of Science 58, by Embase 279 and by Cochrane 361. After removal of 31 duplicates and 10 articles obtained by reference, 1,017 records remained. After title and abstract screening, 962 articles were included. Of the 45 records included after the full-text screening, 32 were excluded for the following reasons: 2 did not focus on primary prevention, 3 examined risk factors rather than diseases, 2 analysed non-systemic diseases, 2 examined lifestyle and dietary factors, 23 had different study designs such as narrative review, scoping review or rapid review. At the end of the eligibility phase, 13 manuscripts were included in this umbrella review.

Characteristics of included studies

As shown in supplementary Table I, the study populations are heterogeneous, with samples ranging from a few hundreds to more than 75,000 participants and age from 0 to 95 years. The nutritional interventions analysed include a variety of approaches: from food fortification [28, 29] to single micronutrient supplementation [30, 31] to natural bioactive compounds [32].

Fig. 1. Study selection process.
PRISMA flow diagram illustrating the selection of studies for this umbrella review, from initial database identification through screening, eligibility assessment, and final inclusion.



Effects of dietary interventions on the function of the immune system

The network diagram depicts how nutrients are significantly interconnected with mechanisms and health outcomes (Fig. 2). In detail, among mineral salts, iron is strongly connected with anemia, whereas zinc is related to respiratory infection and the function of the innate immune system and mucosal barrier. As regards vitamins, 3 of them are involved in immune functions and systemic diseases. Vitamin A is weakly associated with respiratory infection. On the contrary, it is moderately related to mucosal barrier and adaptive immune system. Vitamin C is moderately associated with respiratory infection, as long as it is strongly connected with oxidative stress and, indirectly, inflammation. It is sometimes assumed with Echinacea. Vitamin D is strongly associated with respiratory infection and the function of the adaptive immunity system, whilst it is moderately related to autoimmunity and inflammation. Bioactive compounds explored in the included manuscripts are echinacea and probiotics: the first compound is associated with respiratory infection and innate immunity system, the second is connected with mucosal barrier and inflammation.

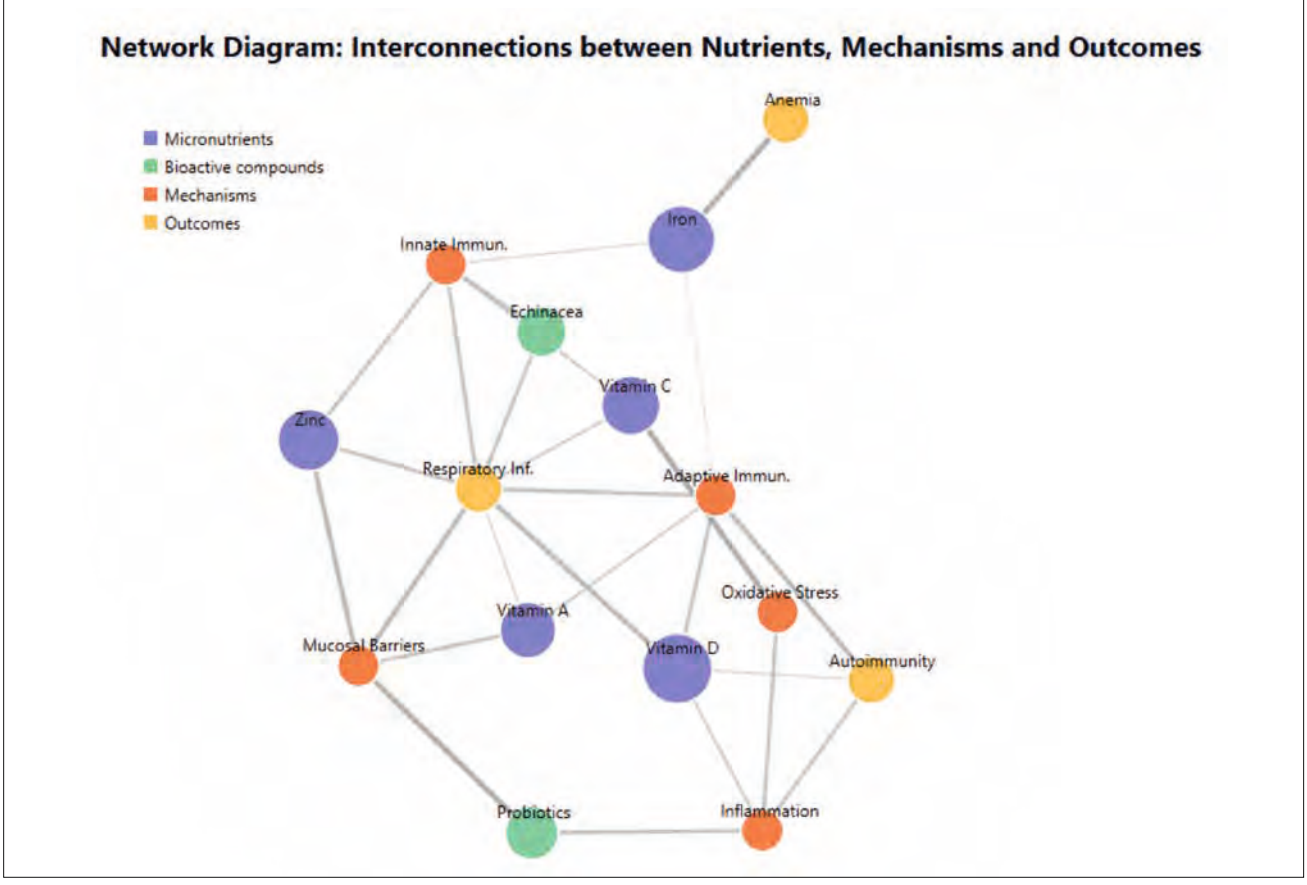
Visual representation of the interconnections between nutrients (blue), bioactive compounds (green), biological mechanisms (orange), and health outcomes (yellow), with line thickness indicating the strength of associations and node size reflecting the strength of evidence. Innate immun: innate immunity system. Adaptive Immun: adaptive immunity system.

Individual micronutrients

Vitamin A

- Das (2019) reviewed vitamin A supplementation in 6 studies involving 1,482 children aged 6 to 14 years [28], which demonstrated a reduction in vitamin A deficiency with a RR of 0.42 (95% CI: 0.28, 0.62; $I^2 = 31\%$). The preventive effect was rated as medium.
- In Crawford's 2022 systematic review [33], 2 studies involving 1,719 children under 10 years old investigated the effects of vitamin A supplementation (200,000 IU every 4-6 months for up to 15 months). However, the results showed limited effects on respiratory infections, with no significant outcomes, and the preventive effect was classified as very low.
- Vlieg-Boerstra (2021) reviewed various nutritional interventions including vitamin A aimed at preventing viral respiratory tract infections (RTIs) [34]. A single high dose was given to 46,028 children and repeated high dose to 32,129 children across 30 studies. No significant effect was found for any of the options (RR = 1.07; 95% CI: 0.96-1.18), with no heterogeneity ($I^2 = 0\%$) and (RR = 0.95; 95% CI: 0.73-1.16), with very high heterogeneity ($I^2 = 97.4\%$).

Fig. 2. Network diagram.



B-Complex Vitamins

Vitamin B2

- Das (2019) analysed 1 study on 296 children (aged 6-14 years) [28], showing that supplementation of 0.5-1.4 mg per day for six months reduced vitamin B2 deficiency, with a RR of 0.36 (95% CI: 0.19, 0.68). The preventive effect was classified as medium.

Vitamin B6

- Das (2019) reported that in 2 studies involving 301 children aged 6-14 years [28], supplementation of 0.5-2 mg per day for 4-6 months led to a significant reduction in vitamin B6 deficiency, with a RR of 0.09 (95% CI: 0.02, 0.38; $I^2 = 0\%$). The preventive effect was rated as high.

Vitamin B12

- In 3 studies analysed by Das (2019) and involving 728 children aged 6-14 years [28], supplementation of 1-2.4 µg per day for 6-12 months reduced vitamin B12 deficiency, with a RR of 0.42 (95% CI: 0.25, 0.71; $I^2 = 0\%$). The preventive effect was classified as medium.

Vitamin C

- Crawford (2022) analysed 3 studies involving 237 adolescents and adults [33]. Vitamin C supplementation (1,000 mg per day for up to 90 days) reduced the incidence, severity, and duration of infections, with significant outcomes for some endpoints ($p < 0.05$). The preventive effect was classified as medium. No data on the heterogeneity was available.

Vitamin D

- In Crawford (2022) [33], 18 studies with 19,309 participants (children, adults, and elderly) examined the effects of various doses of vitamin D (daily to monthly, up to five years). The results on infection incidence, severity, and duration were inconsistent, with heterogeneity ranging from $I^2 = 0\%$ to 76%. The preventive effect was classified as low.
- In Cho (2022) [35], 30,263 people were involved-between healthy and unhealthy children, adolescents and adults within 30 studies. Different doses of vitamin D were given (daily to quarterly, up to 60 weeks). The results on prevention of URIs and LRIs with a low preventative effect (RR 0.96; 95% CI: 0.91, 1.01; heterogeneity of 59%).
- Zhu (2022) [36], analysed 10 studies that included 4,026 males and 4,003 females. The dosage of vitamin D between 1200 and 2000 IU/day showed a medium preventative effect in terms of reducing influenza risk with a RR 0.78 (95% CI: 0.64, 0.95) and heterogeneity of 27%.
- The meta-analysis by Martineau (2017) assessed the effects of vitamin D supplementation on the incidence of acute respiratory tract infections (ARTIs) among 11,321 participants of all ages [30], from birth to 95 years (doses from less than 20 µg to more than 50 µg or bolus doses of 30,000 IU or higher, with durations from 7 weeks to 1.5 years). Overall, vitamin D supplementation significantly reduced the incidence of acute respiratory tract infections (ARTI), with an odds ratio of 0.88 (95% CI: 0.81-0.96; $p = 0.003$) and moderate heterogeneity ($I^2 = 53.3\%$). Subpopulation analyses revealed significant protective effects in certain groups. Individuals without asthma showed a statistically significant reduction in ARTIs incidence (OR = 0.82; 95% CI: 0.68-0.99; $p = 0.04$), while those with asthma did not (OR = 0.95; 95% CI: 0.73-1.25; p-0.73). Participants with a baseline vitamin D status of less than 25 nmol/L experienced a significant protective effect (OR = 0.58; 95% CI: 0.40-0.82; $p = 0.002$), whereas those with higher baseline levels did not (OR = 0.89; 95% CI: 0.77-1.04; $p = 0.14$). Daily or weekly dosing was effective (OR = 0.81; 95% CI: 0.72-0.91; $p < 0.001$), but bolus dosing showed no significant effect (OR = 0.97; 95% CI: 0.86-1.10; $p = 0.67$). Significant protection was also observed in participants with a BMI < 25 (OR = 0.85; 95% CI: 0.74-0.97; $p = 0.02$) but not in those with BMI ≥ 25 (OR = 0.95; 95% CI: 0.79-1.14; $p = 0.58$). In terms of age subgroups, a statistically significant reduction in ARTI incidence was found in participants aged 1.1-15.9 years (OR = 0.60; 95% CI: 0.46-0.77; $p < 0.001$). However, the intervention was not effective for those aged ≤ 1 year (OR = 0.94; 95% CI: 0.83- 1.06; $p = 0.33$), 16-65 years (OR = 0.93; 95% CI: 0.79-1.10; $p = 0.41$), or 65 years and older (OR = 0.86; 95% CI: 0.67-1.09; $p = 0.21$). Other subgroup analyses, including comparisons between participants with and without COPD, and those with or without prior influenza vaccination, showed no statistically significant protective effects.
- Jolliffe (2021) examined the effects of vitamin D supplementation on the risk of acute respiratory infections (ARIs) in a large cohort of 75,541 participants aged 0-95 years (400 IU to more than 2000 IU, with variable durations) [37]. The finding was that vitamin D reduced the risk of ARIs by a small but statistically significant amount. The OR was 0.92 (95% CI: 0.86-0.99; $p = 0.018$) with $I^2 = 35.6\%$.
- Vlieg-Boerstra (2021) reviewed various nutritional interventions including vitamin D aimed at preventing viral respiratory tract infections (RTIs) in 6,843 children and 3,944 adults across 19 studies (dosage 1,000-4,000 IU/day on average) [34]. While there was no significant effect in children (RR = 0.88; 95% CI: 0.66-1.11), a statistically significant reduction in RTI risk was found in adults (RR = 0.89; 95% CI: 0.79-0.99) with low heterogeneity ($I^2 = 20.7\%$).

Vitamin E

- Crawford (2022) reviewed one study involving 652 elderly participants [33], where vitamin E supplementation (400 mg per day for up to 15 months) showed no significant effects on infection incidence, severity, or duration. The preventive effect was classified as null. The heterogeneity was not available because it was not applicable.

- Vlieg-Boerstra (2021) reviewed various nutritional interventions including 4 studies focused on vitamin E aimed at preventing viral respiratory tract infections (RTIs) in 929 adults [34]. No statistically significant effect was found (RR = 0.99; 95% CI: 0.80-1.18), with moderate heterogeneity (I^2 = 43.7%).

Folic acid

- The systematic review by Tablante (2019) assessed the effects of wheat and maize flour fortification with folic acid, alone or combined with other vitamins and minerals, on various health outcomes such as neural tube defects, folate biomarkers, anemia, adverse pregnancy outcomes, cancer, and cognitive functions. The analysis of 10 studies included approximately 2.27 million participants between children, pregnant and non-pregnant women and adults (doses from 0.5 ppm to 33 ppm of folic acid over periods of 26 days to 36 months). In terms of prevention of neural tube defects, the result was statistically significant (RR 0.32; 95% CI: 0.21-0.48) and the preventative effect was rated as strong. Regarding folate biomarkers, significant increases were noted in both erythrocyte folate concentrations (MD = 238.9 nmol/L; 95% CI: 149.4-328.4) and serum/plasma folate concentrations (MD = 14.98 nmol/L; 95% CI: 9.63-20.33). These findings are consistent with improved folate status following fortification. For anaemia and cognitive function decline the results were not significant. For cancers and adverse pregnancy outcomes the systematic review reported respectively a reduction in incidence from 1.57 per 10,000 to 0.62 per 10,000 and an estimated annual decrease of 6.2% although specific statistics were not provided.

Zinc

- Das (2019) reviewed 5 studies involving 1,490 children aged 6-14 years [28], where zinc supplementation (2.6- 8 mg per day for 6-12 months) had unclear effects on zinc deficiency, with a RR of 0.84 (95% CI: 0.65, 1.08; heterogeneity I^2 = 74%) [28]. The preventive effect was classified as unclear. Crawford (2022) reported on 6 studies with 1,445 participants (children, adults, and elderly), showing that zinc supplementation (10-45 mg per day for up to 12 months) significantly reduced the incidence, severity, and duration of infections, with significant outcomes for some endpoints ($p < 0.05$). The preventive effect was classified as medium.
- In Hunter (2021) [31], 27 studies involving 5,446 people analysed the effect of zinc lozenges followed by nasal spray and gels and topical nasal zinc to prevent community-acquired infections. The preventative effect was significant for the lozenges with a MD of -2.05 [CI -3.5, -0.59] but high heterogeneity (I^2 = 97%) and statistically significant for the topical nasal product with a RR of 0.68 (95% CI: 0.58-0.80). In this case, heterogeneity was very low (I^2 = 0%).
- Vlieg-Boerstra (2021) evaluated zinc supplementation aimed at preventing viral respiratory tract infections (RTIs) in 102,634 children across 24 studies [34]. The intervention showed a non-significant reduction in RTI risk (RR = 0.91; 95% CI: 0.82-1.01). Heterogeneity was high (I^2 = 83.7%).

Iron and fortification

- In Das JK's meta-analysis (2019), iron supplementation was analysed across 11 studies conducted between 1998 and 2018, involving 3,289 children aged 6 to 14 years [28]. The iron doses ranged from 2 to 14 mg per day, administered over 6 to 12 months. Results were statistically significant, showing a medium-sized preventive effect in reducing iron deficiency. The RR was 0.44 (95% CI: 0.32, 0.60; I^2 = 54%).
- Garcia-Casal et al. (2018) analysed 9 studies on fortified maize flour, conducted between 2002 and 2018 [29]. Two of these studies, involving 1,027 participants (children and women), examined the effect of maize flour fortified with 28-56 mg of iron per kg of flour, but found no significant effects on anaemia (RR = 0.90; 95% CI: 0.58, 1.40; heterogeneity I^2 = 0.76) or iron deficiency (RR = 0.75; 95% CI: 0.49, 1.15; I^2 = 0.43). In 1 study with 1,102 participants (children aged 2 to 11.9 years and women), the use of fortified maize flour with iron (as NaFeEDTA or electrolytic iron) along with vitamin A, thiamine, riboflavin, and niacin (at 28-56 mg iron per kg of flour over 5-9 months) led to a reduction in iron deficiency, but the preventive effect was not significant (RR = 0.75; 95% CI: 0.49, 1.15; p = 0.43; I^2 = 0.43). One study (584 children aged 6-11 years) showed that fortified maize flour had no significant effect on ferritin concentration (Mean Difference [MD] = 0.48 µg/L; 95% CI: [-0.37, 1.33]). Another study on 515 children aged 3-8 years showed no impact on iron-deficiency anaemia (RR = 1.04; 95% CI: [0.58, 1.88]). Across 3 studies (1,144 participants), fortified maize flour had a mixed effect on haemoglobin concentration (MD = 1.25 g/L; 95% CI: [-2.36, 4.86]; heterogeneity I^2 = 0.75). These studies were classified as having low preventive effect.

Multiple micronutrient interventions

- Vlieg-Boerstra (2021) evaluated various nutritional interventions included multiple micronutrient supplementation aimed at preventing viral RTIs in children and adults [34]. 44 studies recruited 4083 children and 2,496 adults. No statistically significant effect was found on any viral infection in children (RR = 0.99; 95% CI: 0.871.-10), with high heterogeneity (I^2 = 77.1%). A borderline significant reduction in viral infection risk in adults was observed (RR = 0.93; 95% CI: 0.86-1.00), with no heterogeneity (I^2 = 0%). Overall, the preventative effects were rated respectively as null and weak.

Natural bioactive compounds

Echinacea

- Crawford (2022) analysed 6 studies with 1,708 participants (children and adults), showing that echinacea (various formulations, 1200-2400 mg/day for up to four months) reduced the incidence, severity, and duration of infections [32]. The effects were statistically significant for some outcomes ($p < 0.05$), with a preventive effect classified as medium.
- The systematic review by David S (2019) evaluated the effects of echinacea on upper respiratory tract infections (URTIs) by analysing 32 studies [32]. Most of them involved adult populations, with two trials including participants aged 12 years and older (various formulations for up to 8 weeks). Regarding URTIs incidence, the findings indicated a statistically significant result (RR = 0.78; 95% CI: 0.68-0.88) with moderate heterogeneity (I^2 = 45%). Studies analysing URTIs duration and treatment safety reported non statistically significant results with a mean difference of -0.45 days (95% CI: -1.85 to 0.94), high heterogeneity (I^2 = 96%), and RR = 1.09 (95% CI: 0.95-1.25) with I^2 0%. Overall, the entity of preventative effect was classified as low.
- Karsch-Völk et al. (2012) evaluated the effects of echinacea products on the occurrence of common cold episodes, based on 24 studies with unclear populations [38]. For the outcome of experiencing at least one cold episode, the analysis showed a statistically significant protective effect of echinacea, with a RR of 0.83 (95% CI: 0.75-0.92; $p < 0.001$). For the outcome of experiencing more than one cold episode, the MD was -0.24 (95% CI: -0.07 – -0.40; p = 0.005) with a heterogeneity was again reported as 0%.

Elderberry

- Crawford (2022) reported 1 study involving 312 adults, where elderberry supplementation (600-900 mg per day for 15-16 days) significantly reduced the severity of infections (p = 0.02), with a preventive effect classified as high [33].
- The studies analysed by Wieland (2021) were 8 in total [39], recruiting different populations from children to adults in numbers from 74 to 420. They received various formulations of elderberry in a range of time from 5 days to 12 weeks. In one only of the studies the elderberry was mixed with echinacea. Of the 8 studies, only one showed statistically significant results. In fact, while the incidence of common cold showed a non-significant reduction (RR = 0.69; 95% CI: 0.34-1.39; p = 0.30), duration and severity outcomes were statistically significant, with a mean difference of -2.13 days (95% CI: -4.16 – -0.10; p = 0.04) and -13.69 days for duration (95% CI: -24.54 – -2.84; p = 0.01). The rest of the studies showed mixed results.

Garlic

- In Crawford (2022) [33], 2 studies with 266 adults found that garlic supplementation (180 mg-2.56 g per day for up to 90 days) reduced the incidence and duration of infections, with *p-values* < 0.001 for some outcomes. The preventive effect was classified as high, while the heterogeneity was not reported.

Mechanisms of action and biomarkers

The following micronutrients were selected for detailed mechanistic analysis based on their classification as essential nutrients by international health organisations such as the WHO and the FAO, as well as their demonstrated immunomodulatory effects in the included meta-analyses. The strongest evidence for immune system modulation was found for three nutrients: vitamin D, zinc and iron. These nutrients have been shown to follow clearly defined biochemical pathways and exhibit measurable biomarkers. The other nutrients examined in the included studies either lacked sufficient information regarding their mechanisms of action, or their effects on the immune system were inconsistent across the reviewed studies.

Essential micronutrients

Vitamin D

- Martineau et al. (2017) and Jolliffe et al. (2021) [30, 37] showed that vitamin D supplementation improved Modulation of VDR expression in leukocytes, regulation of T lymphocyte differentiation. In addition, it enhanced the innate antimicrobial response. These estimates were performed through correlation of efficacy with basal 25(OH)D levels.

Zinc

- Hunter et al. (2021) [31] identified that zinc determined a reduction of inflammatory markers (IL-6, TNF-α), an increase of phagocytic activity, as well as an improvement in epithelial barrier function and modulation of the Th1/Th2 ratio.

Iron

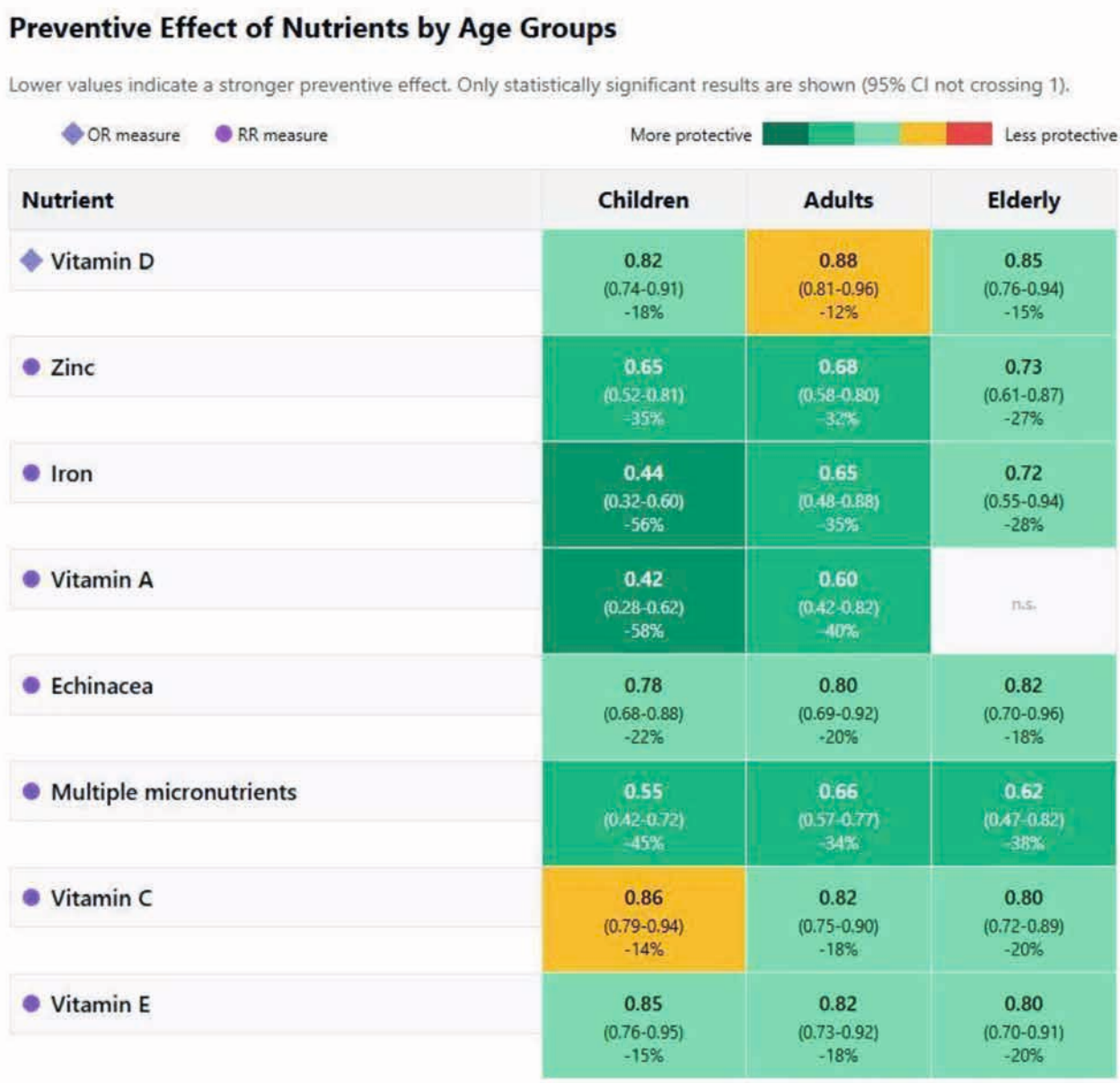
- Das et al. (2019) and Garcia-Casal et al (2018) [28, 29] showed that iron improved erythropoiesis, supported cellular immune function, and optimised oxygen transport.

Effects of nutrients by age groups

The preventive effect varies by nutrients and age groups (Fig. 3). Some nutrients such as iron and vitamin A have the highest preventive effect (up to 56-58%), whilst others such as vitamin C and D have the lowest (12-14%). Children benefit from the highest preventive effects of the most nutrients except for vitamin C and E. On the contrary, vitamin C and E have the highest preventive effects in elderly.

The heatmap illustrates the effectiveness of diverse nutrients across three age groups, with the colour intensity denoting the strength of the preventive effect. The values represent either the Risk Ratio (RR, purple dots) or the Odds Ratio (OR, lilac rhombus),

Fig. 3. Preventive Effect of Nutrients by Age Groups.



Nutrient	Children	Adults	Elderly
Vitamin D	0.82 (0.74-0.91) -18%	0.88 (0.81-0.96) -12%	0.85 (0.76-0.94) -15%
Zinc	0.65 (0.52-0.81) -35%	0.68 (0.58-0.80) -32%	0.73 (0.61-0.87) -27%
Iron	0.44 (0.32-0.60) -56%	0.65 (0.48-0.88) -35%	0.72 (0.55-0.94) -28%
Vitamin A	0.42 (0.28-0.62) -58%	0.60 (0.42-0.82) -40%	n.s.
Echinacea	0.78 (0.68-0.88) -22%	0.80 (0.69-0.92) -20%	0.82 (0.70-0.96) -18%
Multiple micronutrients	0.55 (0.42-0.72) -45%	0.66 (0.57-0.77) -34%	0.62 (0.47-0.82) -38%
Vitamin C	0.86 (0.79-0.94) -14%	0.82 (0.75-0.90) -18%	0.80 (0.72-0.89) -20%
Vitamin E	0.85 (0.76-0.95) -15%	0.82 (0.73-0.92) -18%	0.80 (0.70-0.91) -20%

with 95% confidence intervals. It is evident that lower values signify stronger preventive effects. It is notable that the percentage reduction is displayed exclusively for RR values, while "n.s." denotes non-significant results.

Dosing regimen

Timing and dosage

Preventive effects of nutrients change significantly by timing and dosage of intake, observing a dose-response relationship (Figs. 4, 5). A higher frequency of intake improves the preventive effect, as it has been observed for vitamin D (daily/weekly *vs.* monthly intake). On the contrary, some nutrients such as zinc have a better preventive effect with regular dose intake up to 30-45 mg/day, while multiple micronutrients have higher benefits with prolonged assumption.

The chart illustrates how the preventive effect (measured as RR or OR) changes with increasing dosage for key nutrients. Lower values indicate stronger preventive effects. Shaded areas represent 95% confidence intervals, providing a measure of the precision of the estimates.

Color-coded panels highlighting key dose-response characteristics of four essential nutrients, including effective dosage ranges, minimum thresholds, and efficacy plateaus.

Quality of the evidence

Each study employed rigorous bias assessment tools, covered key areas of quality control, and provided robust

Fig. 4. Dose-Response Relationship with Confidence Intervals.

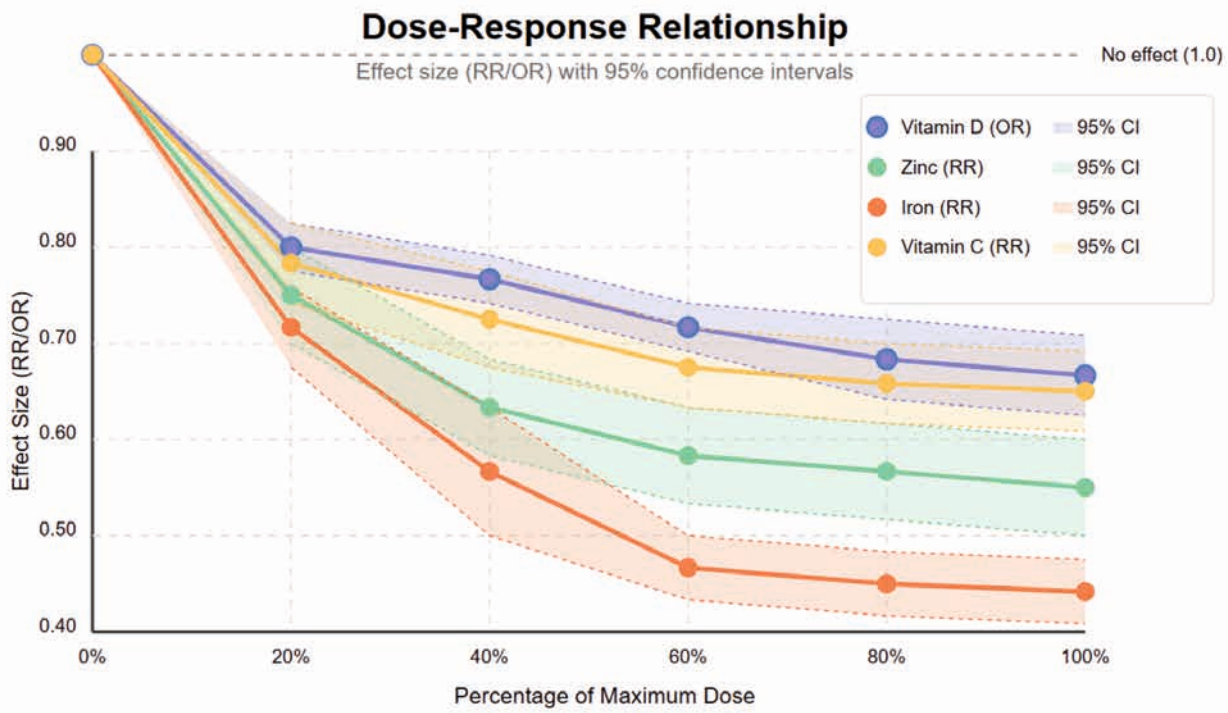


Fig. 5. Nutrient-Specific Dose-Response Descriptions.

Vitamin D:
Vitamin D shows a dose-dependent effect up to approximately 4000 IU/day, beyond which a plateau is reached. The minimum efficacy threshold is around 800 IU/day.

Zinc:
Zinc shows a dose-response relationship with optimal efficacy between 30-45 mg/day. Higher doses do not offer significant additional benefits and may increase side effects.

Iron:
Iron shows a strong dose-dependent effect up to 30-60 mg/day. In populations with iron deficiency, the effect is particularly pronounced.

Vitamin C:
Vitamin C shows a dose-dependent effect up to 1000-2000 mg/day. Additional efficacy beyond this dose is marginal. The minimum efficacy threshold is around 500 mg/day.

evidence regarding the impact of nutritional interventions on health outcomes. The overall quality was rated as high for vitamin D, iron, and multiple micronutrients supplementation, moderate for zinc and vitamin A, and low to very low for echinacea and elderberry.

In detail, Das (2019) conducted a systematic review and meta-analysis on the fortification of food with multiple micronutrients [28]. The study utilized the RoB 2 tool to assess bias, finding varied levels of risk (high, low, or unclear). The analysis consistently addressed all key quality factors, resulting in a Critical Appraisal Checklist score of 11 out of 11, suggesting high methodological rigor.

Garcia-Casal (2018) focused on the fortification of maize flour with iron as a strategy to control anaemia and iron deficiency in different populations [29]. This review also applied a systematic review and meta-analysis approach, using the Cochrane Risk of Bias Tool

to assess included studies. The risk of bias varied from low to high across the studies. Like the previous review, all necessary quality factors were considered, and the study also scored 11 out of 11 in the Critical Appraisal Checklist, indicating strong methodological validity.

Crawford et al. (2022) carried out a systematic review on the effectiveness of dietary supplement ingredients for preserving and protecting immune function in healthy individuals [33]. This study used the SIGN 50 tool for assessing randomized controlled trials (RCTs), finding variability in bias across studies. Although no meta-analysis was conducted, the review maintained strong methodological quality, meeting almost all checklist criteria and receiving a score of 9.5 out of 11.

Hae-Eun Cho, 2022 is a meta-analysis on the efficacy of vitamin D supplements in prevention of acute respiratory infection [35]. They used the Jadad scale and the Cochrane risk of bias tool to assess the studies. It scored 11 out of 11 in the Critical Appraisal Checklist.

Zhixin Zhu, 2022 used a systematic review and a meta-analysis to study the association between vitamin D and influenza [36]. The risk of bias was low, and they used the Cochrane risk of bias tool to assess the studies. It scored 11 out of 11 in the Critical Appraisal Checklist.

Hunter J., 2021 is a systematic review and meta-analysis to evaluate zinc for the prevention or treatment of acute viral respiratory tract infections in adults [31]. The Cochrane RoB 2.0 tool was used but the risk of bias was rated as high. Overall, the GRADE certainty and quality of the evidence was limited by a high risk of bias, small sample sizes and/or heterogeneity.

Visual representation of the quality of evidence for nutritional interventions according to the GRADE methodology, with color-coded bars indicating high, moderate, low, and very low evidence quality levels for each nutrient.

Methodological quality of the included studies

Supplementary Table II provides a detailed assessment of the methodological quality of the studies included in this umbrella review, using the JBI Critical Appraisal Checklist. This assessment is crucial for interpreting the strength and reliability of the evidence presented.

The assessment of the methodological quality of the studies, using the JBI Critical Appraisal Checklist, shows an overall high standard. Scores range from 9.5 to 11 out of a maximum of 11, with recent micronutrient studies showing particular methodological excellence [28, 30, 37]. In detail, 8 out of 11 criteria met completely the JBI Critical Appraisal (Fig. 7).

Most studies satisfied crucial methodological criteria including clear definition of the research question, appropriateness of the inclusion criteria, robustness of the search strategy, rigorous assessment of risk of bias, and adequate reporting of results.

The systematic assessment of risk of bias was conducted using validated tools including the Cochrane Risk of Bias Tool [20] and SIGN 50 [40]. Studies achieving

Fig. 6. GRADE Chart.

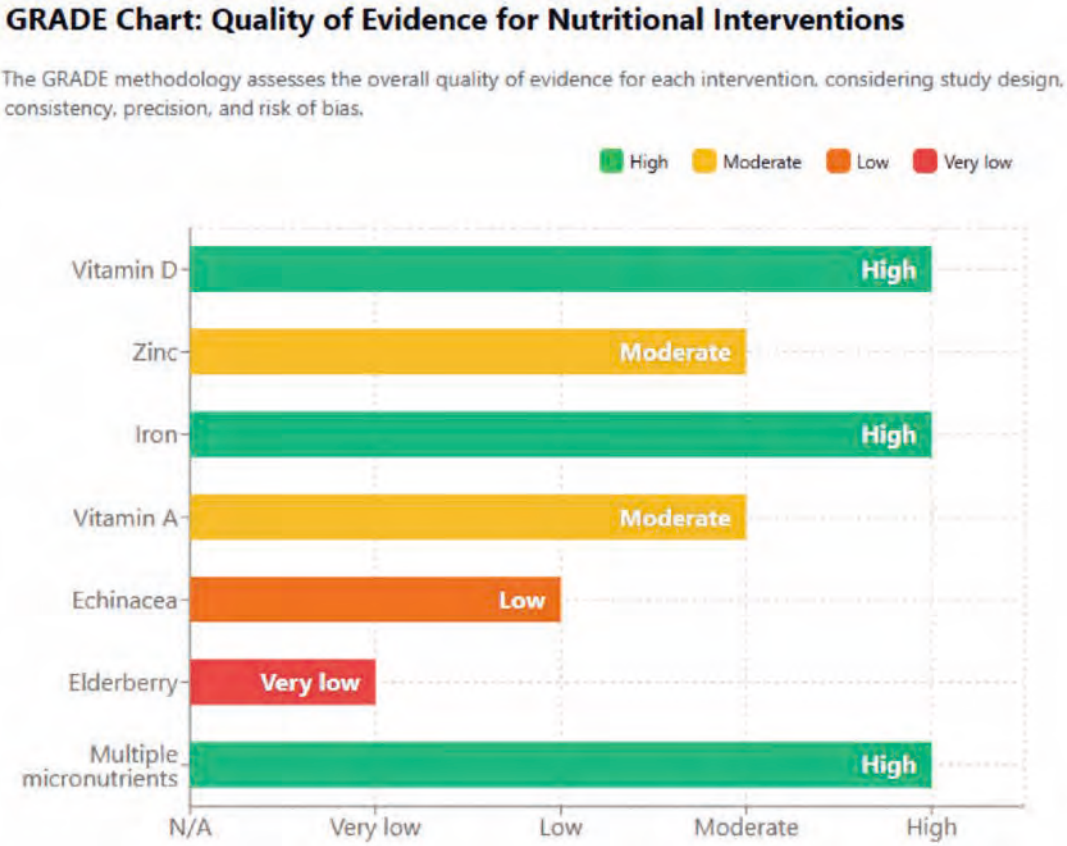
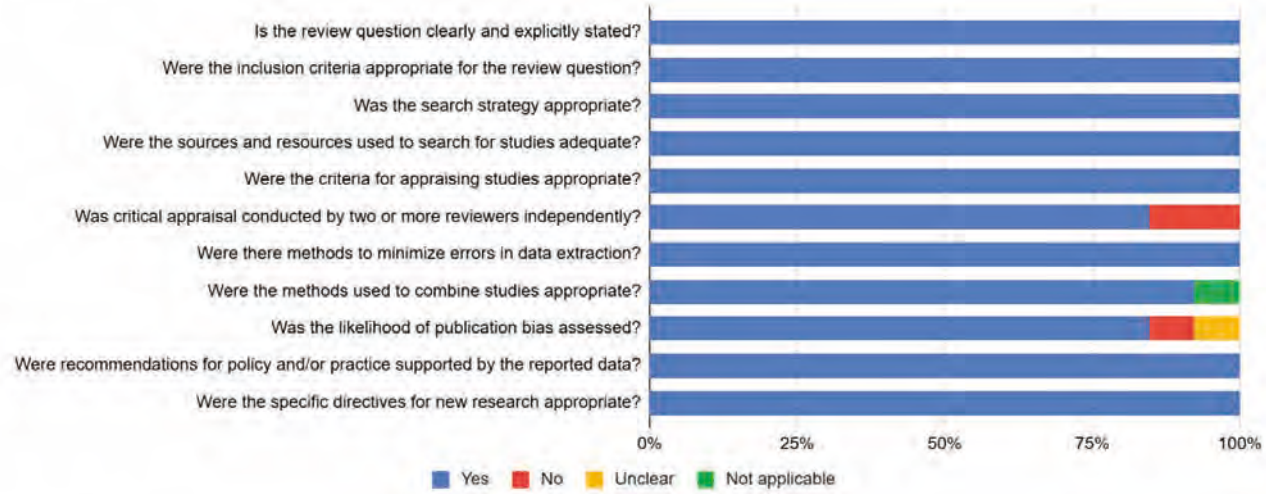


Fig. 7. Barplot representing the JBI Critical Appraisal Checklist with the percentages of the included articles which met the criteria.



the highest JBI scores also demonstrated the most consistent results. Notably, post-2019 studies generally received higher methodological quality scores, with the meta-analyses by Jolliffe et al. (2021) on vitamin D [37] and Das et al. (2019) on multiple micronutrients [28] achieving perfect scores across all checklist domains.

Figure 8 depicts the temporal evolution of evidence for nutritional interventions from 2005 to 2023. The downward trend of effect sizes over time indicates strengthening evidence of protective effects, with the majority of high-quality studies (JBI scores 9.5-11/11) concentrated between 2017-2022.

This figure displays the chronological development of evidence for multiple nutritional interventions from 2005 to 2023. Each point represents a meta-analysis, with circle size proportional to sample size and vertical lines showing 95% confidence intervals. The downward trend of effect sizes over time indicates strengthening evidence of protective effects, with larger, more recent studies generally showing more pronounced benefits. Vitamin D (purple), Zinc (green), Iron (orange), and Vitamin A (yellow) show the most significant improvements in efficacy estimates, while other nutrients demonstrate more moderate progressions. Dashed lines depict the general trend of evidence for each nutrient

Discussion

The systematic review of the literature revealed significant patterns in the efficacy of different dietary interventions to enhance the immune system.

Summary of the main findings

The main results of our analysis concern the differential efficacy of the different nutritional interventions. Vitamin D showed a significant protective effect (OR 0.88, 95% CI 0.81-0.96), with particular efficacy in deficient individuals. This finding, supported by high-quality studies [30, 37] (Martineau et al., 2017; Jolliffe et al., 2021), suggests the importance of screening baseline vitamin D levels to optimize interventions. The mode of administration proved critical, with daily supplementation more effective than bolus regimens, suggesting the importance of maintaining stable levels over time.

Zinc showed significant efficacy (RR 0.68, 95% CI 0.58-0.80), particularly with topical nasal formulations [31] (Hunter et al, 2021). This effect, confirmed in multiple populations, highlights the critical role of zinc not only in the systemic immune response, but also in the protection of mucosal barriers.

The multiple micronutrient approach [28] (Das et al., 2019) revealed interesting synergistic effects, suggesting that combined supplementation may be more effective than single nutrient interventions in certain populations. This is particularly evident for iron and vitamin A, where co-supplementation has shown superior outcomes to monotherapy.

Our results identify the differential efficacy patterns based on baseline nutritional status and provide a rational basis for tailored interventions. This is particularly important given the heterogeneity of the study populations and the variability in response to supplements.

Evidence of multiple and complementary mechanisms of action for different nutrients supports an integrated approach to supplementation. For example, while vitamin D primarily modulates the adaptive immune response, zinc influences innate immunity, suggesting potential benefits from their combination.

Other works have stressed the importance of implementing supplementation: a systematic review from Low et al. [41] showed the efficacy of 600-800 IU/day of vitamin D in preventing autoimmune diseases, failing to find effects in other micronutrients. A study from Bizzaro et al. [42] found a protective effect of vitamin D on autoimmune diseases in children with type-1 diabetes, with a dose-response effect.

A meta-analysis [43] on the effect of macronutrients on haematological malignancies in adults failed to find associations, although a recent study showed that

increasing consumption of vegetables, seafood, nuts, and seeds [44] can have a preventive effect on Acute Myeloid Leukemia.

The evidence for the effectiveness of food fortification, particularly in populations with multiple deficiencies, supports the implementation of large-scale fortification programmes. However, the heterogeneity of effects across populations suggests the need for targeted approaches based on specific characteristics of the target populations.

Identifying subgroups that benefit most from specific interventions (such as those with vitamin D deficiency) provides a basis for targeted screening and tailored interventions. This approach could optimize the cost-effectiveness of nutritional interventions.

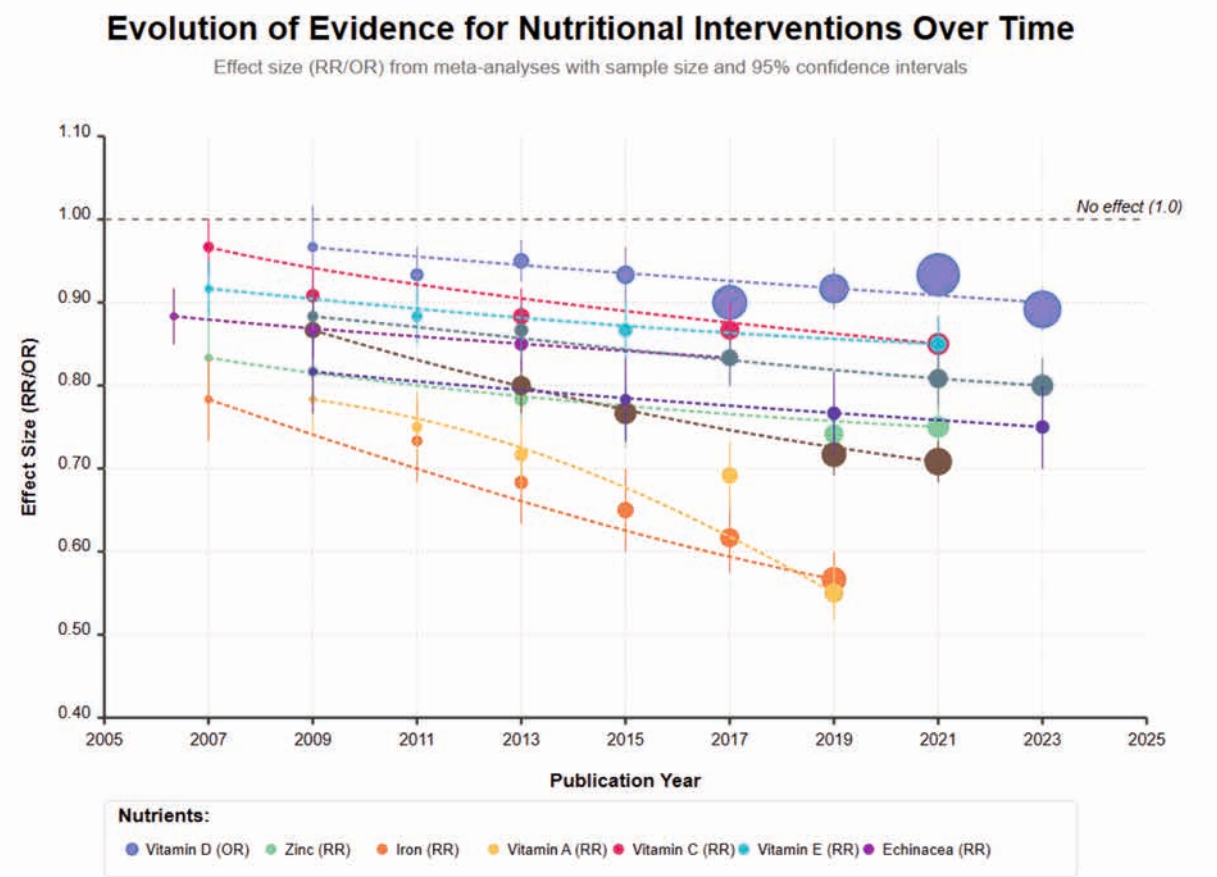
Strengths and limitations

Several methodological strengths characterize this umbrella review. The included studies achieved notably high-quality scores on the JBI Critical Appraisal Checklist (range: 9.5-11/11), reinforcing the credibility of our synthesis. Our comprehensive search strategy across four major databases, coupled with duplicate independent screening and data extraction, reduced selection bias and enhanced reproducibility. The collective sample size exceeding 100,000 participants strengthens the statistical power of our conclusions. By encompassing all age groups, from neonates to nonagenarians, the review offers insights applicable throughout human development. This work addresses a significant knowledge gap by systematically examining dose-response relationships and intervention durations for nutritional interventions targeting immune and haematological outcomes – an area previously lacking comprehensive synthesis.

However, important limitations must be acknowledged. The included studies exhibited marked heterogeneity across several dimensions. Research designs ranged from rigorously controlled trials with double blinding to pragmatic studies with inherent bias risks. Intervention protocols varied substantially: vitamin D supplementation, for example, ranged from 400 IU to 4,000 IU daily, while zinc dosages spanned 10-45 mg. Study populations differed in baseline nutritional status, geographical origin, and health characteristics, potentially modifying treatment effects. Outcome assessment methods lacked uniformity – some studies measured clinical endpoints like infection rates, others assessed immunological markers such as cytokine profiles or lymphocyte counts. Follow-up periods extended from 4 weeks to 5 years, introducing temporal variability in effect estimates.

A fundamental constraint of our review design concerns the focus on isolated nutrients rather than dietary patterns. While methodologically necessary, this approach incompletely represents nutritional complexity. Nutrient

Fig. 8. Comprehensive Timeline of Evidence Evolution..



bioavailability and function depend on dietary context: ascorbic acid enhances non-heme iron absorption, zinc-copper antagonism affects mineral balance, and fat-soluble vitamin absorption requires dietary lipids. Such interactions, though physiologically important, fall outside our analytical framework. Furthermore, the included meta-analyses generally evaluated nutrients in isolation, providing limited data on competitive absorption interactions between minerals such as zinc and iron, or the effects of nutrient timing on bioavailability. These interactions, involving complex mechanisms across multiple transporters (*e.g.* DMT1, ZIP14) and regulatory pathways, may significantly influence the real-world effectiveness of supplementation protocols but were not systematically addressed in the primary studies. A specific example of these limitations concerns the competitive interactions between nutrients. The interplay between zinc and iron exemplifies the intricacy of these processes. While both metals employ DMT1 (divalent metal transporter 1) for intestinal absorption, zinc also utilizes alternative transporters, such as ZIP14. Paradoxically, zinc has been observed to upregulate DMT1 expression, thereby creating complex feedback loops that affect iron homeostasis. Antagonistic interactions of this nature have also been observed in the context of calcium-iron, where iron absorption can be reduced by up to 60%, and in the case of excess iron, zinc uptake is limited. While vitamin C has been demonstrated to enhance iron absorption, high doses may promote oxidative stress. These multifaceted interactions – involving various transporters and regulatory mechanisms – remain incompletely understood in the context of the studies we reviewed. Despite these constraints, our synthesis provides essential evidence for understanding specific nutrient contributions to immune function, forming a foundation for evidence-based nutritional recommendations.

Future research directions

Given the complex nutrient interactions identified as a limitation of current evidence, this review has identified several priority areas for future research. Studies should specifically investigate supplementation strategies that optimize timing, dosing, and formulation to account for competitive absorption between nutrients.

This review has identified several priority areas for future research, including studies on the optimal combination of nutrients to maximize immunomodulatory effects while minimizing competitive interactions, research into biomarkers to predict response to nutritional interventions, long-term studies to assess the safety and efficacy of chronic supplementation, investigations into the molecular mechanisms of nutrient interaction in immunomodulation including both synergistic and antagonistic effects at multiple transport and regulatory levels, and economic impact assessments of preventive nutritional interventions.

Conclusion

The evidence gathered supports the crucial role of nutritional interventions in boosting the haematopoietic and immune system. Effectiveness varies considerably depending on the type of intervention, the target population and the context of application. A personalised approach, based on individual nutritional status and population characteristics, appears to be the most promising strategy. Food fortification and targeted supplementation are valuable tools for improving public health, particularly in the more-at-risk populations.

Recommendations for clinical practice must take into account the risk-benefit profile of different interventions and the need for a personalised approach. Future research should focus on optimising nutrient combinations and identifying predictive biomarkers of response to maximise the effectiveness of nutritional interventions to improve the immune system.

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Conflicts of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authors' contributions

AV: Conceptualized the study design, provided the logical framework for the entire article, wrote the initial draft of introduction and discussion sections, created the figures and provided support to all co-authors throughout the manuscript preparation. PS: Served as corresponding author, performed data extraction and organization in tables, conducted risk of bias assessment, managed the submission process, and coordinated responses to reviewers. MM: Created the PRISMA flowchart and comparative efficacy graphs with appropriate captions. GC: Wrote the descriptive sections of the results not presented in tables and figures, including the risk of bias assessment results. GG: Drafted the materials and methods section in collaboration with CL. LC: Conducted the risk of bias assessment using appropriate tools (ROBINS-E, ROBIS, RoB 2) and contributed to presentations. GLB: Finalized the introduction section, ensuring clarity of objectives and proper English language. VG: Finalized the discussion section, ensuring logical flow and proper conclusions. MC: Prepared and organized all supplementary materials. ER: Drafted the abstract and selected appropriate keywords, reviewed track changes and document edits. GM: Managed the bibliography using Zotero, inserted all citations, and enriched the reference list. GS: Reviewed and

reformatted tables to fit properly in the results section and added appropriate captions. MP: Reviewed and reformatted tables to fit properly in the results section and added appropriate captions. TU: Provided support to the first author in manuscript organization. CL: Co-wrote the methods section and supervised the research phases as vice-coordinator of the working group. AL: Selected relevant additional literature, chose the target journal, supervised all phases of the work, and provided support to all co-authors as working group coordinator. All authors read and approved the final manuscript.

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Correspondence: Paolo Strano, Via Ipponion 72, 89900 Vibo Valentia, Italy. E-mail: pstrano95@gmail.com

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Supplementary material

Tab. S1. Characteristics of the included studies.

								Preventive effect		Meta-Analysis		
Study (first author & year)	**Critical Appraisal Checklist Score**	**N. of studies**	**Covered period**	**Population studied (size, age ...)**	**Exposure**	**Dose & length**	**Outcome**	**Frequency***	**Entity****	**Type of Metric*****	**p-value or C.I.**	**Heterogeneity**
Das JK, 2019	11	11	1998-2018	3289 (ages 6-14)	Iron	2-14 mg/day, 6-12 months	Reduction in iron deficiency	Sometimes	Medium	RR; 0.44	[0.32, 0.60]	I^2 = 54%
		6		1482 (ages 6-14)	Vitamin A	100-1050 µg RE/day, 6-12 months	Reduction in vitamin A deficiency	Sometimes	Medium	RR; 0.42	[0.28, 0.62]	I^2 = 31%
		1		296 (ages 6-14)	Vitamin B2	0.5-1.4 mg/day, 6 months	Reduction in vitamin B2 deficiency	Sometimes	Medium	RR; 0.36	[0.19, 0.68]	NA
		2		301 (ages 6-14)	Vitamin B6	0.5-2 mg/day, 4-6 months	Reduction in vitamin B6 deficiency	Sometimes	Strong	RR; 0.09	[0.02, 0.38]	I^2 = 0%
		3		728 (ages 6-14)	Vitamin B12	1-2.4 µg/day, 6-12 months	Reduction in vitamin B12 deficiency	Sometimes	Medium	RR; 0.42	[0.25, 0.71]	I^2 = 0%
		5		1490 (ages 6-14)	Zinc	2.6-8 mg/day, 6-12 months	Reduction in zinc deficiency	Unclear	Unclear	RR; 0.84	[0.65, 1.08]	I^2 = 74%
Garcia-Casal MN, 2018	11	2	2002-2018	1027 (ages 2-11.9 and females aged >18)	Maize flour fortified with iron (as NaFeEDTA or electrolytic iron) plus vitamin A, thiamin, riboflavin, and niacin	28-56 mg iron/kg flour, 5-9 months	Anaemia	Sometimes	Low	RR	[0.58, 1.40]	0,76
		2		1102 (ages 2-11.9 and females aged >18)	Maize flour fortified with iron (as NaFeEDTA or electrolytic iron) plus vitamin A, thiamin, riboflavin, and niacin	28-56 mg iron/kg flour, 5-9 months	Iron deficiency	Sometimes	Low	RR	[0.49, 1.15]	0,43
		3		1144 (ages 2-11.9 and females aged >18)	Maize flour fortified with iron (as NaFeEDTA, electrolytic iron, or ferrous fumarate) plus other vitamins and minerals	28-56 mg iron/kg flour or 42.4 mg/100g, 5-10 months	Haemoglobin concentration	Sometimes	Low	MD	[-2.36, 4.86]	0,75
		1		584 (ages 6-11)	Nixtamalised corn flour fortified with iron (as reduced iron or NaFeEDTA) plus thiamin, riboflavin, niacin, folic acid and zinc	30 mg iron/kg flour, 9 months	Ferritin concentrations	Sometimes	Low	MD	[-0.37, 1.33]	Not applicable
		1		515 (ages 3-8)	Whole maize flour fortified with iron (as NaFeEDTA or electrolytic iron) plus vitamin A, thiamin, riboflavin, and niacin	28-56 mg iron/kg flour, 5 months	Iron-deficiency anaemia	Sometimes	Low	RR	[0.58, 1.88]	Not applicable
Crawford C, 2022	9,5	6	2001-2021	1,708 (ages 4-12 and >18)	Echinacea	Various formulations, 1200-2400 mg/day, up to 4 months	Incidence of infection, severity, duration of symptoms	Sometimes	Medium	RR, SMD, MD	p < 0.05 for some outcomes	NA
		1		312 (ages >18)	Elderberry	600-900 mg/day, 15-16 days	Incidence of infection, severity, duration of symptoms	Always	Strong	RR, descriptive statistics	p = 0.02 for severity	Not applicable
		2		266 (ages >18)	Garlic	180 mg - 2.56 g/day, up to 90 days	Incidence of infection, duration of symptoms	Always	Strong	RR, descriptive statistics	p < 0.001 for some outcomes	NA
		2		1,719 (ages <10)	Vitamin A	200,000 IU every 4-6 months, up to 15 months	Incidence of respiratory infections	Few	Very low	RR, descriptive statistics	Not significant	NA
		3		237 (adolescents and ages >18)	Vitamin C	1000 mg/day, up to 90 days	Incidence of infection, severity, duration of symptoms	Sometimes	Medium	RR, SMD, MD	p < 0.05 for some outcomes	NA
		18		19,309 (children, adults, seniors)	Vitamin D	Various doses, daily to monthly, up to 5 years	Incidence of infection, severity, duration of symptoms	Few	Low	RR, SMD, MD	Mixed results	I^2 = 0% - 76%
		1		652 (seniors)	Vitamin E	400 mg/day, up to 15 months	Incidence of infection, severity, duration of symptoms	Never	Never	RR, descriptive statistics	Not significant	Not applicable
		6		1,445 (children, adults, seniors)	Zinc	10-45 mg/day, up to 12 months	Incidence of infection, severity, duration of symptoms	Sometimes	Medium	RR, MD	p < 0.05 for some outcomes	NA

Tab. S1 *(follows).*

Hae-Eun Cho, 2022	11	30	2009-2021 (June)	30,263 (healthy and non healthy children, adolescents, adults)	Vitamin D	300-10,000 IU daily 14,000-50,000 IU weekly 60,000-200,000 IU monthly 100,000-300,000 IU quarterly from 1 to 60 weeks	symptoms or prevention of: URIs (n = 23) LRIs (n = 6) both URIs and LRIs (n = 1)	Sometimes	Low	RR= 0.96	[0.91–1.01]	59.0
Zhixin Zhu, 2022	11	10	2010-2021	4026 males and 4003 females	Vitamin D	1200-2000 IU/day	Reduced influenza risk	Sometimes	Medium	RR = 0.78	95% CI: 0.64–0.95	I^2 = 27%
Hunter J., 2021		27	april-august 2020	5446	zinc lozenges followed by nasal spray and gels	15 mg or 45 mg for 7 or 12 months respectively	preventing community-acquired infections	Sometimes	low	RR = -2.05	[-3,5 - -0,59]	I^2 = 97%
					topical nasal zinc to prevent or treat community-acquired infections	0.9–2.6 mg/day	community acquired mild to moderate RTIs (person-month)	Sometimes	low	RR = 0,68	[0,58-0,80]	I^2 = 0
Wieland S, 2021	11	1	1995-2016	312 (adults)	Elderberry	Capsule, 300 mg 2-3 times/day, 15-16 days	Incidence of common cold, duration and severity	Sometimes	Low	RR = 0.69	95% CI: 0.34-1.39; p=0.30	NA
								Few	Very low	MD; -2.13 MD; -13.69	95% CI: -4.16- -0.10; p=0.04 95% CI: -24.54- -2.84.10; p=0.01	NA
		3		151 (children, adolescents, adults)	Elderberry	Various formulations, up to 175 mg 4 times/day, up to 5 days	Improvement of influenza symptoms, duration of symptoms	Few	Very low	RR, MD	Mixed results	I^2 = 94%
		1		420 (adults)	Elderberry and echinacea	5 ml echinaforce, 3-5 times/day	Improvement of influenza symptoms, duration of symptoms	Sometimes	Low	RR	Mixed results	NA
		3		74 (adults, post-menopausal women)	Elderberry	Various formulations, up to 12 weeks	Cytokine production	Unclear	Unclear	MD	Mixed results	NA
Sholto D, 2019	10	9	1980-2018	Not reported, majority of trials from adult populations, 2 trials from 12 years	Echinacea	Various formulations. Mean durations of treatments min 1.6 max 8.0	URTI incidence	Always	Low	RR 0.78	[0.68-0.88]	I2 45%
		7			Echinacea		URTI duration	Sometimes	Null	MD -0.45	[-1.85 - 0.94]	I2 96%
		16			Echinacea		Safety	Always	NA	RR 1.09	[0.95-1.25]	I2 0%
Adrian R. Martineau, 2017	11	25	2009-2015	11321 (ages 0 - 95)	Vitamin D	From <20 µg/day to >50 µg/day from 7 weeks to 1.5 years or bolus doses	Reduction in incidence of acute respiratory tract infection (ARTI)	Few	Low	Overall results: 0.88	0.003 (overall protective effect) 95% [0.81–0.96]	I2 53.3%
							Subpopulation analysis	Few		No asthma: OR: 0.82 Asthma: OR: 0.95	No asthma: p=0.04 95% [0.68–0.99] Asthma: p=0.73 95% [0.73–1.25]	NA
							Subpopulation analysis	Few		Chronic Obstructive Pulmonary Disease (COPD): No COPD: OR: 1.00 COPD: OR: 0.84	No COPD: p=0.98 95% [0.80–1.26] COPD: p=0.38 (95% [0.57–1.24]	NA
							Subpopulation analysis	Few		No influenza vaccination: OR: 0.74 Influenza Vaccination: OR: 0.86	No influenza vaccination: p=0.08 95% [0.52–1.03] Influenza Vaccination: OR: p=0.22 95% [0.68–1.09]	NA
							Subpopulation analysis	Few		BMI <25: OR: 0.85 BMI ≥25: OR: 0.95	BMI <25: p=0.02 95% [0.74–0.97] BMI ≥25: p=0.58 95% [0.79–1.14]	NA
							Subpopulation analysis	Few		Baseline Vitamin D Status (<25 nmol/L): OR: 0.58 Baseline Vitamin D Status (≥25 nmol/L): OR: 0.89	Baseline Vitamin D Status (<25 nmol/L): OR: 0.58 95% [0.40–0.82] Baseline Vitamin D Status (≥25 nmol/L): OR: 0.89 95% [0.77–1.04]	NA
							Subpopulation analysis	Few		Dosing Regimen Daily or Weekly: OR: 0.81 Bolus Doses: OR: 0.97	Daily or Weekly: p-value: <0.001 95% [0.72–0.91] Bolus Doses: p-value: 0.67 95% [0.86–1.10]	NA
							Subpopulation analysis	Few		Age Subgroups: ≤1 year: OR: 0.94 1.1–15.9 years: OR: 0.60 16–65 years: OR: 0.93 65 years: OR: 0.86	Age Subgroups: ≤1 year: p=0.33 95% [0.83–1.06] 1.1–15.9 years: p<0.001 95% [0.46–0.77] 16–65 years: p=0.41 95% [0.79–1.10] 65 years: p=0.21 95% [0.67–1.09]	NA

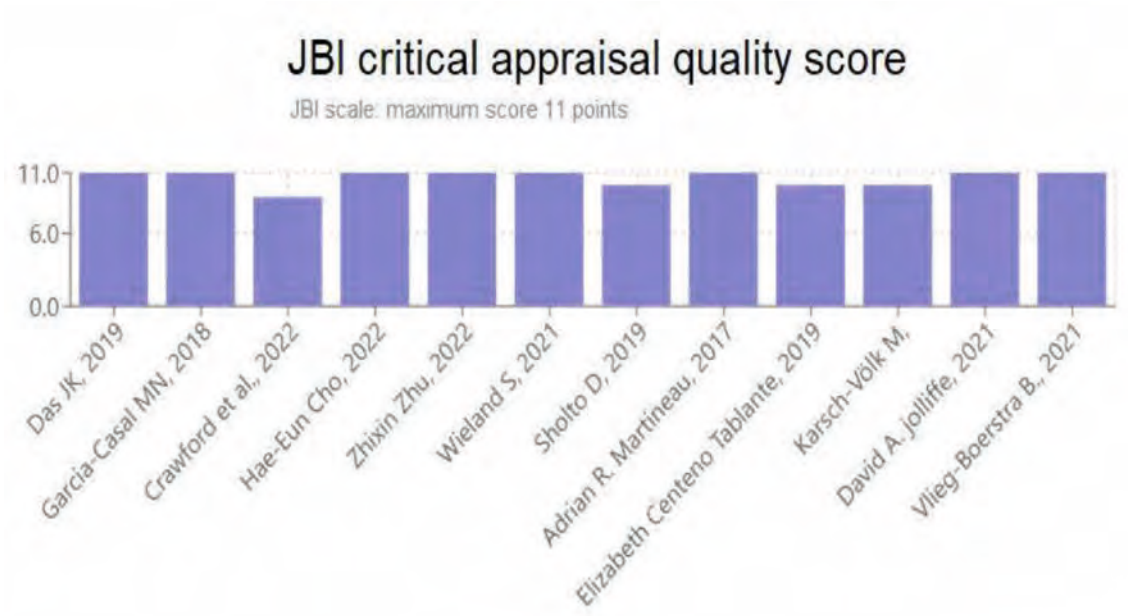
Tab. S1 *(follows).*

Elizabeth Centeno Tablante, 2019	10	10 (4 for quantitative analyses)	1974-2019	~2268000 (Pregnant women: 23723; Non-pregnant women: 1412; Children: 2242772; Adults (men and women): 45)	Fortification of wheat flour and maize flour: Folic acid alone or combined with other vitamins and minerals.	Dose 0.5 ppm to 33 ppm of folic acid (varied by study), by 26 days to 36 months	Neural tube defects	Always	Strong	RR; 0.32	0.21, 0.48	Not reported
							Folate biomarkers: Erythrocyte folate concentrations (nmol/L). Serum/plasma folate concentrations (nmol/L).	Always	Strong	Erythrocyte Folate Concentrations (nmol/L): MD; 238.9 nmol/L Serum/Plasma Folate Concentrations (nmol/L): MD; 14.98 nmol/L	Erythrocyte Folate Concentrations (nmol/L): (149.4, 328.4) Serum/Plasma Folate Concentrations (nmol/L): (9.63, 20.33)	
							Anaemia: Prevalence and haemoglobin concentrations (g/L).	Sometimes	Medium	Anaemia Prevalence: RR; 0.87 Haemoglobin Concentrations (g/L): MD; 3.26 g/L	Anaemia Prevalence: [0.68, 1.11] Haemoglobin Concentrations (g/L): [1.31, 5.22]	
							Adverse pregnancy outcomes: Low birth weight (< 2500 g). Preterm delivery (< 37 weeks gestation). Congenital anomalies (e.g., heart defects).	Sometimes	Null / Medium	Annual decrease of 6.2%		
							Cancers	Few	Medium	Reduction from 1.57/10,000 to 0.62/10,000		
							Cognitive function and decline (older populations).	Never	Null			
Karsch-Völk M, et al	10	24 (2 of 10 trials)	1992-2012	Unclear	Echinacea products	Unclear	at least 1 cold episode.	Always	Medium	RR 0.83	95% CI 0.75 to 0.92;P < 0.001	0%
		24 (5 trials)	1992-2012				more than 1 cold episode.	Always	Weak	MD -0.24	95% CI -0.07 to -0.40; P = 0.005	0%
David A. jolliffe, 2021	11	46	2009-2021	75541 participants (aged 0-95 years)	vitamin d supplemention	from less than 400 IU to more than 2000 IU and variable lenght	reduced the risk of ARIs by a small but statistically significant amount in specific subgroups	Always	Medium	OR 0.92	p 0,018 CI 0,86-0,99	35·6%,
Vlieg-Boerstra B., 2021	11	22 (9 for meta-analysis)	2003-2015	4083 children (2088 intervention group + 1995 control group)	multiple micronutrient supplementation	NR	any viral infection in children	Sometimes	Null	RR of RTI: 0.99	0.87-1.10	77.1 %
		22 (6 for meta-analysis)	1999-2007	2496 adults (1257 intervention group + 1239 control group)	multiple micronutrient supplementation	NR	any viral infection in adults	Sometimes	Weak	RR of RTI: 0.93	0.86-1.00	0%
		24 (18 for meta-analysis)	2002-2018	102,634 children (51,290 intervention group + 51,344 control group)	zinc supplementation	NR	any viral infection in children	Sometimes	Weak	RR of RTI: 0.91	0.82-1.01	83.7%
		10 (6 for meta-analysis)	2010-2019	6843 children (3400 intervention group + 3443 control group)	vitamin D supplementation	ges 1,000–2,000 IU/day on ave	any viral infection in children	Sometimes	Medium	RR of RTI: 0.88	0.66-1.11	80.4%
		9 (7 for meta-analysis)	2009-2017	3944 adults (2028 intervention group + 1966 control group)	vitamin D supplementation	ges 1,000–4,000 IU/day on ave	any viral infection in adults	Sometimes	Medium	RR of RTI: 0.89	0.79-0.99	20.7%
		15 (3 for meta-analysis)	1994-2015	46,028 children (23,005 intervention group + 23,023 control group)	single high dose vitamin A	supplementation (50.000–200	any viral infection in children	Sometimes	Weak	RR of RTI: 1.07	0.96-1.18	0%
		15 (9 for meta-analysis)	1994-2016	32,129 children (16,625 intervention group + 15,504 control group)	repeated high dose vitamin A	dose supplementation (10.000	any viral infection in children	Sometimes	Null	RR of RTI: 0.95	0.73-1.16	97.4%
		4 (2 for meta-analysis)	2002-2004	929 adults (470 intervention group + 459 control group)	vitamin E	NR	any viral infection in adults	Sometimes	Null	RR of RTI: 0.99	0.80-1.18	43.7%

Tab. S2. Assessment of the methodological quality of the included studies.

Study information			Risk of Bias (ROB)		JBI Critical Appraisal Checklist											
Study (first author & year)	Title	Type of study	Type of Risk of Bias (ROB) or Appraisal	ROB rating	Is the review question clearly and explicitly stated?	Were the inclusion criteria appropriate for the review question?	Was the search strategy appropriate?	Were the sources and resources used to search for studies adequate?	Were the criteria for appraising studies appropriate?	Was critical appraisal conducted by two or more reviewers independently?	Were there methods to minimize errors in data extraction?	Were the methods used to combine studies appropriate?	Was the likelihood of publication bias assessed?	Were recommendations for policy and/or practice supported by the reported data?	Were the specific directives for new research appropriate?	Quality of evidence (0-11)
Das JK, 2019	Food fortification with multiple micronutrients: impact on health outcomes in general population (Review)	Systematic Review and Meta-Analysis	RoB 2	high; low; unclear	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	11
Garcia-Casal MN, 2018	Fortification of maize flour with iron for controlling anaemia and iron deficiency in populations	Systematic Review and Meta-Analysis	Cochrane Risk of Bias	Low to High (varies by included study)	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	11
Crawford et al., 2022	Select Dietary Supplement Ingredients for Preserving and Protecting the Immune System in Healthy Individuals: A Systematic Review	Systematic Review	SIGN 50 for RCTs	Varied across studies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable (no meta-analysis)	No	Yes	Yes	9,5
Hae-Eun Cho, 2022	Efficacy of Vitamin D Supplements in Prevention of Acute Respiratory Infection: A Meta-Analysis for Randomized Controlled Trials	Meta-Analysis	Jadad scale Cochrane risk of bias	4.5 5	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Zhixin Zhu, 2022	Association Between Vitamin D and Influenza: Meta-Analysis and Systematic Review of Randomized Controlled Trials	Meta-Analysis and Systematic Review	Cochrane Risk of Bias	Low	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Hunter J., 2021	Zinc for the prevention or treatment of acute viral respiratory tract infections in adults: a rapid systematic review and meta-analysis of randomised controlled trials	Systematic Review and Meta-Analysis (of randomised controlled trials)	Cochrane Risk of Bias	high	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	NA
Wieland S, 2021	Elderberry for prevention and treatment of viral respiratory illnesses: a systematic review	Systematic Review and Meta-analysis	Cochrane Risk of Bias	Low to High (varies by included study)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Sholto D, 2019	Echinacea for the prevention and treatment of upper respiratory tract infections: A systematic review and meta-analysis	Systematic Review and Meta-Analysis	Cochrane Risk of Bias	5 low risk, 7 at least one high risk domain, 17 mix of high and low risk domains	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	10
Adrian R. Martineau, 2017	Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data	Systematic Review and Meta-Analysis (of individual participant data (IPD))	Cochrane Risk of Bias	50 low risk, 2 unclear to high rate of loss to follow-up.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Elizabeth Centeno Tablante, 2019	Fortification of Wheat and Maize Flour with Folic Acid for Population Health Outcomes	Systematic Review and Meta-Analysis.	Cochrane Risk of Bias	Moderate to High (low for RCTs, high risk for non-RCTs and ITS (Interrupted Time Series)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	Yes	10
Karsch-Völk M,	Echinacea for preventing and treating the common cold (Review)	Systematic Review	Cochrane Risk of bias	Low for 10 studies, high for 8 studies, unclear for 6 studies	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	10
David A. Jolliffe, 2021	Vitamin D supplementation to prevent acute respiratory infections: a systematic review and meta-analysis of aggregate data from randomised controlled trials	Systematic Review and Meta-Analysis	Cochrane Risk of Bias	low	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	11
Vlieg-Boerstra B., 2021	Nutrient supplementation for prevention of viral respiratory tract infections in healthy subjects: A systematic review and meta-analysis	Systematic Review and Meta-Analysis	Cochrane Risk of Bias	Moderate	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	11

Fig. S1. JBI Appraisal Score of the included studies.



e-Health

Digital Resources as a Tool for Physical Activity Promotion and Attendance among University Students: a Pilot Study

MAURO DE SANTI[1], GIULIA BALDELLI[1], PAOLA FRISINA[1], PAOLA ITALIANO[1], VERONICA GENTILINI[1], GIUDITTA FIORELLA SCHIAVANO[2], GIORGIO BRANDI[1], GIULIA AMAGLIANI[1]
[1] University of Urbino Carlo Bo, Department of Biomolecular Sciences, Urbino (PU), Italy;
[2] University of Urbino Carlo Bo, Department of Humanities, Urbino (PU), Italy

Keywords

Digital resources • Physical activity • University students • Perceived well-being • COVID-19

Summary

Background. *Various digital resources (DR) to support people in staying physically active have recently been developed and diffused, especially among young people. Our study aimed to evaluate how the epidemiological scenario determined by the COVID-19 pandemic may have influenced the current methods of carrying out physical activity (PA) among university students.*
Methods. *An online survey was conducted to analyze DR usage habits as a tool useful for PA attendance before, during, and after the COVID-19 pandemic. Data from the World Health Organization (WHO)-5 questionnaire and the Body Mass Index were also collected.*
Results. *The survey, conducted on 656 university students (77.0 % female, 22.2 % male, 0.8 % not specified), revealed increased use of DRs during the confinement period, from 21.3% to 74.3%, as expected. Interestingly, DR usage remained 7% higher than before. Moreover, PA levels were related to higher perceived well-being (WHO-5), and DRs were associated with low/moderate PA intensity and lower BMI values. Specifically, DR use was revealed in 32% of those having a BMI under 24.9 and 17% of those with a BMI higher than 25.*
Conclusion. *This research highlights how DRs can represent a simple and economical way to stay active. Considering the importance of an active lifestyle for general well-being and health status maintenance, DR could be considered a good tool and included in policies to promote PA attendance in university students.*

Introduction

Physical activity (PA) plays a fundamental role in overall health, body composition, and perceived well-being, representing a key component of a healthy lifestyle. Keeping active physical habits leads to a wide range of benefits, such as an improvement in cardiovascular health and a decreased risk in type 2 diabetes and some types of cancer risks [1, 2]. PA positively impacts body weight distribution [3]; additionally, it can also have a positive impact on mental health, helping to reduce stress, anxiety, and depression in people of all ages and improving mood, sleep quality, and cognitive function [4]. In contrast, sedentary behavior has been associated with an increased risk of several chronic non-communicable diseases [5].
Unfortunately, the proportion of adults engaged in exercise, sport, or lifestyle PA, in general, has constantly decreased over the years [6], while sedentary time has increased over the last 10-year period among the entire population, including university students [7]. Although university students attending PA sciences and kinesiology programs are more prone to exercise and self-report more activity than students of other faculties [8], a recent study showed a decrease in fitness level and higher abdominal adiposity in a cohort of students, with respect to another group of students from the same institution and program, 30 years prior, potentially attributed to excessive stationary time [9].
Web-based technology and screen time have usually been considered as counterparts of active lifestyle behaviors. However, due to their appreciation and popularity, especially among young adults and children, but with increasing diffusion in other age groups, different technological devices aimed at active gaming and exercise have been developed [10]. Recent technologies provide various strategies for exercising, even in individual settings and at home. This has been particularly useful in maintaining activity during the COVID-19 pandemic: indeed, it has been reported that the use of digital supports has been associated with a positive attitude towards exercise at home during isolation [11]. Apart from simple fitness tracking apps, several examples of technologies aimed at supporting exercise are available, such as fitness programs that utilize interactive online equipment (treadmills, stationary bikes), virtual reality headsets, consoles designed to wirelessly monitor the user's movement, tele-exercise and eHealth, on-demand workout services or live streaming exercise sessions, distance learning classes, and webinars [12].
When the use of such innovative training devices was

analyzed in the context of health recommendations in pre-pandemic era, it proved to possibly constitute a sufficiently useful tool to perform PA to meet the needs of leisure time activities, and to reach the recommended intensity of PA to obtain pro-health benefits [13]. Therefore, digital resources (DR) have the potential to be effective tools for increasing participation in health-oriented PA.

In response to the spread of the SARS-CoV-2 virus in several countries, including Italy, quarantine measures were implemented to prevent infection transmission [14]. Among these measures, there was the closure of gyms, swimming pools, clubs, sports centers, and associations, except for those engaging in individual activities. Due to the stringent limitations on leaving home, lifestyle habits underwent significant changes, leading to a notable decrease in overall PA and an increase in sedentary behavior, along with the associated well-known risks of insufficient PA [15, 16].

In connection with the above, the PA "at home" was promoted by WHO during the pandemic confinement to maintain PA benefits in that challenging situation [17]. In that scenario, the use of DRs appeared to be convenient to stay active and continue exercising. With these premises, further use of PA-related technologies is likely to occur. This study aims to analyze PA habits of university students before, during, and after the COVID-19 restriction period in relation to BMI and perceived well-being, with a particular focus on the exploitation of using DRs and their impact on current PA habits in such populations.

Methods

Study design

A descriptive cross-sectional study was carried out to analyze DR usage habits as a useful tool for PA attendance before, during, and after the COVID-19 pandemic. The study involved university students attending the University of Urbino Carlo Bo, Urbino, Italy. All participants were fully informed about the study requirements and were asked to accept the data sharing and privacy policy (in compliance with the privacy guarantee rules; EU Regulation 2016/679) before participating in the study. The study has been approved by the Ethics Committee of the University of Urbino Carlo Bo (Approval Number: 66/23.02.2023).

Data collection methods

Data were obtained from an online questionnaire, "The use of technologies and social media for the practice of physical activity," designed to collect information on physical habits in terms of frequency, intensity, duration, type, use of DRs such as electronic devices or use of online platforms, before, during, and after the COVID-19 pandemic restriction period, to date. Data were also related to BMI and perceived well-being. Data was collected using an *ad hoc* online questionnaire created on Google Forms and distributed through an email sent by the university secretariat following authorization from the ethics committee.

Sample characteristics

The study population considered was all students attending the University of Urbino Carlo Bo in the academic year 2022/2023. Specifically, the questionnaire was sent to a total of 14,127 students, 9,254 females, and 4,873 males. The sample size was estimated using the standard formula for calculating the sample size needed in population analyses, assuming a 95% confidence level ($Z = 1.96$), an estimated proportion of 0.5 ($p = 0.5$), and a margin of error of 5% ($E = 0.05$); applying the finite population correction and estimating data collection from 14,127 students, we obtain a needed sample size of 374. Details about the academic fields of students attending the University of Urbino are reported in the Supplementary Materials (Fig. S1).

Survey administration

The survey was conducted between 7th March 2023 and 28th April 2023. Students were asked to indicate their PA habits before (8th March 2020), during (in Italy from 8th March 2020 to 25th May 2020 [14]), and after the end of the pandemic home confinement period (from the moment in which sports facilities were reopened and the practice of PA was again possible; the dates were different according to local epidemiological data about COVID-19 incidence at the regional level). Multiple participation was prevented by making mandatory the use of the university account to fill out the questionnaire and limiting each participant to one reply.

The questionnaire, reported in the Supplementary Materials (Tab. S1), was divided into three main sections. In the introductory part, personal data were requested, such as the province of origin, sex, age, height, and whether the student's home had an uncovered area available/private garden, outdoor area/common garden, or no outdoor area/garden. The second part aimed to collect information on PA practice before, during, and after the COVID-19 restriction period in terms of indoor/outdoor PA, frequency (days per week), and perceived intensity (vigorous, moderate/vigorous, moderate/low, low). The weight was asked in order to calculate the body mass index (BMI) in each period. The survey also investigated the attendance or the use of courses, online or digital platforms, multimedia tools or equipment, apps, online lessons, or social media to practice PA. The questions included the type of services used by the student [Streaming services for exercise/Lessons facilitated online live or recorded, via platforms/Free apps /Social media/Active electronic games (*e.g.* games using Wii Balance Board, Xbox Kinect, *etc.*)/Equipment connected to the internet/Fitness programs for subscribers, via app or online/Online or digital training or running platforms] and the frequency of use (Rarely/Sometimes/Often/Always). Students were specifically asked to indicate the use of DRs only if actively used for carrying out the exercise, and not only for monitoring the activities. Those who continued to use technology to practice PA even after the end of the state of emergency were asked to indicate the reasons for their choice.

The last part of the survey included the World Health

Organization-Five Well-Being Index (WHO-5), which referred to the last 14 days [18]. The WHO-5 items are: (1) "I have felt cheerful and in good spirits", (2) "I have felt calm and relaxed", (3) "I have felt active and vigorous", (4) "I woke up feeling fresh and rested" and (5) "My daily life has been filled with things that interest me". Each of the five items is scored from 5 (all of the time) to 0 (none of the time). The raw score, therefore, theoretically ranges from 0 (absence of well-being) to 25 (maximal well-being). Because scales measuring health-related quality of life are conventionally translated to a percentage scale from 0 (absent) to 100 (maximal), the perceived well-being raw score obtained from the WHO-5 questionnaire was multiplied by 4 [18].

Statistical analysis

Exploratory statistical analyses were conducted in order to find differences in the distribution of the physically active students according to gender, availability of outdoor spaces, and BMI. Differences in the distribution of PA attendance according to gender and availability of outdoor spaces were evaluated by chi-square test. Differences in BMI between active and sedentary students were evaluated by students' t-test. Differences in DR use, considering PA type and intensity, were evaluated using the chi-square test.

Spearman's rho coefficients were calculated to find correlations between BMI (POST) and WHO-5 score and age, PA frequency (days per week, POST), PA intensity (POST), and the frequency of DR use (POST).

Results

Study population

A total of 656 students attending the University of Urbino participated in the study (77.0 % female, 22.2 % male, 0.8% not specified). Considering that the student population of the academic year in which the study was conducted was 14,127 students, of whom 9,254 were female, the sample in this study was 5.49% and 3.01% representative for females and males attending the university, respectively. Considering students' responses based on academic fields, we didn't find any differences between the percentages of students attending the University and the adherence to the study from each group (Fig. S1). The mean age of participants was 26.0 and 27.8 for females and males, respectively. Although the mean age is relatively high, suggesting greater interest in the survey from older students, the median age was 23 for females and 22 for males. This discrepancy was due to the presence of a subset of the adult student population. Responders were: 21.6% in the first, 16.7% in the second, 18.5% in the third, 16.4% in the fourth, and 17.5% in the fifth year of study; 9.5% exceeded the normal duration of the years of study.

PA attendance and Body Mass Index

In Table 1, differences in PA attendance in the study population are reported. PA attendance was about 70% in each of the time periods investigated, without significant differences between periods ($p > 0.05$). Males were more active than females during the pre- and post-restriction period ($p < 0.05$), differing by about 10%. PA attendance was also evaluated considering the availability of outdoor spaces (*i.e.* none, shared, or private gardens), revealing no significant differences in the three periods considered.

Concerning the BMI distribution in the study group, 69.31% of participants showed a BMI under 24.9, while 11.69% and 2.69% were overweight and obese, respectively, without differences between periods considered ($p > 0.05$; chi-squared test), and 16.31% of participants did not indicate their body weight. Significant differences in BMI between active and non-active students were found in female "pre" and male "during" only. BMI values remained essentially stable,

Tab. I. Physical activity attendance in the study population.

		Pre			During			Post		
		PA	no PA		PA	no PA		PA	no PA	
Total[a]	656	445 (67.8)	211 (34.7)		460 (70.1)	196 (29.9)		447 (68.1)	209 (31.9)	
Female[a]	505	330 (65.3)	175 (34.6)		355 (70.3)	150 (29.7)		334 (66.1)	171 (33.9)	
Male[a]	146	111 (76.0)	35 (24.0)		102 (69.9)	44 (30.1)		110 (75.3)	36 (24.7)	
Pns[a]	5	4 (80.0)	1 (20.0)	*p = 0.015*[c]	3 (70.1)	2 (29.9)	*ns*[c]	3 (60.0)	2 (40.0)	*p = 0.035*[c]
Outdoor spaces										
None[a]	212	132 (62.3)	80 (37.7)		139 (65.6)	73 (34.4)		132 (62.3)	80 (37.7)	
Shared[a]	118	84 (71.2)	34 (28.8)		84 (71.2)	34 (28.8)		80 (67.8)	38 (32.2)	
Private[a]	326	229 (70.2)	97 (29.8)	*ns*[c]	237 (72.7)	89 (27.3)	*ns*[c]	235 (72.1)	91 (27.9)	*ns*[c]
BMI										
Female[b]		21.7 ± 3.8	22.7 ± 5.4	*p = 0.035*[d]	22.0 ± 4.7	22.6 ± 4.3	*ns*[d]	22.1 ± 4.6	22.0 ± 3.9	*ns*[d]
Male[b]		22.5 ± 2.9	24.1 ± 4.6	*ns*[d]	22.3 ± 2.8	24.6 ± 4.5	*p = 0.007*[d]	23.6 ± 3.0	23.0 ± 3.6	*ns*[d]
Pns[b]		21.0 ± 2.8	21.4 ± n.c.	n.c.[d]	21.4 ± 3.8	21.4 ± n.c.	n.c.[d]	18.7 n.c.	22.7 ± n.c.	n.c.[d]

[a] *n* (%); [b] mean ± standard deviation; [c] chi-squared test; [d] t-test; *ns*: not significant; n.c.: not calculable; *Pns*: "*prefer not to say*"; PA: physical activity.

without significant variations among the three time intervals (paired ANOVA, not shown).

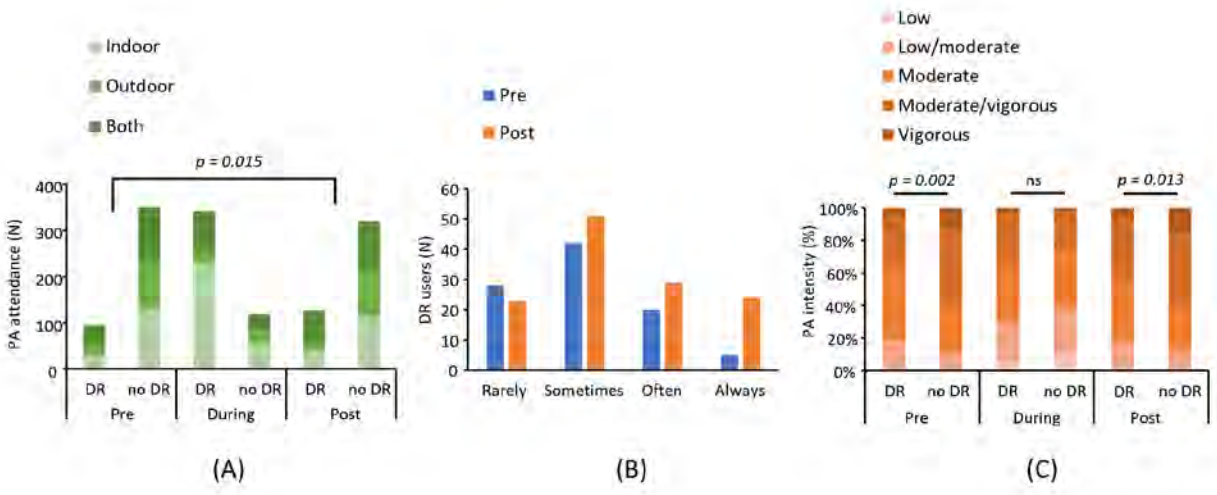
Trends in the use of DRs for PA

The use of DRs in the student population and the influence of the COVID-19 pandemic on their use were then evaluated in physically active participants (Fig. 1). Results revealed a marked increase in DR use during the restriction period, as expected, with a prevalence rising from a starting value of 21.3% to 74.3% and a statistically significant growth ($p < 0.001$) (Fig. 1A). Interestingly, after the end of the restriction period, their use remained more popular than before; in fact, the percentage of students that kept the habit of DRs use for PA attendance was 28.4%, a proportion significantly higher than that of the period before the pandemic restrictions (+7%; $p < 0.05$) (Fig. 1A). DRs were mainly used by female students, representing 77.9 %, 83.6 %, and 79.5 % of total users before, during, and after the pandemic period, respectively. The DRs were mainly used by participants who performed both indoor and outdoor activities during pre- ($p < 0.05$) and post- ($p < 0.01$) restriction periods, whereas, during the pandemic confinement, since PA was forcedly conducted indoors, DR use was more frequent for the at-home PA (Fig. 1A).

Figure 1B outlines the increase in the use of DRs in the period post-COVID-19 restrictions. Specifically, the distribution of DRs frequency changed significantly ($p < 0.01$), with a decrease in the participants who rarely used DRs, and an increase in those who used them often and always. The association between DR use and PA intensity was also analyzed. Results showed a different distribution of PA intensity between DR users and non-users (Fig. 1C). Particularly, low/moderate and moderate PA were more frequent in DR users, with respect to no DR ones, both pre ($p < 0.01$) and post ($p < 0.001$) pandemic restriction periods (Fig. 1C), whereas no significant differences were found during. In other words, except for the home confinement period, people prone to use DRs for PA attendance were likely those practicing recreational activities at low/moderate intensity instead of competitive athletes or exercisers at high fitness levels. However, these considerations need to be confirmed in larger studies. The main type of DRs used was streaming services for exercise, chosen by 40.1% of participants; these services offer a wide range of fitness-related video content accessible for on-demand streaming, including diverse disciplines such as yoga, pilates, high-intensity workouts, dance, and cardio workouts (Fig. 2A). Free apps and social media were chosen by 17.6% and 17.3% of participants, respectively. Live or recorded online lessons were used by 12% of participants. Finally, 8.5% chose fitness programs by subscription, 3.8% chose active electronic games, and only 0.7% chose internet-connected equipment (Fig. 2A).

The reasons why participants continued to use DRs in the post-restriction period were practicality, lower cost, feeling more comfortable, and less waste of time; moreover, approximately 16% of participants learned about DRs during the pandemic period, appreciated these resources, and decided to maintain the new habit (Fig. 2B). Finally, correlations between healthy parameters and age, PA habits, and DR use were analyzed in the post-restriction period. The BMI was chosen as the anthropometric value associated with physical health status. Among active participants, 32% of those having a BMI under 24.9 and 17% of those with a BMI higher than 25 (overweight and obese) use DR. In fact, the univariate analysis showed a slight but significant negative correlation between BMI and DR use, hypothesizing a positive role of DR use in influencing anthropometric values (Tab. III). Moreover, a significant positive correlation between BMI (Post) and age was found.

Fig. 1. Physical activity (PA) and Digital Resource (DR) use in the study population. A) Attendance of PA performed outdoors, indoors, or both in DRs and non-DRs users. B) Frequency of DR use before and post-COVID-19 pandemic restrictions. C) PA intensity in DRs and non-DRs users. Exact p-values are reported; ns, not significant; chi-squared test.



Tab. II. Spearman's correlation coefficients between body mass index and WHO-5, and physical activity habits and digital resource use.

		PA habits		
	Age (n = 656)	Days/week (n = 656)	Intensity (n = 656)	DR use (n = 447)[a]
BMI (Post)	0.191**	*ns*	*ns*	-0.142*
WHO-5 score	*ns*	0.228**	0.260**	*ns*

[a] Active participants only. BMI: Body Mass Index; PA: Physical Activity; DR: Digital Resource. * $p = 0.005$. ** $p < 0.001$.

Perceived mental well-being in DR users

The World Health Organization-Five Well-Being Index (WHO-5), a self-reported measure of current mental well-being based on a short assessment of respondents' feelings over five items, was used to evaluate perceived well-being in survey participants [18]. Physically active and inactive participants have significantly different mean scores ($p < 0.001$), with mean values of 57.3 ± 18.8 and 49.1 ± 20.2, respectively. Regarding PA habits, both frequency and intensity showed a significant positive correlation with the WHO-5 score, regardless of the use of DRs (Tab. III).

Discussion

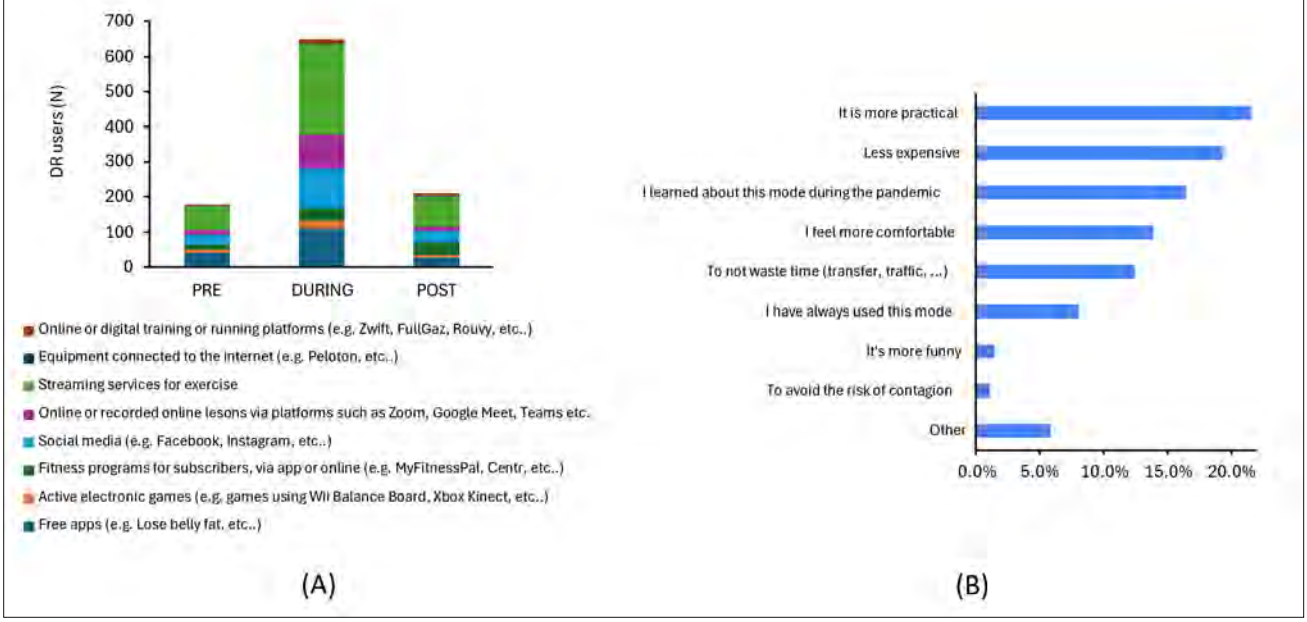
The emergency determined by the COVID-19 pandemic, which resulted in a restriction of all activities and home confinement in 2020, strongly affected people's habits, with particular concern for those related to PA and nutrition. Data collected by Ferrara et al. [19] among university students confirmed, also in this age group, the decrease in the time spent in PA, the change in the type and level of PA, and the increase in sitting time and sedentary behaviors were confirmed, especially for females. The unavailability of specific equipment and facilities understandably played a major role in this scenario [15].

These results were slightly in contrast with those obtained by the present work, in which we observe a constant PA attendance level throughout the considered period (pre-,during, and post-restrictions time), with an average value of about 70%, which is much higher than the one reported by Ferrara et al. (mean value 50%) [19]. However, in accordance with previously shown data, males were more physically active, at least in the pre-pandemic era.

During the pandemic restrictions, an increase in the outdoor PA practice and at-home activities, and a decline in sports center membership have been reported, while online services (free or not) were increasingly preferred [11]. López-Carril et al. [20], highlighted the role of social media and DRs during the COVID-19 lockdown in improving PA practice in university students, being used as channels to motivate people to perform PA, promote it, or learn about new training disciplines.

The WHO Global Action Plan on Physical Activity 2018-2030 [21] aims to reduce global levels of physical inactivity through the development of innovative digital approaches for promotion, such as the mobile-phone-based mActive program [22], which is consistent with the new WHO guidelines on physical activity and sedentary behaviour [23]. Indeed, recent intervention studies reported the successful promotion of PA behaviour change through mobile devices [24-26]. In accordance

Fig. 2. Digital Resource types and reasons for using them. A) Digital Resource (DR) types chosen by study participants in the three periods considered. B) Reasons for using DRs after pandemic restrictions.



with these data, our results show that the use of DRs to practice PA during the pandemic period strongly increased in the participants, from 21.3% to 74.3%. This significant rise could also explain the trend of PA attendance during restriction times, maybe maintained over time and improved also thanks to the increased use of DRs.

Many technologies have been designed to support people in staying physically active, ranging from exergames, activity trackers, and motivational apps. Besides those, the opportunity to practice PA by means of online video tutorials or lessons provided in tele-exercise mode is increasingly considered convenient. The underlying reasons, as arising from the results of this survey, are linked to money and time saving, along with a more comfortable feeling associated with the "at home" exercising mode. As underlined in a recent systematic review by Valeriani et al., being habitually active and using DRs may be associated with a positive attitude towards exercise at home during isolation. Moreover, the promotion of exercise through DRs is particularly important in those groups who are usually less engaged in PA [11]. The results from our study confirm this relevant consideration: participants who used DRs for PA are mainly engaged in moderate and low/moderate activities, suggesting that DR promotion should be useful, especially for recreational activities, instead of professional ones.

Considering the gender variable, our data fully agree with previously reported ones [20], with DRs mainly used by females (average value of 80% before, during, and after the pandemic period). This difference could be partially explained by the fact that in the present study there was a higher prevalence of women. However, also López-Carril et al. also indicated the same trend in DR users, even if most of the participants in their study were men [20].

It has been shown that excessive use of social media is associated with an increasing sense of loneliness and anxiety levels [27]. Notably, in this study, the WHO-5 score data assessed in DR users is not significantly different from that of non-users, leading to the hypothesis that PA attendance through DR does not affect/impact mental well-being. Interestingly, we found a preliminary correlation between the use of DRs and lower BMI and age, which may suggest a possible usefulness of DRs in the weight control of younger people. However, this finding should be deeply investigated through larger studies.

University students experience higher levels of sedentary time compared to the general young adult population, with an increasing trend in the last ten years [28]. Accordingly, levels of sedentary time accumulated by university students have been associated with an increased risk for detrimental health outcomes. This aspect has been confirmed by the WHO-5 questionnaire, through which we found that the self-reported measure of participants' mental well-being was positively correlated and improved with PA attendance, intensity, and frequency. Unfortunately, this result was not related to the use of DRs. A larger study could be useful to better investigate this variable.

Considering that many adult health-related behaviours are established during late adolescence and young adulthood, the university years are an important period for developing future life patterns [7], making imperative the development of effective evidence-based interventions to increase university students' PA [29]. Scientific literature offers a wide range of strategies to promote PA among university students, and DRs have emerged as particularly promising tools. In fact, it has been recently reported that mobile apps and fitness trackers to support PA self-monitoring [30], social media, and text messaging to deliver motivational reminders and create virtual support groups [31], digital health platforms such as web-based programs and gamified apps (*e.g.* exergames) [32], and real-time feedback systems [33].

A limitation of this study could be the possibility of a selection bias due to the way in which the questionnaire was distributed and the adherence to the survey. More active students could be attracted to participate, underestimating the real proportion of people with sedentary lifestyles. Notably, the percentage of sedentary students among participants is in line with the recent statistics [7]. Another limitation of the study is the validity of self-reported measures, which could lead to overestimating or underestimating PA behaviors and being prone to inaccuracies. However, this study represents an explorative survey for the evaluation of DR use in a university population. In fact, further evidence from larger studies involving several Universities is needed to confirm these findings and explore the PA habits of using DRs and possible health implications in the post-pandemic era.

Conclusion

In conclusion, these findings highlight the need for future initiatives and policies targeting sedentary behavior among college students. Indeed, this particular target population would greatly benefit from PA promotion interventions, taking into account strategies that appeal to younger age groups and involving DRs as a cost-effective and easy tool for daily use. In terms of practical considerations, this study strengthens the role of DRs in creating opportunities to attend higher levels of PA, also to connect with customers and offer innovative PA proposals.

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Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of Interest Statement

The Authors declare that there is no conflict of interest.

Human Subjects Approval Statement

The study has been approved by the Ethics Committee of the University of Urbino Carlo Bo (Approval Number: 66/23.02.2023).

Authors' contributions

GA and MDS conceived the study; GBa, PF, and PI, optimized the questionnaire and collected data; MDS, VG, and GBa, data elaboration and statistical analysis; GFS and GBr, conceptualization and revision; MDS and GA, drafted the manuscript. All authors revised and approved the final manuscript.

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Correspondence: Giulia Baldelli, PhD; University of Urbino Carlo Bo, Department of Biomolecular Sciences, Urbino (PU), Italy. E-mail: giulia.baldelli@uniurb.it

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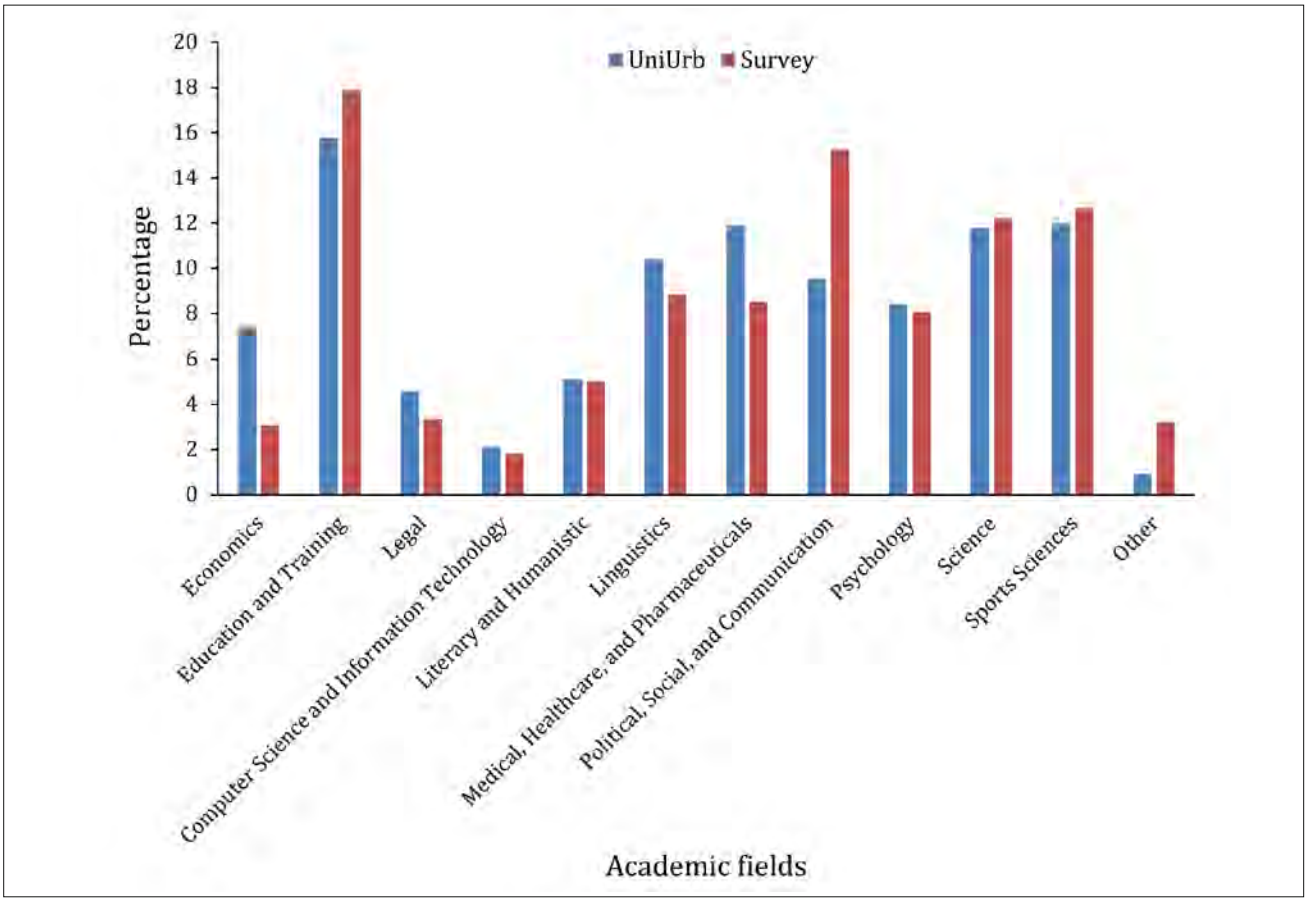
Supplementary material

Fig. S1. Academic fields of students attending the University of Urbino in the academic year 2022/2023 (Blue) and students participating in the survey (Orange). Data are represented as percentages. Source: https://ustat.mur.gov.it/.



Tab. S1. Questionnaire.

THE USE OF TECHNOLOGIES AND SOCIAL MEDIA FOR THE PRACTICE OF PHYSICAL ACTIVITY
The purpose of the questionnaire is to investigate physical activity habits in terms of frequency, intensity, duration, type, use of electronic devices, or use of online platforms, before, during, and after the COVID-19 pandemic, up to now, in relation to BMI and perceived well-being. The questionnaire is multiple-choice and should take approximately 5 minutes to complete.
SECTION 1: INFORMED CONSENT
Please be advised that data collection will be conducted in compliance with privacy regulations (EU Regulation 2016/679 and Legislative Decree 196/2003). The data will be reported in aggregate form, without identifying details, to ensure anonymity and will not be communicated or disseminated in any way except for research purposes.
Do you consent to data processing?
• I consent *(continue to the next section)*
• I deny consent *(submit the form)*
SECTION 2: ANAGRAFIC INFORMATION
- Which province are you from? (Please use CAPITAL LETTERS to indicate your province's abbreviation, *e.g.* RC, RM, AG, AL, *etc.)*
- Gender:
• Female
• Male
• I prefer not to answer
-Age:
-Your height: (indicate height in centimeters)
-Specify your degree class: *(e.g.* L22, L01, L02, LM4, LM67, *etc.*)
-Year of study
• o First
• o Second
• o Third
• o Fourth
• o Fifth
• o Not yet completed
-Does your HOME have:
• o Outdoor area/private garden
• o Outdoor area/shared garden
• o No outdoor area/garden
SECTION 3: BEFORE
- BEFORE the health emergency (before March 8, 2020), your body weight was:
(indicate weight in kilograms)
IT IS USED EXCLUSIVELY TO CALCULATE YOUR BMI
IF YOU DO NOT WISH TO PROVIDE THIS INFORMATION, ANSWER: no
- Did you engage in physical activity BEFORE the health emergency (before March 8, 2020)?
• Yes, INDOOR physical activity *(goes to section 4)*
• Yes, OUTDOOR physical activity *(goes to section 4)*
• Yes, both INDOOR and OUTDOOR physical activity *(goes to section 4)*
• No *(goes to section 6)*
SECTION 4: IF YES
- BEFORE the health emergency, how many DAYS per week did you engage in physical activity?
• 1
• 2
• 3
• 4
• 5

▶

• 6
• 7
- BEFORE the health emergency, how many HOURS/MINUTES of physical activity did you perform in TOTAL per week?
(EXAMPLE: If you performed 2 hours of physical activity 3 times a week, you would answer this question: 6 hours)
• 30 minutes
• 1 hour
• 2 hours
• 3 hours
• 4 hours
• 5 hours
• 6 hours
• 7 hours
• 8 hours
• 9 hours
• 10 hours
• 11 hours
• 12 hours
Other.
-BEFORE the health emergency, at what INTENSITY physical activity was performed?
• Mostly Vigorous Intensity
• Between Moderate and Vigorous
• Mostly Moderate Intensity
• Between Moderate and Low
• Mostly Low Intensity
- BEFORE the health emergency, did you use courses, online or digital platforms, multimedia tools or equipment, apps, online lessons, or social media to practice physical activity?
(*e.g.* YouTube, online courses organized by my gym via Zoom or Google Meet, Instagram, Facebook, Lose Belly Fat, Wii Balance, Peloton, *etc.*)
• NO TRACKING APPS (Google Fit, Huawei Health, Runtastic, RunKeeper, *etc.*)
• Yes *(goes to section 5)*
• No *(goes to section 6)*
SECTION 5: IF YES
WHICH courses, online or digital platforms, multimedia tools or equipment, apps, online lessons, or social media did you use to exercise? You can select multiple answers.
(*e.g.* YouTube, online classes organized by my gym, Instagram, Facebook, Lose Belly Fat, Wii Balance, Peloton, *etc.*)
NO TRACKING APPS (Google Fit, Huawei Health, Runtastic, RunKeeper, *etc.*)
• Exercise streaming services (*e.g.* YouTube, Dailymotion, *etc.*)
• Live or recorded online classes facilitated via platforms such as Zoom, Google Meet, Teams, *etc.* (*e.g.* dance, sports training, and fitness classes)
• Free apps (*e.g.* Lose Belly Fat, *etc.*)
• Social media (*e.g.* Facebook, Instagram, *etc.*)
• Active electronic games (*e.g.* games using the Wii Balance Board, Xbox Kinect, *etc.*)
• Internet-connected equipment (*e.g.* Peloton, *etc.*)
• Subscriber fitness programs, via app or online (*e.g.* MyFitnessPal, Centr, *etc.*)
• Online or digital training or running platforms (*e.g.* Zwift, FullGaz, Rouvy, *etc.*)
- BEFORE the pandemic, HOW OFTEN did you exercise using multimedia tools or equipment, apps, courses, online lessons, or social media?
• Rarely
• Sometimes

▶

• Often
• Always
SECTION 6: DURING
- DURING the health emergency (between March 8, 2020, and May 25, 2020), your body weight was:
(indicate weight in kilograms)
IT IS USED EXCLUSIVELY TO CALCULATE YOUR BMI
IF YOU DO NOT WISH TO PROVIDE THIS INFORMATION, ANSWER: no
- Did you engage in physical activity DURING the health emergency (between March 8, 2020, and May 25, 2020)?
• Yes, INDOOR physical activity *(goes to section 7)*
• Yes, OUTDOOR physical activity *(goes to section 7)*
• Yes, both INDOOR and OUTDOOR physical activity *(goes to section 7)*
• No *(goes to section 9)*
SECTION 7: IF YES
- BEFORE the health emergency, how many DAYS per week did you engage in physical activity?
• 1
• 2
• 3
• 4
• 5
• 6
• 7
- DURIING the health emergency, how many HOURS/MINUTES of physical activity did you perform in TOTAL per week?
(EXAMPLE: If you performed 2 hours of physical activity 3 times a week, you would answer this question: 6 hours)
• 30 minutes
• 1 hour
• 2 hours
• 3 hours
• 4 hours
• 5 hours
• 6 hours
• 7 hours
• 8 hours
• 9 hours
• 10 hours
• 11 hours
• 12 hours
• Other
- DURING the health emergency, at what INTENSITY physical activity was performed?
• Mostly Vigorous Intensity
• Between Moderate and Vigorous
• Mostly Moderate Intensity
• Between Moderate and Low
• Mostly Low Intensity
- DURING the health emergency, did you use courses, online or digital platforms, multimedia tools or equipment, apps, online lessons, or social media to practice physical activity?
(*e.g.* YouTube, online courses organized by my gym via Zoom or Google Meet, Instagram, Facebook, Lose Belly Fat, Wii Balance, Peloton, *etc.*)
NO TRACKING APPS (Google Fit, Huawei Health, Runtastic, RunKeeper, *etc.)*
• Yes *(goes to section 8)*

▶

• No *(goes to section 9)*
SECTION 8: IF YES
WHICH courses, online or digital platforms, multimedia tools or equipment, apps, online lessons, or social media did you use to exercise? You can select multiple answers.
(*e.g.* YouTube, online classes organized by my gym, Instagram, Facebook, Lose Belly Fat, Wii Balance, Peloton, *etc.)*
NO TRACKING APPS (Google Fit, Huawei Health, Runtastic, RunKeeper, *etc.)*
• Exercise streaming services *(e.g.* YouTube, Dailymotion, *etc.*)
• Live or recorded online classes facilitated via platforms such as Zoom, Google Meet, Teams, *etc.* (*e.g.* dance, sports training, and fitness classes)
• Free apps (*e.g.* Lose Belly Fat, *etc.*)
• Social media (*e.g.* Facebook, Instagram, *etc.*)
• Active electronic games (*e.g.* games using the Wii Balance Board, Xbox Kinect, *etc.*)
• Internet-connected equipment (*e.g.* Peloton, *etc.*)
• Subscriber fitness programs, via app or online (*e.g.* MyFitnessPal, Centr, *etc.*)
• Online or digital training or running platforms (*e.g.* Zwift, FullGaz, Rouvy, *etc.*)
- DURING the pandemic, HOW OFTEN did you exercise using multimedia tools or equipment, apps, courses, online lessons, or social media?
• Rarely
• Sometimes
• Often
• Always
SEZIONE 9: AFTER
- NOW, your body weight IS:
(indicate weight in kilograms)
• IT IS USED EXCLUSIVELY TO CALCULATE YOUR BMI
• IF YOU DO NOT WISH TO PROVIDE THIS INFORMATION, ANSWER: no
……
- NOW that the health emergency period is over (*i.e.*, from the time you were able to resume physical activity until sports facilities reopened, depending on your region), are you exercising?
• Yes, INDOOR physical activity *(goes to section 10)*
• Yes, OUTDOOR physical activity *(goes to section 10)*
• Yes, both INDOOR and OUTDOOR physical activity *(goes to section 10)*
• No *(goes to section 12)*
SECTION 10: IF YES
-NOW, how many DAYS per week did you engage in physical activity?
• 1
• 2
• 3
• 4
• 5
• 6
• 7
-NOW, how many HOURS/MINUTES of physical activity did you perform in TOTAL per week?
(EXAMPLE: If you performed 2 hours of physical activity 3 times a week, you would answer this question: 6 hours)
• 30 minutes
• 1 hour
• 2 hours
• 3 hours
• 4 hours
• 5 hours

▶

• 6 hours
• 7 hours
• 8 hours
• 9 hours
• 10 hours
• 11 hours
• 12 hours
• Other
-NOW, at what INTENSITY physical activity was performed?
• Mostly Vigorous Intensity
• Between Moderate and Vigorous
• Mostly Moderate Intensity
• Between Moderate and Low
• Mostly Low Intensity
- NOW, did you use courses, online or digital platforms, multimedia tools or equipment, apps, online lessons, or social media to practice physical activity?
(e.g. YouTube, online courses organized by my gym via Zoom or Google Meet, Instagram, Facebook, Lose Belly Fat, Wii Balance, Peloton*, etc.)*
• NO TRACKING APPS (Google Fit, Huawei Health, Runtastic, RunKeeper, *etc.)*
• Yes *(goes to section 11)*
• No *(goes to section 12)*
SECTION 11: IF YES
-WHICH courses, online or digital platforms, multimedia tools or equipment, apps, online lessons, or social media did you use to exercise? You can select multiple answers.
(*e.g.* YouTube, online classes organized by my gym, Instagram, Facebook, Lose Belly Fat, Wii Balance, Peloton, *etc.*)
NO TRACKING APPS (Google Fit, Huawei Health, Runtastic, RunKeeper, *etc.*)
• Exercise streaming services (*e.g.* YouTube, Dailymotion, *etc.*)
• Live or recorded online classes facilitated via platforms such as Zoom, Google Meet, Teams, *etc.* (*e.g.* dance, sports training, and fitness classes)
• Free apps (*e.g.* Lose Belly Fat, *etc.*)
• Social media (*e.g.* Facebook, Instagram, *etc.*)
• Active electronic games (*e.g.* games using the Wii Balance Board, Xbox Kinect, *etc.*)
• Internet-connected equipment (*e.g.* Peloton, *etc.*)
• Subscriber fitness programs, via app or online (*e.g.* MyFitnessPal, Centr, *etc.*)
• Online or digital training or running platforms (*e.g.* Zwift, FullGaz, Rouvy, *etc.*)
- NOW, HOW OFTEN did you exercise using multimedia tools or equipment, apps, courses, online lessons, or social media?
• Rarely
• Sometimes
• Often
• Always
-NOW that the state of emergency is over, why do you use these technologies to exercise? You can choose several options.
• Because I've always done it
• To avoid the possibility of contagion
• To avoid wasting time (*e.g.* getting stuck in traffic on my way to the gym or another place where I exercise)
• Because I discovered this option during the pandemic and want to continue using it
• Because it saves money
• Because it's more convenient
• Because I feel more comfortable
• Because I prefer to socialize online with people like me who use classes or apps to stay fit
• Because it's more fun

▶

• Other...
SECTION 12: WHO-5
-For each of the 5 statements, please indicate the one that most closely matches how you felt over the past 2 weeks. (TABLE)
• I felt cheerful and in a good mood.
• I felt calm and relaxed
• I felt active and vigorous
• I woke up feeling refreshed and rested
• My daily life has been full of things that interest me
• All the time
• Most of the time
• More than half the time
• Less than half the time
• Sometimes
• Not at all

Non comunicable diseases

Association between blood pressure and waist-to-height ratio in schoolchildren aged 6 to 8 years in the Valparaíso Region, Chile

MIRTA CROVETTO[1], KATHERINE CONCHA[1]
[1] Departamento de Salud, Comunidad y Gestión, Facultad de Ciencias de la Salud, Universidad de Playa Ancha, Valparaíso, Chile

Keywords

Hypertension • Blood pressure • Obesity • Nutritional status • Waist circumference

Summary

Background. *Hypertension is a serious obesity-related disease that affects the paediatric population. Objective: To examine the positive association between systolic and diastolic blood pressure and waist-to-height ratio in schoolchildren Methods: Cross-sectional study. Convenience sample of 300 schoolchildren aged 6 to 8 years from Valparaíso. Blood pressure, waist circumference and height were evaluated. Data were collected in non-consecutive years (2015, 2018, 2019, 2022) due to logistical constraints. Blood pressure was assessed according to the criteria of the American Academy of Pediatrics (2017). Statistical analysis: Results were expressed as mean, 95% confidence interval (95% CI) for quantitative variables and qualitative variables were expressed in absolute (n) and relative (%) frequencies. Normality was verified with the Shapiro Wilk test ($p > 0.05$). Associations were made between altered blood pressure and anthropometric variables (BMI, waist circumference, nutritional status) using the Proportion test and Chi Square test. Three different models were developed to determine the association between altered BP with WHR, WC and NS, adjusting for age in all models.*
Results. *A significant positive association was found between systolic blood pressure and waist-to-height ratio ($p = 0.0073$).*
Conclusion. *Higher WHR is associated with increased blood pressure, highlighting its potential as a screening tool for metabolic risk.*

Introduction

Over the past two decades, the prevalence of arterial hypertension (AHT) has risen significantly in both adults and children [1]. AHT is a serious disease that poses a risk for various pathologies and is a cause of premature death. It affects more than one in three adults worldwide, representing a high burden of disease, especially in low- and middle-income countries [2]. The World Health Organization (WHO) has shown that from 1990 to 2019 the worldwide prevalence of AHT has doubled [3].
It is estimated that 1.28 billion adults aged 30-79 years suffer from AHT, and about two-thirds are unaware of their condition [4]. In the Region of the Americas, it affects between 20% and 40% of the adult population and is the main risk factor for cardiovascular disease. In total, this condition causes the death of 1.6 million people, of which more than half a million are premature deaths in people under 70 years of age [5].
In Chile, the latest National Health Survey (Encuesta Nacional de Salud, ENS) conducted in the population over 15 years of age indicated that suspected AHT reached 27.6% between 2016 and 2017, representing an increase of 1.1% over the previous period (2009-2010) [6].
The prevalence of paediatric hypertension is increasing worldwide, driven by rising rates of childhood obesity [7, 8]. Globally, it is estimated that the prevalence of hypertension in children and adolescents ranges from 3.5% to 5% [9]. In Latin America, recent studies have reported rates of altered blood pressure (ABP) that vary between 0.7% and 40.5% in children and adolescents [10]. In Chile, a prevalence of 20.8% has been observed in the child population. Other studies examining AHT in the Chilean school population have found rates of 13.6% in children aged 6-14 years, and 3.4% in children whose average age was 10.6 years, associated with obesity and other parameters related to metabolic syndrome [11, 12].
In this context, one of the most relevant risk factors for AHT and metabolic syndrome is obesity, which affects 2 billion people worldwide [13]. Obesity is defined as an energy imbalance between caloric intake and expenditure, resulting in excess energy stored in adipose cells [14].
In 2022, 43% of adults aged 18 years and older were overweight and 16% were obese. In addition, more than 390 million children and adolescents aged 5 - 19 years were overweight, of whom 160 million were obese [15, 16]. In the case of Latin America and the Caribbean, a recent UNICEF study has reported that more than 4 million children under 5 years of age are overweight, as well as almost 50 million of the population between 5 and 19 years of age, with this rate being higher than the world average [17]. The World Obesity Atlas indicates that in the Region of the Americas (North, Central and South America) the prevalence of obesity will increase

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between 20% and 33% between 2020 and 2035 [18].
In Chile, data from the nutritional map of the National School and Scholarship Board (JUNJI) for the year 2023 showed that 49.3% of children entering the first year of elementary school in public schools are overweight and obese, and of these, 25.8% are severely obese, that is, 3 out of every 5 schoolchildren in Chile already have weight problems at an early age [19]. This situation, if maintained over time, will prematurely confront them with cardiovascular risks, high blood pressure, metabolic alterations, diabetes and metabolic syndrome in adolescence, which will possibly extend into adulthood [20].
In this sense, it is worth noting the rise in the rates of metabolic syndrome (MS) in young age and the importance of early diagnosis. MS is defined as a cluster of risk factors that include central obesity, hypertension, insulin resistance, and dyslipidaemia, that determine an increased risk for cardiovascular disease and diabetes mellitus (DM), and which incidence has increased among paediatric population [21]. Body Mass Index (BMI) measurement has been traditionally used to assess obesity and, therefore, to evaluate its impact on cardiovascular and metabolic risk factors. However, waist circumference WC measurement has gained relevance when it comes to assessment of central adiposity, which is closely linked to the risk of developing cardiovascular conditions [22].
In this context, recent studies have shown that waist-to-height ratio (WHR) is a better predictor of mortality and cardiovascular risk factors than BMI, both in adults and children [23]. WHR measures abdominal circumference adjusted for height, improving its predictive ability for cardiovascular risk. This results in an improved ability to predict cardiovascular risk factors related to body fat distribution, thus replacing the BMI measurement [24].
In adults, it has been observed that an increase in WHR above 0.5% is associated with an increased risk of AHT [25]. However, the application of these anthropometric measurements as predictors of AHT in the paediatric population is a developing area of study [26].
Prevention and early diagnosis are key strategies to prevent serious diseases such as myocardial infarction, heart failure, aneurysms, stroke, renal failure, blindness, blood vessel rupture, and cognitive impairment [27].
This background underscores the need to enhance early identification and management of risk factors at an early age to prevent future diseases that begin in childhood [28].
In this context, the aim of this study is to associate systolic and diastolic blood pressure with waist-to-height ratio in a public elementary school population in the region of Valparaíso, Chile.

Methods

Design and subjects: Cross-sectional study. Convenience sample. Please change wording to "Of 399 eligible schoolchildren from 7 educational institutions in the Valparaíso region, Chile, 300 were included after applying inclusion criteria (*e.g.* incomplete measurements or lack of consent), from 7 educational institutions in the Valparaíso region, Chile. Schoolchildren (males aged 6 to 8 years, 11 months and 29 days; females aged 6 to 7 years, 1 month and 29 days) who agreed to participate on the day of data collection and whose parents, guardians and/or tutors signed the informed consent form were included. Those who were physically unable to participate in the measurements on the day of the evaluation were excluded. After applying inclusion and exclusion criteria, the final sample consisted of 300 schoolchildren aged 6 to 8 years, 11 months, and 29 days.
Dependent variables: Systolic blood pressure (SBP) and diastolic blood pressure (DBP), classified according to the diagnostic criteria of the AAP 2017 guidelines: normal BP, high BP, stage 1 AHT, and stage 2 AHT [29].
Independent variables: Waist circumference and height.
Data collection: Data were gathered between 2015, 2018, 2019, and 2022 in specific non-consecutive months by fifth-year students of the Nutrition and Dietetics undergraduate program of the Universidad de Playa Ancha, who had been previously trained on the standardization of measurement protocols. This process was supervised by a nutritionist from the Faculty of Health Sciences of the aforementioned institution. The evaluations and data recording were carried out in a space provided by the educational institutions, previously prepared and adapted to ensure the privacy of each participant.
BP was measured in millimetres of mercury (mm Hg); height and waist circumference were measured in centimetres (cm). Measurements were directly tabulated on the record sheet.
An OMRON brand digital pressure monitor, Model number HEM- 7114 with adapter input to OMRON brand paediatric cuff, Model number H- 003DS, was used in the 2015 sample. A BOKANG paediatric aneroid sphygmomanometer, with a BOKANG brand paediatric cuff; and a LITTMANN phonendoscope were used in the 2018, 2019 and 2022 samples. Instrument variation was minimized through standardized training and calibration. The technique considered that each participant took a 10-minute rest before the performance of the measurements, remaining seated in the room set up for the study. Subsequently, two BP measurements were taken, 30 seconds apart, on the right arm; this was done with the student seated with the legs uncrossed and the cuff at the level of the heart.
Data recording was performed by automatic BP measurement in 2015 and 2018. In 2019 and 2022 it was performed by the paediatric cuff insufflation through the sphygmomanometer and BP was recorded by means of Korotkoff sounds in phase I and phase V, as systolic and diastolic measurements, respectively.
BP classification parameters: BP classification corresponded to "normal" BP (< p90), high BP (> p90 to < p95 or 120/80 mm Hg to < p90; whichever is lower), stage 1 AHT (≥ p95 to < p95 + 12 mm Hg or 130/80 to 139/89 mm Hg, whichever is lower), and stage 2 AHT

(≥ p95 + 12 mm Hg or 140/90 mm Hg, whichever is lower). The above, using as reference the "Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents" by the AAP, 2017 [29]. The reference is included since it was used as a guideline for the anthropometric measurement of height for BP assessment and classification.

In this study, BP measurement was performed on one day without follow-up, thus identifying suspicion of high BP and suspicion of AHT.

Anthropometric measurement of height and classification parameters: Height measurement. A TANITA brand portable wall-mounted mechanical measuring rod was used in 2015; a SECA portable measuring rod, Model 213, was used in 2018, 2019, 2022. The technique employed was based on the 2014 MINSAL regulations [30], that is, the schoolchild standing barefoot on a flat, horizontal surface with their back against the instrument, feet parallel or with toes slightly apart. The heels, buttocks, shoulders and head were in contact with the posterior plane, the head comfortably upright. An imaginary horizontal line should pass through the external angle of the eye and the external auditory canal, arms hanging at the sides of the body in a natural way, the child not wearing hair accessories. The upper attachment of the rod is lowered at a right angle gently flattening the hair and making contact with the vertex of the head [31]. Height was used to calculate waist-to-height ratio (WHR).

Anthropometric weight measurement and nutritional status classification parameters according to Body Mass Index (BMI): Weight measurement. An OMRON brand body composition analyser was used in 2015, and a TANITA IRONMAN digital scale was used in 2018 and 2019. The technique used consisted of the child barefoot, with minimal clothing (no vest or sweatshirt and no pants). The scale was placed on a smooth surface with no foreign objects under it. The child was placed with the feet in the centre of the calibrated scale platform, where it was observed that between one patient and another the instrument will indicate zero. Weight was recorded in kilograms, to the nearest 100 grams [31]. With the above data, BMI calculation was performed, this corresponding to the ratio between weight (expressed in kg) and height squared (expressed in meters): BMI = weight/height^2.

Classification parameters of nutritional status according to BMI: BMI-for-age (BMI/A) was assessed and classified as undernutrition (≤ -2SD), risk of undernutrition (≤ -1SD and > -2SD), normal (> -1SD and < +1SD), overweight (≥ +1SD and < +2SD), obesity (≥ +2SD and < +3SD) and severe obesity (≥ +3SD) [32]: Anthropometric measurements. Waist circumference was measured according to 2014 MINSAL regulations [30]. A SECA Model 201 measuring tape was used every year. The child was required to remain with the least amount of clothing possible. In a standing posture, the measuring tape was placed around the waist and then positioned above the iliac crest, passing above the navel, asking the infant to take a breath and exhale, the measurement being taken post exhalation, with the abdomen relaxed. This procedure was done twice, recording the average of both measurements [30].

Classification parameters (cm) of waist circumference according to WHR: Waist circumference was assessed by calculating WHR, both measured in centimetres (waist/height). A cut-off point of 0.5 was used to differentiate low WHR index (< 0.5) and high WHR index (≥ 0.5) [33].

Statistical analysis

Results were expressed as mean, 95% confidence interval (95% CI) for quantitative variables and qualitative variables were expressed as absolute (n) and relative (%) frequencies. Normality was verified with the Shapiro Wilk test ($p > 0.05$). Associations were made between altered blood pressure and anthropometric variables (BMI, WC, nutritional status) using the Proportion test and the Chi square test. Three different models were developed to determine the association between altered BP with WHR, WC and NS, adjusting all models for age. Logistic regression models adjusted for age assumed linearity and no multicollinearity.

Data were analysed using the Statistical Package for Social Sciences (SPSS) software, version 13.0 (SPSS Inc. Chicago, IL, USA).

Ethical aspects: The study was validated by the Bioethics Committee of the Universidad de Playa Ancha (RES: 13/2015; 21/2018; 19/2019; 40/2022).

Results

General Background: The sample consisted of 300 subjects (males 50.6% and females 49.3%). P-values have been added for each variable in Table I in order to specify which differences are significant.

Suspected arterial hypertension. For systolic blood pressure (SBP), 81.7% had normal SBP, 6.3% had high BP, 8.7% had stage 1 hypertension and 3.3% had stage 2 hypertension. In the case of DBP, 75.7% had normal BP, 10.0% had high BP, 9.0% had stage 1 AHT, and 5.3% had stage 2 AHT (Tab. II).

Regarding the association between anthropometric variables (high WHR, obesity WC, nutritional status) and sex, it was observed that the waist-to-height ratio and obesity according to WC did not differ according to sex, and a significant association was found between nutritional status and sex (p=0.043) (Tab. III).

Altered BP (high BP, stage 1 or 2 AHT) was associated with anthropometric variables (WHR, obesity WC and nutritional status (normal weight, overweight and obesity)). It was observed that: i) WHR was significantly higher in children whose BP was altered (39.2%); ii) obesity according to WC is significantly higher in children with altered BP (41.2%); and iii) there is a significant association between nutritional status and altered BP in children with normal nutritional status (58.8%), overweight children (11.3%), and obese children (29.9%) (Tab. IV).

In turn, three different models were generated for the

Tab. I. Sample characterization by sex.

Variables	Males n = 152 (50.6%)	Females n = 148 (49.3%)	Total n = 300 (100%)	*p* -value
Age - years‡	6.8 ± 0.6	6.7 ± 0.5	6.8 ± 0.6	0.0129
95% CI	(6.7 - 6.9)	(6.6 - 6.8)	(6.7 - 6.8)	
SBP mm Hg[2]	96.7 ± 13.2	97.2 ± 13.0	97.0 ± 13.1	0.7359
95% CI	(94.6 - 98.8)	(95.1 - 99.3)	(95.5 - 98.4)	
DBP mm Hg‡	62.8 ± 9.5	65.2 ± 11.1	64.0 ± 10.4	0.0411
95% CI	(61.3 - 64.3)	(63.4 - 67.0)	(62.8 - 65.2)	
Weight kg‡	28.9 ± 6.6	27.1 ± 5.9	28.0 ± 6.3	0.0128
95% CI	(27.8 - 30.0)	(26.1 - 28.0)	(27.3 - 28.7)	
Height cm‡	125.4 ± 6.3	123.5 ± 6.0	124.4 ± 6.2	0.0097
95% CI	(124.3 - 126.4)	(122.5 - 124.5)	(123.7 - 125.1)	
WC cm‡	60.7 ± 7.3	58.6 ± 7.2	59.6 ± 7.30	0.0126
95% CI	(59.5 - 61.9)	(57.4 - 59.7)	(58.8 - 60.5)	
BMI‡ kg/m[2]	18.1 ± 3.0	17.3 ± 2.7	17.7 ± 2.9	0.0210
95% CI	(17.6 - 18.6)	(16.9 - 17.8)	(17.4 - 18.0)	
WHR	0.48 ± 0.05	0.47 ± 0.06	0.48 ± 0.05	0.1306
95% CI	(0.48 - 0.49)	(0.47 - 0.48)	(0.47 - 0.49)	

Results expressed as Mean ± Standard Deviation (SD) and Confidence Interval. ‡: T Test. *p*-value < 0.05.

Tab. II. Blood pressure classification (2017 AAP guidelines).

	Systolic Blood Pressure (SBP)	Diastolic Blood Pressure (DBP)
Normal	245 (81.7%)	227 (75.7%)
High BP	19 (6.3%)	30 (10.0%)
Stage 1 AHT	26 (8.7%)	27 (9.0%)
Stage 2 AHT	10 (3.3%)	16 (5.3%)

Results expressed in number of subjects (percentage).

Tab. III. Association between anthropometric variables and sex.

	M	F	*p*-value
High WHR*	48 (31.6%)	39 (26.4%)	0.3185‡
Obesity WC	96 (36.8%)	105 (29.1%)	0.1515‡
Nutritional Status			
Normal weight	81 (53.3%)	97 (65.5%)	
Overweight	32 (21.1%)	29 (19.6%)	0.043¥
Obesity	39 (25.7%)	22 (14.9%)	

*> 0.05 weight-to-height ratio. ‡: Proportion test. ¥: Chi square test

Tab. IV. Association between altered blood pressure and anthropometric variables.

	Normal BP	Altered BP	*p*-value
High WHR*	49 (24.1%)	38 (39.2%)	0.0073‡
Obesity WC	59 (29.1%)	40 (41.2%)	0.0360‡
Nutritional Status			
Normal weight	121 (59.6%)	57 (58.8%)	
Overweight	50 (24.6%)	11 (11.3%)	0.002¥
Obesity	32 (15.8%)	29 (29.9%)	

*> 0.05 weight-to-height ratio. ‡: Proportion test. ¥: Chi square test.

Tab. V. Association between altered BP with WHR, WC and NS, adjusted for age.

Model 1			
Variables	**OR**	**CI**	***p* value**
High WHR	2.2	(1.3 - 3.7)	0.005‡
Females	1.3	(0.8 - 2.2)	0.315
Hosmer - Lemeshow	0.7754		
Model 2			
Variables	**OR**	**CI**	
High WC	1.7	(1.0 - 2.9)	0.040‡
Females	1.3	(0.8 - 2.2)	0.325
Hosmer - Lemeshow	0.7013		
Model 3			
Variables	**OR**	**CI**	
NS Over+ob	1.0	(0.6 - 1.7)	0.901
Females	1.2	(0.7 - 2.1)	0.409
Hosmer - Lemeshow	0.8718		

A logistic regression was conducted, and reference values are: WHR normal; sex: male; normal WC; NS normal weight.

association of altered BP with WHR, WC and age-adjusted NS in all models. In Model 1 it was observed that a child has 2.2 times more chance of having high BP compared to children with normal WHR; in Model 2 it was observed that a child with high WC has 1.7 times more chance of having high BP compared to children with normal WHR. In Model 3, nutritional status was not significantly associated with altered BP ($p = 0.901$) (Tab. V). It was concluded that the WHR variable has more weight than the WC variable and that the NS variable does not have greater weight with respect to high BP.

Discussion

BMI has traditionally been the primary anthropometric measurement to evaluate obesity and to associate it with metabolic and cardiovascular risks in children and

adults. In an epidemiological context that includes a high prevalence of obesity from an early age, waist-to-height ratio is proposed for the early detection of central obesity and its associated risks, since it combines the measurement of WC and corrects it for height, exhibiting a greater ability to diagnose cardiovascular risk factors in obese populations as well as in those with normal BMI and in children with chronic kidney disease and hyperinsulinemia, among others [34, 35, 36].

Different studies on waist-to-height ratio, such as one conducted in Brazil in children aged 8-10 years, determined that the WC variable was better correlated with the increase in blood pressure, since an increase of 1.22 times in the probability of children to become hypertensive was observed for each centimetre of increased waist circumference [37]. Our study has also found similar evidence, since it has observed that WHR is 2.2 times higher in children with altered BP ($p < 0.005$) and 1.7 times higher in those with high central obesity compared to children with normal central obesity ($p < 0.040$). 005), and 1.7 times higher in those with high central obesity compared to children with normal WHR.

Similar results on the importance of controlling WC were found in China, concluding that within each BMI category (normal weight, overweight, and obese), children with a WC ≥ P 90 had higher blood pressure levels than those with a WC < P 90 [38]. It was also observed that 43.6% of students with high waist-to-height ratio had alterations in one or more of their blood pressures [33]. At the same time, it has been shown that compared with BMI and WC, waist-to-height ratio was the anthropometric measurement with the highest area under the curve in both sexes for hypertension. Our study also showed that 39.2% of children with altered BP had a high waist-to-height ratio ($p < 0.0073$) and 41.2% with altered BP had central adiposity ($p < 0.0360$). Other studies conducted in Mexico and in the Dominican Republic, which purpose was to detect metabolic risks in school population using the waist-to-height index, showed that this index is a better predictor to detect metabolic alterations early in school age and noted the need to study risk factors for metabolic syndrome [39-42]. Our study has shown similar results, since the models to assess the associations between altered BP with WHR, WC and age-adjusted nutritional status showed that children with high WHR had 2.2 times higher odds of altered BP compared to children whose WHR is normal, and that an individual with high WC is 1.7 times more likely to have altered BP compared to those with normal WHR.

Although age groups studied differ, similar findings were reported in a study conducted in Spain including 1,511 schoolchildren aged 6-16 years, which examined weight, height, waist circumference, adiposity and blood pressure. It was found that 3.17% of boys and 3.05% of girls had high blood pressure and the risk increased 10.56 times in boys and 7.87 times in girls with a high waist-to-height index [43]. These results were also observed in our study, noting that children with a high waist-to-height ratio are 2.2 times more likely to have altered BP than those with a normal waist-to-height ratio.

In Iran, two studies have shown the importance of waist-to-height ratio; one observed that waist-to-height ratio, unlike BMI and waist-to-hip ratio, was significantly associated with an increased risk of developing hypertension, considering that the distribution of adipose tissue is an important factor in the development of cardiovascular diseases [26]. Researchers concluded that after waist-to-height control, the correlations that remained significant were WC and systolic blood pressure, and between WC and diastolic blood pressure in individuals with type 2 diabetes [26]. The other research, in the context of the Mashhad Stroke and Heart Atherosclerotic Disorder (MASHAD) study [44], evaluated 9,704 participants aged 35-65 years. Logistic regression including data mining algorithms was applied, showing that the most important indicators for discriminating hypertensive patients from normotensive patients were body roundness index (BRI), body mass index (BMI) and visceral adiposity index (VAI), which were significantly associated with AHT in both sexes ($p < 0.0001$). BRI showed the strongest association with AHT (OR = 1.276, 95% CI = (1.224, 1.330)). For BMI we had OR = 1.063, 95% CI = (1.047, 1.080), for VAI we had OR = 1.029, 95% CI = (1.020, 1.038), *i.e.* one of the most significant anthropometric indices for discriminating hypertensive patients from normotensive patients was BRI which is an indicator of body adiposity [44].

Studies conducted in Chile in both children and adults have noted the increase in cardiometabolic diseases and the importance of gathering more evidence and measurement instruments that contribute to their early detection, in order to reduce their current and future prevalence [45, 46]. A study carried out in Chile in the adult population on the three National Health Surveys (ENS) that are applied to the population from 15 years of age compared the predictive capacity of cardiometabolic risk, AHT and diabetes between BMI, WC, and WHR and concluded that WHR has greater sensitivity as a predictor of cardiometabolic risk [47].

Studies on children and adolescents suffering from chronic kidney disease (CKD) and insulinemia, respectively, have shown that cardiovascular risk is high among children with CKD as well as in those with hyperinsulinemia, with no measurements available to assess cardiovascular risk in these populations, which emphasizes the importance of using the waist-to-height ratio as a better predictor of CVR in these patients [35, 36].

The increase in the prevalence of childhood obesity and cardiometabolic alterations associated with central adiposity require the availability of indicators for the evaluation of cardiovascular risk in both obese and normal-weight populations, in order to allow early diagnosis of metabolic syndrome and risk factors for which evidence is being generated, both for the indicator to be used and the cut-off points, which is in line with studies that have been conducted in Chile and other countries [48, 49].

Conclusion

The waist-to-height ratio abdominal obesity index is a useful predictor of hypertension and cardiovascular and metabolic risks, since it allows the detection of central adiposity in the paediatric population. BMI is less effective than WHR for early detection of metabolic disorders. Detecting BP alterations and risk factors in early stages of life may facilitate the implementation of corrective measures in order to decrease the burden of cardiovascular and metabolic diseases in the population and to decrease CVR in adulthood. The results of this study provide evidence for the use of waist-to-height ratio in the paediatric population.

Recommendation

According to the latest studies, BMI is less effective than WHR for early detection of metabolic disorders. WHR should be integrated into routine paediatric screenings to identify children at risk of hypertension. It is a predictor and an early-warning index for the possibility of developing cardiovascular diseases in childhood, such as hypertension. One of the last studies conducted in Chile regarding hypertension in schoolchildren concluded that, currently, it is necessary to update the regulations for the evaluation of hypertension in the country. The guidelines of the AAP (2017) introduced a more rigorous instrument that achieves sensitivity to identify more cases of hypertension, which may be found in the onset of the disease, thus eventually contributing to decrease the present and future disease burden in the country.
Additionally, the measurement of waist and height is easy to apply, the calculation of its index is simple and of great relevance for the early detection of central obesity as a cardiometabolic risk factor, and for the implementation of policy actions in the context of primary public health care.

Limitations

Participation in 2022 was limited by COVID-19 protocols, potentially affecting data collection. Although the measurements were obtained using different instruments, the individuals who performed the measurements were previously trained; however, all measurements were performed under the supervision of the same researcher.
Convenience sampling prevents the establishment of causality.
Researchers did not include a question on the consumption of drugs and/or medicines that may have been prescribed to some of the schoolchildren at the time the measurements were collected.

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Conflict of Interests Statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

MC: Conceptualization, Methodology, Validation, Formal Analysis, Investigation, Data curation, Writing-Original draft preparation, Writing-Reviewing and Editing. KC: Conceptualization, Methodology, Validation, Data curation.

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Correspondence: Mirta Crovetto, Avenida Playa Ancha 850, Edificio Puntangeles, Valparaíso, Chile. E-mail: mcrovetto@upla.cl

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Non comunicable diseases

Awareness towards Cancer Attributable to Infections (CAI): A Lebanese study with a special focus on young adults, and adults

FARAH ZEINEH[1], SALIM MOUSSA[1]
[1] Medical Laboratory Technology Department, Beirut Arab University, Beirut, Lebanon

Keywords

CAI • Vaccine • Awareness level • Socio-demographics • Middle East • Young adults • Adults

Summary

Introduction. *Around two million cancer cases per year are caused by infections. Currently, there is a lack of studies assessing awareness of the link between infections and cancer in Lebanon. This knowledge is essential for the effective prevention, early detection, and management of these cancers. Thus, the aim of this study was to determine the level of awareness of cancer attributable to infections (CAI) in Lebanon especially among young adults, and adults.*
Methods. *A cross-sectional, descriptive research study was conducted for two months in Beirut, Beqaa, Mount Lebanon, South Lebanon, and North Lebanon. A valid and reliable survey was distributed to participants. The survey was divided into two sections: socio-demographic information and awareness of CAI.*
Result. *Approximately 43.4% of participants knew that hepatitis B virus (HBV) and hepatitis C virus (HCV) cause liver cancer. Around 34.9% knew that human papillomavirus (HPV) causes cervical cancer. About 33.5% knew that stomach cancer is caused by Helicobacter pylori. Around 20% were aware of the association between Kaposi sarcoma-associated herpesvirus (KSHV) and Kaposi sarcoma, Epstein-Barr virus (EBV) and human T-cell lymphotropic virus type 1 (HTLV-1) and lymphoma. Around 27.7% of them had received the HBV vaccine. Only 11.8% of them had received the HPV vaccine.*
Conclusion. *In Lebanon, young adults, and adults did not demonstrate the same level of awareness regarding the various types of CAI. Awareness levels increased among females, Lebanese individuals, healthcare workers, highly educated individuals, and those with a middle family income.*

Introduction

Infection is emerging as a major risk factor for cancer worldwide. The International Agency for Research on Cancer (IARC) considers certain viruses, bacteria, and parasites to be carcinogenic to humans. *Helicobacter pylori* and the tumor viruses: human papillomavirus (HPV), and hepatitis B (HBV) and C (HCV) viruses, were among the top infectious agents associated with cancer cases based on the latest *GLOBOCAN* 2020 (http://gco.iarc.fr/). China, Egypt, South Africa, Romania, and some countries in South America had the highest rates of cancer attributable to infections (CAI) (≥ 27.8 per 100 000). In contrast, Australia, northern Europe, Canada, the United States of America (USA) and most of the countries in the Middle East and North Africa (MENA) region, such as Lebanon, had a low rate of CAI (< 15.8 per 100 000).
Infectious agents related to cancer can alter survival pathways and disrupt host cell genomic integrity through a variety of mechanisms, leading to malignancy rather than death [1, 2]. For example, the E6 and E7 oncoproteins produced by HPV could degrade the tumor suppressor p53 and pRb proteins, respectively, thereby disrupting cell cycle control and initiating cancer development [3]. Another example, the contribution of the Epstein-Barr virus nuclear antigen 1 (EBNA1) to tumorigenesis of infected epithelial cells [4].
Screening for pathogens associated with cancer would be a proactive strategy to reduce cancer incidence by eliminating the presence of these infections. Eradication of *Helicobacter pylori* is highly effective in preventing gastric cancer [5, 6]. Improvements in antiviral therapies for hepatitis B and C have reduced the incidence of liver cancer, as demonstrated by the successful use of direct-acting antivirals (DAAs) against HCV [7]. Unfortunately, available effective therapies don't cover all CAI types, and many are still in clinical trials [8]. Vaccination would be an alternative approach to CAI prevention and it is widely used worldwide. For example, HBV and HPV vaccines have shown to effectively reduce the risk of infection and development of hepatocellular carcinoma (HCC) and cervical cancer, respectively [9, 11]. Evidence also points to the possibility of herd immunity effects, with declining rates of HPV infection in unvaccinated people as a result of less transmission in vaccinated populations [12].
With the dramatic increase in CAI rates, especially in developing countries, there is an urgent need to educate people about the underlying link between infection and cancer development and management. In Lebanon, a small country that represents the middle east, people's

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awareness of CAI has very rarely been assessed [13]. This study therefore aimed to determine awareness level of CAI mainly among the young adults, and adults of the Lebanese population.

Methods

Study design

The study design was a descriptive cross-sectional study done between May 2023 and July 2023. The study was conducted in five main Lebanese districts Beirut, Beqaa, Mount Lebanon, South Lebanon, and North Lebanon.

Study procedure

A valid and reliable survey was distributed via social media and professional platforms including WhatsApp, Instagram, and LinkedIn since almost all Lebanese people primarily use these platforms for communication. The survey was divided into two sections: socio-demographic information and awareness related to CAI.

Data analysis and presentation

The data was manually entered into SPSS version 24 for Windows software. Descriptive statistics were used to present the socio-demographic characteristics of the participants. A chi-square test was used in order to identify the relationship between variables. A p-value < 0.05 was considered statistically significant. Additionally, binary logistic regression was used to examine the relationship between a few dependent variables and a number of independent variables.

Sample size and sampling

We used a convenient sampling method. The sample consists of 415 Lebanese residents mainly young adults, and adults (minimum required is 385, software sample size calculator). Females and males residing in Lebanon who are of age 18 and above were included in the study.

Study tool

The questionnaire was developed to assess the awareness of the population of infection-related cancers. The survey includes 10 questions about socio-demographic characteristics and 22 questions about infection-related cancer knowledge. Evidence for the reliability and validity of the measurement tool was measured by the Center of Applied Statistics (CAS) at Beirut Arab University.

Evidence for the reliability and validity of the measurement Model is available in Table S1.

Ethics approval

This study was performed according to the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Beirut Arab University (No: 2023-H-0155-HS-M-0549).

Results

Socio-Demographics characteristics

A total of 415 participants completed the survey. Females made up 53.3% (n = 221) of the sample. The majority of participants, 68% (n = 282), were between 18 and 29 years old. 90.1% had tertiary education (n = 374), 66.5% were in non-health occupations (n = 276) (Tab. I). Furthermore, 26.7% (n = 111) of the participants lived in Beirut, 38.6% (n = 160) in Beqaa, 14.2% (n = 59) in Mount Lebanon, 10.6% (n = 44) in North Lebanon and 9.9% (n = 41) in South Lebanon. 27.5% were non-Lebanese (n = 114), while 72.5% were Lebanese (n = 301). In addition, 67.5% (n = 280) had a medium family income and 17.8% (n = 74) had a high family income. 28.4% (n = 118) were married and 67.7% (n = 281) were single. A total of 1.9% (n = 8) of participants reported a personal history of cancer, while 35.7% (n = 148) reported a family history of cancer.

Awareness about CAI

A high percentage of participants (59.3%) had not heard

Tab. I. Socio-demographic characteristics of participants.

Variables		Frequency (N = 415)	Percentage (%)
Age(years)	18-29	282	68%
	30-49	118	28.4%
	50-64	14	3.4%
	> 64	1	0.2%
Gender	Female	221	53.3%
	Male	194	46.7%
Education Level	Primary	3	0.7%
	Secondary	38	9.2%
	Tertiary	374	90.1%
Occupation	Non-healthcare	276	66.5%
	Healthcare	139	33.5%
Place of residence	Beirut Beqaa Mount Lebanon North Lebanon South Lebanon	111 160 59 44 41	26.7% 38.6% 14.2% 10.6% 9.9%
Nationality	Non- Lebanese Lebanese	114 301	27.5% 72.5%
Family income	Low Middle High	61 280 74	14.7% 67.5% 17.8%
Marital status	Divorced Married Single	16 118 281	3.9% 28.4% 67.7%
Diagnosed with cancer	Yes No	8 407	1.9% 98.1%
Family History of Cancer	Yes No	148 267	35.7% 64.3%

of some cancers associated with bacteria, 55.4% had not heard of some cancers associated with viruses, 74.5% had not heard of oncovirus, viruses that causes 12% of all human cancers [14], and 69.1% did not know that vaccines can prevent some cancers.

56.1% of participants had not heard of human papillomavirus, 65.1% did not know that HPV causes cervical cancer, 63.4% had not heard of the HPV vaccine, 70.1% did not know that HPV vaccines can prevent cervical cancer, and 88.2% had not received the HPV vaccine. The main sources of information for those who heard about the vaccine were distributed, 7.2% were from awareness campaigns, 36.8% were from doctors, 27% were from social media, and 29% were from other sources. The majority of people who have heard about HPV know that it causes cervical cancer and that a vaccine exists. While 81.75% of people who have heard of the vaccine know it is effective, only few of them have received it. The majority of participants (62.7%) had heard about hepatitis B and C viruses and 52.5% had heard about the HBV vaccine. However, 56.6% did not know that HBV and HCV cause liver cancer, 63.4% did not know that HBV vaccines can prevent liver cancer, and 72.3% had not received the HBV vaccine. About 70% of people who have heard about the vaccine are aware of its effectiveness, and 58.3% of those people have received it. 75.4% of participants had never heard of Kaposi's sarcoma herpesvirus (KSHV), and 80% did not know that KSHV causes Kaposi's sarcoma. 75.7% of participants had never heard of the Epstein-Barr virus (EBV), and 78.3% did not know that EBV causes lymphoma. In addition, 74.9% had never heard of HTLV-1 and 77.6% did not know that HTLV-1 causes lymphoma. 62.2% had never heard of *Helicobacter pylori* and 66.5% did not know that it causes stomach cancer (Tab. II).

Association between socio-demographic characteristics and awareness to CAI

The results show that there was no relationship between the difference in age and the level of awareness of CAI. However, female participants were more aware of CAI than males. Participants who are not married heard more about CAI than married and divorced people. Lebanese people showed a higher awareness level towards CAI than other nationalities. However, both Lebanese and non-Lebanese didn't show any difference in awareness level regarding EBV and HTLV1 as causes of lymphoma ($p > 0.05$) and both respondents didn't show any difference in HPV vaccine practice ($p = 0.063$). Surprisingly participants who had reached tertiary education level had more awareness only about oncoviruses ($p = 0.047$). However, they didn't show a higher knowledge about importance of vaccine in cancer

Tab. II. Awareness levels to CAI.

Question	YES		NO	
	N	%	N	%
Have you heard about some cancer types associated with bacteria?	169	40.7	246	59.3
Have you heard about some cancer types associated with viruses?	185	44.6	230	55.4
Have you heard of 'Oncovirus'?	106	25.5	309	74.5
Do you know that vaccines can prevent some cancer types?	158	38.1	257	61.9
Cervical Ca				
Have you heard about the human papillomavirus?	182	43.9	233	56.1
Do you know that HPV causes cervical cancer?	145	34.9	270	65.1
Have you heard of the HPV vaccine?	152	36.6	363	63.4
Do you know that the HPV vaccine can prevent cervical cancer?	124	29.9	291	70.1
Have you received the HPV vaccine?	49	11.8	366	88.2
Liver Ca				
Have you heard about the hepatitis B and C viruses?	260	62.7	155	37.3
Do you know that HBV and HCV cause liver cancer?	180	43.4	235	56.6
Have you heard of the HBV vaccine?	218	52.5	197	47.5
Do you know that the HBV vaccine can prevent liver cancer?	152	36.6	263	63.4
Have you received the HBV vaccine?	115	27.7	300	72.3
Kaposi Sarcoma				
Have you heard about the Kaposi sarcoma herpes virus?	102	24.6	313	75.4
Do you know that KSHV causes Kaposi sarcoma?	83	20	332	80
Lymphoma				
Have you heard about the Epstein-Barr virus?	101	24.3	314	75.7
Do you know that EBV causes lymphoma?	90	21.7	325	78.3
Have you heard about the HTLV-1?	104	25.1	311	74.9
Do you know that HTLV-1 causes lymphoma?	93	22.4	322	77.6
Gastric Ca				
Have you heard about the *Helicobacter pylori* bacteria?	157	37.8	258	62.2
Do you know that *Helicobacter pylori* causes stomach cancer?	139	33.5	276	66.5

Tab. III. Association between socio-demographic characteristics and awareness to CAI.

Item	Sex	Marital status	Nationality	Age	Education level	Occupation	Family Income	Diagnosed with cancer	Family history
	p-value								
Heard about some cancer types associated with bacteria	*0.003	*0.047	*0.000	0.251	*0.024	*0	*0	0.59	*0.042
Heard about some cancer types associated with viruses	*0	*0.006	*0.000	0.095	*0.007	*0	*0	0.303	*0.013
Heard of 'Oncovirus'	*0	0.071	*0.000	0.753	*0.047	*0	*0	0.434	*0.009
Vaccine can prevent some cancer types	*0	0.323	*0.000	0.548	*0.156	*0	*0	0.973	0.16

* ($p < 0.05$), statistically significant.

prevention and vaccine practice ($p > 0.05$). As expected, there was a significant relationship between occupation level and participants awareness towards CAI, where healthcare workers had shown a higher awareness level ($p = 0.000$). Participants who had middle family income had more awareness about CAI compared to participants who had low and high family income ($p = 0.000$). There was no relationship between place of residence and awareness to CAI. Surprisingly, people diagnosed with cancer didn't show a difference in their answers compared to healthy ones. Finally, a family history of cancer was associated with a higher awareness level to CAI except for the importance of vaccine in cancer prevention (Tab. III).

Cervical cancer and HPV

Females showed a much higher level of awareness regarding cervical cancer and HPV as the causative agent than males ($p = 0.000$). The results revealed no association between marital status and awareness level towards this type of CAI. Lebanese people were more aware about all aspects of the disease ($p = 0.000$) but have a low practice towards the HPV vaccine (13.6%) as other nationalities (7.0%). Place of residence and difference in age have no effect on participants results ($p > 0.05$). Importantly, a higher education level had a positive impact on awareness level towards this type of CAI ($p < 0.05$). The HPV vaccine practice was low even among people in higher education, with 13.2% of secondary school students and 11.8% of university students receiving the vaccine. Working in healthcare setting or having a middle income were associated with a better participants score ($p < 0.05$). Having a family history of cancer, but not a personal one, increased awareness of the disease and its causes. However, the practice of getting the HPV vaccine was significantly higher among people with a personal or family history of cancer ($p < 0.05$) (Tab. IV). Two participants diagnosed with cervical cancer had opposite different awareness levels to this CAI. Majority of participants with a family history of cervical cancer were aware to the disease and its prevention.

A detailed statistical analysis of the association between participants' characteristics and their awareness of CAI is available in Table S2, Table S3.

Liver cancer and HBV and HCV

Females also had a much higher level of awareness of liver cancer and related viruses compared to males ($p < 0.05$). However, the marital status didn't much affect

Tab. IV. Association between socio-demographic characteristics and awareness to cervical cancer and HPV.

Item	Sex	Marital status	Nationality	Age	Education level	Occupation	Family Income	Diagnosed with cancer	Family history
	p-value								
Heard of HPV	*0	0.179	*0	0.11	*0.02	*0	*0	0.724	*0
HPV infection causes cervical cancer	*0	0.223	*0	0.171	*0.033	*0	*0.001	0.367	*0
Heard of the HPV vaccine	*0	0.262	*0	0.208	80.043	*0	*0.002	0.428	*0
HPV vaccine can prevent cervical cancer	*0	0.762	*0.001	0.634	0.232	*0	*0.017	0.634	*0.002
you received HPV vaccine	*0	0.719	0.063	0.947	0.791	*0	*0.012	*0.001	*0.007

* ($p < 0.05$), statistically significant.

participants answers ($p > 0.05$). As with cervical cancer, Lebanese people were more aware of all aspects of the disease ($p = 0.000$). However, they were more likely to receive the hepatitis B vaccine (31.2%), which is significantly higher than the percentage of non-Lebanese people who received the vaccine (18.4%). Age difference was not associated with participants awareness to this type of CAI ($p > 0.05$). People of the North had the lowest scores regarding the infections causing the liver cancer (22.7%). Here, too, awareness increased significantly with higher education levels. However, the practice of getting the HBV vaccine was not affected by education level and remains low. Healthcare workers were very aware of all aspects of the disease. 53.2% of them had received the HBV vaccine. Middle income category had the highest level of awareness. Interestingly, the same pattern of association between personal and family history and awareness level was observed here as in cervical cancer. However, a family history of cancer only influenced HBV vaccine practices. Thirty-three percent of people with a family history of cancer received the vaccine, compared to 24.3% of people without a family history ($p = 0.04$) (Tab. V). Two of the three participants diagnosed with liver cancer were aware of the disease and causative infection but not towards the vaccine and practice. The majority of participants with a family history of liver cancer were aware about this CAI but their vaccine practice remains very low (5.3%).

A detailed statistical analysis of the association between participants' characteristics and their awareness of CAI is available in Table S2, Table S3.

Other types of CAI

Regarding Kaposi sarcoma, lymphoma, and gastric cancer, as well as their causative infections, females demonstrated a higher level of awareness of these CAI than males did ($p < 0.05$). There was no association between the difference in marital status and level of awareness to Kaposi sarcoma and cancer of the stomach ($p > 0.05$). Married people were the least aware of lymphoma caused by HTLV-1 or EBV, with 13.6% of them reporting this knowledge. Lebanese people had scored higher in questions about cancer of the stomach ($p = 0.002$) and lymphoma caused by HTLV-1 but not EBV ($p = 0.047$) compared to non-Lebanese. However, the difference in nationality didn't influence their knowledge that Kaposi sarcoma herpes virus causes Kaposi sarcoma ($p = 0.062$). Place of residence, education level, and age did not influence participants' scores ($p > 0.05$). However, people with a tertiary education level had better answers, especially regarding *Helicobacter pylori* (39.8%). Here is a clear association between occupational category with level of awareness of CAI. Working in a healthcare setting significantly increases awareness of all CAI ($p < 0.05$). The most aware of infections causing these diseases were middle-class families, as observed in cervical and liver cancers. Finally, having a family history of cancer, but not a personal one, increased awareness of the CAI mentioned here ($p < 0.05$). 33.3% of participants with stomach cancer had a better awareness level towards this CAI (Tab. VI). Around half of participants with a lymphoma family history were aware about this disease and related infections. Only one participant had a family history of Kaposi sarcoma and was not aware of the herpes virus that causes the disease.

A detailed statistical analysis of the association between participants' characteristics and their awareness of CAI is available in Table S2, Table S3.

Logistic regression analysis

We determined which of the socio-demographic characteristics predicts the 4 items of the awareness towards infection-associated cancers (1. Have you heard about some cancer types associated with bacteria? 2. Have you heard about some cancer types associated with virus? 3. Have you heard of "Oncovirus"? 4. Know that vaccine can prevent some cancer types?)**.** The two most significant variables in predicting awareness about cancer types associated with bacteria are nationality and occupation ($p = 0.001$ and < 0.001) respectively. Healthcare workers were 4 times as likely to be aware significant about

Tab. V. Association between socio-demographic characteristics and awareness to liver cancer and HBV and HCV.

Item	Sex	Marital status	Nationality	Age	Education level	Occupation	Family Income	Diagnosed with cancer	Family history
	p-value								
Heard of the hepatitis B and C viruses	*0	*0.014	*0	0.214	*0.004	*0	*0	0.466	*0
Hepatitis B and C viruses cause liver cancer	*0	0.271	*0	0.52	*0.024	*0	*0	0.068	*0.004
Heard of the hepatitis B vaccine	*0	0.076	*0	0.298	*0.004	*0	*0	0.569	*0
Hepatitis B vaccine can prevent liver cancer	*0	0.088	*0	0.335	0.152	*0	*0	0.428	*0
Received HBV vaccine	*0	0.482	*0.009	0.631	0.121	*0	*0	0.155	*0.04

* ($p < 0.05$), statistically.

Tab. VI. Association between socio-demographic characteristics and awareness to infections related to Kaposi sarcoma, lymphoma and cancer stomach.

Item	Sex	Marital status	Nationality	Age	Education level	Occupation	Family Income	Diagnosed with cancer	Family history
	p-value								
Heard of KSHV	*0.004	0.446	*0.021	0.758	0.134	*0	*0.007	0.391	*0.003
Kaposi sarcoma herpes virus causes Kaposi sarcoma	*0.002	0.429	0.062	0.758	0.204	*0	*0.004	0.211	*0.031
Heard of EBV	*0	0.177	0.084	0.58	0.259	*0	*0.001	0.381	*0.004
EBV causes lymphoma	*0	*0.034	0.073	0.352	0.136	*0	*0	0.273	*0.007
Heard of HTLV-1	*0	*0.014	*0.007	0.335	0.118	*0	*0.001	0.412	*0.01
HTLV-1 causes lymphoma	*0	*0.024	*0.047	0.481	0.113	*0	*0.004	0.301	*0.008
Heard of the bacteria *Helicobacter pylori*	*0	0.249	*0	0.756	*0.03	*0	*0	0.474	*0.034
Helicobacter pylori is associated to cancer of the stomach	*0	0.299	*0.002	0.635	0.052	*0	*0	0.318	*0.024

* ($p < 0.05$), statistically significant.

cancer types associated with bacteria when compared to non-healthcare workers. Similarly, Lebanese respondents were 2.5 times as likely as non-Lebanese respondents to be aware about cancer types associated with bacteria. The two most significant variables in predicting awareness about cancer types associated with viruses are Occupation and Family Income ($p < 0.001$ and 0.01) respectively. Healthcare workers were 1.7 times as likely to be aware about cancer types associated with viruses when compared to non-healthcare workers. Similarly, respondents with low and middle family incomes were 5.7 and 15.4 times as likely to be aware of cancers associated with viruses compared to respondents with high family incomes. The most significant variables in predicting awareness about 'Oncovirus' are Occupation, Nationality, Place of Residence, and Family Income, with corresponding *p*-values of < 0.001, 0.027, 0.01, and 0.018 respectively. Lebanese respondents were 2.6 times as likely to be aware about oncovirus when compared to non-Lebanese respondents. Similarly, healthcare workers were 17.5 times as likely to be aware of it as non-healthcare workers. In addition, respondents with low and middle family incomes were 0.187 and 1.047 times, respectively, likely to be aware of oncovirus when compared to respondents with high family income. Respondents from Beirut, Beqaa, Mount Lebanon, and North Lebanon were respectively 0.898, 0.309, 0.799, and 1.441 times as likely to be aware of 'Oncovirus' when compared to respondents from south Lebanon. The most significant variables in predicting awareness about vaccines being able to prevent some cancer types are gender and occupation. Female respondents were 2.75 times as likely to be aware about vaccines being able to prevent some types of cancer when compared to male respondents. Similarly, healthcare workers were 4.25 times as likely to be aware of it as non-healthcare workers.

The result of the logistic regression analysis is available in Table S4.

Discussion

Cancer continues to be a global health concern, with its incidence steadily rising over the years. Interestingly, a significant portion of cancer cases can be attributed to infections. Recent data shows that the number of cancer cases attributable to infections (CAI) has increased from 2.2 to 2.3 million between 2018 and 2020 worldwide [15]. They were distributed according to the type of infection as follows: *Helicobacter pylori* (36.3%), HPV (31.1%), HBV (16.4%), HCV (7.4 %) and other agents (8.9%) based on the latest GLOBOCAN 2020 data. Infection prevention and control strategies play a crucial role in reducing the incidence of CAI such as vaccination and safety precautions. Lebanon, a developing country of the middle east and with a low income, was ranked with high cancer rates in the region. Thus, the present study aimed to evaluate the awareness level of young adults, and adults residing in Lebanon with respect to CAI. By identifying any gaps in knowledge, we can implement targeted actions to enhance awareness, promote preventive measures, and mitigate the impact of cancer in Lebanon.

The majority of participants were young Lebanese who had completed their higher education degree. The sample includes a similar proportion of females and males. Less than half were aware about CAI and that vaccines can serve as a preventive measure against cancer. Additionally, a large number of respondents were not familiar with the term "Oncovirus." People in Lebanon had mainly heard of HBV and HCV, and knew that they cause liver cancer. They demonstrated moderate awareness of HPV and *Helicobacter pylori*, which cause cervical and gastric cancer, respectively. Unfortunately, their awareness of EBV, KSHV, and HTLV-1, as well

as their association with hematological malignancies, was poor. This could be explained by the fact that the local awareness campaigns focused primarily on HBV and HPV, and not on the lymphoma-related infections. More attention should be given to these other CAI types that have not been extensively studied in the Lebanese context [16-18].

In Lebanon, liver cancer, was mainly associated with HCV (40%) and HBV (28%) [19]. Vaccine preventive measure would be the most appropriate choice to reduce the liver cancer incidence. Despite the Lebanese government's recommendations for mandatory premarital screening in 1994 and hepatitis B vaccinations for newborns in 1998, only 36.6% of participants were aware that the hepatitis B vaccine is effective in preventing liver cancer and 27.7% had only been vaccinated. This result may be explained by the fact that a large percentage of participants were single (67.75%), and thus probably not educated about the hepatitis B virus (HBV) recommendations issued by Lebanese public health policies. Interestingly, the group of healthcare workers had the highest percentage of vaccinated participants which reflects Lebanese healthcare settings' adherence to the CDC's recommendation regarding vaccination for high-risk groups and explains the low prevalence of hepatitis locally [20]. The high percentage of unvaccinated people is alarming, especially since the HBV vaccine has been included in the national vaccination schedule since 1998 as mentioned above. Thus, regular visits to pediatricians are essential to keep track of vaccination progress. Also, only 11.8% of participants had received the HPV vaccine despite that 29.9% knew its effectiveness. The HPV vaccine is still considered too expensive in a country with a severe economic crisis, and a national guideline is still absent.

It was clear that females were significantly more aware than males towards all types of CAI, not only the one related to HPV and cervical cancer. Moreover, awareness toward CAI was significantly predicted by nationality. Interestingly, people who were Lebanese showed greater understanding of CAI than those who weren't. Furthermore, awareness of malignancies caused by viruses and bacteria was shown to be significantly influenced by occupation and income level, with healthcare professionals being much more likely to be aware of them than non-healthcare workers, and middle-income levels also being more aware. Additionally, the findings revealed some fascinating patterns about regional differences. Residence had a significant impact on respondents' awareness of "Oncovirus" ($p = 0.01$); respondents from North Lebanon, Mount Lebanon, Beqaa, and Beirut had varying degrees of awareness compared to those from South Lebanon. Surprisingly, having a family history of cancer significantly increased awareness of CAI. However, being diagnosed with cancer didn't affect the awareness level. On the other hand, age and marital status did not show a significant association with awareness levels.

Although this is the first report in Lebanon to focus exclusively on awareness level of CAI, some limitations deserve further attention. The convenience sampling method primarily reached young, highly educated people, while those with other levels of education were underrepresented. Furthermore, the two districts of South and North Lebanon were underrepresented. Therefore, it is not possible to generalize the findings to all people in Lebanon. However, the present study provides insight into the awareness level of educated young adults and adults in Lebanon towards CAI.

It is important to create and implement customized educational initiatives that consider differences in cultural origins, geographic regions, and socioeconomic status [21]. Stakeholders, such as the Ministry of Public Health, healthcare providers, and educational institutions, should provide the community with essential recommendations about CAI, preventive techniques, and the value of vaccination. Continuing medical education programs should emphasize the role of healthcare professionals as providers of accurate, trustworthy cancer prevention information, enhancing their ability to interact efficiently and effectively with patients and communities. Prioritizing the integration of cancer vaccine programs into national immunization schedules, while ensuring accessibility and affordability, is imperative for public health strategies. These findings underscore the necessity of comprehensive awareness campaigns and targeted educational programs to promote the use and acceptance of preventive vaccinations against cancer.

Conclusion

The Lebanese community, especially the young adults, and adults, demonstrated different levels of awareness of the different CAI types. The awareness level towards CAI was significantly impacted by the gender, nationality, occupation, education level, and family income of the participants. These findings highlight the need of focused health education campaigns that take certain sociodemographic groups into account.

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Conflict of interest

The authors have no conflict of interest to disclose.

Authors' contributions

S.M. designed the research work, analyzed the data and wrote the manuscript. F.Z. recruited participants and collected and analyzed the data.

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Correspondence: Salim Moussa, Beirut Arab University, Beirut, Lebanon. E-mail: s.moussa@bau.edu.lb

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Supplementary material

Tab. S1. Evidence for the reliability and validity of the measurement model.

Reliability and Validity results					
	Factor loadings		***Cronbach's alpha***	***KMO***	***AVE***
Awareness of HPV association with cancer	HPV1	0.879	.899	.832	.712
	HPV2	0.918			
	HPV3	0.921			
	HPV4	0.88			
	HPV5	0.569			
Awareness of Hepatitis B and C association with cancer	HBV1	0.842	.890	.799	.693
	HBV2	0.858			
	HBV3	0.882			
	HBV4	0.85			
	HBV5	0.724			
Awareness of Kaposi sarcoma herpes virus association with cancer	KSHV1	0.958	.908	.500	.917
	KSHV2	0.958			
Awareness of Epstein-Barr virus association with cancer	EBV1	0.982	.962	.500	.964
	EBV2	0.982			
Awareness of Human T-Lymphotropic virus association with cancer	HTLV1	0.972	.941	.500	.944
	HTLV2	0.972			
Awareness of *Helicobacter pylori* bacteria association with cancer	HPYL1	0.977	.953	.500	.954
	HPYL2	0.977			

The measurement Model was tested for reliability and validity.
First, the Kaiser-Meyer-Olkin (KMO) measure was calculated for each construct. All values were found to be greater than 0.5, which is considered an acceptable value according to Norusis (2008), Field (2013), and Kaiser (1974). This indicates that the sample size is adequate for factor analysis.
Next, Cronbach's alpha values were obtained for each construct. All values were greater than 0.7, indicating high internal consistency and scale reliability. Confirmatory factor analysis was then used to obtain the factor loadings for each item. All obtained values were above 0.5, demonstrating that each item was statistically significant and significantly loaded onto its respective construct. This suggests that the items measure the intended constructs well.
Finally, Average Variance Extracted (AVE) was calculated for each measure. All AVE values were greater than the threshold of 0.5 (Fornell & Larcker, 1981), supporting the convergent validity of the measurement model. This means that the constructs explain a sufficient amount of the variance in the measures.
These results provide evidence for the reliability and validity of the measurement model, suggesting that the measures are appropriate for capturing the intended constructs.

Tab. S2. A detailed statistical analysis of the association between participants characteristics' and awareness towards CAI.

Relation	Test	Test statistic	Significance
Q2.1 (sex)x Q3.1 (Have you heard about some cancer types associated with bacteria?)	Pearson Chi-Square	9.025	0.003
Q2.1 (sex)x Q3.2 (Have you heard about some cancer types associated with viruses?)	Pearson Chi-Square	16.436	0
Q2.1 (sex)x Q3.3 (Have you heard of 'Oncovirus')	Pearson Chi-Square	21.497	0
Q2.1 (sex)x Q3.4 (Know that vaccine can prevent some cancer types)	Pearson Chi-Square	41.673	0
Q2.1 (sex)x Q4.1 (Have you heard of Human papillomavirus (HPV))	Pearson Chi-Square	51.173	0
Q2.1 (sex)x Q4.2 (Know that HPV infection causes cervical cancer)	Pearson Chi-Square	57.612	0
Q2.1 (sex)x Q4.3 (Have you ever heard of the HPV vaccine)	Pearson Chi-Square	51.246	0
Q2.1 (sex)x Q4.3.1 (main source of info)	Pearson Chi-Square	1.703	0.636
Q2.1 (sex)x Q4.4 (Know that HPV vaccine can prevent cervical cancer)	Pearson Chi-Square	31.15	0
Q2.1 (sex)x Q4.5 (Have you received HPV vaccine)	Pearson Chi-Square	20.654	0
Q2.1 (sex)x Q5.1 (Have you heard of the hepatitis B and C viruses)	Pearson Chi-Square	36.102	0
Q2.1 (sex)x Q5.2 Know that hepatitis B and C viruses cause liver cancer	Pearson Chi-Square	26.938	0
Q2.1 (sex)x Q5.3 Have you heard of the hepatitis B vaccine	Pearson Chi-Square	39.522	0

▶

Tab. S2. *(follows).*

Relation	Test	Test statistic	Significance
Q2.1 (sex)x Q5.3.1 main source of info	Pearson Chi-Square	3.58	0.311
Q2.1 (sex)x Q5.4 Know that Hepatitis B vaccine can prevent liver cancer	Pearson Chi-Square	24.131	0
Q2.1 (sex)x Q5.5 Have you received HBV vaccine	Pearson Chi-Square	22.878	0
Q2.1 (sex)x Q6.1 Heard of Kaposi sarcoma herpes virus (KSHV)	Pearson Chi-Square	8.398	0.004
Q2.1 (sex)x Q6.2 Know that Kaposi sarcoma herpes virus causes Kaposi sarcoma	Pearson Chi-Square	9.912	0.002
Q2.1 (sex)x Q7.1 Heard of Epstein Barr Virus (EBV)	Pearson Chi-Square	19.407	0
Q2.1 (sex)x Q7.2 Know that Epstein Barr virus causes lymphoma	Pearson Chi-Square	18.614	0
Q2.1 (sex)x Q7.3 Heard of Human T-lymphotropic virus 1 (HTLV-1)	Pearson Chi-Square	15.996	0
Q2.1 (sex)x Q7.4 Know that HTLV-1 causes lymphoma	Pearson Chi-Square	16.999	0
Q2.1 (sex)x Q8.1 Heard of the bacteria *Helicobacter pylori*	Pearson Chi-Square	35.556	0
Q2.1 (sex)x Q8.2 Know that *Helicobacter pylori* is associated to cancer of the stomach	Pearson Chi-Square	36.49	0
Q2.2 (marital status)x Q3.1 (Have you heard about some cancer types associated with bacteria?)	Pearson Chi-Square	6.116	0.047
Q2.2 (marital status)x Q3.2 (Have you heard about some cancer types associated with viruses?)	Pearson Chi-Square	10.227	0.006
Q2.2 (marital status)x Q3.3 (Have you heard of 'Oncovirus')	Pearson Chi-Square	5.296	0.071
Q2.2 (marital status)x Q3.4 (Know that vaccine can prevent some cancer types)	Pearson Chi-Square	2.26	0.323
Q2.2 (marital status)x Q4.1 (Have you heard of Human papillomavirus (HPV))	Pearson Chi-Square	3.44	0.179
Q2.2 (marital status)x Q4.2 (Know that HPV infection causes cervical cancer)	Pearson Chi-Square	3.001	0.223
Q2.2 (marital status)x Q4.3 (Have you ever heard of the HPV vaccine)	Pearson Chi-Square	2.677	0.262
Q2.2 (marital status)x Q4.3.1 (main source of info)	Pearson Chi-Square		
Q2.2 (marital status)x Q4.4 (Know that HPV vaccine can prevent cervical cancer)	Pearson Chi-Square	0.545	0.762
Q2.2 (marital status)x Q4.5 (Have you received HPV vaccine)	Pearson Chi-Square	0.659	0.719
Q2.2 (marital status)x Q5.1 (Have you heard of the hepatitis B and C viruses)	Pearson Chi-Square	8.48	0.014
Q2.2 (marital status)x Q5.2 Know that hepatitis B and C viruses cause liver cancer	Pearson Chi-Square	2.608	0.271
Q2.2 (marital status)x Q5.3 Have you heard of the hepatitis B vaccine	Pearson Chi-Square	5.157	0.076
Q2.2 (marital status))x Q5.3.1 main source of info	Pearson Chi-Square	6.069	0.415
Q2.2 (marital status)x Q5.4 Know that Hepatitis B vaccine can prevent liver cancer	Pearson Chi-Square	4.86	0.088
Q2.2 (marital status)x Q5.5 Have you received HBV vaccine	Pearson Chi-Square	1.461	0.482
Q2.2 (marital status)x Q6.1 Heard of Kaposi sarcoma herpes virus (KSHV)	Pearson Chi-Square	1.613	0.446
Q2.2 (marital status)x Q6.2 Know that Kaposi sarcoma herpes virus causes Kaposi sarcoma	Pearson Chi-Square	1.692	0.429
Q2.2 (marital status))x Q7.1 Heard of Epstein Barr Virus (EBV)	Pearson Chi-Square	3.468	0.177
Q2.2 (marital status)x Q7.2 Know that Epstein Barr virus causes lymphoma	Pearson Chi-Square	6.791	0.034
Q2.2 (marital status)x Q7.3 Heard of Human T-lymphotropic virus 1 (HTLV-1)	Pearson Chi-Square	8.583	0.014
Q2.2 (marital status)x Q7.4 Know that HTLV-1 causes lymphoma	Pearson Chi-Square	7.436	0.024
Q2.2 (marital status)x Q8.1 Heard of the bacteria *Helicobacter pylori*	Pearson Chi-Square	2.78	0.249
Q2.2 (marital status)x Q8.2 Know that *Helicobacter pylori* is associated to cancer of the stomach	Pearson Chi-Square	2.412	0.299
Q2.3 (nationality)x Have you heard about some cancer types associated with bacteria?	Pearson Chi-Square	22.996	0
Q2.3 (nationality)x Have you heard about some cancer types associated with viruses?	Pearson Chi-Square	15.544	0
Q2.3 (nationality)x Have you heard of 'Oncovirus'?	Pearson Chi-Square	14.535	0
Q2.3 (nationality)x Do you know that vaccine can prevent some cancer types?	Pearson Chi-Square	19.311	0
Q2.3 (nationality)x Have you heard of Human papillomavirus (HPV)?	Pearson Chi-Square	30.687	0

Tab. S2. *(follows).*

Relation	Test	Test statistic	Significance
Q2.3 (nationality)x Do you know that HPV infection causes cervical cancer?	Pearson Chi-Square	23.087	0
Q2.3 (nationality)x Have you ever heard of the HPV vaccine?	Pearson Chi-Square	20.333	0
Q2.3 (nationality)x main source of info?	Pearson Chi-Square		
Q2.3 (nationality)x Do you know that HPV vaccine can prevent cervical cancer?	Pearson Chi-Square	11.415	0.001
Q2.3 (nationality)x Have you received HPV vaccine?	Pearson Chi-Square	3.463	0.063
Q2.3 (nationality)x Have you heard of the hepatitis B and C viruses?	Pearson Chi-Square	51.03	0
Q2.3 (nationality)x Do you know that hepatitis B and C viruses cause liver cancer?	Pearson Chi-Square	22.647	0
Q2.3 (nationality)x Have you heard of the hepatitis B vaccine?	Pearson Chi-Square	32.496	0
Q2.3 (nationality)x main source of info?	Pearson Chi-Square	2.728	0.435
Q2.3 (nationality)xDo you know that Hepatitis B vaccine can prevent liver cancer?	Pearson Chi-Square	24.658	0
Q2.3 (nationality)x Have you received HBV vaccine?	Pearson Chi-Square	6.771	0.009
Q2.3 (nationality)x Have you heard of Kaposi sarcoma herpes virus (KSHV)?	Pearson Chi-Square	5.307	0.021
Q2.3 (nationality)x Do you know that Kaposi sarcoma herpes virus causes Kaposi sarcoma?	Pearson Chi-Square	3.495	0.062
Q2.3 (nationality)x Have you heard of Epstein Barr Virus (EBV)?	Pearson Chi-Square	2.988	0.084
Q2.3 (nationality)x Do you know that Epstein Barr virus causes lymphoma?	Pearson Chi-Square	3.219	0.073
Q2.3 (nationality)x Have you heard of Human T-lymphotropic virus 1 (HTLV-1)?	Pearson Chi-Square	7.193	0.007
Q2.3 (nationality)x Do you know that HTLV-1 causes lymphoma?	Pearson Chi-Square	3.962	0.047
Q2.3 (nationality)x Have you heard of the bacteria *Helicobacter pylori*?	Pearson Chi-Square	13.375	0
Q2.3 (nationality)x Do you know that *Helicobacter pylori* is associated to cancer of the stomach?	Pearson Chi-Square	9.436	0.002
Q2.4 (place of residence)x Have you heard about some cancer types associated with bacteria?	Pearson Chi-Square	7.065	0.132
Q2.4 (place of residence)x Have you heard about some cancer types associated with viruses?	Pearson Chi-Square	5.427	0.246
Q2.4 (place of residence)x Have you heard of 'Oncovirus'?	Pearson Chi-Square	3.383	0.496
Q2.4 (place of residence)x Do you know that vaccine can prevent some cancer types?	Pearson Chi-Square	5.011	0.286
Q2.4 (place of residence)x Have you heard of Human papillomavirus (HPV)?	Pearson Chi-Square	7.594	0.108
Q2.4 (place of residence)x Do you know that HPV infection causes cervical cancer?	Pearson Chi-Square	5.179	0.269
Q2.4 (place of residence)x Have you ever heard of the HPV vaccine?	Pearson Chi-Square	4.382	0.357
Q2.4 (place of residence)x main source of info?	Pearson Chi-Square	9.668	0.645
Q2.4 (place of residence)x Do you know that HPV vaccine can prevent cervical cancer?	Pearson Chi-Square	3.041	0.551
Q2.4 (place of residence)x Have you received HPV vaccine?	Pearson Chi-Square	3.218	0.522
Q2.4 (place of residence)x Have you heard of the hepatitis B and C viruses?	Pearson Chi-Square	11.226	0.024
Q2.4 (place of residence)x Do you know that hepatitis B and C viruses cause liver cancer?	Pearson Chi-Square	10.226	0.037
Q2.4 (place of residence)x Have you heard of the hepatitis B vaccine?	Pearson Chi-Square	8.167	0.086
Q2.4 (place of residence)x main source of info?	Pearson Chi-Square	16.561	0.167
Q2.4 (place of residence)xDo you know that Hepatitis B vaccine can prevent liver cancer?	Pearson Chi-Square	6.336	0.175
Q2.4 (place of residence) x Have you received HBV vaccine?	Pearson Chi-Square	4.551	0.337
Q2.4 (place of residence)x Have you heard of Kaposi sarcoma herpes virus (KSHV)?	Pearson Chi-Square	6.427	0.169
Q2.4 (place of residence)x Do you know that Kaposi sarcoma herpes virus causes Kaposi sarcoma?	Pearson Chi-Square	4.299	0.367
Q2.4 (place of residence)x Have you heard of Epstein Barr Virus (EBV)?	Pearson Chi-Square	4.337	0.362

Tab. S2. *(follows).*

Relation	Test	Test statistic	Significance
Q2.4 (place of residence)x Do you know that Epstein Barr virus causes lymphoma?	Pearson Chi-Square	6.232	0.182
Q2.4 (place of residence)x Have you heard of Human T-lymphotropic virus 1 (HTLV-1)?	Pearson Chi-Square	4.096	0.393
Q2.4 (place of residence)x Do you know that HTLV-1 causes lymphoma?	Pearson Chi-Square	6.478	0.166
Q2.4 (place of residence)x Have you heard of the bacteria *Helicobacter pylori*?	Pearson Chi-Square	4.291	0.368
Q2.4 (place of residence)x Do you know that *Helicobacter pylori* is associated to cancer of the stomach?	Pearson Chi-Square	3.224	0.521
Q2.5 (age)x Have you heard about some cancer types associated with bacteria?	Pearson Chi-Square	4.101	0.251
Q2.5 (age)x Have you heard about some cancer types associated with viruses?	Pearson Chi-Square	6.371	0.095
Q2.5 (age)x Have you heard of 'Oncovirus'?	Pearson Chi-Square	1.201	0.753
Q2.5 (age)x Do you know that vaccine can prevent some cancer types?	Pearson Chi-Square	2.118	0.548
Q2.5 (age)x Have you heard of Human papillomavirus (HPV)?	Pearson Chi-Square	6.032	0.11
Q2.5 (age)x Do you know that HPV infection causes cervical cancer?	Pearson Chi-Square	5.008	0.171
Q2.5 (age)x Have you ever heard of the HPV vaccine?	Pearson Chi-Square	4.543	0.208
Q2.5 (age)x main source of info?	Pearson Chi-Square	10.021	0.124
Q2.5 (age)x Do you know that HPV vaccine can prevent cervical cancer?	Pearson Chi-Square	1.713	0.634
Q2.5 (age)x Have you received HPV vaccine?	Pearson Chi-Square	0.366	0.947
Q2.5 (age)x Have you heard of the hepatitis B and C viruses?	Pearson Chi-Square	4.483	0.214
Q2.5 (age)x Do you know that hepatitis B and C viruses cause liver cancer?	Pearson Chi-Square	2.259	0.52
Q2.5 (age)x Have you heard of the hepatitis B vaccine?	Pearson Chi-Square	3.681	0.298
Q2.5 (age)x main source of info?	Pearson Chi-Square	6.905	0.33
Q2.5 (age)xDo you know that Hepatitis B vaccine can prevent liver cancer?	Pearson Chi-Square	3.395	0.335
Q2.5 (age)x Have you received HBV vaccine?	Pearson Chi-Square	1.728	0.631
Q2.5 (age)x Have you heard of Kaposi sarcoma herpes virus (KSHV)?	Pearson Chi-Square	1.181	0.758
Q2.5 (age)x Do you know that Kaposi sarcoma herpes virus causes Kaposi sarcoma?	Pearson Chi-Square	1.181	0.758
Q2.5 (age)x Have you heard of Epstein Barr Virus (EBV)?	Pearson Chi-Square	1.965	0.58
Q2.5 (age)x Do you know that Epstein Barr virus causes lymphoma?	Pearson Chi-Square	3.266	0.352
Q2.5 (age)x Have you heard of Human T-lymphotropic virus 1 (HTLV-1)?	Pearson Chi-Square	3.396	0.335
Q2.5 (age)x Do you know that HTLV-1 causes lymphoma?	Pearson Chi-Square	2.47	0.481
Q2.5 (age)x Have you heard of the bacteria *Helicobacter pylori*?	Pearson Chi-Square	1.187	0.756
Q2.5 (age)x Do you know that *Helicobacter pylori* is associated to cancer of the stomach?	Pearson Chi-Square	1.707	0.635
Q2.6 (education level)x Have you heard about some cancer types associated with bacteria?	Pearson Chi-Square	7.424	0.024
Q2.6 (education level)x Have you heard about some cancer types associated with viruses?	Pearson Chi-Square	9.847	0.007
Q2.6 (education level)x Have you heard of 'Oncovirus'?	Pearson Chi-Square	6.123	0.047
Q2.6 (education level)x Do you know that vaccine can prevent some cancer types?	Pearson Chi-Square	3.722	0.156
Q2.6 (education level)x Have you heard of Human papillomavirus (HPV)?	Pearson Chi-Square	7.783	0.02
Q2.6 (education level)x Do you know that HPV infection causes cervical cancer?	Pearson Chi-Square	6.804	0.033
Q2.6 (education level)x Have you ever heard of the HPV vaccine?	Pearson Chi-Square	6.272	0.043
Q2.6 (education level)x main source of info?	Pearson Chi-Square	3.272	0.352
Q2.6 (education level)x Do you know that HPV vaccine can prevent cervical cancer?	Pearson Chi-Square	2.922	0.232
Q2.6 (education level)x Have you received HPV vaccine?	Pearson Chi-Square	0.469	0.791
Q2.6 (education level)x Have you heard of the hepatitis B and C viruses?	Pearson Chi-Square	11.106	0.004
Q2.6 (education level)x Do you know that hepatitis B and C viruses cause liver cancer?	Pearson Chi-Square	7.459	0.024
Q2.6 (education level)x Have you heard of the hepatitis B vaccine?	Pearson Chi-Square	10.984	0.004

▶

Tab. S2. *(follows).*

Relation	Test	Test statistic	Significance
Q2.6 (education level)x main source of info?	Pearson Chi-Square	3.324	0.344
Q2.6 (education level)xDo you know that Hepatitis B vaccine can prevent liver cancer?	Pearson Chi-Square	3.764	0.152
Q2.6 (education level)x Have you received HBV vaccine?	Pearson Chi-Square	4.23	0.121
Q2.6 (education level)x Have you heard of Kaposi sarcoma herpes virus (KSHV)?	Pearson Chi-Square	4.023	0.134
Q2.6 (education level)x Do you know that Kaposi sarcoma herpes virus causes Kaposi sarcoma?	Pearson Chi-Square	3.176	0.204
Q2.6 (education level)x Have you heard of Epstein Barr Virus (EBV)?	Pearson Chi-Square	2.703	0.259
Q2.6 (education level)x Do you know that Epstein Barr virus causes lymphoma?	Pearson Chi-Square	3.994	0.136
Q2.6 (education level)x Have you heard of Human T-lymphotropic virus 1 (HTLV-1)?	Pearson Chi-Square	4.266	0.118
Q2.6 (education level)x Do you know that HTLV-1 causes lymphoma?	Pearson Chi-Square	4.366	0.113
Q2.6 (education level)x Have you heard of the bacteria *Helicobacter pylori*?	Pearson Chi-Square	7.016	0.03
Q2.6 (education level)x Do you know that *Helicobacter pylori* is associated to cancer of the stomach?	Pearson Chi-Square	5.931	0.052
Q2.7 (occupation)x Have you heard about some cancer types associated with bacteria?	Pearson Chi-Square	53.014	0
Q2.7 (occupation)x Have you heard about some cancer types associated with viruses?	Pearson Chi-Square	70.182	0
Q2.7 (occupation)x Have you heard of 'Oncovirus'?	Pearson Chi-Square	128.315	0
Q2.7 (occupation)x Do you know that vaccine can prevent some cancer types?	Pearson Chi-Square	63.081	0
Q2.7 (occupation)x Have you heard of Human papillomavirus (HPV)?	Pearson Chi-Square	73.999	0
Q2.7 (occupation)x Do you know that HPV infection causes cervical cancer?	Pearson Chi-Square	85.686	0
Q2.7 (occupation)x Have you ever heard of the HPV vaccine?	Pearson Chi-Square	74.899	0
Q2.7 (occupation)x main source of info?	Pearson Chi-Square	12.947	0.005
Q2.7 (occupation)x Do you know that HPV vaccine can prevent cervical cancer?	Pearson Chi-Square	68.662	0
Q2.7 (occupation)x Have you received HPV vaccine?	Pearson Chi-Square	25.242	0
Q2.7 (occupation)x Have you heard of the hepatitis B and C viruses?	Pearson Chi-Square	66.459	0
Q2.7 (occupation)x Do you know that hepatitis B and C viruses cause liver cancer?	Pearson Chi-Square	96.098	0
Q2.7 (occupation)x Have you heard of the hepatitis B vaccine?	Pearson Chi-Square	76.462	0
Q2.7 (occupation)x main source of info?	Pearson Chi-Square	13.898	0.003
Q2.7 (occupation)xDo you know that Hepatitis B vaccine can prevent liver cancer?	Pearson Chi-Square	98.996	0
Q2.7 (occupation)x Have you received HBV vaccine?	Pearson Chi-Square	67.985	0
Q2.7 (occupation)x Have you heard of Kaposi sarcoma herpes virus (KSHV)?	Pearson Chi-Square	62.919	0
Q2.7 (occupation)x Do you know that Kaposi sarcoma herpes virus causes Kaposi sarcoma?	Pearson Chi-Square	88.597	0
Q2.7 (occupation)x Have you heard of Epstein Barr Virus (EBV)?	Pearson Chi-Square	119.864	0
Q2.7 (occupation)x Do you know that Epstein Barr virus causes lymphoma?	Pearson Chi-Square	122.501	0
Q2.7 (occupation)x Have you heard of Human T-lymphotropic virus 1 (HTLV-1)?	Pearson Chi-Square	97.613	0
Q2.7 (occupation)x Do you know that HTLV-1 causes lymphoma?	Pearson Chi-Square	119.628	0
Q2.7 (occupation)x Have you heard of the bacteria *Helicobacter pylori*?	Pearson Chi-Square	121.583	0
Q2.7 (occupation)x Do you know that *Helicobacter pylori* is associated to cancer of the stomach?	Pearson Chi-Square	143.942	0
Q2.8 (family income)x Have you heard about some cancer types associated with bacteria?	Pearson Chi-Square	20.241	0
Q2.8 (family income)x Have you heard about some cancer types associated with viruses?	Pearson Chi-Square	20.107	0

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Tab. S2. *(follows).*

Relation	Test	Test statistic	Significance
Q2.8 (family income)x Have you heard of 'Oncovirus'?	Pearson Chi-Square	18.369	0
Q2.8 (family income)x Do you know that vaccine can prevent some cancer types?	Pearson Chi-Square	15.866	0
Q2.8 (family income)x Have you heard of Human papillomavirus (HPV)?	Pearson Chi-Square	15.552	0
Q2.8 (family income)x Do you know that HPV infection causes cervical cancer?	Pearson Chi-Square	14.555	0.001
Q2.8 (family income)x Have you ever heard of the HPV vaccine?	Pearson Chi-Square	12.004	0.002
Q2.8 (family income)x main source of info?	Pearson Chi-Square	12.297	0.056
Q2.8 (family income)x Do you know that HPV vaccine can prevent cervical cancer?	Pearson Chi-Square	8.11	0.017
Q2.8 (family income)x Have you received HPV vaccine?	Pearson Chi-Square	8.815	0.012
Q2.8 (family income)x Have you heard of the hepatitis B and C viruses?	Pearson Chi-Square	47.598	0
Q2.8 (family income)x Do you know that hepatitis B and C viruses cause liver cancer?	Pearson Chi-Square	37.241	0
Q2.8 (family income)x Have you heard of the hepatitis B vaccine?	Pearson Chi-Square	28.472	0
Q2.8 (family income)x main source of info?	Pearson Chi-Square	8.18	0.225
Q2.8 (family income)xDo you know that Hepatitis B vaccine can prevent liver cancer?	Pearson Chi-Square	24.454	0
Q2.8 (family income) x Have you received HBV vaccine?	Pearson Chi-Square	19.045	0
Q2.8 (family income)x Have you heard of Kaposi sarcoma herpes virus (KSHV)?	Pearson Chi-Square	9.909	0.007
Q2.8 (family income)x Do you know that Kaposi sarcoma herpes virus causes Kaposi sarcoma?	Pearson Chi-Square	10.958	0.004
Q2.8 (family income)x Have you heard of Epstein Barr Virus (EBV)?	Pearson Chi-Square	14.86	0.001
Q2.8 (family income)x Do you know that Epstein Barr virus causes lymphoma?	Pearson Chi-Square	15.69	0
Q2.8 (family income)x Have you heard of Human T-lymphotropic virus 1 (HTLV-1)?	Pearson Chi-Square	13.803	0.001
Q2.8 (family income)x Do you know that HTLV-1 causes lymphoma?	Pearson Chi-Square	11.002	0.004
Q2.8 (family income)x Have you heard of the bacteria *Helicobacter pylori*?	Pearson Chi-Square	41.983	0
Q2.8 (family income)x Do you know that *Helicobacter pylori* is associated to cancer of the stomach?	Pearson Chi-Square	31.305	0
Q2.9 (have you been diagnosed with cancer)x Have you heard about some cancer types associated with bacteria?	Pearson Chi-Square	0.291	0.59
Q2.9 (have you been diagnosed with cancer)x Have you heard about some cancer types associated with viruses?	Pearson Chi-Square	1.06	0.303
Q2.9 (have you been diagnosed with cancer)x Have you heard of 'Oncovirus'?	Pearson Chi-Square	0.613	0.434
Q2.9 (have you been diagnosed with cancer)x Do you know that vaccine can prevent some cancer types?	Pearson Chi-Square	0.001	0.973
Q2.9 (have you been diagnosed with cancer)x Have you heard of Human papillomavirus (HPV)?	Pearson Chi-Square	0.125	0.724
Q2.9 (have you been diagnosed with cancer)x Do you know that HPV infection causes cervical cancer?	Pearson Chi-Square	0.814	0.367
Q2.9 (have you been diagnosed with cancer)x Have you ever heard of the HPV vaccine?	Pearson Chi-Square	0.629	0.428
Q2.9 (have you been diagnosed with cancer)x main source of info?	Pearson Chi-Square	6.115	0.106
Q2.9 (have you been diagnosed with cancer)x Do you know that HPV vaccine can prevent cervical cancer?	Pearson Chi-Square	0.226	0.634
Q2.9 (have you been diagnosed with cancer)x Have you received HPV vaccine?	Pearson Chi-Square	11.427	0.001
Q2.9 (have you been diagnosed with cancer)x Have you heard of the hepatitis B and C viruses?	Pearson Chi-Square	0.532	0.466
Q2.9 (have you been diagnosed with cancer)x Do you know that hepatitis B and C viruses cause liver cancer?	Pearson Chi-Square	3.322	0.068
Q2.9 (have you been diagnosed with cancer)x Have you heard of the hepatitis B vaccine?	Pearson Chi-Square	0.325	0.569
Q2.9 (have you been diagnosed with cancer)x main source of info?	Pearson Chi-Square	4.719	0.194

Tab. S2. *(follows).*

Relation	Test	Test statistic	Significance
Q2.9 (have you been diagnosed with cancer)xDo you know that Hepatitis B vaccine can prevent liver cancer?	Pearson Chi-Square	0.629	0.428
Q2.9 (have you been diagnosed with cancer)x Have you received HBV vaccine?	Pearson Chi-Square	2.023	0.155
Q2.9 (have you been diagnosed with cancer)x Have you heard of Kaposi sarcoma herpes virus (KSHV)?	Pearson Chi-Square	0.735	0.391
Q2.9 (have you been diagnosed with cancer)x Do you know that Kaposi sarcoma herpes virus causes Kaposi sarcoma?	Pearson Chi-Square	1.561	0.211
Q2.9 (have you been diagnosed with cancer)x Have you heard of Epstein Barr Virus (EBV)?	Pearson Chi-Square	0.767	0.381
Q2.9 (have you been diagnosed with cancer)x Do you know that Epstein Barr virus causes lymphoma?	Pearson Chi-Square	1.201	0.273
Q2.9 (have you been diagnosed with cancer)x Have you heard of Human T-lymphotropic virus 1 (HTLV-1)?	Pearson Chi-Square	0.672	0.412
Q2.9 (have you been diagnosed with cancer)x Do you know that HTLV-1 causes lymphoma?	Pearson Chi-Square	1.068	0.301
Q2.9 (have you been diagnosed with cancer)x Have you heard of the bacteria *Helicobacter pylori*?	Pearson Chi-Square	0.514	0.474
Q2.9 (have you been diagnosed with cancer)x Do you know that *Helicobacter pylori* is associated to cancer of the stomach?	Pearson Chi-Square	0.998	0.318
Q2.9.1 (what type?)x Have you heard about some cancer types associated with bacteria?	Pearson Chi-Square	3.056	0.383
Q2.9.1 (what type?)x Have you heard about some cancer types associated with viruses?	Pearson Chi-Square	3.254	0.354
Q2.9.1 (what type?)x Have you heard of 'Oncovirus'?	Pearson Chi-Square	4.048	0.256
Q2.9.1 (what type?)x Do you know that vaccine can prevent some cancer types?	Pearson Chi-Square	4.048	0.256
Q2.9.1 (what type?)x Have you heard of Human papillomavirus (HPV)?	Pearson Chi-Square	1.333	0.721
Q2.9.1 (what type?)x Do you know that HPV infection causes cervical cancer?	Pearson Chi-Square	1.333	0.721
Q2.9.1 (what type?)x Have you ever heard of the HPV vaccine?	Pearson Chi-Square	1.333	0.721
Q2.9.1 (what type?)x main source of info?	Pearson Chi-Square	2.4	0.494
Q2.9.1 (what type?)x Do you know that HPV vaccine can prevent cervical cancer?	Pearson Chi-Square	3.75	0.29
Q2.9.1 (what type?)x Have you received HPV vaccine?	Pearson Chi-Square	2.014	0.57
Q2.9.1 (what type?)x Have you heard of the hepatitis B and C viruses?	Pearson Chi-Square	0.972	0.808
Q2.9.1 (what type?)x Do you know that hepatitis B and C viruses cause liver cancer?	Pearson Chi-Square	0.972	0.808
Q2.9.1 (what type?)x Have you heard of the hepatitis B vaccine?	Pearson Chi-Square	1.333	0.721
Q2.9.1 (what type?)x main source of info?	Pearson Chi-Square	10	0.125
Q2.9.1 (what type?)xDo you know that Hepatitis B vaccine can prevent liver cancer?	Pearson Chi-Square	1.333	0.721
Q2.9.1 (what type?) x Have you received HBV vaccine?	Pearson Chi-Square	1.333	0.721
Q2.9.1 (what type?)x Have you heard of Kaposi sarcoma herpes virus (KSHV)?	Pearson Chi-Square	3.75	0.29
Q2.9.1 (what type?)x Do you know that Kaposi sarcoma herpes virus causes Kaposi sarcoma?	Pearson Chi-Square	3.75	0.29
Q2.9.1 (what type?)x Have you heard of Epstein Barr Virus (EBV)?	Pearson Chi-Square	3.75	0.29
Q2.9.1 (what type?) x Do you know that Epstein Barr virus causes lymphoma?	Pearson Chi-Square	3.75	0.29
Q2.9.1 (what type?)x Have you heard of Human T-lymphotropic virus 1 (HTLV-1)?	Pearson Chi-Square	3.75	0.29
Q2.9.1 (what type?)x Do you know that HTLV-1 causes lymphoma?	Pearson Chi-Square	3.75	0.29
Q2.9.1 (what type?) x Have you heard of the bacteria *Helicobacter pylori*?	Pearson Chi-Square	1.333	0.721
Q2.9.1 (what type?)x Do you know that *Helicobacter pylori* is associated to cancer of the stomach?	Pearson Chi-Square	1.333	0.721
Q2.10 (family history of cancer)x Have you heard about some cancer types associated with bacteria?	Pearson Chi-Square	4.119	0.042

Tab. S2. *(follows).*

Relation	Test	Test statistic	Significance
Q2.10 (family history of cancer)x Have you heard about some cancer types associated with viruses?	Pearson Chi-Square	6.146	0.013
Q2.10 (family history of cancer)x Have you heard of 'Oncovirus'?	Pearson Chi-Square	6.924	0.009
Q2.10 (family history of cancer)x Do you know that vaccine can prevent some cancer types?	Pearson Chi-Square	1.972	0.16
Q2.10 (family history of cancer)x Have you heard of Human papillomavirus (HPV)?	Pearson Chi-Square	18.978	0
Q2.10 (family history of cancer)x Do you know that HPV infection causes cervical cancer?	Pearson Chi-Square	13.81	0
Q2.10 (family history of cancer)x Have you ever heard of the HPV vaccine?	Pearson Chi-Square	19.561	0
Q2.10 (family history of cancer)x main source of info?	Pearson Chi-Square	2.099	0.552
Q2.10 (family history of cancer)x Do you know that HPV vaccine can prevent cervical cancer?	Pearson Chi-Square	9.516	0.002
Q2.10 (family history of cancer)x Have you received HPV vaccine?	Pearson Chi-Square	7.33	0.007
Q2.10 (family history of cancer)x Have you heard of the hepatitis B and C viruses?	Pearson Chi-Square	14.993	0
Q2.10 (family history of cancer)x Do you know that hepatitis B and C viruses cause liver cancer?	Pearson Chi-Square	8.152	0.004
Q2.10 (family history of cancer)x Have you heard of the hepatitis B vaccine?	Pearson Chi-Square	19.028	0
Q2.10 (family history of cancer)x main source of info?	Pearson Chi-Square	0.74	0.864
Q2.10 (family history of cancer)xDo you know that Hepatitis B vaccine can prevent liver cancer?	Pearson Chi-Square	12.759	0
Q2.10 (family history of cancer) x Have you received HBV vaccine?	Pearson Chi-Square	4.235	0.04
Q2.10 (family history of cancer)x Have you heard of Kaposi sarcoma herpes virus (KSHV)?	Pearson Chi-Square	9.029	0.003
Q2.10 (family history of cancer)x Do you know that Kaposi sarcoma herpes virus causes Kaposi sarcoma?	Pearson Chi-Square	4.631	0.031
Q2.10 (family history of cancer)x Have you heard of Epstein Barr Virus (EBV)?	Pearson Chi-Square	8.186	0.004
Q2.10 (family history of cancer)x Do you know that Epstein Barr virus causes lymphoma?	Pearson Chi-Square	7.352	0.007
Q2.10 (family history of cancer)x Have you heard of Human T-lymphotropic virus 1 (HTLV-1)?	Pearson Chi-Square	6.657	0.01
Q2.10 (family history of cancer)x Do you know that HTLV-1 causes lymphoma?	Pearson Chi-Square	7.089	0.008
Q2.10 (family history of cancer)x Have you heard of the bacteria *Helicobacter pylori*?	Pearson Chi-Square	4.474	0.034
Q2.10 (family history of cancer)x Do you know that *Helicobacter pylori* is associated to cancer of the stomach?	Pearson Chi-Square	5.128	0.024
Q2.10.1 (what type)x Have you heard about some cancer types associated with bacteria?	Pearson Chi-Square	13.136	0.285
Q2.10.1 (what type)x Have you heard about some cancer types associated with viruses?	Pearson Chi-Square	17.993	0.082
Q2.10.1 (what type)x Have you heard of 'Oncovirus'?	Pearson Chi-Square	15.381	0.166
Q2.10.1 (what type)x Do you know that vaccine can prevent some cancer types?	Pearson Chi-Square	16.004	0.141
Q2.10.1 (what type)x Have you heard of Human papillomavirus (HPV)?	Pearson Chi-Square	12.988	0.294
Q2.10.1 (what type)x Do you know that HPV infection causes cervical cancer?	Pearson Chi-Square	19.238	0.057
Q2.10.1 (what type)x Have you ever heard of the HPV vaccine?	Pearson Chi-Square	11.521	0.401
Q2.10.1 (what type)x main source of info?	Pearson Chi-Square	68.555	0
Q2.10.1 (what type)x Do you know that HPV vaccine can prevent cervical cancer?	Pearson Chi-Square	17.152	0.103
Q2.10.1 (what type)x Have you received HPV vaccine?	Pearson Chi-Square	20.376	0.04
Q2.10.1 (what type)x Have you heard of the hepatitis B and C viruses?	Pearson Chi-Square	13.031	0.291
Q2.10.1 (what type)x Do you know that hepatitis B and C viruses cause liver cancer?	Pearson Chi-Square	8.342	0.682
Q2.10.1 (what type)x Have you heard of the hepatitis B vaccine?	Pearson Chi-Square	9.878	0.541

Tab. S2. *(follows).*

Relation	Test	Test statistic	Significance
Q2.10.1 (what type)x main source of info?	Pearson Chi-Square	36.414	0.195
Q2.10.1 (what type)xDo you know that Hepatitis B vaccine can prevent liver cancer?	Pearson Chi-Square	9.416	0.584
Q2.10.1 (what type)x Have you received HBV vaccine?	Pearson Chi-Square	22.056	0.024
Q2.10.1 (what type)x Have you heard of Kaposi sarcoma herpes virus (KSHV)?	Pearson Chi-Square	16.667	0.118
Q2.10.1 (what type)x Do you know that Kaposi sarcoma herpes virus causes Kaposi sarcoma?	Pearson Chi-Square	18.577	0.069
Q2.10.1 (what type)x Have you heard of Epstein Barr Virus (EBV)?	Pearson Chi-Square	20.631	0.037
Q2.10.1 (what type)x Do you know that Epstein Barr virus causes lymphoma?	Pearson Chi-Square	16.372	0.128
Q2.10.1 (what type)x Have you heard of Human T-lymphotropic virus 1 (HTLV-1)?	Pearson Chi-Square	17.663	0.09
Q2.10.1 (what type)x Do you know that HTLV-1 causes lymphoma?	Pearson Chi-Square	10.763	0.463
Q2.10.1 (what type)x Have you heard of the bacteria *Helicobacter pylori*?	Pearson Chi-Square	9.279	0.596
Q2.10.1 (what type) Do you know that *Helicobacter pylori* is associated to cancer of the stomach?	Pearson Chi-Square	8.915	0.63

($p < 0.05$), statistically significant.

Tab. S3. Cross-tabulation of participants characteristics and awareness levels to CAI.

Have you heard about some cancer types associated with bacteria?					Total
			No	Yes	
Sex	Male	Count	130	64	194
		%	67.0%	33.0%	100.0%
	Female	Count	116	105	221
		%	52.5%	47.5%	100.0%
Total		Count	246	169	415
		%	59.3%	40.7%	100.0%
Have you heard about some cancer types associated with viruses?					**Total**
			No	**Yes**	
Sex	Male	Count	128	66	194
		%	66.0%	34.0%	100.0%
	Female	Count	102	119	221
		%	46.2%	53.8%	100.0%
Total		Count	230	185	415
		%	55.4%	44.6%	100.0%
Have you heard of 'Oncovirus'					**Total**
			No	**Yes**	
Sex	Male	Count	165	29	194
		%	85.1%	14.9%	100.0%
	Female	Count	144	77	221
		%	65.2%	34.8%	100.0%
Total		Count	309	106	415
		%	74.5%	25.5%	100.0%
Know that vaccine can prevent some cancer types					**Total**
			No	**Yes**	
Sex	Male	Count	152	42	194
		%	78.4%	21.6%	100.0%
	Female	Count	105	116	221
		%	47.5%	52.5%	100.0%
Total		Count	257	158	415
		%	61.9%	38.1%	100.0%

Tab. S3 (*follows*).

Have you heard of Human papillomavirus (HPV)					Total
			No	Yes	
Sex	Male	Count	145	49	194
		%	74.7%	25.3%	100.0%
	Female	Count	88	133	221
		%	39.8%	60.2%	100.0%
Total		Count	233	182	415
		%	56.1%	43.9%	100.0%
Know that HPV infection causes cervical cancer					**Total**
			No	**Yes**	
Sex	Male	Count	163	31	194
		%	84.0%	16.0%	100.0%
	Female	Count	107	114	221
		%	48.4%	51.6%	100.0%
Total		Count	270	145	415
		%	65.1%	34.9%	100.0%
Have you ever heard of the HPV vaccine					**Total**
			No	**Yes**	
Sex	Male	Count	158	36	194
		%	81.4%	18.6%	100.0%
	Female	Count	105	116	221
		%	47.5%	52.5%	100.0%
Total		Count	263	152	415
		%	63.4%	36.6%	100.0%
Know that HPV vaccine can prevent cervical cancer					**Total**
			No	**Yes**	
Sex	Male	Count	162	32	194
		%	83.5%	16.5%	100.0%
	Female	Count	129	92	221
		%	58.4%	41.6%	100.0%
Total		Count	291	124	415
		%	70.1%	29.9%	100.0%
Have you received HPV vaccine					**Total**
			No	**Yes**	
Sex	Male	Count	186	8	194
		%	95.9%	4.1%	100.0%
	Female	Count	180	41	221
		%	81.4%	18.6%	100.0%
Total		Count	366	49	415
		%	88.2%	11.8%	100.0%
Have you heard of the hepatitis B and C viruses					**Total**
			No	**Yes**	
Sex	Male	Count	102	92	194
		%	52.6%	47.4%	100.0%
	Female	Count	53	168	221
		%	24.0%	76.0%	100.0%
Total		Count	155	260	415
		%	37.3%	62.7%	100.0%
Know that hepatitis B and C viruses cause liver cancer					**Total**
			No	**Yes**	
Sex	Male	Count	136	58	194
		%	70.1%	29.9%	100.0%
	Female	Count	99	122	221
		%	44.8%	55.2%	100.0%
Total		Count	235	180	415
		%	56.6%	43.4%	100.0%

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Tab. S3 (*follows*).

Have you heard of the hepatitis B vaccine					Total
			No	Yes	
Sex	Male	Count	124	70	194
		%	63.9%	36.1%	100.0%
	Female	Count	73	148	221
		%	33.0%	67.0%	100.0%
Total		Count	197	218	415
		%	47.5%	52.5%	100.0%
Know that Hepatitis B vaccine can prevent liver cancer					**Total**
			No	**Yes**	
Sex	Male	Count	147	47	194
		%	75.8%	24.2%	100.0%
	Female	Count	116	105	221
		%	52.5%	47.5%	100.0%
Total		Count	263	152	415
		%	63.4%	36.6%	100.0%
Have you received HBV vaccine					**Total**
			No	**Yes**	
Sex	Male	Count	162	32	194
		%	83.5%	16.5%	100.0%
	Female	Count	138	83	221
		%	62.4%	37.6%	100.0%
Total		Count	300	115	415
		%	72.3%	27.7%	100.0%
Heard of Kaposi sarcoma herpes virus (KSHV)					**Total**
			No	**Yes**	
Sex	Male	Count	159	35	194
		%	82.0%	18.0%	100.0%
	Female	Count	154	67	221
		%	69.7%	30.3%	100.0%
Total		Count	313	102	415
		%	75.4%	24.6%	100.0%
Know that Kaposi sarcoma herpes virus causes Kaposi sarcoma					**Total**
			No	**Yes**	
Sex	Male	Count	168	26	194
		%	86.6%	13.4%	100.0%
	Female	Count	164	57	221
		%	74.2%	25.8%	100.0%
Total		Count	332	83	415
		%	80.0%	20.0%	100.0%
Heard of Epstein Barr Virus (EBV)					**Total**
			No	**Yes**	
Sex	Male	Count	166	28	194
		%	85.6%	14.4%	100.0%
	Female	Count	148	73	221
		%	67.0%	33.0%	100.0%
Total		Count	314	101	415
		%	75.7%	24.3%	100.0%
Know that Epstein Barr virus causes lymphoma					**Total**
			No	**Yes**	
Sex	Male	Count	170	24	194
		%	87.6%	12.4%	100.0%
	Female	Count	155	66	221
		%	70.1%	29.9%	100.0%
Total		Count	325	90	415
		%	78.3%	21.7%	100.0%

Tab. S3 (*follows*).

Heard of Human T-lymphotropic virus 1 (HTLV-1)					Total
			No	Yes	
Sex	Male	Count	163	31	194
		%	84.0%	16.0%	100.0%
	Female	Count	148	73	221
		%	67.0%	33.0%	100.0%
Total		Count	311	104	415
		%	74.9%	25.1%	100.0%
Know that HTLV-1 causes lymphoma					**Total**
			No	**Yes**	
Sex	Male	Count	168	26	194
		%	86.6%	13.4%	100.0%
	Female	Count	154	67	221
		%	69.7%	30.3%	100.0%
Total		Count	322	93	415
		%	77.6%	22.4%	100.0%
Heard of the bacteria *Helicobacter pylori*					**Total**
			No	**Yes**	
Sex	Male	Count	150	44	194
		%	77.3%	22.7%	100.0%
	Female	Count	108	113	221
		%	48.9%	51.1%	100.0%
Total		Count	258	157	415
		%	62.2%	37.8%	100.0%
Know that *Helicobacter pylori* is associated to cancer of the stomach					**Total**
			No	**Yes**	
Sex	Male	Count	158	36	194
		%	81.4%	18.6%	100.0%
	Female	Count	118	103	221
		%	53.4%	46.6%	100.0%
Total		Count	276	139	415
		%	66.5%	33.5%	100.0%
Have you heard about some cancer types associated with bacteria?					**Total**
			No	**Yes**	
Marital status	Divorced/ widowed	Count	11	5	16
		%	68.8%	31.3%	100.0%
	Married	Count	80	38	118
		%	67.8%	32.2%	100.0%
	Single	Count	155	126	281
		%	55.2%	44.8%	100.0%
Total		Count	246	169	415
		%	59.3%	40.7%	100.0%
Have you heard about some cancer types associated with viruses?					**Total**
			No	**Yes**	
Marital status	Divorced/ widowed	Count	12	4	16
		%	75.0%	25.0%	100.0%
	Married	Count	77	41	118
		%	65.3%	34.7%	100.0%
	Single	Count	141	140	281
		%	50.2%	49.8%	100.0%
Total		Count	230	185	415
		% s	55.4%	44.6%	100.0%

Tab. S3 (*follows*).

Have you heard of 'Oncovirus'					Total
			No	Yes	
Marital status	Divorced/ widowed	Count	14	2	16
		%	87.5%	12.5%	100.0%
	Married	Count	95	23	118
		%	80.5%	19.5%	100.0%
	Single	Count	200	81	281
		%	71.2%	28.8%	100.0%
Total		Count	309	106	415
		%	74.5%	25.5%	100.0%
Know that vaccine can prevent some cancer types					**Total**
			No	**Yes**	
Marital status	Divorced/ widowed	Count	12	4	16
		%	75.0%	25.0%	100.0%
	Married	Count	77	41	118
		%	65.3%	34.7%	100.0%
	Single	Count	168	113	281
		%	59.8%	40.2%	100.0%
Total		Count	257	158	415
		%	61.9%	38.1%	100.0%
Have you heard of Human papillomavirus (HPV)					**Total**
			No	**Yes**	
Marital status	Divorced/ widowed	Count	10	6	16
		%	62.5%	37.5%	100.0%
	Married	Count	74	44	118
		%	62.7%	37.3%	100.0%
	Single	Count	149	132	281
		%	53.0%	47.0%	100.0%
Total		Count	233	182	415
		%	56.1%	43.9%	100.0%
Know that HPV infection causes cervical cancer					**Total**
			No	**Yes**	
Marital status	Divorced/ widowed	Count	11	5	16
		%	68.8%	31.3%	100.0%
	Married	Count	84	34	118
		%	71.2%	28.8%	100.0%
	Single	Count	175	106	281
		%	62.3%	37.7%	100.0%
Total		Count	270	145	415
		%	65.1%	34.9%	100.0%
Have you ever heard of the HPV vaccine					**Total**
			No	**Yes**	
Marital status	Divorced/ widowed	Count	10	6	16
		%	62.5%	37.5%	100.0%
	Married	Count	82	36	118
		%	69.5%	30.5%	100.0%
	Single	Count	171	110	281
		%	60.9%	39.1%	100.0%
Total		Count	263	152	415
		%	63.4%	36.6%	100.0%

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Tab. S3 (*follows*).

Know that HPV vaccine can prevent cervical cancer					Total
			No	Yes	
Marital status	Divorced/ widowed	Count	12	4	16
		%	75.0%	25.0%	100.0%
	Married	Count	85	33	118
		%	72.0%	28.0%	100.0%
	Single	Count	194	87	281
		%	69.0%	31.0%	100.0%
Total		Count	291	124	415
		%	70.1%	29.9%	100.0%
Have you received HPV vaccine					**Total**
			No	**Yes**	
Marital status	Divorced/ widowed	Count	15	1	16
		%	93.8%	6.3%	100.0%
	Married	Count	105	13	118
		%	89.0%	11.0%	100.0%
	Single	Count	246	35	281
		%	87.5%	12.5%	100.0%
Total		Count	366	49	415
		%	88.2%	11.8%	100.0%
Have you heard of the hepatitis B and C viruses					**Total**
			No	**Yes**	
Marital status	Divorced/ widowed	Count	5	11	16
		%	31.3%	68.8%	100.0%
	Married	Count	57	61	118
		%	48.3%	51.7%	100.0%
	Single	Count	93	188	281
		%	33.1%	66.9%	100.0%
Total		Count	155	260	415
		%	37.3%	62.7%	100.0%
Know that hepatitis B and C viruses cause liver cancer					**Total**
			No	**Yes**	
Marital status	Divorced/ widowed	Count	8	8	16
		%	50.0%	50.0%	100.0%
	Married	Count	74	44	118
		%	62.7%	37.3%	100.0%
	Single	Count	153	128	281
		%	54.4%	45.6%	100.0%
Total		Count	235	180	415
		%	56.6%	43.4%	100.0%
Have you heard of the hepatitis B vaccine					**Total**
			No	**Yes**	
Marital status	Divorced/ widowed	Count	10	6	16
		%	62.5%	37.5%	100.0%
	Married	Count	64	54	118
		%	54.2%	45.8%	100.0%
	Single	Count	123	158	281
		%	43.8%	56.2%	100.0%
Total		Count	197	218	415
		%	47.5%	52.5%	100.0%

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Tab. S3 (*follows*).

Know that Hepatitis B vaccine can prevent liver cancer					Total
			No	Yes	
Marital status	Divorced/ widowed	Count	11	5	16
		%	68.8%	31.3%	100.0%
	Married	Count	84	34	118
		%	71.2%	28.8%	100.0%
	Single	Count	168	113	281
		%	59.8%	40.2%	100.0%
Total		Count	263	152	415
		%	63.4%	36.6%	100.0%
Have you received HBV vaccine					**Total**
			No	Yes	
Marital status	Divorced/ widowed	Count	12	4	16
		%	75.0%	25.0%	100.0%
	Married	Count	90	28	118
		%	76.3%	23.7%	100.0%
	Single	Count	198	83	281
		%	70.5%	29.5%	100.0%
Total		Count	300	115	415
		%	72.3%	27.7%	100.0%
Heard of Kaposi sarcoma herpes virus (KSHV)					**Total**
			No	Yes	
Marital status	Divorced/ widowed	Count	12	4	16
		%	75.0%	25.0%	100.0%
	Married	Count	94	24	118
		%	79.7%	20.3%	100.0%
	Single	Count	207	74	281
		%	73.7%	26.3%	100.0%
Total		Count	313	102	415
		%	75.4%	24.6%	100.0%
Know that Kaposi sarcoma herpes virus causes Kaposi sarcoma					**Total**
			No	Yes	
Marital status	Divorced/ widowed	Count	12	4	16
		%	75.0%	25.0%	100.0%
	Married	Count	99	19	118
		%	83.9%	16.1%	100.0%
	Single	Count	221	60	281
		%	78.6%	21.4%	100.0%
Total		Count	332	83	415
		%	80.0%	20.0%	100.0%
Heard of Epstein Barr Virus (EBV)					**Total**
			No	Yes	
Marital status	Divorced/ widowed	Count	13	3	16
		%	81.3%	18.8%	100.0%
	Married	Count	96	22	118
		%	81.4%	18.6%	100.0%
	Single	Count	205	76	281
		%	73.0%	27.0%	100.0%
Total		Count	314	101	415
		%	75.7%	24.3%	100.0%

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Tab. S3 (*follows*).

Know that Epstein Barr virus causes lymphoma					Total
			No	Yes	
Marital status	Divorced/ widowed	Count	13	3	16
		%	81.3%	18.8%	100.0%
	Married	Count	102	16	118
		%	86.4%	13.6%	100.0%
	Single	Count	210	71	281
		%	74.7%	25.3%	100.0%
Total		Count	325	90	415
		%	78.3%	21.7%	100.0%
Heard of Human T-lymphotropic virus 1 (HTLV-1)					**Total**
			No	Yes	
Marital status	Divorced/ widowed	Count	12	4	16
		%	75.0%	25.0%	100.0%
	Married	Count	100	18	118
		%	84.7%	15.3%	100.0%
	Single	Count	199	82	281
		%	70.8%	29.2%	100.0%
Total		Count	311	104	415
		%	74.9%	25.1%	100.0%
Know that HTLV-1 causes lymphoma					**Total**
			No	Yes	
Marital status	Divorced/ widowed	Count	12	4	16
		%	75.0%	25.0%	100.0%
	Married	Count	102	16	118
		%	86.4%	13.6%	100.0%
	Single	Count	208	73	281
		%	74.0%	26.0%	100.0%
Total		Count	322	93	415
		%	77.6%	22.4%	100.0%
Heard of the bacteria *Helicobacter pylori*					**Total**
			No	Yes	
Marital status	Divorced/ widowed	Count	11	5	16
		%	68.8%	31.3%	100.0%
	Married	Count	80	38	118
		%	67.8%	32.2%	100.0%
	Single	Count	167	114	281
		%	59.4%	40.6%	100.0%
Total		Count	258	157	415
		%	62.2%	37.8%	100.0%
Know that *Helicobacter pylori* is associated to cancer of the stomach					**Total**
			No	Yes	
Marital status	Divorced/ widowed	Count	11	5	16
		%	68.8%	31.3%	100.0%
	Married	Count	85	33	118
		%	72.0%	28.0%	100.0%
	Single	Count	180	101	281
		%	64.1%	35.9%	100.0%
Total		Count	276	139	415
		%	66.5%	33.5%	100.0%

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Tab. S3 (*follows*).

Have you heard about some cancer types associated with bacteria?					Total
			No	Yes	
Nationality	Non-Lebanese	Count	89	25	114
		%	78.1%	21.9%	100.0%
	Lebanese	Count	157	144	301
		%	52.2%	47.8%	100.0%
Total		Count	246	169	415
		%	59.3%	40.7%	100.0%
Have you heard about some cancer types associated with viruses?					**Total**
			No	**Yes**	
Nationality	Non-Lebanese	Count	81	33	114
		%	71.1%	28.9%	100.0%
	Lebanese	Count	149	152	301
		%	49.5%	50.5%	100.0%
Total		Count	230	185	415
		%	55.4%	44.6%	100.0%
Have you heard of 'Oncovirus'					**Total**
			No	**Yes**	
Nationality	Non-Lebanese	Count	100	14	114
		%	87.7%	12.3%	100.0%
	Lebanese	Count	209	92	301
		%	69.4%	30.6%	100.0%
Total		Count	309	106	415
		%	74.5%	25.5%	100.0%
Know that vaccine can prevent some cancer types					**Total**
			No	**Yes**	
Nationality	Non-Lebanese	Count	90	24	114
		%	78.9%	21.1%	100.0%
	Lebanese	Count	167	134	301
		%	55.5%	44.5%	100.0%
Total		Count	257	158	415
		%	61.9%	38.1%	100.0%
Have you heard of Human papillomavirus (HPV)					**Total**
			No	**Yes**	
Nationality	Non-Lebanese	Count	89	25	114
		%	78.1%	21.9%	100.0%
	Lebanese	Count	144	157	301
		%	47.8%	52.2%	100.0%
Total		Count	233	182	415
		%	56.1%	43.9%	100.0%
Know that HPV infection causes cervical cancer					**Total**
			No	**Yes**	
Nationality	Non-Lebanese	Count	95	19	114
		%	83.3%	16.7%	100.0%
	Lebanese	Count	175	126	301
		%	58.1%	41.9%	100.0%
Total		Count	270	145	415
		%	65.1%	34.9%	100.0%
Have you ever heard of the HPV vaccine					**Total**
			No	**Yes**	
Nationality	Non-Lebanese	Count	92	22	114
		%	80.7%	19.3%	100.0%
	Lebanese	Count	171	130	301
		%	56.8%	43.2%	100.0%
Total		Count	263	152	415
		%	63.4%	36.6%	100.0%

Tab. S3 (*follows*).

Know that HPV vaccine can prevent cervical cancer					Total
			No	Yes	
Nationality	Non-Lebanese	Count	94	20	114
		%	82.5%	17.5%	100.0%
	Lebanese	Count	197	104	301
		%	65.4%	34.6%	100.0%
Total		Count	291	124	415
		%	70.1%	29.9%	100.0%
Have you received HPV vaccine					**Total**
			No	**Yes**	
Nationality	Non-Lebanese	Count	106	8	114
		%	93.0%	7.0%	100.0%
	Lebanese	Count	260	41	301
		%	86.4%	13.6%	100.0%
Total		Count	366	49	415
		%	88.2%	11.8%	100.0%
Have you heard of the hepatitis B and C viruses					**Total**
			No	**Yes**	
Nationality	Non-Lebanese	Count	74	40	114
		%	64.9%	35.1%	100.0%
	Lebanese	Count	81	220	301
		%	26.9%	73.1%	100.0%
Total		Count	155	260	415
		%	37.3%	62.7%	100.0%
Know that hepatitis B and C viruses cause liver cancer					**Total**
			No	**Yes**	
Nationality	Non-Lebanese	Count	86	28	114
		%	75.4%	24.6%	100.0%
	Lebanese	Count	149	152	301
		%	49.5%	50.5%	100.0%
Total		Count	235	180	415
		%	56.6%	43.4%	100.0%
Have you heard of the hepatitis B vaccine					**Total**
			No	**Yes**	
Nationality	Non-Lebanese	Count	80	34	114
		%	70.2%	29.8%	100.0%
	Lebanese	Count	117	184	301
		%	38.9%	61.1%	100.0%
Total		Count	197	218	415
		%	47.5%	52.5%	100.0%
Know that Hepatitis B vaccine can prevent liver cancer					**Total**
			No	**Yes**	
Nationality	Non-Lebanese	Count	94	20	114
		%	82.5%	17.5%	100.0%
	Lebanese	Count	169	132	301
		%	56.1%	43.9%	100.0%
Total		Count	263	152	415
		%	63.4%	36.6%	100.0%
Have you received HBV vaccine					**Total**
			No	**Yes**	
Nationality	Non-Lebanese	Count	93	21	114
		%	81.6%	18.4%	100.0%
	Lebanese	Count	207	94	301
		%	68.8%	31.2%	100.0%
Total		Count	300	115	415
		%	72.3%	27.7%	100.0%

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Tab. S3 (*follows*).

Heard of Kaposi sarcoma herpes virus (KSHV)					Total
			No	Yes	
Nationality	Non-Lebanese	Count	95	19	114
		%	83.3%	16.7%	100.0%
	Lebanese	Count	218	83	301
		%	72.4%	27.6%	100.0%
Total		Count	313	102	415
		%	75.4%	24.6%	100.0%
Know that Kaposi sarcoma herpes virus causes Kaposi sarcoma					Total
			No	Yes	
Nationality	Non-Lebanese	Count	98	16	114
		%	86.0%	14.0%	100.0%
	Lebanese	Count	234	67	301
		%	77.7%	22.3%	100.0%
Total		Count	332	83	415
		%	80.0%	20.0%	100.0%
Heard of Epstein Barr Virus (EBV)					Total
			No	Yes	
Nationality	Non-Lebanese	Count	93	21	114
		%	81.6%	18.4%	100.0%
	Lebanese	Count	221	80	301
		%	73.4%	26.6%	100.0%
Total		Count	314	101	415
		%	75.7%	24.3%	100.0%
Know that Epstein Barr virus causes lymphoma					Total
			No	Yes	
Nationality	Non-Lebanese	Count	96	18	114
		%	84.2%	15.8%	100.0%
	Lebanese	Count	229	72	301
		%	76.1%	23.9%	100.0%
Total		Count	325	90	415
		%	78.3%	21.7%	100.0%
Heard of Human T-lymphotropic virus 1 (HTLV-1)					Total
			No	Yes	
Nationality	Non-Lebanese	Count	96	18	114
		%	84.2%	15.8%	100.0%
	Lebanese	Count	215	86	301
		%	71.4%	28.6%	100.0%
Total		Count	311	104	415
		%	74.9%	25.1%	100.0%
Know that HTLV-1 causes lymphoma					Total
			No	Yes	
Nationality	Non-Lebanese	Count	96	18	114
		%	84.2%	15.8%	100.0%
	Lebanese	Count	226	75	301
		%	75.1%	24.9%	100.0%
Total		Count	322	93	415
		%	77.6%	22.4%	100.0%
Heard of the bacteria *Helicobacter pylori*					Total
			No	Yes	
Nationality	Non-Lebanese	Count	87	27	114
		%	76.3%	23.7%	100.0%
	Lebanese	Count	171	130	301
		%	56.8%	43.2%	100.0%
Total		Count	258	157	415
		%	62.2%	37.8%	100.0%

Tab. S3 (*follows*).

Know that *Helicobacter pylori* is associated to cancer of the stomach					Total
			No	Yes	
Nationality	non-Lebanese	Count	89	25	114
		%	78.1%	21.9%	100.0%
	Lebanese	Count	187	114	301
		%	62.1%	37.9%	100.0%
Total		Count	276	139	415
		%	66.5%	33.5%	100.0%
Have you heard about some cancer types associated with bacteria?					**Total**
			No	**Yes**	
Place of residence	Beirut	Count	62	49	111
		%	55.9%	44.1%	100.0%
	Bekaa	Count	88	72	160
		%	55.0%	45.0%	100.0%
	mount Lebanon	Count	36	23	59
		%	61.0%	39.0%	100.0%
	north Lebanon	Count	33	11	44
		%	75.0%	25.0%	100.0%
	south Lebanon	Count	27	14	41
		%	65.9%	34.1%	100.0%
Total		Count	246	169	415
		%	59.3%	40.7%	100.0%
Have you heard about some cancer types associated with viruses?					**Total**
			No	**Yes**	
Place of residence	Beirut	Count	63	48	111
		%	56.8%	43.2%	100.0%
	Bekaa	Count	83	77	160
		%	51.9%	48.1%	100.0%
	mount Lebanon	Count	30	29	59
		%	50.8%	49.2%	100.0%
	north Lebanon	Count	31	13	44
		%	70.5%	29.5%	100.0%
	south Lebanon	Count	23	18	41
		%	56.1%	43.9%	100.0%
Total		Count	230	185	415
		%	55.4%	44.6%	100.0%
Have you heard of 'Oncovirus'					**Total**
			No	**Yes**	
Place of residence	Beirut	Count	80	31	111
		%	72.1%	27.9%	100.0%
	Bekaa	Count	124	36	160
		%	77.5%	22.5%	100.0%
	mount Lebanon	Count	43	16	59
		%	72.9%	27.1%	100.0%
	north Lebanon	Count	35	9	44
		%	79.5%	20.5%	100.0%
	south Lebanon	Count	27	14	41
		%	65.9%	34.1%	100.0%
Total		Count	309	106	415
		%	74.5%	25.5%	100.0%

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Tab. S3 (*follows*).

Know that vaccine can prevent some cancer types					Total
			No	Yes	
Place of residence	Beirut	Count	67	44	111
		%	60.4%	39.6%	100.0%
	Bekaa	Count	93	67	160
		%	58.1%	41.9%	100.0%
	mount Lebanon	Count	36	23	59
		%	61.0%	39.0%	100.0%
	north Lebanon	Count	33	11	44
		%	75.0%	25.0%	100.0%
	south Lebanon	Count	28	13	41
		% e	68.3%	31.7%	100.0%
Total		Count	257	158	415
		%	61.9%	38.1%	100.0%
Have you heard of Human papillomavirus (HPV)					Total
			No	Yes	
Place of residence	Beirut	Count	57	54	111
		%	51.4%	48.6%	100.0%
	Bekaa	Count	87	73	160
		%	54.4%	45.6%	100.0%
	mount Lebanon	Count	33	26	59
		%	55.9%	44.1%	100.0%
	north Lebanon	Count	33	11	44
		%	75.0%	25.0%	100.0%
	south Lebanon	Count	23	18	41
		%	56.1%	43.9%	100.0%
Total		Count	233	182	415
		%	56.1%	43.9%	100.0%
Know that HPV infection causes cervical cancer					Total
			No	Yes	
Place of residence	Beirut	Count	71	40	111
		%	64.0%	36.0%	100.0%
	Bekaa	Count	101	59	160
		%	63.1%	36.9%	100.0%
	mount Lebanon	Count	39	20	59
		%	66.1%	33.9%	100.0%
	north Lebanon	Count	35	9	44
		%	79.5%	20.5%	100.0%
	south Lebanon	Count	24	17	41
		%	58.5%	41.5%	100.0%
Total		Count	270	145	415
		%	65.1%	34.9%	100.0%
Have you ever heard of the HPV vaccine					Total
			No	Yes	
Place of residence	Beirut	Count	69	42	111
		%	62.2%	37.8%	100.0%
	Bekaa	Count	97	63	160
		%	60.6%	39.4%	100.0%
	mount Lebanon	Count	38	21	59
		%	64.4%	35.6%	100.0%
	north Lebanon	Count	34	10	44
		%	77.3%	22.7%	100.0%
	south Lebanon	Count	25	16	41
		%	61.0%	39.0%	100.0%
Total		Count	263	152	415
		%	63.4%	36.6%	100.0%

Tab. S3 (*follows*).

Know that HPV vaccine can prevent cervical cancer					Total
			No	Yes	
Place of residence	Beirut	Count	80	31	111
		%	72.1%	27.9%	100.0%
	Bekaa	Count	105	55	160
		%	65.6%	34.4%	100.0%
	mount Lebanon	Count	43	16	59
		%	72.9%	27.1%	100.0%
	north Lebanon	Count	34	10	44
		%	77.3%	22.7%	100.0%
	south Lebanon	Count	29	12	41
		%	70.7%	29.3%	100.0%
Total		Count	291	124	415
		%	70.1%	29.9%	100.0%
Have you received HPV vaccine					**Total**
			No	**Yes**	
Place of residence	Beirut	Count	98	13	111
		%	88.3%	11.7%	100.0%
	Bekaa	Count	141	19	160
		%	88.1%	11.9%	100.0%
	mount Lebanon	Count	50	9	59
		%	84.7%	15.3%	100.0%
	north Lebanon	Count	42	2	44
		%	95.5%	4.5%	100.0%
	south Lebanon	Count	35	6	41
		%	85.4%	14.6%	100.0%
Total		Count	366	49	415
		%	88.2%	11.8%	100.0%
Have you heard of the hepatitis B and C viruses					**Total**
			No	**Yes**	
Place of residence	Beirut	Count	43	68	111
		%	38.7%	61.3%	100.0%
	Bekaa	Count	54	106	160
		%	33.8%	66.3%	100.0%
	mount Lebanon	Count	18	41	59
		%	30.5%	69.5%	100.0%
	north Lebanon	Count	26	18	44
		%	59.1%	40.9%	100.0%
	south Lebanon	Count	14	27	41
		%	34.1%	65.9%	100.0%
Total		Count	155	260	415
		%	37.3%	62.7%	100.0%
Know that hepatitis B and C viruses cause liver cancer					**Total**
			No	**Yes**	
Place of residence	Beirut	Count	63	48	111
		%	56.8%	43.2%	100.0%
	Bekaa	Count	85	75	160
		%	53.1%	46.9%	100.0%
	mount Lebanon	Count	34	25	59
		%	57.6%	42.4%	100.0%
	north Lebanon	Count	34	10	44
		%	77.3%	22.7%	100.0%
	south Lebanon	Count	19	22	41
		%	46.3%	53.7%	100.0%
Total		Count	235	180	415
		%	56.6%	43.4%	100.0%

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Tab. S3 (*follows*).

Have you heard of the hepatitis B vaccine					Total
			No	Yes	
Place of residence	Beirut	Count	54	57	111
		%	48.6%	51.4%	100.0%
	Bekaa	Count	67	93	160
		%	41.9%	58.1%	100.0%
	mount Lebanon	Count	27	32	59
		%	45.8%	54.2%	100.0%
	north Lebanon	Count	29	15	44
		%	65.9%	34.1%	100.0%
	south Lebanon	Count	20	21	41
		%	48.8%	51.2%	100.0%
Total		Count	197	218	415
		%	47.5%	52.5%	100.0%
Know that Hepatitis B vaccine can prevent liver cancer					**Total**
			No	Yes	
Place of residence	Beirut	Count	72	39	111
		%	64.9%	35.1%	100.0%
	Bekaa	Count	92	68	160
		%	57.5%	42.5%	100.0%
	mount Lebanon	Count	39	20	59
		%	66.1%	33.9%	100.0%
	north Lebanon	Count	34	10	44
		%	77.3%	22.7%	100.0%
	south Lebanon	Count	26	15	41
		%	63.4%	36.6%	100.0%
Total		Count	263	152	415
		%	63.4%	36.6%	100.0%
Have you received HBV vaccine					**Total**
			No	Yes	
Place of residence	Beirut	Count	75	36	111
		%	67.6%	32.4%	100.0%
	Bekaa	Count	114	46	160
		%	71.3%	28.8%	100.0%
	mount Lebanon	Count	44	15	59
		% place	74.6%	25.4%	100.0%
	north Lebanon	Count	37	7	44
		%	84.1%	15.9%	100.0%
	south Lebanon	Count	30	11	41
		%	73.2%	26.8%	100.0%
Total		Count	300	115	415
		%	72.3%	27.7%	100.0%
Heard of Kaposi sarcoma herpes virus (KSHV)					**Total**
			No	Yes	
Place of residence	Beirut	Count	75	36	111
		%	67.6%	32.4%	100.0%
	Bekaa	Count	125	35	160
		%	78.1%	21.9%	100.0%
	mount Lebanon	Count	46	13	59
		%	78.0%	22.0%	100.0%
	north Lebanon	Count	37	7	44
		%	84.1%	15.9%	100.0%
	south Lebanon	Count	30	11	41
		%	73.2%	26.8%	100.0%
Total		Count	313	102	415
		%	75.4%	24.6%	100.0%

Tab. S3 (*follows*).

Know that Kaposi sarcoma herpes virus causes Kaposi sarcoma					Total
			No	Yes	
Place of residence	Beirut	Count	84	27	111
		%	75.7%	24.3%	100.0%
	Bekaa	Count	132	28	160
		%	82.5%	17.5%	100.0%
	mount Lebanon	Count	48	11	59
		%	81.4%	18.6%	100.0%
	north Lebanon	Count	38	6	44
		%	86.4%	13.6%	100.0%
	south Lebanon	Count	30	11	41
		%	73.2%	26.8%	100.0%
Total		Count	332	83	415
		%	80.0%	20.0%	100.0%
Heard of Epstein Barr Virus (EBV)					**Total**
			No	Yes	
Place of residence	Beirut	Count	80	31	111
		%	72.1%	27.9%	100.0%
	Bekaa	Count	127	33	160
		%	79.4%	20.6%	100.0%
	mount Lebanon	Count	43	16	59
		%	72.9%	27.1%	100.0%
	north Lebanon	Count	36	8	44
		%	81.8%	18.2%	100.0%
	south Lebanon	Count	28	13	41
		%	68.3%	31.7%	100.0%
Total		Count	314	101	415
		%	75.7%	24.3%	100.0%
Know that Epstein Barr virus causes lymphoma					**Total**
			No	Yes	
Place of residence	Beirut	Count	82	29	111
		%	73.9%	26.1%	100.0%
	Bekaa	Count	132	28	160
		%	82.5%	17.5%	100.0%
	mount Lebanon	Count	46	13	59
		%	78.0%	22.0%	100.0%
	north Lebanon	Count	37	7	44
		%	84.1%	15.9%	100.0%
	south Lebanon	Count	28	13	41
		%	68.3%	31.7%	100.0%
Total		Count	325	90	415
		%	78.3%	21.7%	100.0%
Heard of Human T-lymphotropic virus 1 (HTLV-1)					**Total**
			No	Yes	
Place of residence	Beirut	Count	84	27	111
		%	75.7%	24.3%	100.0%
	Bekaa	Count	120	40	160
		%	75.0%	25.0%	100.0%
	mount Lebanon	Count	45	14	59
		%	76.3%	23.7%	100.0%
	north Lebanon	Count	36	8	44
		%	81.8%	18.2%	100.0%
	south Lebanon	Count	26	15	41
		%	63.4%	36.6%	100.0%
Total		Count	311	104	415
		%	74.9%	25.1%	100.0%

Tab. S3 (*follows*).

Know that HTLV-1 causes lymphoma					Total
			No	Yes	
Place of residence	Beirut	Count	85	26	111
		%	76.6%	23.4%	100.0%
	Bekaa	Count	126	34	160
		%	78.8%	21.3%	100.0%
	mount Lebanon	Count	48	11	59
		%	81.4%	18.6%	100.0%
	north Lebanon	Count	37	7	44
		%	84.1%	15.9%	100.0%
	south Lebanon	Count	26	15	41
		%	63.4%	36.6%	100.0%
Total		Count	322	93	415
		%	77.6%	22.4%	100.0%
Heard of the bacteria *Helicobacter pylori*					Total
			No	Yes	
Place of residence	Beirut	Count	71	40	111
		%	64.0%	36.0%	100.0%
	Bekaa	Count	94	66	160
		%	58.8%	41.3%	100.0%
	mount Lebanon	Count	36	23	59
		%	61.0%	39.0%	100.0%
	north Lebanon	Count	33	11	44
		%	75.0%	25.0%	100.0%
	south Lebanon	Count	24	17	41
		%	58.5%	41.5%	100.0%
Total		Count	258	157	415
		%	62.2%	37.8%	100.0%
Know that *Helicobacter pylori* is associated to cancer of the stomach					Total
			No	Yes	
Place of residence	Beirut	Count	74	37	111
		%	66.7%	33.3%	100.0%
	Bekaa	Count	103	57	160
		%	64.4%	35.6%	100.0%
	mount Lebanon	Count	40	19	59
		%	67.8%	32.2%	100.0%
	north Lebanon	Count	34	10	44
		%	77.3%	22.7%	100.0%
	south Lebanon	Count	25	16	41
		%	61.0%	39.0%	100.0%
Total		Count	276	139	415
		%	66.5%	33.5%	100.0%
Have you heard about some cancer types associated with bacteria?					Total
			No	Yes	
Age	18-29 years	Count	160	122	282
		%	56.7%	43.3%	100.0%
	30-49 years	Count	77	41	118
		%	65.3%	34.7%	100.0%
	50-64 years	Count	9	5	14
		%	64.3%	35.7%	100.0%
	64+ years	Count	0	1	1
		%	0.0%	100.0%	100.0%
Total		Count	246	169	415
		%	59.3%	40.7%	100.0%

Tab. S3 (*follows*).

Have you heard about some cancer types associated with viruses?					Total
			No	Yes	
Age	18-29 years	Count	146	136	282
		%	51.8%	48.2%	100.0%
	30-49 years	Count	75	43	118
		% e	63.6%	36.4%	100.0%
	50-64 years	Count	9	5	14
		%	64.3%	35.7%	100.0%
	64+ years	Count	0	1	1
		%	0.0%	100.0%	100.0%
Total		Count	230	185	415
		%	55.4%	44.6%	100.0%
Have you heard of 'Oncovirus'					Total
			No	Yes	
Age	18-29 years	Count	206	76	282
		%	73.0%	27.0%	100.0%
	30-49 years	Count	91	27	118
		%	77.1%	22.9%	100.0%
	50-64 years	Count	11	3	14
		%	78.6%	21.4%	100.0%
	64+ years	Count	1	0	1
		%	100.0%	0.0%	100.0%
Total		Count	309	106	415
		%	74.5%	25.5%	100.0%
Know that vaccine can prevent some cancer types					Total
			No	Yes	
Age	18-29 years	Count	172	110	282
		%	61.0%	39.0%	100.0%
	30-49 years	Count	77	41	118
		%	65.3%	34.7%	100.0%
	50-64 years	Count	7	7	14
		%	50.0%	50.0%	100.0%
	64+ years	Count	1	0	1
		%	100.0%	0.0%	100.0%
Total		Count	257	158	415
		%	61.9%	38.1%	100.0%
Have you heard of Human papillomavirus (HPV)					Total
			No	Yes	
Age	18-29 years	Count	149	133	282
		%	52.8%	47.2%	100.0%
	30-49 years	Count	72	46	118
		%	61.0%	39.0%	100.0%
	50-64 years	Count	11	3	14
		%	78.6%	21.4%	100.0%
	64+ years	Count	1	0	1
		%	100.0%	0.0%	100.0%
Total		Count	233	182	415
		%	56.1%	43.9%	100.0%

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Tab. S3 (*follows*).

Know that HPV infection causes cervical cancer					Total
			No	Yes	
Age	18-29 years	Count	174	108	282
		%	61.7%	38.3%	100.0%
	30-49 years	Count	84	34	118
		%	71.2%	28.8%	100.0%
	50-64 years	Count	11	3	14
		%	78.6%	21.4%	100.0%
	64+ years	Count	1	0	1
		%	100.0%	0.0%	100.0%
Total		Count	270	145	415
		%	65.1%	34.9%	100.0%
Have you ever heard of the HPV vaccine					Total
			No	Yes	
Age	18-29 years	Count	170	112	282
		%	60.3%	39.7%	100.0%
	30-49 years	Count	81	37	118
		%	68.6%	31.4%	100.0%
	50-64 years	Count	11	3	14
		%	78.6%	21.4%	100.0%
	64+ years	Count	1	0	1
		%	100.0%	0.0%	100.0%
Total		Count	263	152	415
		%	63.4%	36.6%	100.0%
Know that HPV vaccine can prevent cervical cancer					Total
			No	Yes	
Age	18-29 years	Count	193	89	282
		%	68.4%	31.6%	100.0%
	30-49 years	Count	86	32	118
		%	72.9%	27.1%	100.0%
	50-64 years	Count	11	3	14
		%	78.6%	21.4%	100.0%
	64+ years	Count	1	0	1
		%	100.0%	0.0%	100.0%
Total		Count	291	124	415
		%	70.1%	29.9%	100.0%
Have you received HPV vaccine					Total
			No	Yes	
Age	18-29 years	Count	250	32	282
		%	88.7%	11.3%	100.0%
	30-49 years	Count	103	15	118
		%	87.3%	12.7%	100.0%
	50-64 years	Count	12	2	14
		%	85.7%	14.3%	100.0%
	64+ years	Count	1	0	1
		%	100.0%	0.0%	100.0%
Total		Count	366	49	415
		%	88.2%	11.8%	100.0%

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Tab. S3 (*follows*).

Have you heard of the hepatitis B and C viruses					Total
			No	Yes	
Age	18-29 years	Count	99	183	282
		%	35.1%	64.9%	100.0%
	30-49 years	Count	51	67	118
		%	43.2%	56.8%	100.0%
	50-64 years	Count	4	10	14
		%	28.6%	71.4%	100.0%
	64+ years	Count	1	0	1
		%	100.0%	0.0%	100.0%
Total		Count	155	260	415
		%	37.3%	62.7%	100.0%
Know that hepatitis B and C viruses cause liver cancer					Total
			No	Yes	
Age	18-29 years	Count	155	127	282
		%	55.0%	45.0%	100.0%
	30-49 years	Count	72	46	118
		%	61.0%	39.0%	100.0%
	50-64 years	Count	7	7	14
		%	50.0%	50.0%	100.0%
	64+ years	Count	1	0	1
		%	100.0%	0.0%	100.0%
Total		Count	235	180	415
		%	56.6%	43.4%	100.0%
Have you heard of the hepatitis B vaccine					Total
			No	Yes	
Age	18-29 years	Count	126	156	282
		%	44.7%	55.3%	100.0%
	30-49 years	Count	63	55	118
		%	53.4%	46.6%	100.0%
	50-64 years	Count	7	7	14
		%	50.0%	50.0%	100.0%
	64+ years	Count	1	0	1
		%	100.0%	0.0%	100.0%
Total		Count	197	218	415
		%	47.5%	52.5%	100.0%
Know that Hepatitis B vaccine can prevent liver cancer					Total
			No	Yes	
Age	18-29 years	Count	171	111	282
		%	60.6%	39.4%	100.0%
	30-49 years	Count	82	36	118
		%	69.5%	30.5%	100.0%
	50-64 years	Count	9	5	14
		%	64.3%	35.7%	100.0%
	64+ years	Count	1	0	1
		%	100.0%	0.0%	100.0%
Total		Count	263	152	415
		%	63.4%	36.6%	100.0%

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Tab. S3 (*follows*).

Have you received HBV vaccine					Total
			No	Yes	
Age	18-29 years	Count	203	79	282
		%	72.0%	28.0%	100.0%
	30-49 years	Count	84	34	118
		%	71.2%	28.8%	100.0%
	50-64 years	Count	12	2	14
		%	85.7%	14.3%	100.0%
	64+ years	Count	1	0	1
		%	100.0%	0.0%	100.0%
Total		Count	300	115	415
		%	72.3%	27.7%	100.0%
Heard of Kaposi sarcoma herpes virus (KSHV)					**Total**
			No	**Yes**	
Age	18-29 years	Count	211	71	282
		%	74.8%	25.2%	100.0%
	30-49 years	Count	89	29	118
		%	75.4%	24.6%	100.0%
	50-64 years	Count	12	2	14
		%	85.7%	14.3%	100.0%
	64+ years	Count	1	0	1
		%	100.0%	0.0%	100.0%
Total		Count	313	102	415
		%	75.4%	24.6%	100.0%
Know that Kaposi sarcoma herpes virus causes Kaposi sarcoma					**Total**
			No	**Yes**	
Age	18-29 years	Count	222	60	282
		%	78.7%	21.3%	100.0%
	30-49 years	Count	97	21	118
		%	82.2%	17.8%	100.0%
	50-64 years	Count	12	2	14
		%	85.7%	14.3%	100.0%
	64+ years	Count	1	0	1
		%	100.0%	0.0%	100.0%
Total		Count	332	83	415
		%	80.0%	20.0%	100.0%
Heard of Epstein Barr Virus (EBV)					**Total**
			No	**Yes**	
Age	18-29 years	Count	208	74	282
		%	73.8%	26.2%	100.0%
	30-49 years	Count	94	24	118
		%	79.7%	20.3%	100.0%
	50-64 years	Count	11	3	14
		%	78.6%	21.4%	100.0%
	64+ years	Count	1	0	1
		%	100.0%	0.0%	100.0%
Total		Count	314	101	415
		%	75.7%	24.3%	100.0%

Tab. S3 (*follows*).

Know that Epstein Barr virus causes lymphoma					Total
			No	Yes	
Age	18-29 years	Count	214	68	282
		%	75.9%	24.1%	100.0%
	30-49 years	Count	98	20	118
		%	83.1%	16.9%	100.0%
	50-64 years	Count	12	2	14
		%	85.7%	14.3%	100.0%
	64+ years	Count	1	0	1
		%	100.0%	0.0%	100.0%
Total		Count	325	90	415
		%	78.3%	21.7%	100.0%
Heard of Human T-lymphotropic virus 1 (HTLV-1)					Total
			No	Yes	
Age	18-29 years	Count	204	78	282
		%	72.3%	27.7%	100.0%
	30-49 years	Count	95	23	118
		%	80.5%	19.5%	100.0%
	50-64 years	Count	11	3	14
		%	78.6%	21.4%	100.0%
	64+ years	Count	1	0	1
		%	100.0%	0.0%	100.0%
Total		Count	311	104	415
		%	74.9%	25.1%	100.0%
Know that HTLV-1 causes lymphoma					Total
			No	Yes	
Age	18-29 years	Count	213	69	282
		%	75.5%	24.5%	100.0%
	30-49 years	Count	96	22	118
		%	81.4%	18.6%	100.0%
	50-64 years	Count	12	2	14
		%	85.7%	14.3%	100.0%
	64+ years	Count	1	0	1
		%	100.0%	0.0%	100.0%
Total		Count	322	93	415
		%	77.6%	22.4%	100.0%
Heard of the bacteria *Helicobacter pylori*					Total
			No	Yes	
Age	18-29 years	Count	175	107	282
		%	62.1%	37.9%	100.0%
	30-49 years	Count	72	46	118
		%	61.0%	39.0%	100.0%
	50-64 years	Count	10	4	14
		%	71.4%	28.6%	100.0%
	64+ years	Count	1	0	1
		%	100.0%	0.0%	100.0%
Total		Count	258	157	415
		%	62.2%	37.8%	100.0%
Know that *Helicobacter pylori* is associated to cancer of the stomach					Total
			No	Yes	
Age	18-29 years	Count	184	98	282
		%	65.2%	34.8%	100.0%
	30-49 years	Count	80	38	118
		%	67.8%	32.2%	100.0%
	50-64 years	Count	11	3	14
		%	78.6%	21.4%	100.0%
	64+ years	Count	1	0	1
		%	100.0%	0.0%	100.0%
Total		Count	276	139	415
		%	66.5%	33.5%	100.0%

Tab. S3 (*follows*).

Have you heard about some cancer types associated with bacteria?					Total
			No	Yes	
Education level	Primary	Count	1	2	3
		%	33.3%	66.7%	100.0%
	Secondary	Count	30	8	38
		%	78.9%	21.1%	100.0%
	Tertiary	Count	215	159	374
		%	57.5%	42.5%	100.0%
Total		Count	246	169	415
		%	59.3%	40.7%	100.0%
Have you heard about some cancer types associated with viruses?					**Total**
			No	**Yes**	
Education level	Primary	Count	1	2	3
		%	33.3%	66.7%	100.0%
	Secondary	Count	30	8	38
		%	78.9%	21.1%	100.0%
	Tertiary	Count	199	175	374
		%	53.2%	46.8%	100.0%
Total		Count	230	185	415
		%	55.4%	44.6%	100.0%
Have you heard of 'Oncovirus'					**Total**
			No	**Yes**	
Education level	Primary	Count	3	0	3
		%	100.0%	0.0%	100.0%
	Secondary	Count	34	4	38
		%	89.5%	10.5%	100.0%
	Tertiary	Count	272	102	374
		%	72.7%	27.3%	100.0%
Total		Count	309	106	415
		%	74.5%	25.5%	100.0%
Know that vaccine can prevent some cancer types					**Total**
			No	**Yes**	
Education level	Primary	Count	2	1	3
		%	66.7%	33.3%	100.0%
	Secondary	Count	29	9	38
		%	76.3%	23.7%	100.0%
	Tertiary	Count	226	148	374
		%	60.4%	39.6%	100.0%
Total		Count	257	158	415
		%	61.9%	38.1%	100.0%
Have you heard of Human papillomavirus (HPV)					**Total**
			No	**Yes**	
Education level	Primary	Count	3	0	3
		%	100.0%	0.0%	100.0%
	Secondary	Count	28	10	38
		%	73.7%	26.3%	100.0%
	Tertiary	Count	202	172	374
		%	54.0%	46.0%	100.0%
Total		Count	233	182	415
		%	56.1%	43.9%	100.0%

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Tab. S3 (*follows*).

Know that HPV infection causes cervical cancer					Total
			No	Yes	
Education level	Primary	Count	3	0	3
		%	100.0%	0.0%	100.0%
	Secondary	Count	31	7	38
		%	81.6%	18.4%	100.0%
	Tertiary	Count	236	138	374
		%	63.1%	36.9%	100.0%
Total		Count	270	145	415
		%	65.1%	34.9%	100.0%
Have you ever heard of the HPV vaccine					**Total**
			No	**Yes**	
Education level	Primary	Count	3	0	3
		%	100.0%	0.0%	100.0%
	Secondary	Count	30	8	38
		%	78.9%	21.1%	100.0%
	Tertiary	Count	230	144	374
		%	61.5%	38.5%	100.0%
Total		Count	263	152	415
		%	63.4%	36.6%	100.0%
Know that HPV vaccine can prevent cervical cancer					**Total**
			No	**Yes**	
Education level	Primary	Count	3	0	3
		%	100.0%	0.0%	100.0%
	Secondary	Count	30	8	38
		%	78.9%	21.1%	100.0%
	Tertiary	Count	258	116	374
		%	69.0%	31.0%	100.0%
Total		Count	291	124	415
		%	70.1%	29.9%	100.0%
Have you received HPV vaccine					**Total**
			No	**Yes**	
Education level	Primary	Count	3	0	3
		%	100.0%	0.0%	100.0%
	Secondary	Count	33	5	38
		%	86.8%	13.2%	100.0%
	Tertiary	Count	330	44	374
		%	88.2%	11.8%	100.0%
Total		Count	366	49	415
		%	88.2%	11.8%	100.0%
Have you heard of the hepatitis B and C viruses					**Total**
			No	**Yes**	
Education level	Primary	Count	3	0	3
		%	100.0%	0.0%	100.0%
	Secondary	Count	21	17	38
		% l	55.3%	44.7%	100.0%
	Tertiary	Count	131	243	374
		%	35.0%	65.0%	100.0%
Total		Count	155	260	415
		%	37.3%	62.7%	100.0%

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Tab. S3 (*follows*).

Know that hepatitis B and C viruses cause liver cancer					Total
			No	Yes	
Education level	Primary	Count	3	0	3
		%	100.0%	0.0%	100.0%
	Secondary	Count	28	10	38
		%	73.7%	26.3%	100.0%
	Tertiary	Count	204	170	374
		%	54.5%	45.5%	100.0%
Total		Count	235	180	415
		%	56.6%	43.4%	100.0%
Have you heard of the hepatitis B vaccine					**Total**
			No	**Yes**	
Education level	Primary	Count	3	0	3
		%	100.0%	0.0%	100.0%
	Secondary	Count	26	12	38
		%	68.4%	31.6%	100.0%
	Tertiary	Count	168	206	374
		%	44.9%	55.1%	100.0%
Total		Count	197	218	415
		%	47.5%	52.5%	100.0%
Know that Hepatitis B vaccine can prevent liver cancer					**Total**
			No	**Yes**	
Education level	Primary	Count	3	0	3
		%	100.0%	0.0%	100.0%
	Secondary	Count	28	10	38
		%	73.7%	26.3%	100.0%
	Tertiary	Count	232	142	374
		%	62.0%	38.0%	100.0%
Total		Count	263	152	415
		%	63.4%	36.6%	100.0%
Have you received HBV vaccine					**Total**
			No	**Yes**	
Education level	Primary	Count	3	0	3
		%	100.0%	0.0%	100.0%
	Secondary	Count	32	6	38
		%	84.2%	15.8%	100.0%
	Tertiary	Count	265	109	374
		%	70.9%	29.1%	100.0%
Total		Count	300	115	415
		%	72.3%	27.7%	100.0%
Heard of Kaposi sarcoma herpes virus (KSHV)					**Total**
			No	**Yes**	
Education level	Primary	Count	3	0	3
		%	100.0%	0.0%	100.0%
	Secondary	Count	33	5	38
		%	86.8%	13.2%	100.0%
	Tertiary	Count	277	97	374
		%	74.1%	25.9%	100.0%
Total		Count	313	102	415
		%	75.4%	24.6%	100.0%

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Tab. S3 (*follows*).

Know that Kaposi sarcoma herpes virus causes Kaposi sarcoma					Total
			No	Yes	
Education level	Primary	Count	3	0	3
		%	100.0%	0.0%	100.0%
	Secondary	Count	34	4	38
		%	89.5%	10.5%	100.0%
	Tertiary	Count	295	79	374
		%	78.9%	21.1%	100.0%
Total		Count	332	83	415
		%	80.0%	20.0%	100.0%
Heard of Epstein Barr Virus (EBV)					**Total**
			No	Yes	
Education level	Primary	Count	3	0	3
		%	100.0%	0.0%	100.0%
	Secondary	Count	32	6	38
		%	84.2%	15.8%	100.0%
	Tertiary	Count	279	95	374
		%	74.6%	25.4%	100.0%
Total		Count	314	101	415
		%	75.7%	24.3%	100.0%
Know that Epstein Barr virus causes lymphoma					**Total**
			No	Yes	
Education level	Primary	Count	3	0	3
		%	100.0%	0.0%	100.0%
	Secondary	Count	34	4	38
		%	89.5%	10.5%	100.0%
	Tertiary	Count	288	86	374
		%	77.0%	23.0%	100.0%
Total		Count	325	90	415
		%	78.3%	21.7%	100.0%
Heard of Human T-lymphotropic virus 1 (HTLV-1)					**Total**
			No	Yes	
Education level	Primary	Count	3	0	3
		%	100.0%	0.0%	100.0%
	Secondary	Count	33	5	38
		%	86.8%	13.2%	100.0%
	Tertiary	Count	275	99	374
		%	73.5%	26.5%	100.0%
Total		Count	311	104	415
		%	74.9%	25.1%	100.0%
Know that HTLV-1 causes lymphoma					**Total**
			No	Yes	
Education level	Primary	Count	3	0	3
		%	100.0%	0.0%	100.0%
	Secondary	Count	34	4	38
		%	89.5%	10.5%	100.0%
	Tertiary	Count	285	89	374
		%	76.2%	23.8%	100.0%
Total		Count	322	93	415
		%	77.6%	22.4%	100.0%

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Tab. S3 (*follows*).

Heard of the bacteria *Helicobacter pylori*					Total
			No	Yes	
Education level	Primary	Count	3	0	3
		%	100.0%	0.0%	100.0%
	Secondary	Count	30	8	38
		%	78.9%	21.1%	100.0%
	Tertiary	Count	225	149	374
		%	60.2%	39.8%	100.0%
Total		Count	258	157	415
		%	62.2%	37.8%	100.0%
Know that *Helicobacter pylori* is associated to cancer of the stomach					**Total**
			No	**Yes**	
Education level	Primary	Count	3	0	3
		%	100.0%	0.0%	100.0%
	Secondary	Count	31	7	38
		%	81.6%	18.4%	100.0%
	Tertiary	Count	242	132	374
		%	64.7%	35.3%	100.0%
Total		Count	276	139	415
		%	66.5%	33.5%	100.0%
Have you heard about some cancer types associated with bacteria?					**Total**
			No	**Yes**	
Occupation	Non-healthcare	Count	198	78	276
		%	71.7%	28.3%	100.0%
	Healthcare	Count	48	91	139
		%	34.5%	65.5%	100.0%
Total		Count	246	169	415
		%	59.3%	40.7%	100.0%
Have you heard about some cancer types associated with viruses?					**Total**
			No	**Yes**	
Occupation	Non-healthcare	Count	193	83	276
		%	69.9%	30.1%	100.0%
	Healthcare	Count	37	102	139
		%	26.6%	73.4%	100.0%
Total		Count	230	185	415
		%	55.4%	44.6%	100.0%
Have you heard of 'Oncovirus'					**Total**
			No	**Yes**	
Occupation	Non-healthcare	Count	253	23	276
		%	91.7%	8.3%	100.0%
	Healthcare	Count	56	83	139
		%	40.3%	59.7%	100.0%
Total		Count	309	106	415
		%	74.5%	25.5%	100.0%
Know that vaccine can prevent some cancer types					**Total**
			No	**Yes**	
Occupation	Non-healthcare	Count	208	68	276
		%	75.4%	24.6%	100.0%
	Healthcare	Count	49	90	139
		%	35.3%	64.7%	100.0%
Total		Count	257	158	415
		%	61.9%	38.1%	100.0%

Tab. S3 (*follows*).

Have you heard of Human papillomavirus (HPV)					Total
			No	Yes	
Occupation	Non-healthcare	Count	196	80	276
		%	71.0%	29.0%	100.0%
	Healthcare	Count	37	102	139
		%	26.6%	73.4%	100.0%
Total		Count	233	182	415
		%	56.1%	43.9%	100.0%
Know that HPV infection causes cervical cancer					**Total**
			No	Yes	
Occupation	Non-healthcare	Count	222	54	276
		%	80.4%	19.6%	100.0%
	Healthcare	Count	48	91	139
		%	34.5%	65.5%	100.0%
Total		Count	270	145	415
		%	65.1%	34.9%	100.0%
Have you ever heard of the HPV vaccine					**Total**
			No	Yes	
Occupation	Non-healthcare	Count	215	61	276
		%	77.9%	22.1%	100.0%
	Healthcare	Count	48	91	139
		%	34.5%	65.5%	100.0%
Total		Count	263	152	415
		%	63.4%	36.6%	100.0%
Know that HPV vaccine can prevent cervical cancer					**Total**
			No	Yes	
Occupation	Non-healthcare	Count	230	46	276
		%	83.3%	16.7%	100.0%
	Healthcare	Count	61	78	139
		%	43.9%	56.1%	100.0%
Total		Count	291	124	415
		%	70.1%	29.9%	100.0%
Have you received HPV vaccine					**Total**
			No	Yes	
Occupation	Non-healthcare	Count	259	17	276
		%	93.8%	6.2%	100.0%
	Healthcare	Count	107	32	139
		%	77.0%	23.0%	100.0%
Total		Count	366	49	415
		%	88.2%	11.8%	100.0%
Have you heard of the hepatitis B and C viruses					**Total**
			No	Yes	
Occupation	Non-healthcare	Count	141	135	276
		%	51.1%	48.9%	100.0%
	Healthcare	Count	14	125	139
		%	10.1%	89.9%	100.0%
Total		Count	155	260	415
		%	37.3%	62.7%	100.0%
Know that hepatitis B and C viruses cause liver cancer					**Total**
			No	Yes	
Occupation	Non-healthcare	Count	203	73	276
		%	73.6%	26.4%	100.0%
	Healthcare	Count	32	107	139
		%	23.0%	77.0%	100.0%
Total		Count	235	180	415
		%	56.6%	43.4%	100.0%

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Tab. S3 (*follows*).

Have you heard of the hepatitis B vaccine					Total
			No	Yes	
Occupation	Non-healthcare	Count	173	103	276
		%	62.7%	37.3%	100.0%
	Healthcare	Count	24	115	139
		%	17.3%	82.7%	100.0%
Total		Count	197	218	415
		%	47.5%	52.5%	100.0%
Know that Hepatitis B vaccine can prevent liver cancer					**Total**
			No	Yes	
Occupation	Non-healthcare	Count	221	55	276
		%	80.1%	19.9%	100.0%
	Healthcare	Count	42	97	139
		%	30.2%	69.8%	100.0%
Total		Count	263	152	415
		%	63.4%	36.6%	100.0%
Have you received HBV vaccine					**Total**
			No	Yes	
Occupation	Non-healthcare	Count	235	41	276
		%	85.1%	14.9%	100.0%
	Healthcare	Count	65	74	139
		%	46.8%	53.2%	100.0%
Total		Count	300	115	415
		%	72.3%	27.7%	100.0%
Heard of Kaposi sarcoma herpes virus (KSHV)					**Total**
			No	Yes	
Occupation	Non-healthcare	Count	241	35	276
		%	87.3%	12.7%	100.0%
	Healthcare	Count	72	67	139
		%	51.8%	48.2%	100.0%
Total		Count	313	102	415
		%	75.4%	24.6%	100.0%
Know that Kaposi sarcoma herpes virus causes Kaposi sarcoma					**Total**
			No	Yes	
Occupation	Non-healthcare	Count	257	19	276
		%	93.1%	6.9%	100.0%
	Healthcare	Count	75	64	139
		%	54.0%	46.0%	100.0%
Total		Count	332	83	415
		%	80.0%	20.0%	100.0%
Heard of Epstein Barr Virus (EBV)					**Total**
			No	Yes	
Occupation	Non-healthcare	Count	254	22	276
		%	92.0%	8.0%	100.0%
	Healthcare	Count	60	79	139
		%	43.2%	56.8%	100.0%
Total		Count	314	101	415
		%	75.7%	24.3%	100.0%
Know that Epstein Barr virus causes lymphoma					**Total**
			No	Yes	
Occupation	Non-healthcare	Count	260	16	276
		%	94.2%	5.8%	100.0%
	Healthcare	Count	65	74	139
		%	46.8%	53.2%	100.0%
Total		Count	325	90	415
		%	78.3%	21.7%	100.0%

Tab. S3 (*follows*).

Heard of Human T-lymphotropic virus 1 (HTLV-1)					Total
			No	Yes	
Occupation	Non-healthcare	Count	248	28	276
		%	89.9%	10.1%	100.0%
	Healthcare	Count	63	76	139
		%	45.3%	54.7%	100.0%
Total		Count	311	104	415
		%	74.9%	25.1%	100.0%
Know that HTLV-1 causes lymphoma					**Total**
			No	**Yes**	
Occupation	Non-healthcare	Count	258	18	276
		%	93.5%	6.5%	100.0%
	Healthcare	Count	64	75	139
		%	46.0%	54.0%	100.0%
Total		Count	322	93	415
		%	77.6%	22.4%	100.0%
Heard of the bacteria *Helicobacter pylori*					**Total**
			No	**Yes**	
Occupation	Non-healthcare	Count	223	53	276
		%	80.8%	19.2%	100.0%
	Healthcare	Count	35	104	139
		%	25.2%	74.8%	100.0%
Total		Count	258	157	415
		%	62.2%	37.8%	100.0%
Know that *Helicobacter pylori* is associated to cancer of the stomach					**Total**
			No	**Yes**	
Occupation	Non-healthcare	Count	238	38	276
		%	86.2%	13.8%	100.0%
	Healthcare	Count	38	101	139
		%	27.3%	72.7%	100.0%
Total		Count	276	139	415
		%	66.5%	33.5%	100.0%
Have you heard about some cancer types associated with bacteria?					**Total**
			No	**Yes**	
Family income	Low	Count	47	14	61
		%	77.0%	23.0%	100.0%
	Middle	Count	145	135	280
		%	51.8%	48.2%	100.0%
	High	Count	54	20	74
		%	73.0%	27.0%	100.0%
Total		Count	246	169	415
		%	59.3%	40.7%	100.0%
Have you heard about some cancer types associated with viruses?					**Total**
			No	**Yes**	
Family income	Low	Count	47	14	61
		%	77.0%	23.0%	100.0%
	Middle	Count	135	145	280
		%	48.2%	51.8%	100.0%
	High	Count	48	26	74
		%	64.9%	35.1%	100.0%
Total		Count	230	185	415
		%	55.4%	44.6%	100.0%

Tab. S3 (*follows*).

Have you heard of 'Oncovirus'					Total
			No	Yes	
Family income	Low	Count	57	4	61
		%	93.4%	6.6%	100.0%
	Middle	Count	192	88	280
		%	68.6%	31.4%	100.0%
	High	Count	60	14	74
		%	81.1%	18.9%	100.0%
Total		Count	309	106	415
		%	74.5%	25.5%	100.0%
Know that vaccine can prevent some cancer types					**Total**
			No	**Yes**	
Family income	Low	Count	47	14	61
		%	77.0%	23.0%	100.0%
	Middle	Count	155	125	280
		%	55.4%	44.6%	100.0%
	High	Count	55	19	74
		%	74.3%	25.7%	100.0%
Total		Count	257	158	415
		%	61.9%	38.1%	100.0%
Have you heard of Human papillomavirus (HPV)					**Total**
			No	**Yes**	
Family income	Low	Count	45	16	61
		%	73.8%	26.2%	100.0%
	Middle	Count	139	141	280
		%	49.6%	50.4%	100.0%
	High	Count	49	25	74
		%	66.2%	33.8%	100.0%
Total		Count	233	182	415
		%	56.1%	43.9%	100.0%
Know that HPV infection causes cervical cancer					**Total**
			No	**Yes**	
Family income	Low	Count	49	12	61
		%	80.3%	19.7%	100.0%
	Middle	Count	165	115	280
		%	58.9%	41.1%	100.0%
	High	Count	56	18	74
		%	75.7%	24.3%	100.0%
Total		Count	270	145	415
		%	65.1%	34.9%	100.0%
Have you ever heard of the HPV vaccine					**Total**
			No	**Yes**	
Family income	Low	Count	48	13	61
		%	78.7%	21.3%	100.0%
	Middle	Count	162	118	280
		%	57.9%	42.1%	100.0%
	High	Count	53	21	74
		%	71.6%	28.4%	100.0%
Total		Count	263	152	415
		%	63.4%	36.6%	100.0%

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Tab. S3 (*follows*).

Know that HPV vaccine can prevent cervical cancer					Total
			no	yes	
Family income	Low	Count	51	10	61
		%	83.6%	16.4%	100.0%
	Middle	Count	185	95	280
		%	66.1%	33.9%	100.0%
	High	Count	55	19	74
		%	74.3%	25.7%	100.0%
Total		Count	291	124	415
		%	70.1%	29.9%	100.0%
Have you received HPV vaccine					**Total**
			no	yes	
Family income	Low	Count	59	2	61
		%	96.7%	3.3%	100.0%
	Middle	Count	238	42	280
		%	85.0%	15.0%	100.0%
	High	Count	69	5	74
		%	93.2%	6.8%	100.0%
Total		Count	366	49	415
		%	88.2%	11.8%	100.0%
Have you heard of the hepatitis B and C viruses					**Total**
			No	Yes	
Family income	Low	Count	42	19	61
		%	68.9%	31.1%	100.0%
	Middle	Count	74	206	280
		%	26.4%	73.6%	100.0%
	High	Count	39	35	74
		%	52.7%	47.3%	100.0%
Total		Count	155	260	415
		%	37.3%	62.7%	100.0%
Know that hepatitis B and C viruses cause liver cancer					**Total**
			No	Yes	
Family income	Low	Count	50	11	61
		%	82.0%	18.0%	100.0%
	Middle	Count	130	150	280
		%	46.4%	53.6%	100.0%
	High	Count	55	19	74
		%	74.3%	25.7%	100.0%
Total		Count	235	180	415
		%	56.6%	43.4%	100.0%
Have you heard of the hepatitis B vaccine					**Total**
			No	Yes	
Family income	Low	Count	45	16	61
		%	73.8%	26.2%	100.0%
	Middle	Count	109	171	280
		%	38.9%	61.1%	100.0%
	High	Count	43	31	74
		%	58.1%	41.9%	100.0%
Total		Count	197	218	415
		%	47.5%	52.5%	100.0%

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Tab. S3 (*follows*).

Know that Hepatitis B vaccine can prevent liver cancer					Total
			No	Yes	
Family income	Low	Count	51	10	61
		%	83.6%	16.4%	100.0%
	Middle	Count	155	125	280
		%	55.4%	44.6%	100.0%
	High	Count	57	17	74
		%	77.0%	23.0%	100.0%
Total		Count	263	152	415
		%	63.4%	36.6%	100.0%
Have you received HBV vaccine					**Total**
			No	Yes	
Family income	Low	Count	56	5	61
		%	91.8%	8.2%	100.0%
	Middle	Count	185	95	280
		%	66.1%	33.9%	100.0%
	High	Count	59	15	74
		%	79.7%	20.3%	100.0%
Total		Count	300	115	415
		%	72.3%	27.7%	100.0%
Heard of Kaposi sarcoma herpes virus (KSHV)					**Total**
			No	Yes	
Family income	Low	Count	55	6	61
		%	90.2%	9.8%	100.0%
	Middle	Count	200	80	280
		%	71.4%	28.6%	100.0%
	High	Count	58	16	74
		%	78.4%	21.6%	100.0%
Total		Count	313	102	415
		%	75.4%	24.6%	100.0%
Know that Kaposi sarcoma herpes virus causes Kaposi sarcoma					**Total**
			No	Yes	
Family income	Low	Count	58	3	61
		%	95.1%	4.9%	100.0%
	Middle	Count	214	66	280
		%	76.4%	23.6%	100.0%
	High	Count	60	14	74
		%	81.1%	18.9%	100.0%
Total		Count	332	83	415
		%	80.0%	20.0%	100.0%
Heard of Epstein Barr Virus (EBV)					**Total**
			no	yes	
Family income	Low	Count	57	4	61
		%	93.4%	6.6%	100.0%
	Middle	Count	198	82	280
		%	70.7%	29.3%	100.0%
	High	Count	59	15	74
		%	79.7%	20.3%	100.0%
Total		Count	314	101	415
		%	75.7%	24.3%	100.0%

▶

Tab. S3 (*follows*).

Know that Epstein Barr virus causes lymphoma					Total
			no	yes	
Family income	Low	Count	58	3	61
		%	95.1%	4.9%	100.0%
	Middle	Count	205	75	280
		%	73.2%	26.8%	100.0%
	High	Count	62	12	74
		%	83.8%	16.2%	100.0%
Total		Count	325	90	415
		%	78.3%	21.7%	100.0%
Heard of Human T-lymphotropic virus 1 (HTLV-1)					Total
			no	yes	
Family income	Low	Count	57	4	61
		%	93.4%	6.6%	100.0%
	Middle	Count	198	82	280
		%	70.7%	29.3%	100.0%
	High	Count	56	18	74
		%	75.7%	24.3%	100.0%
Total		Count	311	104	415
		%	74.9%	25.1%	100.0%
Know that HTLV-1 causes lymphoma					Total
			no	yes	
Family income	Low	Count	57	4	61
		%	93.4%	6.6%	100.0%
	Middle	Count	207	73	280
		%	73.9%	26.1%	100.0%
	High	Count	58	16	74
		%	78.4%	21.6%	100.0%
Total		Count	322	93	415
		%	77.6%	22.4%	100.0%
Heard of the bacteria *Helicobacter pylori*					Total
			No	Yes	
Family income	Low	Count	57	4	61
		%	93.4%	6.6%	100.0%
	Middle	Count	146	134	280
		%	52.1%	47.9%	100.0%
	High	Count	55	19	74
		%	74.3%	25.7%	100.0%
Total		Count	258	157	415
		%	62.2%	37.8%	100.0%
Know that *Helicobacter pylori* is associated to cancer of the stomach					Total
			No	Yes	
Family income	Low	Count	57	4	61
		%	93.4%	6.6%	100.0%
	Middle	Count	163	117	280
		%	58.2%	41.8%	100.0%
	High	Count	56	18	74
		%	75.7%	24.3%	100.0%
Total		Count	276	139	415
		%	66.5%	33.5%	100.0%

▶

Tab. S3 (*follows*).

Have you heard about some cancer types associated with bacteria?					Total
			No	Yes	
Have you been diagnosed with cancer	No	Count	242	165	407
		%	59.5%	40.5%	100.0%
	Yes	Count	4	4	8
		%	50.0%	50.0%	100.0%
Total		Count	246	169	415
		%	59.3%	40.7%	100.0%
Have you heard about some cancer types associated with viruses?					**Total**
			No	**Yes**	
Have you been diagnosed with cancer	No	Count	227	180	407
		%	55.8%	44.2%	100.0%
	Yes	Count	3	5	8
		%	37.5%	62.5%	100.0%
Total		Count	230	185	415
		%	55.4%	44.6%	100.0%
Have you heard of 'Oncovirus'					**Total**
			No	**Yes**	
Have you been diagnosed with cancer	No	Count	304	103	407
		%	74.7%	25.3%	100.0%
	Yes	Count	5	3	8
		%	62.5%	37.5%	100.0%
Total		Count	309	106	415
		%	74.5%	25.5%	100.0%
Know that vaccine can prevent some cancer types					**Total**
			No	**Yes**	
Have you been diagnosed with cancer	No	Count	252	155	407
		%	61.9%	38.1%	100.0%
	Yes	Count	5	3	8
		%	62.5%	37.5%	100.0%
Total		Count	257	158	415
		%	61.9%	38.1%	100.0%
Have you heard of Human papillomavirus (HPV)					**Total**
			No	**Yes**	
Have you been diagnosed with cancer	No	Count	229	178	407
		%	56.3%	43.7%	100.0%
	Yes	Count	4	4	8
		%	50.0%	50.0%	100.0%
Total		Count	233	182	415
		%	56.1%	43.9%	100.0%
Know that HPV infection causes cervical cancer					**Total**
			No	**Yes**	
Have you been diagnosed with cancer	No	Count	266	141	407
		%	65.4%	34.6%	100.0%
	Yes	Count	4	4	8
		%	50.0%	50.0%	100.0%
Total		Count	270	145	415
		%	65.1%	34.9%	100.0%
Have you ever heard of the HPV vaccine					**Total**
			No	**Yes**	
Have you been diagnosed with cancer	No	Count	259	148	407
		%	63.6%	36.4%	100.0%
	Yes	Count	4	4	8
		%	50.0%	50.0%	100.0%
Total		Count	263	152	415
		%	63.4%	36.6%	100.0%

Tab. S3 (*follows*).

Know that HPV vaccine can prevent cervical cancer					Total
			No	Yes	
Have you been diagnosed with cancer	No	Count	286	121	407
		%	70.3%	29.7%	100.0%
	Yes	Count	5	3	8
		%	62.5%	37.5%	100.0%
Total		Count	291	124	415
		%	70.1%	29.9%	100.0%
Have you received HPV vaccine					**Total**
			No	**Yes**	
Have you been diagnosed with cancer	No	Count	362	45	407
		%	88.9%	11.1%	100.0%
	Yes	Count	4	4	8
		%	50.0%	50.0%	100.0%
Total		Count	366	49	415
		%	88.2%	11.8%	100.0%
Have you heard of the hepatitis B and C viruses					**Total**
			No	**Yes**	
Have you been diagnosed with cancer	No	Count	153	254	407
		%	37.6%	62.4%	100.0%
	Yes	Count	2	6	8
		%	25.0%	75.0%	100.0%
Total		Count	155	260	415
		%	37.3%	62.7%	100.0%
Know that hepatitis B and C viruses cause liver cancer					**Total**
			No	**Yes**	
Have you been diagnosed with cancer	No	Count	233	174	407
		%	57.2%	42.8%	100.0%
	Yes	Count	2	6	8
		%	25.0%	75.0%	100.0%
Total		Count	235	180	415
		%	56.6%	43.4%	100.0%
Have you heard of the hepatitis B vaccine					**Total**
			No	**Yes**	
Have you been diagnosed with cancer	No	Count	194	213	407
		%	47.7%	52.3%	100.0%
	Yes	Count	3	5	8
		%	37.5%	62.5%	100.0%
Total		Count	197	218	415
		%	47.5%	52.5%	100.0%
Know that Hepatitis B vaccine can prevent liver cancer					**Total**
			No	**Yes**	
Have you been diagnosed with cancer	No	Count	259	148	407
		%	63.6%	36.4%	100.0%
	Yes	Count	4	4	8
		%	50.0%	50.0%	100.0%
Total		Count	263	152	415
		%	63.4%	36.6%	100.0%
Have you received HBV vaccine					**Total**
			No	**Yes**	
Have you been diagnosed with cancer	No	Count	296	111	407
		%	72.7%	27.3%	100.0%
	Yes	Count	4	4	8
		%	50.0%	50.0%	100.0%
Total		Count	300	115	415
		%	72.3%	27.7%	100.0%

Tab. S3 (*follows*).

Heard of Kaposi sarcoma herpes virus (KSHV)					Total
			No	Yes	
Have you been diagnosed with cancer	No	Count	308	99	407
		%	75.7%	24.3%	100.0%
	Yes	Count	5	3	8
		%	62.5%	37.5%	100.0%
Total		Count	313	102	415
		%	75.4%	24.6%	100.0%
Know that Kaposi sarcoma herpes virus causes Kaposi sarcoma					**Total**
			No	Yes	
Have you been diagnosed with cancer	No	Count	327	80	407
		%	80.3%	19.7%	100.0%
	Yes	Count	5	3	8
		%	62.5%	37.5%	100.0%
Total		Count	332	83	415
		%	80.0%	20.0%	100.0%
Heard of Epstein Barr Virus (EBV)					**Total**
			No	Yes	
Have you been diagnosed with cancer	No	Count	309	98	407
		%	75.9%	24.1%	100.0%
	Yes	Count	5	3	8
		%	62.5%	37.5%	100.0%
Total		Count	314	101	415
		%	75.7%	24.3%	100.0%
Know that Epstein Barr virus causes lymphoma					**Total**
			No	Yes	
Have you been diagnosed with cancer	No	Count	320	87	407
		%	78.6%	21.4%	100.0%
	Yes	Count	5	3	8
		%	62.5%	37.5%	100.0%
Total		Count	325	90	415
		%	78.3%	21.7%	100.0%
Heard of Human T-lymphotropic virus 1 (HTLV-1)					**Total**
			No	Yes	
Have you been diagnosed with cancer	No	Count	306	101	407
		%	75.2%	24.8%	100.0%
	Yes	Count	5	3	8
		%	62.5%	37.5%	100.0%
Total		Count	311	104	415
		%	74.9%	25.1%	100.0%
Know that HTLV-1 causes lymphoma					**Total**
			No	Yes	
Have you been diagnosed with cancer	No	Count	317	90	407
		%	77.9%	22.1%	100.0%
	Yes	Count	5	3	8
		%	62.5%	37.5%	100.0%
Total		Count	322	93	415
		%	77.6%	22.4%	100.0%
Heard of the bacteria *Helicobacter pylori*					**Total**
			No	Yes	
Have you been diagnosed with cancer	No	Count	254	153	407
		%	62.4%	37.6%	100.0%
	Yes	Count	4	4	8
		%	50.0%	50.0%	100.0%
Total		Count	258	157	415
		%	62.2%	37.8%	100.0%

Tab. S3 (*follows*).

Know that *Helicobacter pylori* is associated to cancer of the stomach					Total
			No	Yes	
Have you been diagnosed with cancer	No	Count	272	135	407
		%	66.8%	33.2%	100.0%
	Yes	Count	4	4	8
		%	50.0%	50.0%	100.0%
Total		Count	276	139	415
		%	66.5%	33.5%	100.0%
Have you heard about some cancer types associated with bacteria?					**Total**
			No	**Yes**	
Family history of cancer	No	Count	168	99	267
		%	62.9%	37.1%	100.0%
	Yes	Count	78	70	148
		%	52.7%	47.3%	100.0%
Total		Count	246	169	415
		%	59.3%	40.7%	100.0%
Have you heard about some cancer types associated with viruses?					**Total**
			No	**Yes**	
Family history of cancer	No	Count	160	107	267
		%	59.9%	40.1%	100.0%
	Yes	Count	70	78	148
		%	47.3%	52.7%	100.0%
Total		Count	230	185	415
		%	55.4%	44.6%	100.0%
Have you heard of 'Oncovirus'					**Total**
		no	**Yes**		
Family history of cancer	No	Count	210	57	267
		%	78.7%	21.3%	100.0%
	Yes	Count	99	49	148
		%	66.9%	33.1%	100.0%
Total		Count	309	106	415
		%	74.5%	25.5%	100.0%
Know that vaccine can prevent some cancer types					**Total**
			No	**Yes**	
Family history of cancer	No	Count	172	95	267
		%	64.4%	35.6%	100.0%
	Yes	Count	85	63	148
		%	57.4%	42.6%	100.0%
Total		Count	257	158	415
		%	61.9%	38.1%	100.0%
Have you heard of Human papillomavirus (HPV)					**Total**
			No	**Yes**	
Family history of cancer	No	Count	171	96	267
		%	64.0%	36.0%	100.0%
	Yes	Count	62	86	148
		%	41.9%	58.1%	100.0%
Total		Count	233	182	415
		%	56.1%	43.9%	100.0%
Know that HPV infection causes cervical cancer					**Total**
			No	**Yes**	
Family history of cancer	No	Count	191	76	267
		%	71.5%	28.5%	100.0%
	Yes	Count	79	69	148
		%	53.4%	46.6%	100.0%
Total		Count	270	145	415
		%	65.1%	34.9%	100.0%

Tab. S3 (*follows*).

Have you ever heard of the HPV vaccine					Total
			No	Yes	
Family history of cancer	no	Count	190	77	267
		%	71.2%	28.8%	100.0%
	yes	Count	73	75	148
		%	49.3%	50.7%	100.0%
Total		Count	263	152	415
		%	63.4%	36.6%	100.0%
Know that HPV vaccine can prevent cervical cancer					**Total**
			No	**Yes**	
Family history of cancer	no	Count	201	66	267
		%	75.3%	24.7%	100.0%
	yes	Count	90	58	148
		%	60.8%	39.2%	100.0%
Total		Count	291	124	415
		%	70.1%	29.9%	100.0%
Have you received HPV vaccine					**Total**
			No	**Yes**	
Family history of cancer	no	Count	244	23	267
		%	91.4%	8.6%	100.0%
	yes	Count	122	26	148
		%	82.4%	17.6%	100.0%
Total		Count	366	49	415
		%	88.2%	11.8%	100.0%
Have you heard of the hepatitis B and C viruses					**Total**
			No	**Yes**	
Family history of cancer	no	Count	118	149	267
		%	44.2%	55.8%	100.0%
	yes	Count	37	111	148
		%	25.0%	75.0%	100.0%
Total		Count	155	260	415
		%	37.3%	62.7%	100.0%
Know that hepatitis B and C viruses cause liver cancer					**Total**
			No	**Yes**	
Family history of cancer	no	Count	165	102	267
		%	61.8%	38.2%	100.0%
	yes	Count	70	78	148
		%	47.3%	52.7%	100.0%
Total		Count	235	180	415
		%	56.6%	43.4%	100.0%
Have you heard of the hepatitis B vaccine					**Total**
			No	**Yes**	
Family history of cancer	no	Count	148	119	267
		%	55.4%	44.6%	100.0%
	yes	Count	49	99	148
		%	33.1%	66.9%	100.0%
Total		Count	197	218	415
		%	47.5%	52.5%	100.0%
Know that Hepatitis B vaccine can prevent liver cancer					**Total**
			No	**Yes**	
Family history of cancer	no	Count	186	81	267
		%	69.7%	30.3%	100.0%
	yes	Count	77	71	148
		%	52.0%	48.0%	100.0%
Total		Count	263	152	415
		%	63.4%	36.6%	100.0%

Tab. S3 (*follows*).

Have you received HBV vaccine					Total
			No	Yes	
Family history of cancer	No	Count	202	65	267
		%	75.7%	24.3%	100.0%
	Yes	Count	98	50	148
		%	66.2%	33.8%	100.0%
Total		Count	300	115	415
		%	72.3%	27.7%	100.0%
Heard of Kaposi sarcoma herpes virus (KSHV)					**Total**
			No	**Yes**	
Family history of cancer	No	Count	214	53	267
		%	80.1%	19.9%	100.0%
	Yes	Count	99	49	148
		%	66.9%	33.1%	100.0%
Total		Count	313	102	415
		%	75.4%	24.6%	100.0%
Know that Kaposi sarcoma herpes virus causes Kaposi sarcoma					**Total**
			No	**Yes**	
Family history of cancer	No	Count	222	45	267
		%	83.1%	16.9%	100.0%
	Yes	Count	110	38	148
		%	74.3%	25.7%	100.0%
Total		Count	332	83	415
		%	80.0%	20.0%	100.0%
Heard of Epstein Barr Virus (EBV)					**Total**
			No	**Yes**	
Family history of cancer	No	Count	214	53	267
		%	80.1%	19.9%	100.0%
	Yes	Count	100	48	148
		%	67.6%	32.4%	100.0%
Total		Count	314	101	415
		%	75.7%	24.3%	100.0%
Know that Epstein Barr virus causes lymphoma					**Total**
			No	**Yes**	
Family history of cancer	No	Count	220	47	267
		%	82.4%	17.6%	100.0%
	Yes	Count	105	43	148
		%	70.9%	29.1%	100.0%
Total		Count	325	90	415
		%	78.3%	21.7%	100.0%
Heard of Human T-lymphotropic virus 1 (HTLV-1)					**Total**
			No	**Yes**	
Family history of cancer	No	Count	211	56	267
		%	79.0%	21.0%	100.0%
	Yes	Count	100	48	148
		%	67.6%	32.4%	100.0%
Total		Count	311	104	415
		%	74.9%	25.1%	100.0%
Know that HTLV-1 causes lymphoma					**Total**
			No	**Yes**	
Family history of cancer	No	Count	218	49	267
		%	81.6%	18.4%	100.0%
	Yes	Count	104	44	148
		%	70.3%	29.7%	100.0%
Total		Count	322	93	415
		%	77.6%	22.4%	100.0%

▶

Tab. S3 (*follows*).

Heard of the bacteria *Helicobacter pylori*					Total
			No	Yes	
Family history of cancer	No	Count	176	91	267
		%	65.9%	34.1%	100.0%
	Yes	Count	82	66	148
		%	55.4%	44.6%	100.0%
Total		Count	258	157	415
		% r	62.2%	37.8%	100.0%
Know that *Helicobacter pylori* is associated to cancer of the stomach					Total
			No	Yes	
Family history of cancer	No	Count	188	79	267
		%	70.4%	29.6%	100.0%
	Yes	Count	88	60	148
		%	59.5%	40.5%	100.0%
Total		Count	276	139	415
		%	66.5%	33.5%	100.0%

Tab. S4. Logistic regression results.

Variables	df	Sig.	Exp(B)
Have you heard about some cancer types associated with bacteria?			
Nationality	1	.001	.405
Occupation	1	.000	.240
Constant	1	.000	2.153
Have you heard about some cancer types associated with virus?			
Occupation	1	.000	.173
Family income (low)	1	.174	.570
Family income (middle)	1	.140	1.539
Constant	1	.023	2.054
Have you heard of "Oncovirus"?			
Nationality	1	.027	.383
Occupation	1	.000	.057
POR (Beirut)	1	.838	.898
POR (Bekaa)	1	.022	.309
POR (Mount Lebanon)	1	.705	.799
POR (North Lebanon)	1	.593	1.441
Family Income 1	1	.019	.187
Family Income 2	1	.917	1.047
Constant	1	.065	3.385
Do you know that vaccine can prevent some cancer types?			
Nationality	1	.001	.405
Occupation	1	.000	.240
Constant	1	.000	2.153

Non comunicable diseases

The Role of SGLT2 Inhibitors in Preventing the Progression of Chronic Kidney Disease in Patients with Type 2 DM: A Systematic Review

AIDI ALIFIA PUTRI[1], AUGRIS SHANDRIANTI[2], ICHE ANDRIYANI LIBERTY[3]
[1] Medical Profession Program, Faculty of Medicine, Universitas Sriwijaya, Palembang; [2] Department of Internal Medicine, Faculty of Medicine, Universitas Sriwijaya, Palembang; [3] Department of Public Health and Community Medicine, Faculty of Medicine, Universitas Sriwijaya, Palembang

Keywords

SGLT2 inhibitors • Chronic Kidney Disease • Diabetes Mellitus type 2

Summary

Background. *Type 2 diabetes mellitus is the most common type of diabetes and is the leading cause of chronic kidney disease globally. Currently, the medications recommended for treatment are not fully effective for treating CKD. Recent findings from the DAPA-CKD and EMPA-KIDNEY clinical trials have revealed that SGLT-2 inhibitors offer significant benefits in improving kidney function and preventing the progression of kidney disease.*
Objective. *This review aims to evaluate the efficacy and safety of SGLT2 inhibitors in delaying CKD progression and reducing dialysis dependency in patients with type 2 diabetes.*
Methods. *This research is a systematic literature study using PRISMA 2020 Protocols. Article searches were carried out in PubMed, Cochrane Library, Sage Journals, and Europe PMC, covering the period from January 2019 to March 2024. The search strategy used the keywords "SGLT2 Inhibitor" AND "Prevention" AND "Chronic Kidney Disease" AND "Type 2 Diabetes". Articles that met the criteria were assessed for risk of bias using RoB2.*
Results. *From 7 articles with a total of 15,927 participants included in this systematic review, the overall risk of bias was low. Patients with type 2 diabetes and CKD who received SGLT2 inhibitors had a significantly lower risk of renal composite outcomes compared to placebo (e.g. HR 0.70, 95% CI 0.59-0.82). A modest initial decrease in eGFR was observed in the SGLT2i group compared to placebo, followed by stabilization over time.*
Conclusion. *SGLT2 inhibitors can be proposed as an effective treatment option for renal protection in patients with type 2 diabetes mellitus and chronic kidney disease, with moderate certainty of evidence from consistent RCT findings.*

Introduction

Diabetes mellitus or diabetes is a disease that often occurs around the world and still poses a significant threat to health to this day. About 537 million adults (ages 20-79) live with diabetes. The International Diabetes Federation projects that 1 in 8 adults or about 783 million people will live with diabetes by 2045. One in 11 adults (90 million) in Southeast Asia lives with diabetes. Indonesia ranks 5th in the country with the highest diabetic population (19.5 million people) in the world. Type 2 diabetes mellitus is the most common type of diabetes, covering 90-95% of diabetic subjects, and is caused by inadequate insulin secretion combined with insulin resistance [1, 2].

Diabetes and chronic kidney disease (CKD) generally occur together and are associated with a high risk of morbidity and mortality in patients. Diabetes is the leading cause of CKD globally, accounting for nearly half of all cases of kidney failure requiring kidney replacement therapy [3]. Diabetic kidney disease or better known as CKD in diabetes is a common microvascular complication associated with diabetes, affecting about 20-40% of diabetic patients. This condition can develop into *end-stage kidney disease* (ESKD) in some cases. Currently, renin-angiotensin system inhibitors are recommended as the main drug according to guidelines for treating CKD. However, the drug is not completely adequate for the treatment of CKD due to the potential for increased risk of ESKD and acute kidney failure [4, 5].

Glucose-2 glucose-sodium inhibitor (SGLT-2) is a glucose-lowering drug that works by reducing glucose reabsorption by the kidneys in the S1 segment of the proximal tubules in the kidneys. This drug causes glycosuria and natriuresis and is associated with a decrease in glycated hemoglobin (Hb1Ac), blood pressure, albuminuria, and body weight. This class of hypoglycemic drugs works completely without relying on the hormone insulin and functions according to serum glucose levels, so the risk of hypoglycemia can be avoided. Recent findings from the DAPA-CKD and EMPA-KIDNEY clinical trials have revealed that SGLT-2 inhibitors offer significant benefits in improving cardiovascular and renal function, as well as delaying the progression of kidney disease in CKD patients, regardless of their diabetic status. The effectiveness and safety of SGLT-2 inhibitors, have been validated

for the therapy of CKD, so the 2022 KDIGO guidelines recommend its use for PGL patients with a glomerular filtration rate (eGFR) ≥ 20 mL/min/1.73 m^2 [1, 6-9].
Slowing the progression of CKD and avoiding dialysis or kidney transplantation is the main goal of all proposed therapeutic modalities, given the impact of dialysis and kidney transplantation on the quality of life and morbidity and mortality of patients, as well as the large costs associated with kidney replacement therapy. Therefore, this systematic review was made to comprehensively review the role of SGLT2 inhibitors in slowing the progression of chronic kidney disease given the high prevalence of diabetes as a major cause of CKD and its impact on quality of life and costs incurred by kidney replacement therapy. Therefore, this systematic review aims to evaluate how SGLT2 inhibitors contribute to delaying CKD progression and reducing dialysis dependency in patients with type 2 diabetes, thereby aligning with preventive medicine and community health priorities. Unlike previous reviews, this study updates and synthesizes recent evidence following the 2022 KDIGO guidelines, providing an up-to-date perspective on the renal-protective role of SGLT2 inhibitors.

Methods

This study is a systematic literature study using data obtained from the search results of related articles using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 Protocols method [10]. Article searches were conducted through four electronic data-based publication centers, namely PubMed, Cochrane Library, Sage Journal, and Europe PMC. The full search string for PubMed was: ("SGLT2 Inhibitor" AND "Chronic Kidney Disease" AND "Type 2 Diabetes") and adapted appropriately for other databases. The search was carried out for articles published between 2019 and 2024.
The articles used in this systematic review must meet the inclusion criteria, including: 1) Studies with populations of individuals aged ≥ 18 years with type 2 diabetes mellitus and chronic kidney disease (CKD defined as *eGFR* < 90 ml/min/1.73 m²); 2) Studies evaluating the use of SGLT2 inhibitors as part of treatment compared to other conventional drugs (such as ACE inhibitors, ARBs) or placebo; 3) Studies that reported relevant clinical outcomes in the form of slowing of kidney disease progression, reduced risk of dialysis or kidney-related mortality; 4) The study is an original article using the Randomized Controlled Trial method; and 5) The article was published in the period 2019-2024, in English, and can be accessed in full. *Two reviewers independently screened titles and abstracts and subsequently reviewed the full texts of potentially eligible studies. Any disagreements were resolved by discussion or by consulting a third reviewer.* The main efficacy outcomes assessed in this systematic review included a slowdown in the progression of chronic kidney disease (decreased glomerular filtration rate/GFR, reduction in albuminuria, reduced risk of kidney failure or transition to end-stage kidney disease (EKSD)), decreased dialysis need, or kidney-related mortality. Given the clinical and methodological heterogeneity across included trials, a narrative synthesis was conducted rather than a meta-analysis. This review was not registered, which is acknowledged as a methodological limitation.

Results

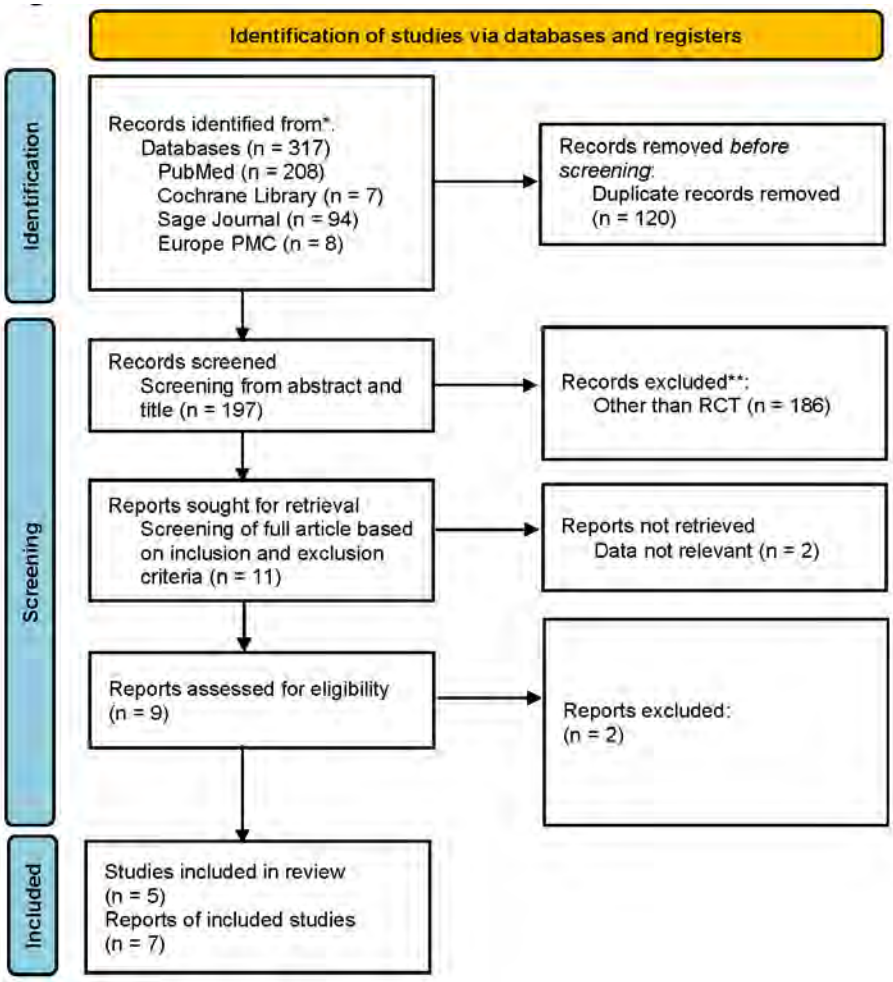
Seven articles from 5 studies that met the inclusion criteria involved a total of 15,927 participants with an average age range of 60-70 years and dominated by male gender. The studies included in this systematic review involved multicenter studies conducted in various countries, including South Africa, the United States, Argentina, Australia, the Netherlands, Belgium, Brazil, the United Kingdom, Bulgaria, Chile, China, Colombia, Denmark, Estonia, the Philippines, Guatemala, Hungary, India, Italy, Israel, Japan, Germany, Canada, South Korea, Latvia, Lithuania, Malaysia, Mexico, Norway, France, Peru, Portugal, Czech Republic, Romania, Russia, New Zealand, Serbia, Slovakia, Spain, Sweden, Taiwan, Turkey, Ukraine, the United Arab Emirates, and Greece. Three SGLT2 inhibitors, namely Canagliflozin, Sotagliflozin, and Ipragliflozin, were used in the 7 articles included in this systematic review. Assessment of study characteristics which include authors, title, study design, study location, study population, intervention, comparison group, assessed findings, and results are presented in Table I. Figure 1 illustrates the study selection process, including screening and eligibility assessment.
In total, 1,234 records were screened, of which 1,180 were excluded after title and abstract review, and 47 were excluded after full-text assessment due to not meeting inclusion criteria. Ultimately, 7 articles were included in the final analysis.
Table II shows the effect of SGLT2 inhibitor on the progression of chronic kidney disease as assessed by the change in eGFR from baseline and composite incidence in the kidneys from the intervention and control groups. Overall, the incidence of renal composite in the intervention group was generally lower when compared to the control group, but did not differ significantly ($p > 0.05$).
The selected articles were then assessed for quality and risk of bias using a risk of bias assessment based on the Revised Cochrane risk-of-bias for randomized trials (RoB2) using the Cochrane Review Manager software (RevMan 5.4). In terms of the assessment of the entire domain, the startification risk of bias of the selected articles is low risk. Figure 2 and 3 presents the risk-of-bias assessment across included studies. Some domains that have high bias risk values are allocation concealment (selection bias) and blinding of participants and personnel (performance bias) domains in the research of Tanaka et al. (2020) and incomplete outcome data (attrition bias)

Tab. I. Characteristics of Enrolled Studies.

Author (Year)	Number of Participants	Intervensi	Outcome
Bakris et al (2020) [11]	A total of 174 participants with type 2 diabetes developed chronic kidney disease and had an eGFR < of 30 ml/min per 1.73 m²	Canagliflozin 100 mg/day	• Canagliflozin did not cause a significant decrease in eGFR in the first week of treatment in this subgroup, in contrast to the general population who showed an initial decrease (Canagliflozin -1.30 ml/min per 1.73 m² per year; Placebo -3.83 ml/min per 1.73 m² per year, Δ = -2.54 ml/min per 1.73 m² per year, 95% CI: 0.9-4.17) • Canagliflozin showed a significant reduction in the risk of renal failure (HR in participants with eGFR < 30 ml/min per 1.73 m² 0.67 (95% CI: 0.35-1.27), for patients with eGFR ≥ 30 ml/min per 1.73 m², HR 0.70 (95% CI: 0.54-0.91)) • Canagliflozin is safe for use in patients with low eGFR, without increasing the risk of adverse side effects, including AKI and the incidence of renal side effects
Bhatt et al (2021) [12]	A total of 10584 participants with type 2 diabetes, HbA1c ≥ 7%, and chronic kidney disease (eGFR 25-60 ml/min/1.73 m²) as well as additional cardiovascular risk factors	Sotaglifozin 200 mg once a day	• Results on renal composites in this study showed that there was no significant difference between the group receiving sotagliflozin and the placebo group (HR 0.71, 95% CI (0.46-1.08) • Although sotagliflozin showed some side effects (diarrhea, genital fungal infections, dehydration, and diabetic ketoacidosis), the overall safety profile did not show significant differences in the incidence of serious side effects between the two groups
Jardine et al (2020) [13]	A total of 4401 participants with type 2 diabetes who also had an eGFR value of 30 - < 90 ml/min/1.73 m²	Canagliflozin 100 mg/day	• Canagliflozin reduced the risk of ESKD by 30% compared to placebo (HR 0.70; 95% CI, 0.59-0.82) • The average decrease in eGFR in the first week was about 2.5 ml/min per 1.73 m², followed by stabilization • The incidence of serious side effects, including urinary tract infections and diabetic ketoacidosis, remained low and comparable between the two groups
Perkovic et al (2019) [14]	A total of 4401 participants with type 2 diabetes mellitus	Canagliflozin 100 mg/day	• The primary composite results of this study included the incidence of end-stage kidney disease (ESKD) or death from renal or cardiovascular causes (HR 0.70 (95% CI, 0.59-0.82), p = 0.00001) • Canagliflozin showed better maintenance of kidney function compared to placebo • Canagliflozin shows an acceptable safety profile in patient populations with type 2 diabetes and nephropathy
Tanaka et al (2020) [15]	A total of 30 participants with type 2 diabetes mellitus	Ipragliflozin 50 mg once a day	• There was a decrease in eGFR in the ipragliflozin group compared to the control group, indicating that ipragliflozin may help maintain kidney function • Ipragliflozin can be safe and effective in improving kidney function and lowering uric acid levels
Wada et al (2022) [16]	A total of 308 CKD patients with type 2 DM	Canagliflozin 100 mg/day	• The incidence of a 30% reduction in eGFR was significantly lower in the canagliflozin group compared to the placebo group, an estimated difference between groups of 5.2% (95% CI 2.3-8.0, $p < 0.001$) • The study reported that the incidence of a 40% decrease in eGFR at week 104 was 10.1% in the canagliflozin group and 13.9% in the placebo group. The estimated difference between groups (placebo - canagliflozin) was 3.8% (95% CI -4.1-11.7, $p = 0.343$) • There were no significant safety concerns associated with the use of canagliflozin in Japanese patients with chronic kidney disease and type 2 diabetes
Wada et al (2022) [17]	A total of 604 participants with type 2 diabetes mellitus and eGFR 30 - < 90 ml/min/1.73 m² were from East and Southeast Asia	Canagliflozin 100 mg/day	Canagliflozin reduced the risk of renal primary composite compared to placebo in EA participants (40.83 *vs.* 73.45 per 1,000-year-patient; HR 0.54, 95% CI 0.35-0.84) Canagliflozin showed significant reductions in UACR and improvements in eGFR Canagliflozin is considered safe for use in patients with type 2 diabetes and nephropathy, with a safety profile comparable to placebo

AKI: acute kidney injury; CI: confidence interval; EA: East Asian and Southeast Asian participants; eGFR: estimated glomerular filtration rate; ESKD: end stage kidney disease; HR: hazard ratio; UACR: urine albumin-creatinine ratio.

Fig. 1. PRISMA flowchart.



domains in the research of Bakris et al. (2020), Jardine et al. (2020), and Wada et al. (b) (2020). Importantly, the presence of attrition bias in Bakris et al. (2020) did not alter the overall trend toward renal protection with SGLT2 inhibitors, suggesting robustness of the pooled conclusions.

Discussion

SGLT2 inhibitors are a group of glucose-lowering drugs that inhibit glucose reabsorption in the renal tubules and induce glucose excretion through the urine by lowering the renal glucose threshold. This class of hypoglycemic drugs works completely independently of the hormone insulin and functions according to the existing serum glucose levels, so it has a very low risk of hypoglycemia [1, 18].

Heterogeneity in the included studies arose from differences in the SGLT2 inhibitors evaluated, patient populations, and duration of follow-up, which precluded a formal meta-analysis. Of the 7 articles included in this systematic review, all articles discuss the role of SGLT2 inhibitors in preventing CKD progression, both as the main and secondary findings. The article written by Bakris et al. (2020), Jardine et al. (2020), Perkovic et al. (2019), and Wada et al. (b) (2022) discussed the inhibitory effect of SGLT2 in preventing renal progression as the main finding, with *the end-points* assessed to include the composite of *end-stage kidney disease,* a 2-fold increase in serum creatinine from baseline, a change in eGFR, or death from kidney disease. In this systematic review, it was found that patients with type 2 diabetes and chronic kidney disease who received SGLT2 inhibitors had a lower risk of priner composite outcomes compared to the placebo group. These results suggest that SGLT2 inhibitors can be proposed as an effective treatment option for renal protection in patients with type 2 diabetes and chronic kidney disease.

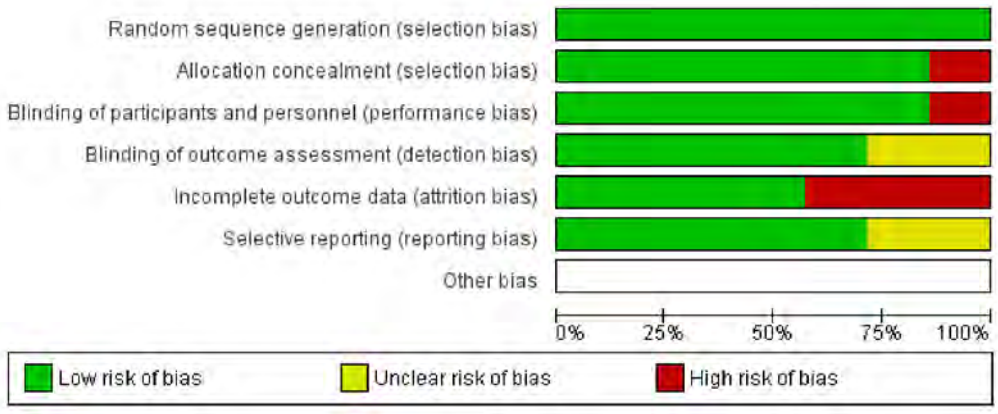
In addition, Bakris et al. (2020) also reported that Canagliflozin, one type of SGLT2 inhibitor, showed a significant reduction in the risk of kidney failure. The hazard ratio (HR) for renal failure in participants with eGFR < 30 ml/min per 1.73 m² was 0.67 (95% CI: 0.35-1.27), for patients with eGFR ≥ 30 ml/min per 1.73 m², HR was 0.70 (95% CI: 0.54-0.91) [11]. Similar

Tab. II. Effect of SGLT2 Inhibitor on Chronic Kidney Disease Progression.

Author (Year)	Type of SGLT2i	Mean baseline eGFR (ml/min/1.73 m²)		Mean change in eGFR from *baseline* (ml/min/1.73 m²)		Effect of SGLT2i on reduction of CKD progression*					
						SGLT2i		Control		HR (95% CI)	*p value***
		SGLT2i	Control	SGLT2i	Control	Participants/events	Events per 1000 patients-year	Participants/events	Events per 1000 patients-year		
Bakris et al. (2020) [11]	Canagliflozin	26 ± 3	27 ± 3	-1.30	-3.38	84/15	75.4	90/25	116.0	0.67 (0.35-1.27	0.77
Bhatt et al. (2021) [12]	Sotaglifozin	44.4	44.5	-0.09	-1.31	5292/37	0.5	5292/52	0.7	0.71 (0.46-1.08)	-
Jardine et al. (2020) [13]	Canagliflozin	56.3 ± 18.2	56.0 ± 18.3	-3.19	-4.71	2202/245	43.2	2199/340	61.2	0.70 (0.59-0.82)	0.0001
Perkovic et al. (2019) [14]	Canagliflozin	56.3 ± 18.2	56.0 ± 18.3	-1.5	-4.5	2202/245	43.2	2199/340	61.2	0.70 (0.59-0.82)	0.0001
Tanaka et al. (2020)	Ipragliflozin	67.3 ± 18.2	67.9 ± 16.9	1.6	-3.5	-	-	-	-	-	-
Wada et al. (2022) [16]	Canagliflozin	56.3 ± 15.5	55.2 ± 13.6	-10.39	-11.49	154/7	24.29	154/11	38.66	0.60 (0.23-1.55)	0.2930
Wada et al. (2022) [17]	Canagliflozin	55.4 ± 16.0	56.1 ± 17.2	-3.38	-5.68	301/31	40.83	303/54	73.45	0.54 (0.35-0.84)	0.2035

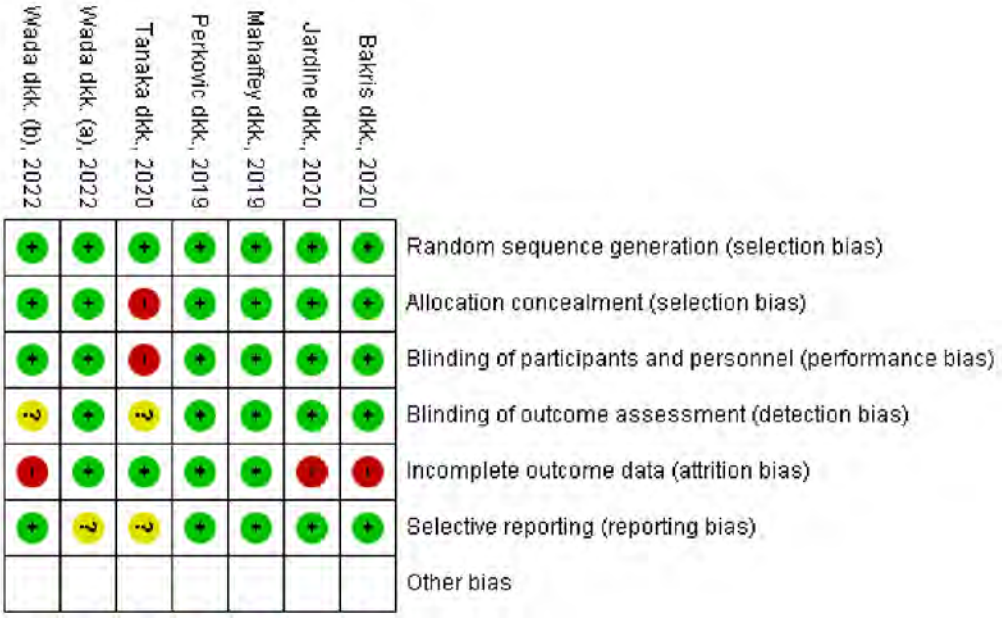
eGFR: estimated glomerular filtration rate; SGLT2i: SGLT2 inhibitor; CI: confidence interval. * Components assessed include the incidence of end-stage kidney disease (ESKD), a 2-fold increase in serum creatinine, kidney failure, kidney death. ** *p* value is considered significant if $p < 0.05$. -: Unreported

Fig. 2. The results of the risk of bias assessment using RoB2 from the included journals.



results were also reported by Jardine et al. (2022) where they found that Canagliflozin reduced the risk of ESKD by 30% compared to placebo (HR 0.70; 95% CI, 0.59-0.82). Perkovic et al. (2019) also reported the results of the primary composite of kidneys including *end-stage kidney disease* (ESKD) or death from renal causes with an HR value for the canagliflozin group compared to placebo of 0.70 (95% CI, 0.59-0.82), *p* value = 0.00001. This suggests that the use of canagliflozin reduces the risk of major composite events by 30% compared to placebo. Perkovic et al. (2019) also reported kidney-specific composite results including a significant decline in kidney function. *The hazard ratio* for this outcome was 0.66 (95% CI, 0.53-0.81), with a *p* value < 0.001 [14]. In a study conducted by Wada et al. (b) (2020) with more demographically specific participants, including participants from East and Southeast Asian countries (China, Philippines,

Fig. 3. Risk of bias summary from the included journals.



Japan, South Korea, Malaysia), canagliflozin reduced the risk of primary outcomes (combined from ESKD, a two-fold increase in serum creatinine, or renal or cardiovascular mortality) compared to placebo in EA participants (40.83 *vs.* 73.45 per 1,000-patient-year-old; HR 0.54, 95% CI 0.35-0.84). In addition, the study also reported that canagliflozin showed a significant reduction in UACR and improvement in eGFR, which showed additional benefits in managing renal risk[17] In contrast to the effects of canagliflozin, Bhatt et al. (2021) reported below results on renal composites in their study showing that there was no significant difference between the group receiving sotagliflozin and the placebo group (HR 0.71, 95% CI (0.46-1.08)) [12].

Six of the 7 articles reported in this systematic review showed a decrease in eGFR in the SGLT2 inhibitor group when compared to the comparison group. However, Bakris et al. (2020) reported that Canagliflozin did not cause a significant decrease in eGFR in the first week of treatment in this subgroup, in contrast to the general population which showed an initial decrease (Canagliflozin -1.30 ml/min per 1.73 m² per year; Placebo -3.83 ml/min per 1.73 m² per year, Δ = - 2.54 ml/min per 1.73 m² per year, 95% CI: 0.9-4.17) [11]. Jardine et al. (2020) also reported canagliflozin causes an acute decrease in eGFR followed by stabilization of eGFR loss. The average decrease in eGFR in the first week was about 2.5 ml/min per 1.73 m², followed by stabilization. The decrease in eGFR in the intervention group had a statistically significant difference when compared to placebo ($p = 0.0001$) [13].

Tanaka et al. (2020) also reported a decrease in eGFR in the ipragliflozin group compared to the control group, indicating that ipragliflozin may help maintain kidney function [15]. The SGLT2 inhibitor inhibits the reabsorption of sodium m and glucose in the proximal tubules, leading to increased delivery of sodium and chloride to the macula densa. This results in vasoconstriction of the afferent arterioles caused by adenosine-mediated myogenic activation, thereby reducing intraglomerular pressure and GFR [19]. Maladaptive glomerular hemodynamics play an important role in the progression of kidney disease. All of the articles used in this systematic review reported similar safety profiles, in both the SGLT2 inhibitor and placebo groups. Bakris et al. (2020) reported that Canagliflozin is safe for use in patients with low eGFR (≤ 30 ml/min/1.73 m^2) without increasing the risk of adverse side effects, including the incidence of AKI and other renal side effects. Jardine et al. (2020) reported the incidence of serious adverse events, including urinary tract infections and diabetic ketoacidosis, remained low and comparable among the SGLT2 and placebo inhibitor groups. Perkovic et al. (2019) [14], Wada et al. (a) (2022) and Wada et al. (b) (2022) reported that Canagliflozin is considered safe for use in patients with type 2 diabetes and nephropathy and there are no significant safety concerns related to the use of this drug in patients with chronic kidney disease and type 2 diabetes. Although sotagliflozin showed some side effects, such as diarrhea, genital fungal infections, dehydration, and diabetic ketoacidosis, Bhatt et al. (2021) reported no significant difference in the incidence of serious side effects in the two groups. Tanaka et al. (2020) reported that Ipragliflozin can be safe and effective in improving kidney function. Using the GRADE approach, the certainty of evidence for renal outcomes was rated as moderate, primarily due to consistency across large multicenter RCTs but with some concerns regarding publication bias. From a public

health perspective, broader implementation of SGLT2 inhibitors could reduce the demand for dialysis and transplantation, particularly in low- and middle-income regions where the burden of diabetic kidney disease is rising. Nonetheless, this review has limitations, including the exclusion of non-English studies, which may limit the generalizability of findings and introduce potential publication bias.

Conclusion

Based on the analysis of seven studies in this systematic review, the authors concluded that patients with type 2 diabetes mellitus and chronic kidney disease who received SGLT2 inhibitors had a lower risk of chronic kidney disease progression compared to those who received a placebo. SGLT2 inhibitors, particularly Canagliflozin, can significantly reduce composite kidney events, including end-stage kidney disease, a two-fold increase in serum creatinine from baseline, changes in eGFR, or death due to kidney disease. These findings suggest that SGLT2 inhibitors could be proposed as an effective treatment option for kidney protection in patients with type 2 diabetes mellitus and chronic kidney disease. Additionally, there were no significant safety issues or adverse effects associated with the use of SGLT2 inhibitors in patients with type 2 diabetes mellitus and chronic kidney disease, indicating that these medications are safe to use.

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Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest statement

The authors declare no competing interests. This study did not receive any industry funding and was not produced as part of any grant supported.

Authors' contributions

All authors made substantial contributions to this study. Conceptualization: AAP, AS, IAL. Literature search and study selection: AAP, AS. Data extraction and quality appraisal: AAP, AS, IAL. Data synthesis and interpretation: AAP, AS, IAL. Writing – original draft: AAP. Writing – review & editing: AS, IAL. Supervision: AS, IAL. All authors have read and approved the final version of the manuscript.

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Correspondence: Iche Andriyani Liberty, Department of Public Health and Community Medicine; Biomedical Department, Universitas Sriwijaya, Faculty of Medicine, Palembang, Indonesia. E-mail: icheandriyaniliberty@fk.unsri.ac.id

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NON COMUNICABLE DISEASES

Health-related quality of life of patients with chronic kidney disease: Does it improve after initiation of haemodialysis? A single-centre study from South India

SWATHI GANESAN[1], JAIPPREETHA JAYARAJ[1], ELAYAPERUMAL INDHUMATHI[2]
[1] Sri Ramachandra Institute of Higher Education and Research, Chennai, India;
[2] Department of Nephrology, Saveetha Medical College and Hospital, Chennai, India

Keywords

Haemodialysis • Health-related quality of life • Chronic Kidney Disease • End-stage renal disease

Summary

Background. *In recent years, research on quality of life has emerged as a valuable tool in assessing the effectiveness of therapeutic interventions in chronic kidney disease. This study aims to assess the health-related quality of life among patients with chronic kidney disease, and draw comparisons between haemodialysis and non-dialysis patients.*
Methods. *This is a prospective questionnaire-based observational study involving 148 patients (81 haemodialysis and 67 non-dialysis patients) with chronic kidney disease (Stage 3-5D) conducted in a tertiary care hospital in South India over six months (July 2023-December 2023). The instrument used was the Kidney Disease Quality of Life Short Form-36.*
Results. *The overall mean health-related quality of life score was better among non-dialysis patients compared to haemodialysis patients. A reduction in various domains, including physical functioning ($p < 0.014$), role limitations due to physical health ($p < 0.001$), role limitations due to emotional problems ($p < 0.001$) and social functioning ($p < 0.007$) were observed in the haemodialysis group. In our population, age, gender, employment status and socioeconomic classes were found to be independent predictors of health-related quality of life.*
Conclusion. *This study highlights the deleterious impact of chronic kidney disease on health-related quality of life, with more significant deterioration among patients undergoing haemodialysis compared to non-dialysis patients. Further, this study advocates potential areas of target for therapeutic intervention.*

Introduction

Chronic Kidney Disease (CKD) and End-Stage Renal Disease (ESRD) have become major global health challenges due to their rapidly growing prevalence characterised by high morbidity and mortality, diminished quality of life, and substantial economic strain on healthcare systems. The global burden of ESRD is growing at around 7% annually and is one of the leading causes of mortality [1]. In India, the reported annual incidence of ESRD is around 232 per million population [2].
Chronic kidney disease is characterised by a progressive decline in renal function, with diabetes and hypertension serving as the primary contributing factors. With the increasing prevalence of these two key risk factors owing to economic growth and urbanisation, CKD has become a global health burden. End-stage renal disease represents the terminal stage of CKD characterised by a glomerular filtration rate (GFR) of less than 15 mL/min/1.73 m², signifying severe irreversible renal damage often requiring kidney replacement therapy (KRT) such as dialysis or renal transplantation [2].
In recent years, there has been growing attention on exploring the physical and psychosocial influence of an illness on the overall quality of life of a patient. The shift of focus towards psychological and social aspects in addition to biomedical measures has been shown to play a vital role in ensuring positive patient outcome from both the patient's and clinician's perspective, and has become a crucial component of outcome measure when evaluating treatment. Quality of life (QOL) is a broad multifaceted concept encompassing physical, psychological, social and environmental domains that are shaped by a person's experience, expectations, beliefs and perceptions. Health-related quality of life (HRQOL) is a subset of QOL, concentrating specifically on the aspects of life that are directly or indirectly influenced by health, disease or therapeutic interventions [3].
The chronic nature of CKD has a profound impact on the HRQOL of patients as well as their caregivers. Although successful kidney transplantation with a well-matched kidney is the most preferred form of KRT, it is not easily attainable making long-term maintenance dialysis the most feasible alternative with a bias towards haemodialysis worldwide. Despite being designed to improve the patient's HRQOL, haemodialysis is time-consuming, resource-intensive, expensive, requires dietary modifications, and often results in loss of independence, reliance on caregivers, reduced physical, emotional and financial stability leading to disruption in marital, family and social life [4]. Hence,

a multidisciplinary approach with timely interventions to improve HRQOL can significantly benefit a patient's health. It is critical to educate healthcare professionals on the methods of using HRQOL tools in assessing patients under their care and the importance of implementing necessary interventions to improve the HRQOL of patients with CKD.

Despite the escalating global burden of CKD, there are very few studies dealing with the HRQOL of CKD patients, with most of these being from developed countries. The main objective of this study is to assess the HRQOL among patients with CKD based on physical, emotional and social domains with an attempt to compare between patients undergoing haemodialysis and non-dialysis patients. We also aim to determine the key socio-demographic factors affecting the HRQOL among patients with CKD. This information is key in helping health professionals deliver patient-centred rehabilitation and care to cater the personal needs of each patient thus improving their overall health outcomes.

Materials and methods

Study design

A prospective questionnaire-based observational study was conducted in an urban tertiary care hospital in South India. Following approval from the institutional ethics committee (CSP/20/FEB/84/89), the study was carried out over six months, from July 2023 to December 2023. A simple random sampling was used to select the participants. Using the single population proportion formula, considering the prevalence of CKD (stage 3 to 5D) as 6% with 95% confidence interval and 10% attrition, the sample size was calculated as 148 patients.

Inclusion and exclusion criteria

Patients with CKD stage 3 to 5D attending the nephrology outpatient department or patients undergoing haemodialysis for at least three months or admitted at this centre were the study participants. Patients with a history of renal transplantation, undergoing peritoneal dialysis, malignancy, psychiatric illness and significant impairment of speech, hearing, or cognitive disturbances were excluded from the study population.

Data collection

Data were collected using pre-structured and pre-tested questionnaires containing socio-demographic characteristics, disease parameters and health-related quality of life questions. The HRQOL was assessed using Kidney Disease Quality of Life Short Form 36-Item (KDQOL SF-36) health survey from RAND Corporation [5]. SF-36 is a 36-item short-form questionnaire not specific to any disease or treatment group. SF-36 assesses the disease burden in an 8-dimensional profile on a 100-point scale; a higher score indicates a better perceived HRQOL. The eight dimensions include physical functioning (PF), role limitations due to physical health (RP), role limitations due to emotional problems (RE), energy/fatigue (E/F), emotional well-being (EW), social functioning (SF), bodily pain (BP) and general health (GH).

The English version of SF-36 has been validated in the Indian population. The questionnaire was translated into the regional language according to instructions given by RAND Corporation. A Nephrologist reviewed and back-translated the translated questionnaire to verify the accuracy of the translated terms. A pilot study with 15 patients assessed the cultural appropriateness and the inputs were used for framing the final version. Even though SF-36 is a self-reported questionnaire, considering the response bias, the authors administered the questionnaire by interviewing all the study participants. Written informed consent was obtained from patients after explaining the objectives of this study in their language.

Data analysis

Data were coded, entered into Microsoft Excel and analysed using SPSS version 26.0. Normality and outliers were assessed using histograms, the Shapiro–Wilk normality test, skewness, and kurtosis indices. The data were found to be normally distributed. Descriptive statistics were conducted for the whole sample population followed by separately for non-dialysis and haemodialysis group. Categorical variables were represented as frequencies and percentages, and all continuous variables were expressed as means and standard deviations (SD). Two summary scores were calculated using these eight domains: Physical Component Summary (PCS) and Mental Component Summary (MCS). PF, RP, BP and GH were included in PCS; and E/F, EW, RE and SF were included in MCS. The mean and SD of PCS and MCS were determined and used to categorise patients into three groups according to the level of HRQOL: one SD above the mean is "good", +/- one SD from the mean is "fair" and one SD below the mean is "poor". Differences between non-dialysis and haemodialysis groups were examined using the Student's unpaired t-test. Associations between socio-demographic variables and SF-36 domains among non-dialysis and haemodialysis patients were assessed using student's unpaired t-test to compare variables containing two groups, and one-way analysis of variance (ANOVA) to compare variables containing more than two groups. Two-tailed p-value < 0.05 was considered statistically significant.

Results

Of the 148 participants, 67 (46.5%) patients were non-dialysis (stages 3 to 5) and 81 (54.7%) were on haemodialysis (stage 5D).

Socio-demographic parameters

The age of patients ranged between 26 and 84 years, with the mean age being 54.57 ± 11.91 years. The majority of the study participants were in the age group 40 to 60 years, which accounted for 46.6%. Among our study

population, 60% were males. More than half were urban dwellers (68.2%). Only a small proportion (25.7%) of patients were currently employed. More than half of the study population belonged to upper-middle (31.8%) and upper-lower (39.2%) socioeconomic classes. The general patient characteristics according to CKD stages are shown in Table I. Based on body mass index, 58% of our study population was within the normal weight range. Nearly one-fifth of the patients were chronic smokers and alcoholics.

Clinical parameters

Overall, patients had been diagnosed with CKD for an average of 3.8 years, ranging from less than two years (47, 31.7%), to 2-5 years (66, 44.6%) and over five years (35, 23.7%). In addition to CKD, it was found that 122 (82.4%) had hypertension, 58 (39.2%) had diabetes, 31 (20.9%) had coronary artery disease and 4 (2.7%) had cerebrovascular accident concomitantly.

The most frequently reported inter-dialytic symptoms were tiredness (77.78%), oedema (56.50%), shortness of breath (46.91%) and muscle cramps (44.44%). Other inter-dialytic symptoms are summarised in Figure 1. In the haemodialysis group, 58 (71.6%) patients had anaemia. In general, haemodialysis patients had slightly more hospital admissions (38.3%) than non-dialysis patients (32.8%).

Health-related quality of life scores and correlations among various domains of SF-36

Haemodialysis group displayed significantly lower scores in 5 out of 8 HRQOL domains compared to non-dialysis group. Although PF, RP, RE, E/F and SF domain scores were better among non-dialysis patients, EW, BP and GH domains were better among haemodialysis patients. The difference in PF, RP, RE and SF scores between haemodialysis and non-dialysis was statistically significant ($p < 0.05$). Analysis of individual scores of SF-36 showed that the highest mean scores among non-dialysis patients were RE (mean = 73) and PF (mean = 67) domains, and among haemodialysis patients were BP (mean = 65) and EW (mean = 65) domains. RP had the lowest mean score among non-dialysis (mean =48) and haemodialysis (mean = 18) patients. Comparison of mean HRQOL scores among haemodialysis and non-dialysis patients is shown in Figure 2. Measurements of HRQOL across

Tab. I. General characteristics of the study population.

Parameter		All (n = 148)	Non-dialysis (n = 67)	Haemodialysis (n = 81)
Age	< 40 years	16 (10.8%)	6 (9%)	10 (12.3%)
	40 - 60 years	69 (46.6%)	29 (43.3%)	40 (49.4%)
	> 60 years	63 (42.6%)	32 (47.8%)	31 (38.3%)
Gender	Female	59 (39.9%)	26 (38.8%)	33 (40.7%)
	Male	89 (60.1%)	41 (61.2%)	48 (59.3%)
Residence	Urban	101 (68.2%)	43 (64.2%)	58 (71.6%)
	Rural	47 (31.8%)	24 (35.8%)	23 (28.4%)
Employment status	Currently working	38 (25.7%)	19 (28.4%)	19 (23.5%)
	Not currently working	110 (74.3%)	48 (71.6%)	62 (76.5%)
Socioeconomic status	Upper	5 (3.4%)	3 (4.5%)	2 (2.5%)
	Upper-middle	47 (31.8%)	16 (23.9%)	31 (38.3%)
	Lower-middle	34 (23%)	13 (19.4%)	21 (25.9%)
	Upper-lower	58 (39.2%)	31 (46.3%)	27 (33.3%)
	Lower-lower	4 (2.7%)	4 (6%)	0 (0%)
Type of family	Nuclear	104 (70.3%)	42 (62.7%)	62 (76.5%)
	Joint	44 (29.7%)	25 (37.3%)	19 (23.5%)
Marital status	Married	140 (94.6%)	64 (95.5%)	76 (93.8%)
	Single	8 (5.4%)	3 (4.5%)	5 (6.2%)
Body mass index (BMI)	Underweight	16 (10.8%)	8 (11.9%)	8 (9.9%)
	Normal	86 (58.1%)	36 (53.7%)	50 (61.7%)
	Overweight	34 (23%)	16 (23.9%)	18 (22.2%)
	Obese	12 (8.11%)	7 (10.45%)	45 (6.17%)
Smoking	Yes	27 (18.2%)	13 (19.4%)	14 (17.3%)
	No	121 (81.8%)	54 (80.6%)	67 (82.7%)
Alcohol consumption	Yes	29 (19.6%)	18 (26.9%)	11 (13.6%)
	No	119 (80.4%)	49 (73.1%)	70 (86.4%)
Co-morbidities	Diabetes	58 (39.1%)	28 (41.8%)	30 (37%)
	Hypertension	122 (82.4%)	48 (71.6%)	74 (91.4%)
	Heart disease	31 (20.9%)	8 (11.9%)	23 (28.4%)
	Stroke	4 (2.7%)	2 (3%)	2 (2.5%)

Fig. 1. Inter-dialytic symptoms experienced by haemodialysis patients (n = 81).

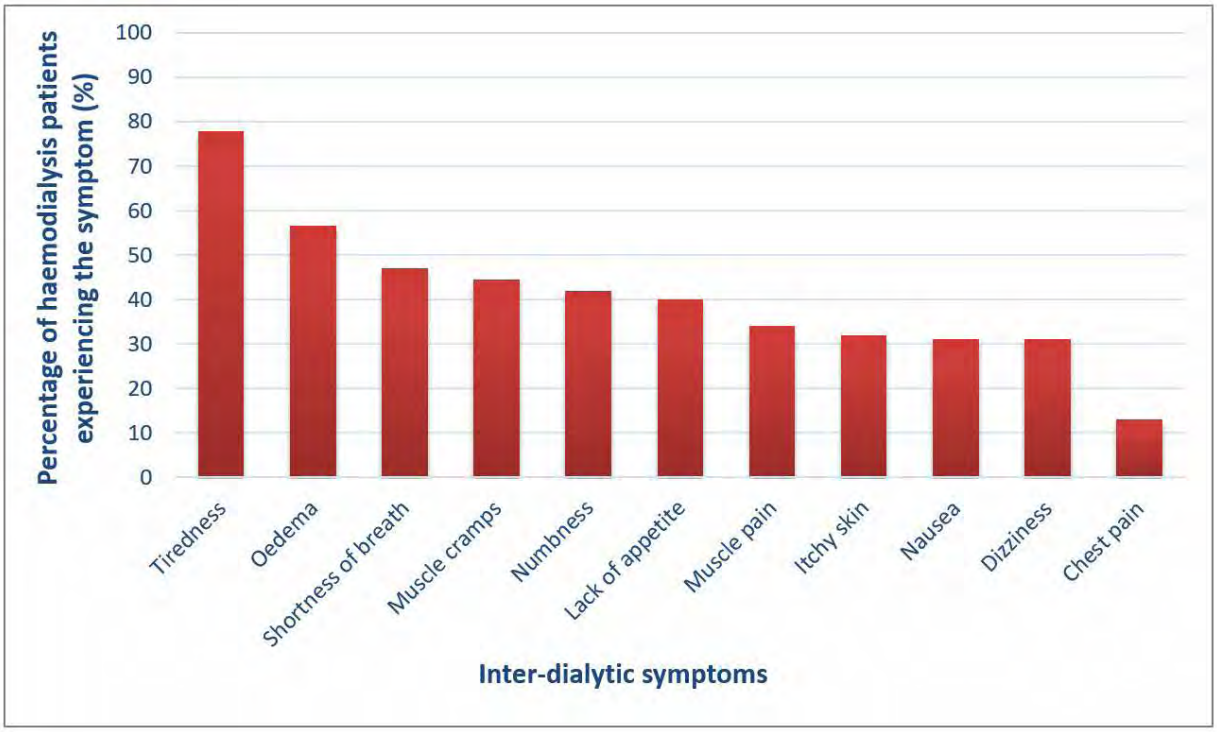
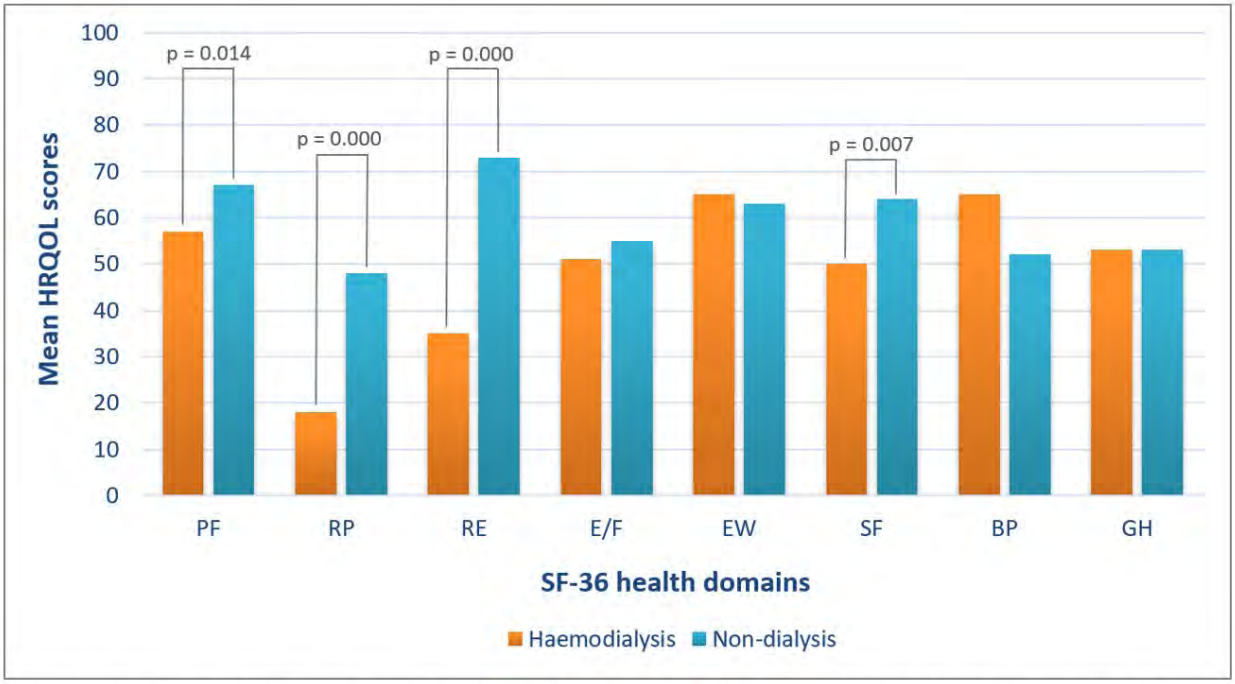


Fig. 2. Comparison of mean HRQOL scores across various domains of SF-36 between non-dialysis and haemodialysis patients.



PF = physical functioning; RP = role limitations due to physical health; RE = role limitations due to emotional problems; E/F = energy/fatigue; EW = emotional well-being; SF = social functioning; BP = bodily pain; GH = general health

*the graph is based on the mean scores of the population under study. #differences did not meet the level of statistical significance unless otherwise specified

Fig. 3. Comparison of mean HRQOL scores among the study population.

PF = physical functioning; RP = role limitations due to physical health; RE = role limitations due to emotional problems; E/F = energy/fatigue; EW = emotional well-being; SF = social functioning; BP = bodily pain; GH = general health

various domains of SF-36 for the entire study population (Fig. 3), and for haemodialysis and non-dialysis groups separately (Fig. 4) are shown in Table II.

In our study population, the PCS and MCS were fair for more than half (62.84% and 60.14%, respectively) of the patients. A higher proportion of non-dialysis patients had better PCS and MCS scores than haemodialysis patients. However, there was a lower proportion of haemodialysis patients with poor PCS and MCS scores than their counterparts (Tab. III). Figure 5 shows the linear relationship between PCS and MCS, represented by a linear equation with R squared 65%, y = 0.8351x + 17.649 (where x is PCS and y is MCS).

Effect of socio-demographic parameters on SF-36 domains

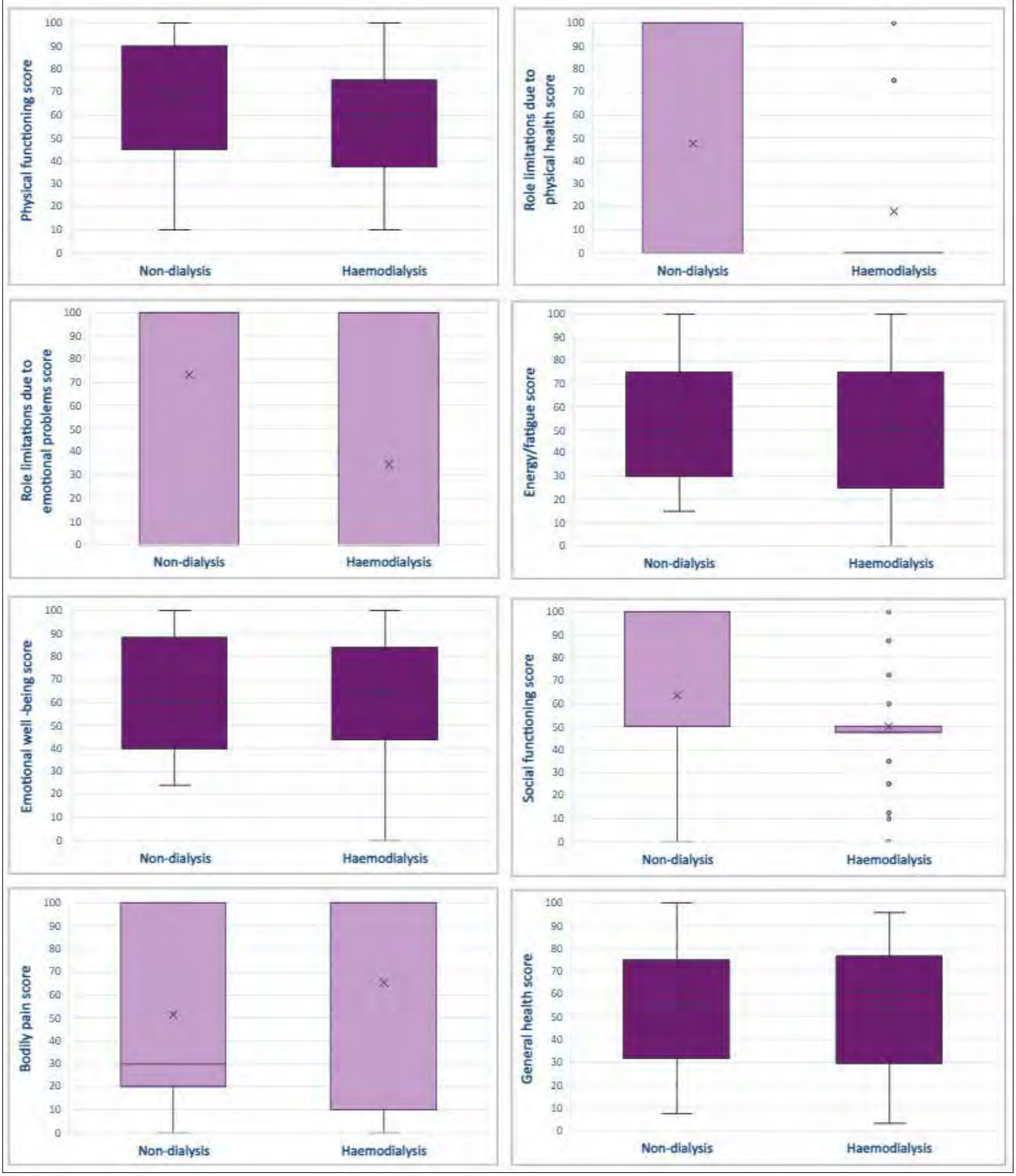
Among the various domains of SF-36, PF significantly declined with advancing age among haemodialysis patients ($p < 0.05$), while age did not affect the PF among non-dialysis patients. In the present study, male patients undergoing haemodialysis had better HRQOL with respect to PF, E/F, EW, SF, BP and GH compared to female patients. In addition, gender was statistically associated with PF ($p = 0.001$), RE ($p = 0.024$), E/F ($p = 0.024$) and BP ($p = 0.044$) among non-dialysis patients. Among both non-dialysis and haemodialysis groups, the working population had better mean HRQOL scores than their counterparts across all domains. Univariate analysis revealed that employment status statistically correlated with PF, RE, E/F, EW, SF and GH among haemodialysis patients ($p < 0.05$) and, RP and RE among non-dialysis patients ($p < 0.05$). Higher socioeconomic groups had higher HRQOL scores in all SF-36 domains in non-dialysis patients,

Tab. II. Mean health-related quality of life scores across various domains of SF-36 among patients with Chronic Kidney Disease.

Health-related quality of life domain	Non-dialysis	Haemodialysis	*p* value
Physical functioning	67 ± 26.8	57.3 ± 23.1	0.014*
Role limitations due to physical health	47.8 ± 50.3	17.9 ± 38	0.000*
Role limitations due to emotional problems	73.1 ± 44.7	34.6 ± 47.3	0.000*
Energy/ fatigue	54.8 ± 26.9	51.2 ± 32.5	0.491
Emotional well-being	62.8 ± 25.8	65.4 ± 24.8	0.459
Social functioning	63.8 ± 37	50.3 ± 28.7	0.007*
Bodily pain	51.6 ± 41.4	65.4 ± 43.2	0.104
General health	52.7 ± 25.3	53.1 ± 25.8	0.730

* Statistically significant at $p < 0.05$

Fig. 4. Box & whisker plot summarising the HRQOL scores across various domains of SF-36.

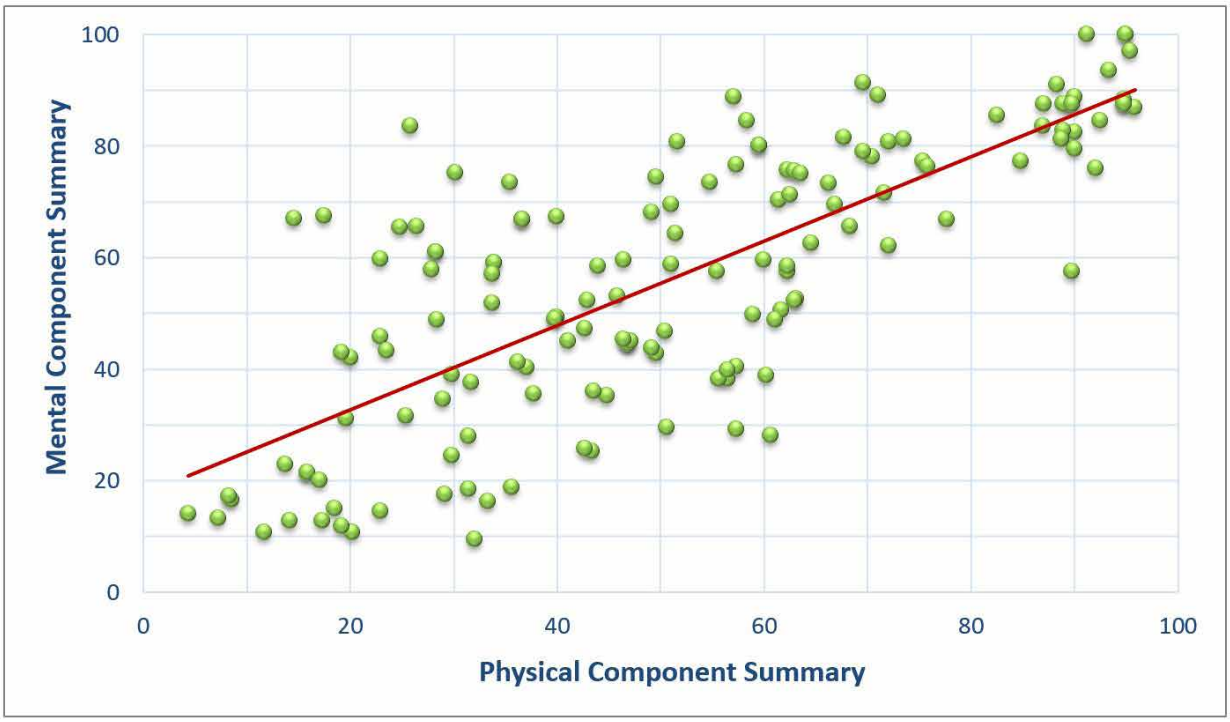


Tab. III. Physical and mental component summary of patients with Chronic Kidney Disease.

	All		Non-dialysis		Haemodialysis	
	PCS	MCS	PCS	MCS	PCS	MCS
Good	18.92%	20.27%	22.39%	25.37%	16.05%	16.05%
Fair	62.84%	60.14%	58.21%	55.23%	66.67%	66.67%
Poor	18.24%	19.59%	19.40%	19.40%	17.28%	17.28%

PCS: physical component summary, MCS: mental component summary.

Fig. 5. Correlation between physical and mental component summary.



while this trend was not noted among haemodialysis patients. The findings of the comparative statistical analysis between SF-36 domains and categorical socio-demographic variables among non-dialysis and haemodialysis patients are summarised in Table IV and Table V, respectively.

Tab. IV. Comparative statistical analysis of mean scores of SF-36 domains among non-dialysis patients, based on socio-demographic variables.

Parameters		PF	RP	RE	E/F	EW	SF	BP	GH
Age	< 40 years	75 ± 31.5	33.3 ± 51.6	83.3 ± 40.8	48.3 ± 29.9	54 ± 35.8	83.3±25.8	30 ± 35.2	32.4 ± 21.5
	40-60 years	55.5 ± 27.4	44.8 ± 50.6	60.5 ± 48.4	57.1 ± 25.9	55.7 ± 23.1	52.3±41.9	59.1 ± 52.9	47.1± 27.7
	> 60 years	66.9 ± 26	53.1 ± 50.7	78.1 ± 42	53.9 ± 27.9	70.9 ± 24.5	70.5±31.1	48.8 ± 40.4	57.8 ± 23.3
	p value	0.644	0.620	0.459	0.656	0.049*	0.077	0.325	0.242
Gender	Female	53.2 ± 25.8	38.5 ± 49.6	57.7 ± 50.4	46.4 ± 28.5	55.9 ± 27.5	62.7±41.3	40.4 ± 42.2	45.6 ± 26.9
	Male	75.7 ± 23.8	53.7 ± 50.5	83 ± 38.1	60.1 ± 24.8	67.2 ± 24	64.5±34.4	58.7 ± 39.8	57.1 ± 23.5
	p value	0.001*	0.228	0.024*	0.024*	0.054	0.929	0.044*	0.060
Residence	Urban	62 ± 28.9	44.2 ± 50.2	67.4 ± 47.4	54.4 ± 27.5	65.4 ± 25.8	57.6 ± 37.7	53.8 ± 42.9	49.8 ± 24.8
	Rural	76 ± 20	54.1 ± 50.9	83.3 ± 38.1	55.4 ± 26.5	58.2 ± 25.8	75 ± 33.6	47.5 ± 39.1	57.7 ± 26.1
	p value	0.559	0.770	0.412	0.474	0.382	0.074	0.083	0.646
Employment status	Currently working	75 ± 25.6	68.4 ± 47.8	94.7 ± 23	63.7 ± 23.6	63 ± 21.8	65.7 ± 37.3	70 ± 38.8	56.8 ± 24.6
	Not currently working	63.9 ± 26.8	39.6 ± 49.4	64.6 ± 48.3	51.3 ± 27.6	62.8 ± 27.5	59.1 ± 36.7	47 ± 41.9	51 ± 25.7
	p value	0.101	0.035*	0.013*	0.062	0.905	0.483	0.111	0.432
Socio-economic status	Upper	83.3 ± 5.8	100±0	100±0	91.7 ± 14.4	85.3 ± 25.4	83.3 ± 28.9	66.7 ± 57.7	85.3 ± 25.5
	Upper-middle	65.9 ± 27	62.5 ± 50	75 ± 44.7	60 ± 24.5	69.3 ± 25.1	47.5 ± 27.5	58.4 ± 45.5	54.6 ± 23.2
	Lower-middle	82.3 ± 23	53.9 ± 51.9	84.7 ± 37.6	63.1 ± 27.6	65 ± 23	67.1 ± 40.3	53.1 ± 42.5	63.1 ± 31
	Upper-lower	60.8 ± 28.3	38.7 ± 49.5	67.7 ± 47.5	46.9 ± 26.3	60.1 ± 26.3	69.1 ± 39	44.8 ± 38.4	46.6 ± 21.6
	Lower-lower	57.5 ± 12.6	0 ± 0	50 ± 57.7	40 ± 11.5	34 ± 12	62.5 ± 43.3	60 ± 46.2	33 ± 8.2
	p value	0.080	0.052	0.478	0.032*	0.048*	0.206	0.911	0.036*

* Statistically significant at $p < 0.05$.

PF: physical functioning, RP: role limitations due to physical health, RE: role limitations due to emotional problems, E/F: energy/fatigue, EW: emotional well-being, SF: social functioning, BP: bodily pain, GH: general health.

Tab. V. Comparative statistical analysis of mean scores of SF-36 domains among haemodialysis patients, based on socio-demographic variables.

Parameters		PF	RP	RE	E/F	EW	SF	BP	GH
Age	< 40 years	66 ± 19.3	30 ± 48.3	40 ± 51.6	48.5 ± 29.7	59.2 ± 28.2	60.3 ± 28.5	56.5 ± 44.1	55.8 ± 24.7
	40-60 years	64.9 ± 22.4	21.3 ± 40.3	44.2 ± 49.7	57.3 ± 34.5	70.5 ± 23.1	54.8 ± 24.9	66 ± 44.1	58.4 ± 23.3
	> 60 years	44.8 ± 19.9	9.7 ± 30.1	20.4 ± 40.1	44.4 ± 30	60.9 ± 25.3	41.4 ± 31.6	54.2 ± 43.2	45.6 ± 28
	p value	0.000*	0.246	0.125	0.277	0.220	0.043*	0.965	0.123
Gender	Female	51.8 ± 24.7	20.5 ± 40.2	37.4 ± 48.4	40.6 ± 30.6	60.2 ± 25.9	46.3 ± 31.1	58.5 ± 44.3	49.4 ± 28.6
	Male	61.1 ± 21.3	16.2 ± 36.6	32.7 ± 46.9	58.5 ± 32	69 ± 23.7	53.1 ± 26.9	70.1 ± 42.3	55.7 ± 23.6
	p value	0.092	0.613	0.597	0.012*	0.119	0.089	0.188	0.351
Residence	Urban	58.6 ± 23.1	18.1 ± 37.9	34.5 ± 47.1	54.2 ± 33.2	68.2 ± 23.5	48.9 ± 29.7	65.3 ± 42.9	55.5 ± 26.7
	Rural	54.1 ± 23.1	17.4 ± 38.8	34.8 ± 48.7	43.7 ± 29.9	58.4 ± 27.1	54 ± 26.1	65.4 ± 44.9	47.3 ± 22.7
	p value	0.466	0.920	0.985	0.245	0.130	0.898	0.963	0.109
Employment status	Currently working	69.5 ± 21.9	31.6 ± 47.7	52.6 ± 51.3	65 ± 33.4	75.4 ± 21.8	62.4 ± 28.5	80 ± 40	64.3 ± 16.7
	Not currently working	53.6 ± 22.3	13.7 ± 33.8	29.1 ± 45	47 ± 31.2	62.4 ± 25	46.7 ± 27.9	60.9 ± 43.5	49.7 ± 27.2
	p value	0.008*	0.078	0.043*	0.027*	0.045*	0.015*	0.097	0.045*
Socio-economic status	Upper	45 ± 35.4	0 ± 0	50 ± 70.7	25 ± 35.4	70 ± 14	43.8 ± 61.9	50 ± 70.7	38.3 ± 14.1
	Upper-middle	53.1 ± 22.9	12.1 ± 32.2	25.8 ± 44.5	44.8 ± 33.8	64.8 ± 26.1	54 ± 26.3	62.4 ± 44.1	53.1 ± 23.7
	Lower-middle	62.1 ± 18.5	13.1 ± 33.2	38.2 ± 47.5	53.1 ± 30.4	61 ± 23.9	41.2 ± 22.5	32.1 ± 41	52.3 ± 27.2
	Upper-lower	59.4 ± 25.8	29.6 46.5	40.7 ± 50.1	59.1 ± 31.7	69.3 ± 25	53.8 ± 33.1	64.6 ± 44.2	55 ± 28.2
	Lower-lower	-	-	-	-	-	-	-	-
	p value	0.507	0.270	0.582	0.217	0.679	0.326	0.873	0.736

* Statistically significant at $p < 0.05$

PF: physical functioning, RP: role limitations due to physical health, RE: role limitations due to emotional problems, E/F: energy/fatigue, EW: emotional well-being, SF: social functioning, BP: bodily pain, GH: general health

Discussion

Over the last few decades, health systems have begun to pay increasing attention towards HRQOL due to the emergence of a holistic approach to health and disease. In this study, there was a decline in the HRQOL across all stages of CKD and more significant HRQOL deterioration was noted among patients undergoing haemodialysis compared to non-dialysis patients. Socioeconomic characteristics were found to have a significant impact on the HRQOL of patients.

The mean age in our cohort was slightly higher compared to patients reported in the Indian CKD registry and a slight male predominance was seen similar to other studies [6-8]. Sex hormones are assumed to be significant in the pathogenic mechanisms associated with gender-specific disease outcomes. In vitro studies with animal models have established oestrogen's protective influence and testosterone's negative influence on several mechanisms involved in kidney injury [8]. Even in the modern Indian context, due to the prevailing male breadwinner tradition, the increased incidence of CKD in men can lead to severe financial distress in the family.

In our study population, diabetes mellitus and hypertension were the common co-morbidities associated with CKD. This finding was in conjunction with the Indian CKD registry. Studies reveal that patients with concomitant CKD and diabetes have markedly lower HRQOL [9, 10]. Prospective health screening is necessary to identify these predisposing factors and to promote an active healthy lifestyle among these individuals.

In our study, haemodialysis patients displayed lower HRQOL scores than non-dialysis patients in most SF-36 domains. Patients experienced significant role limitations due to both physical health (47.8 ± 50.3 in non-dialysis and 17.9 ± 38 in haemodialysis) and emotional health problems (73.1 ± 44.7 in non-dialysis and 34.6 ± 47.3 in haemodialysis). These were the lowest-scoring items in the haemodialysis group and statistically correlated with the stage of kidney disease. These scores were significantly higher than the study performed by Kefale B et al. in the non-dialysis group [11]. At the same time, it was much lower compared to the study by Cruz MC et al. in the haemodialysis group [9]. The SF score among non-dialysis patients was better than haemodialysis patients. This finding was in accordance with Bagasha et al. [12]. This may be attributed to the extensive time spent at haemodialysis centres in conjunction with dependency on machines and healthcare professionals, which entail a significant burden for patients characterised by lifestyle disruption, and feelings of guilt and inadequacy. The mean score of PF among non-dialysis patients was higher than among haemodialysis patients. This finding was coherent with the results of Cruz MC et al. [9]. Impaired PF due to fatigue, muscle weakness and exercise intolerance reduce the ability to perform day-to-day activities among patients undergoing haemodialysis, attributing to the decreased PF scores. Reduced physical functioning limits the ability of a person to work in a paying job in addition to increased treatment expenses leading to financial instability, which in turn affects the emotional and social functioning of the patient. These are interrelated and thus continue as a vicious

cycle affecting the patient's overall HRQOL. A well-founded social and family support network and a stable ambience are crucial in providing holistic care to these patients. There is adequate evidence to suggest a positive relationship between a reliable social support system and lower depression rates resulting in higher compliance to treatment and overall better HRQOL [13, 14].

In general, we observed the PCS and MCS scores to be better in non-dialysis patients compared to haemodialysis patients. In our population, the mean PCS score was 51.3 ± 24.7, which was similar to other studies from developing countries [15, 16]. Varied PCS scores were observed in studies from different countries [11, 17, 18], with higher scores noted in developed countries [19, 20]. Our study determined the mean MCS score as 56.4 ± 24.4, similar to previous studies [15, 21]. Higher MCS score was noted in studies from Western countries [19, 22]. This variation may be attributed to the differences in educational standards, economic status and treatment protocols between countries. Overall, MCS was higher than PCS, reflecting the patients' psychological adaptation to chronic illness. An analysis of nearly 14,000 in-centre haemodialysis patients found that HRQOL scores were critical predictors of hospitalisation and mortality. Their results revealed that each 5-point increase in PCS score was associated with a 10% reduction in the relative risk of hospitalisation and death, and each 5-point increase in MCS was associated with a 5% and 10% reduction in the relative risk of hospitalisation and death, respectively [23].

The presence of two or more concurrent co-morbidities had a negative impact on the domains of PCS, particularly PF and RP. Earlier reports have suggested that the coexistence of multiple co-morbidities is a significant determinant of deterioration in HRQOL [9, 24]. Apart from physical, functional and clinical parameters, factors such as socio-demographic characteristics, employment status and accessibility to medical care play a pivotal role in an individual's perception of life [25, 26]. Among our population, older age was found to be a negative predictor of PF in haemodialysis patients; on the contrary, younger age was a negative predictor of SF among haemodialysis patients and EW among non-dialysis patients. Though older adults may have reduced motivation and energy to perform physical activity, they scored better in emotional domains due to better adaptability and maturity to deal with the disease than younger adults in the face of CKD. In our analysis, female gender emerged as a strong predictor of lower scores in SF-36 domains, particularly in E/F among haemodialysis patients, and PF, RE, E/F and BP among non-dialysis patients. This reflects the vulnerability of women with chronic disease ascribed to their different psychosocial perspectives on life, such as social stigmatisation, higher prevalence of psychological distress and family commitments, compared to men. Through our study, we observed that unemployment adversely affected the HRQOL across most domains. Similar results have also been reported by previous studies conducted in Ethiopia [26], the United States of America [27] and India [28]. The findings of this association may imply that financial constraints to manage the treatment expenses could have resulted in lower HRQOL. To reduce the incidence of unemployment among patients undergoing haemodialysis, flexible haemodialysis shifts to adapt to individuals' lifestyles are essential to ameliorate the employment rate. On careful evaluation, we found that higher socioeconomic status positively predicted E/F, EW and GH among non-dialysis patients. Patients of higher socioeconomic status can afford better treatment to satisfy their needs. In addition, financial security may lead to a better state of mind resulting in higher HRQOL compared to those in lower socioeconomic classes. A similar pattern of HRQOL and its relation with socioeconomic status was found in other studies [25, 29, 30].

In our study population, more than half of the CKD patients across all stages had difficulty falling asleep during the night. Biological, psychological and behavioural factors might contribute to the increasing prevalence of sleep disturbances among patients with CKD. End-stage renal disease is characterised by considerable changes in sleep architecture, circadian rhythm and endogenous melatonin release [31]. Poor quality of sleep in CKD patients has an adverse effect on their HRQOL. Therefore, counselling and advocacy programs should be established to improve the patient's sleep quality and HRQOL.

With rise in prevalence of CKD, it becomes even more essential to evaluate effectiveness of therapeutic approaches in order to enhance the treatment quality, improve operational efficiency, optimise resource allocation and devise individualised care plans. This is elucidated in the study by Guarducci et al., which used EuroQol 5-Dimension 5-Level questionnaire and Cumulative Illness Rating Scale to perform patient-reported and clinical assessments, respectively, in order to evaluate health gains in the form of quality-adjusted life years (QALYs) and related treatment costs in an Italian private healthcare centre [32]. Chronic kidney disease involves a complex interaction between physiological deterioration and HRQOL. This association has been investigated by D'Arrigo et al. in an Italian study cohort, which highlighted that the progressive decline in kidney function (GFR) was significantly associated with reductions in both physical and mental components of HRQOL over a 3-year follow-up period [33]. More such longitudinal studies are required to evaluate the progression of HRQOL across all CKD stages and to assess the precise impact of socioeconomic factors in order to plan context-specific and sustainable interventions.

This was a single-centre study with a relatively small sample size; hence, multi-centre studies involving various geographical locations may be needed. The study's observational nature permitted only to determine associations between various independent and dependent variables and not causal relationships. There may be residual confounding factors affecting the results, such as compliance with therapy, capacity to handle stress, and cultural and religious practices.

Conclusion

The increasing life expectancy, along with the rising prevalence of risk factors, is significantly increasing the burden of chronic diseases like CKD, particularly among resource-poor and medically underserved populations, representing one of the most complex challenges that the future healthcare system must face. Thus, the need to assess and improve the HRQOL of these patients becomes increasingly fundamental. In the present study, we observed a significant decline in the HRQOL of patients with CKD. Socioeconomic characteristics were found to considerably impact the HRQOL of patients in our population. Though haemodialysis is initiated to improve a patient's overall well-being, evidence from several studies including the present study report greater HRQOL deterioration among patients undergoing haemodialysis compared to non-dialysis patients. Therefore, routine utilisation of HRQOL assessments in the care of patients with CKD would allow an improved understanding of HRQOL and its predictors, and help in formulating tailored treatment strategies for each patient with the potential to improve their long-term health outcomes. Future initiatives should prioritise a bench-to-bedside approach which transforms these findings into real-world interventions such as enhanced pharmacological therapies, nutritional counselling, vocational training, standardised HRQOL evaluation criteria, and psychosocial support for patients and caregivers.

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Conflict of interest

There were no potential conflicts of interest among the authors.

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Authors' contribution

SG and JJ formulated the study design, collected data, carried out data analysis and prepared the draft. EI approved the final draft and guided through publication process.

Ethical approval

IRB approval number CSP/20/FEB/84/89.

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Correspondence: Elayaperumal Indhumathi, Professor and HOD, Department of Nephrology, Saveetha Medical College and Hospital, Chennai, India - Email: drindhusrmc@gmail.com

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Occupational medicine and hygiene

Cardiovascular risk in seasonal migrant workers in Southern Italy: clinical-epidemiological evaluation

DOMENICO BASTA[1]
[1] University of Bari Aldo Moro, Italy - Medical Health Area, FARBAS Basilicata Environment Research Foundation, Italy

Keywords

Cardio-vascular risk • Arterial hypertension • Seasonal workers • Electrocardiogram • Spirometry

Summary

Introduction. *As part of the GOV.E.R.NI projects (Effective Government in Reports for New Integrations) and Più Su.Pr.Eme, project that is part of the three-year plan to combat labor exploitation in agriculture and the caporalato approved within the specific Caporalato Table promoted by the Directorate General for Immigration of the Ministry of Labor and Social Security with the aim of combating and overcoming all forms of serious labor exploitation and serious marginality and vulnerability of migrant workers in the territories that present the most critical issues in Southern Italy. The research institute FARBAS has carried out health surveillance activities on migrant workers in Basilicata with the aim of assessing the state of health and conditions that may put the health of workers at risk.*

Materials and Methods. *The epidemiological study concerns the analysis and study of data obtained from a cohort of 135 migrant workers hosting in two reception centers located in the territory of Basilicata (Italy) who have voluntarily joined the health screening activities by means of electrocardiogram examination, spirometry tests, blood pressure measurement and physiological and pathological history. Enlisted come from 12 Central African countries, with a mean age of 37.08 ± 9.8, of male gender.*

Results. *Analysis of clinical and instrumental data shows that 51.1 % of patients have higher than optimal blood pressure values; 42.2 % have higher than normal systolic blood pressure values, 11.1% have above-normal diastolic blood pressure values. From the analysis of the data obtained from the instrumental examinations it is clear that 20% of the subjects present an electrocardiogram indicating a pathological alteration and 14% of the population present an altered spirometry trace attributable to a pathological state. 64% of the population has a normal BMI, the overweight rate is 30.8 % while 1.5% has grade I obesity and the remaining 3.7 % is underweight.*

Discussion and conclusion. *The study shows a significant prevalence of arterial hypertension, cardiovascular disease and pathological changes in the respiratory system. In particular, the presence of risk factors such as high blood pressure associated with work factors such as maintaining difficult postures and working in the presence of heat represent a high risk to the health of seasonal workers working in the field of tomato harvesting in Southern Italy [1]. Future public health and preventive medicine actions should be geared towards precision health surveillance that can control, manage and reduce this risk to the health of workers.*

Background

The Più Su.Pr.Eme. project is part of the three-year plan to combat labor exploitation in agriculture and the caporalato, recently approved within the specific Caporalato Table promoted by the Directorate General for Immigration of the Ministry of Labour and Social Security. The program aims to implement an Integrated Extraordinary Plan of interventions aimed at combating and overcoming all forms of serious labour exploitation and serious marginality and vulnerability of migrant workers in the territories that present the most criticalities in the five Regions of the South that are the subject of the action. Encourage the overcoming of illegal conditions, through actions of prevention, surveillance, control and emergence of situations of serious labour exploitation in agriculture and through the experimentation of pilot projects of social agriculture. In Basilicata, the health and environmental research body FARBAS has been involved, with a team of experts, with surveillance and research on this issue. Health surveillance of migrant workers in Basilicata carries out a strategic action with the objective of protecting the health of migrants and preventing conditions that may endanger the health of workers. Some data with references to the health conditions most commonly encountered among these workers highlight a health picture mainly characterized by musculoskeletal diseases, respiratory disorders, gastrointestinal problems and a high prevalence of undiagnosed chronic diseases, such as hypertension and diabetes. Numerous reviews have shown that 40% of migrant agricultural workers reported musculoskeletal disorders, 25% chronic respiratory diseases and a significant number suffered from undiagnosed hypertension [2]. These data converge to show how precarious working conditions, difficulties in accessing care and exposure to environmental and social risks create a highly vulnerable health profile among migrant seasonal workers. This evidence reinforces the need to study and plan health surveillance actions and improve access to targeted health services for these populations.

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Materials and Methods

- The epidemiological study concerns the analysis and study of data obtained from a cohort of 135 migrant workers hosting two reception facilities located in the territory of Basilicata who have voluntarily joined the health screening activities by means of electrocardiogram examination, spirometry tests, blood pressure measurement and physiological and pathological history. Enlisted come from 12 Central African countries, with a mean age of 37.08 ± 9.8.
- From the descriptive analysis of the sample of workers included in the survey for socio-demographic variables (sex, age, origin, type of profession).
- Subjects are aged between 22-65 years; with an average age ± SD: 37.08 ± 9.8.
- The subjects come from 12 Central African countries: Benin, Burkina Faso, Chad, Ivory Coast, Eritrea, Gambia, Ghana, Guinea, Mali, Niger, Nigeria, Sudan; as shown in Figure 1.

The work activity carried out is that of harvesting vegetables, in particular tomatoes in the fields of southern Italy in the summer season

Anamnestic data

The pathological history was reconstructed by a health professional through the use of a validated annex with the objective of providing clinical data that can complete the vision of the care picture of the migrant in Italy.
From the pathological history it emerges that:

- No subject reports having had an injury that requires hospitalization.
- 7 subjects underwent surgery (3 herniating discs - 2 appendectomy - 1 cholecystectomy - 1 intervention of the cardio-vascular system).
- 8 subjects suffer from hypertension.
- No one has suffered from neurological diseases (including stroke/epilepsy).
- 1 subject is diabetic.
- No one declares problems or pathologies affecting muscle and bone tissue.
- 1 subject declares visual disturbances.
- 1 subject declares to have contracted scabies and tuberculosis.

Anthropometric data

Body weight assessment was carried out using the Body Mass Index (BMI) which relates weight to height. This analysis shows that 64% of the population has a normal BMI, the overweight rate is 30.8%, 1.5% has grade I obesity and the remaining 3.7% is underweight as shown in Figure 2.

Blood pressure

Blood pressure, systolic (PAS) or diastolic (PAD) parameters have been the subject of numerous studies, some of which establish an association between the increase in these parameters and mortality, particularly at middle ages [3]. According to the World Health Organization (WHO) [4], at least 1 in 5 adults in the world suffer from hypertension and this factor is the cause of about half of deaths from heart attack and ischemic stroke. Blood pressure was measured by an experienced operator using an aneroid sphygmomanometer (non-invasive method) according to guidelines provided by the World Health Organization (WHO). The analysis of the data from the reference sample shows that 51.1% of patients have higher than optimal blood pressure values (Fig. 3); 42.2% have higher than normal systolic blood pressure values, 11.1% have higher than normal diastolic blood pressure values, it can therefore be stated that in

Fig. 1. Countries of origin of the enlisted subjects.

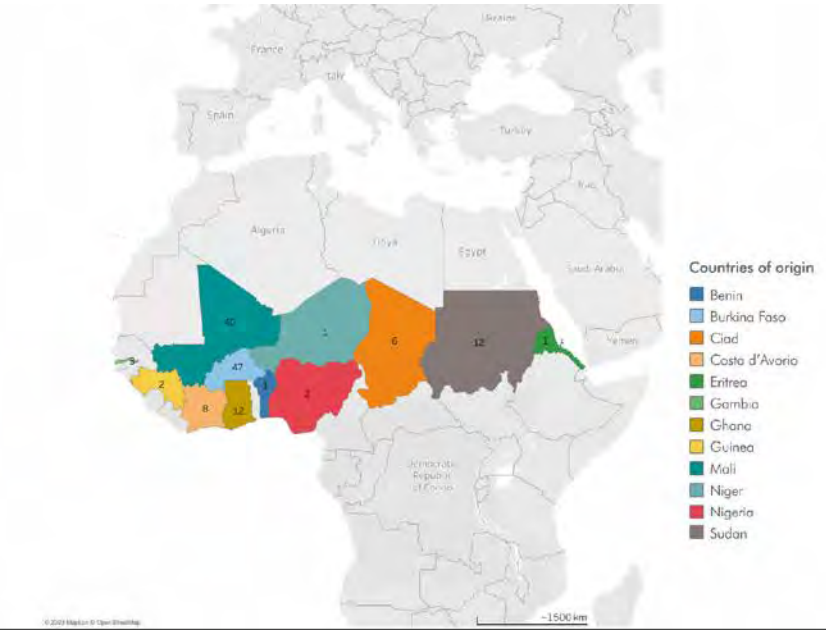
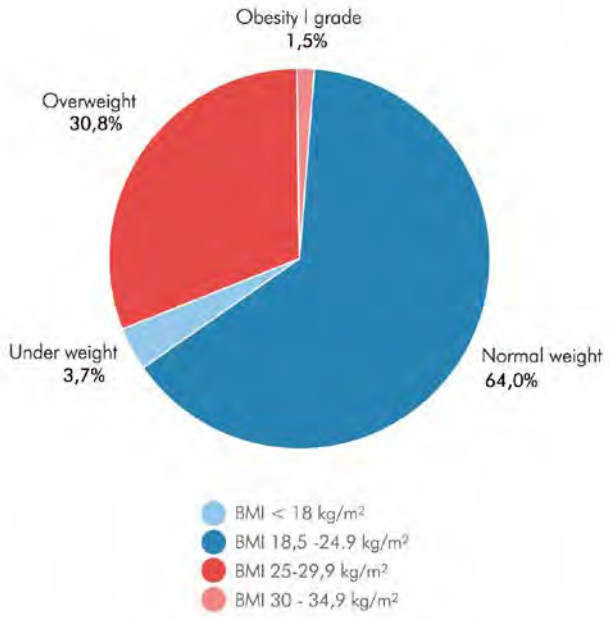


Fig. 2. Percentage representation of BMI in the studied population.



the sample studied 5 out of 10 subjects have abnormal blood pressure values.
From the data collected it was possible to make a diagnosis according to the 2018 ESC/ESH (European Society of Cardiology and European Society of Hypertension) Guidelines as shown in Table I.

Electrocardiogram

From the analysis of the data obtained from the instrumental examinations it is clear that 20% of the subjects (2 out of 10 subjects) have an electrocardiogram indicating a pathological alteration as represented in Figure 4.

Spirometry

Spirometry is the most common test to assess lung function. It is a particularly effective and widespread diagnostic tool as it is standardized, painless, easily reproducible and objective. Spirometry is frequently used in the diagnosis and evaluation of lung function in people with restrictive or obstructive airway diseases. The analysis of the data obtained shows that 14% of the population has an altered spirometry trace attributable to

Fig. 3. Representation of the prevalence of blood pressure values above the norm.

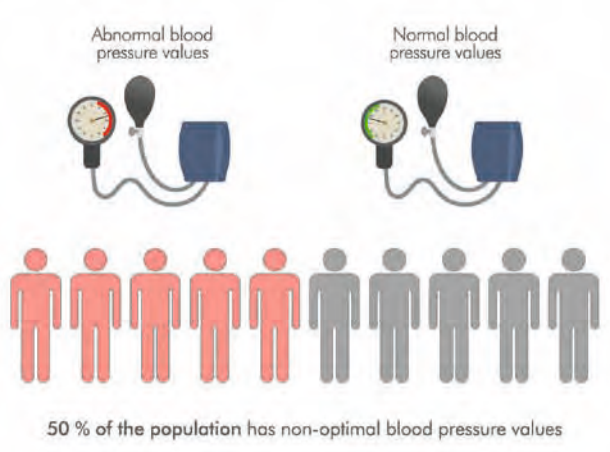
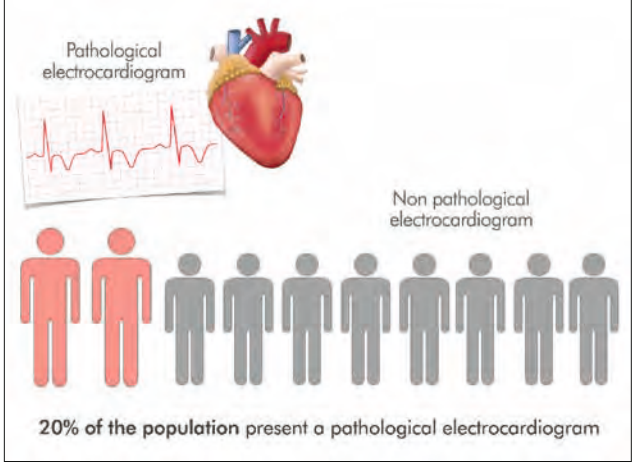


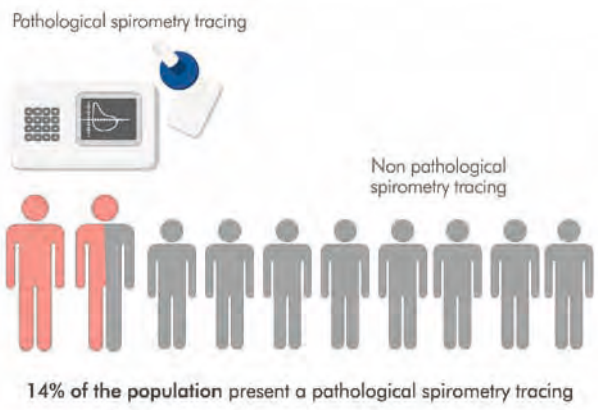
Fig. 4. Representation of the prevalence of pathological electrocardiogram in the sample studied.



Tab. I. SBP and DBP values classification.

Category	Reference values	N. of subjects	Systolic pressure (mmHg) Average ± SD	Diastolic pressure (mmHg) Average ± SD
Optimal	< 120 < 80	66	110 ± 5,0	70,4 ± 3,7
Normal	120-129 80-84	19	120,79 ± 1,8	80 ± 0
Normal - High	130-139 85-89	2	132,5 ± 3,5	87,5 ± 0,7
Grade 1 hypertension	140-159 90-99	15	142,5 ± 3,5	93,5 ± 4,9
Grade 2 hypertension	160-179 100-109	3	160	100
Isolated systolic hypertension	≥ 140 ≤ 90	30	148,72 ± 8,3	79,2 ± 6,0

Fig. 5. Representation of the prevalence of pathological spirometric trace in the studied sample.



a pathological state of a restrictive and instructive nature of the airways, as in Figure 5.

Statistical analysis and correlation

A special professional program of analysis and correlation of the data was used for the statistical analysis. A correlation between age, systolic blood pressure (SBP) and diastolic blood pressure (DBP) was made among subjects with a pathological electrocardiogram. Therefore, there is a significant correlation of increased blood pressure values with increasing age, consequently the cardiovascular risk is increased in the presence of multiple risk factors (abnormal electrocardiogram, arterial hypertension and advanced age) Figure 6.

Linking the body mass index with SBP emerges a positive correlation between increased systolic blood

Fig. 6. Correlation between age, SBP and DBP in subjects with pathological electrocardiogram.

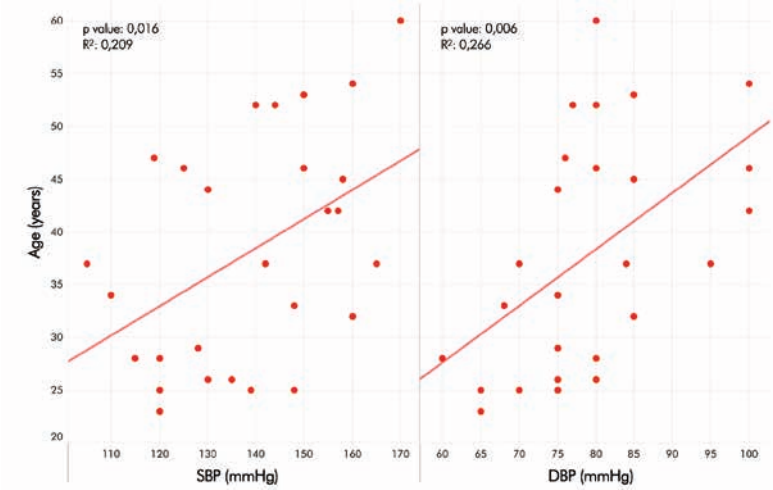
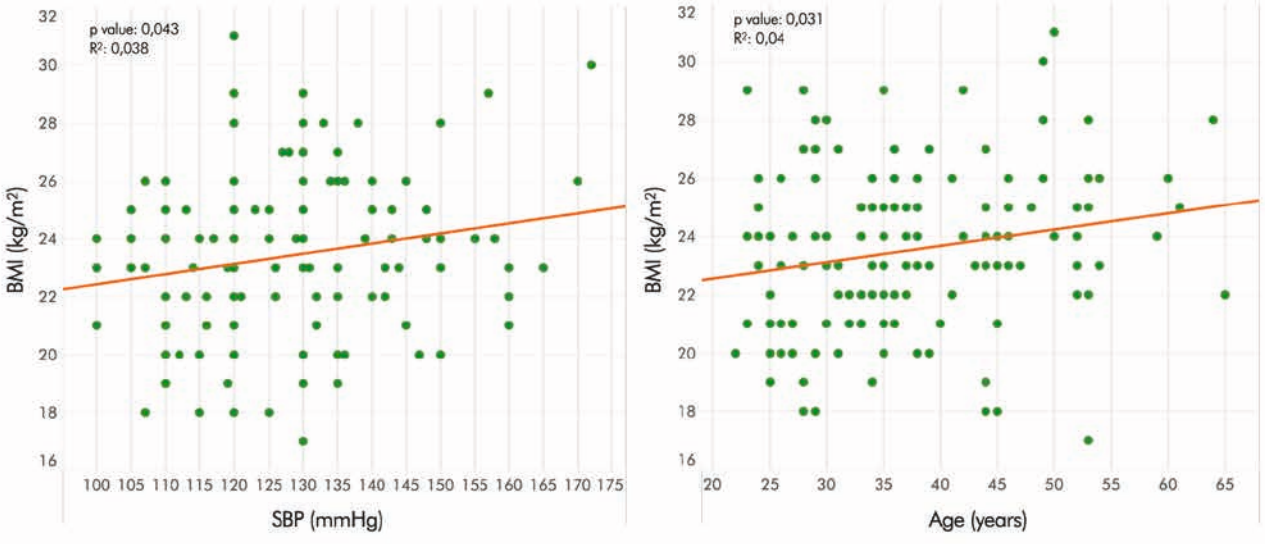


Fig. 7. Linear regressions between SBP and BMI and between BMI and age.



pressure and increased BMI, and the correlation between increased BMI and advancing age is significant (Fig. 7).

Discussion and Conclusion

The analysis of the collected clinical data shows a significant prevalence of arterial hypertension, cardiovascular diseases and pathological alterations of the respiratory system among foreign seasonal workers, despite the average age of the male population being relatively young (37.08 ± 9.8 years). The synergistic presence of risk factors – such as hypertension, cardiovascular and respiratory diseases – together with working determinants (incongruent postures, prolonged exposure to summer heat with temperatures above the seasonal average) determines a high risk for the health of the laborers employed in the tomato harvest in Southern Italy. To these factors are added obstacles to access to public health services, linked to language barriers, irregular legal status and discriminatory phenomena. These results are reflected in numerous international studies on similar populations. A recent meta-analysis conducted on Latino seasonal agricultural workers in the United States reported rates of hypertension ranging from 4% to 68% in males and between 1% to 54% in females, with significant prevalences also for diabetes, obesity and dyslipidemia [5]. Similarly, a study of 3,382 migrant workers in Oregon showed that prolonged stay (≥ 10 years) is associated with a higher risk of hypertension (OR 1.72; 95% CI 1.17-2.54) and obesity (22.8%) [6]. Even in Europe, comparative studies show a higher prevalence of cardiovascular risk factors in migrants compared to native populations, linked to precarious working conditions and difficulties in accessing care [8]. Data on thermal stress also confirm that exposure to high temperatures, particularly among migrants employed in outdoor work, can significantly increase cardiovascular mortality. For example, in contexts such as Qatar and Italy, more than 50% of deaths in the summer among migrant workers were attributable to cardiovascular diseases induced by heat [8]. Respiratory health is also compromised: an extensive review on exposures to agricultural dust and pesticides showed a clear association between agricultural work and acute and chronic respiratory diseases, with incidences between 20% and 35% depending on the context [9].

This study, on the one hand, lays the foundations for future public health and preventive medicine actions aimed at precision health surveillance, capable of monitoring, managing and reducing the risk of cardiovascular diseases among foreign workers; on the other hand, it highlights the urgent need to strengthen health protection interventions aimed at migrants. The strategic assessment of the state of health and the surveillance of diseases in seasonal workers therefore represent an essential cornerstone both for the protection of individual health and for the safeguarding of public health.

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Correspondence: Domenico Basta, University of Bari Aldo Moro - Medical Health Area, FARBAS Basilicata Environment Research Foundation, Italy - Email: domenico.basta@uniba.it

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History of medicine and ethics

Communication and *Cholera Morbus*: measures and fears in 19th Century Italy in the face of an unknown evil. Medical ignorance and ideological paradigms unchanged over time

MARIANO MARTINI[1,2,3,4], FEDERICO DANIELLI[5]
[1] Department of Health Sciences, University of Genoa, Italy; [2] Interuniversity Research Center on Influenza and Other Transmissible Infections (CIRI-IT), Genoa, Italy; [3] UNESCO Chair "Anthropology of Health - Biosphere and Healing System", University of Genoa, Italy; [4] President of section of History of Radiology of Italian Society of History of Medicine, Italy; [5] Independent Scholar, Genoa, Italy

Keywords

Cholera • Disease • Health • Fear • Medical ignorance • History of hygiene

Summary

Abstract. *The arrival of Cholera Morbus in Europe and Italy elicited a prompt institutional reaction. Starting in 1831, preventive measures characteristic of the plagues of the "Ancien Régime" were reactivated. The new disease triggered several instinctive and irrational reactions in the population, which resulted in the most diverse fears: fear of death, of doctors, of food, isolation, and abuse of food and alcohol. Ignorance of the origin of the disease, its etiology and modes of transmission meant that containment measures and treatment were often inefficacious. When patients recovered from the disease, this was due more to their living conditions and underlying state of health than to medical treatment, which was still limited to bloodletting, purgatives, and natural remedies (as emerges from the data from 1835 in the archives of the Genoese hospitals). As revealed by the pamphlets distributed around 1830, the disease was attributed to dietary disorders, personal and domestic hygiene, damp environments, menial occupations, and exposure to cold.*
The medical theories of the time were still closely bound to the "miasmatic-humoral paradigm", as the discoveries of Filippo Pacini, (1812-1883), John Snow (1813-1858) and Heinrich Hermann Robert Koch (1843-1910) had not yet been made. As for preventive measures at the institutional level, "contagionist" theories prevailed, which meant that sanitary cordons were reintroduced, safety measures (e.g. quarantine on people and goods) were implemented and great attention was placed on cleansing and disinfecting streets and public places.
Background. *For centuries, Cholera Morbus was endemic to the territory of Bengal; only with the revolution in transport, starting from 1817, did the disease first spread beyond India [1], replacing the plague as the "scourge of urban populations" [2]. Cholera was localized in Asia until 1817, when a first pandemic spread from India to other regions of the world. Endemic in Asia, (in the delta of the Ganges-India), it remained enclosed to that geographical area until the beginning of the 1800s. It first emerged from the Sundarbans Forest where the bacterium Vibrio cholerae had perhaps been mutating for millennia.*
It afterwards moved to the Mediterranean and Europe as new commerce routes were opened up between East and West and in the 1830s, Western Europe was faced with this totally new and unknown evil [3], which appeared in Italy in 1835.

Introduction

The arrival of this new, aggressive, and unknown disease triggered extraordinary reactions on the part of the population and institutions, which were still tied to rigid mental patterns that dated back to the spread of *Yersinia Pestis* during the *Ancien Régime*.
This situation arose despite the great efforts implemented by the institutions to reassure the population.
According to the medical theories dominant at the time, the disease was caused by fear, dietary disorders and cold [4]. Moreover, there was considerable confusion as to how the disease spread and the nature of the agent that caused it, which was variously indicated in pamphlets and medical publications as: a "morbid germ", a "cholera germ", a "volatile principle", a "choleraic effluvium", a "miasmatic atom", *etc*.
The history of epidemics has been one of the most prominent fields of inquiry in Italian historiography over the past fifty years, with its foundations rooted in the work of Carlo M. Cipolla. A leading economic historian, Cipolla was among the first to examine epidemics through the lens of their socioeconomic consequences. His seminal studies on seventeenth-century epidemics in Italy, published mainly by Il Mulino between the late 1970s and early 1990s, have since been reissued in new editions [5-7], underscoring their lasting significance. These works remain an indispensable point of departure for any scholar approaching the subject, not only with regard to the Italian case but also in comparative perspective. Indeed, the central-northern regions of Italy, particularly the "quadrilateral" formed by Genoa, Florence, Venice, and Milan, where permanent health magistracies had been established in the early modern period, provided a Model subsequently adopted both across the peninsula and, in later centuries, beyond

the Alps and the Channel. As will be shown, English responses to cholera in the nineteenth century drew extensively on Italian precedents, illustrating the centrality of Cipolla's contributions.

Almost contemporaneous with Cipolla's early publications, Lorenzo del Panta's *Le epidemie nella storia demografica italiana* (Loescher, 1980), recently reprinted [8], extended the discussion to the demographic impact of epidemics from the Middle Ages to the contemporary era, thereby developing one of the many lines of inquiry opened by Cipolla. The intellectual vitality of that period also produced a rich series of studies on plague outbreaks in early modern Italy, among them the works of Preto [9, 10] and Restifo [11-13].

Turning to the nineteenth century and the *Cholera Morbus*, the key reference remains Eugenia Tognotti's comprehensive analysis of cholera in Italy [1]. Her study reconstructs the spread of the disease while examining reactions, causes, economic and demographic effects, and the social repercussions in terms of collective imagination and the resurgence of irrational fears, fears that re-emerged after the Enlightenment and nearly ninety years without encounters with a "monster" comparable to the plague. The theme of fear in relation to cholera was further developed by Paolo Sorcinelli in *Nuove epidemie, antiche paure* (Franco Angeli, 1986; reissued by Biblioteca Clueb in 2021 [14]). Focusing on everyday life, diet, interpersonal relations, relations with medical practitioners, and the persistence of irrational anxieties, Sorcinelli demonstrated how these aspects were profoundly disrupted and exacerbated by the sudden arrival of an unfamiliar disease, much as had occurred in earlier centuries.

As Guido Alfani has observed, "*in recent years mortality crises have once again attracted the attention of historical demographers and social and economic historians. This is an international phenomenon, in which Italian scholars have played a particularly visible role*" [15]. Alfani highlights the importance of Tognotti's work, including her collaboration with Alessia Melegaro [16], and notes the proliferation of publications in the first fifteen years of the twenty-first century. Many of these studies, however, focus on specific regions or cities, leaving southern Italy, though the area most severely affected by cholera, relatively understudied, thus revealing a significant gap in the literature. Nevertheless, several recent contributions have begun to address this imbalance [17, 18].

Alfani also points to the concentration of scholarship on the first and third cholera waves (1835-37 and 1854-55, respectively). A broader chronological perspective is offered by Forti Messina [19], whose work covers all cholera outbreaks in nineteenth-century Italy and provides valuable statistical and demographic insights.

Finally, it is worth noting that the post-COVID era has given rise to a renewed wave of scholarship on epidemics, exemplified by Tanturri's 2022 study [20].

The routes of propagation were similar to those of the plague: from miasmas to man, from an infected person to a healthy one, and from contaminated materials or objects to humans.

There were those who maintained that the contagion was spread "more by poor people's dirty clothes made of low-quality materials than by individuals".

They therefore claimed that a "sphere of contagious activity" surrounded the body of the cholera patient and could transmit the disease through the skin or respiratory tract. Some attributed great importance to the individual's way of life, claiming that cholera mainly affected "those with ill-disposed intestines and nerves, those who were poorly protected from the elements and those who led a disorderly life, (...) rather than persons who led a regular life" [1], while others cited geographical factors, climate and freak atmospheric events.

G. Franceschi's pamphlet, entitled *Istruzione al popolo sul cholera morbus contagioso*, published in Cesena in 1832 [21], is emblematic of the very limited knowledge of the time.

The pamphlet provided a set of recommendations: wrapping a woolen belt around the belly, wearing woolen shirts and underwear, washing these garments often and not using them if damp or dirty… [4]. The novelty of the disease prompted a large production of pamphlets, which demonstrated the scant knowledge of the incubation period of the disease and of the fact that the cholera vibrio remained in the feces for at least three weeks.

The liveliest debate between "anti-contagionists" and "contagionists" concerned the nature of the disease:

- on the one hand, the supporters of the epidemic theory, who again attributed the spread of the disease to the miasmas or harmful effluvia caused by stagnant water or by "rebus et corporibus putridis et corruptis", i.e. heaps of manure, garbage and filth that swamped the cities.
- on the other hand, those who believed that contagion was due to the inter-human transmission of germs.

The importance of this debate lay, above all, in its political implications. Indeed, a government that embraced the "anti-contagionist" theses, which held that sanitary cordons (against free trade) were ineffective, would have elicited adverse public reactions against the incautious health policy adopted. By contrast, implementing cordons, isolation, quarantine and seizures (measures supported by the "contagionists") would have limited trade, thereby generating negative psychological repercussions among the population; this, in turn, would have fueled social insecurity, which was regarded as one of the causes of the disease [4].

The "political danger of cholera" was manifested in "the common people's belief that the disease originated from poisons deliberately spread by scoundrels, as was also suggested by the rulers themselves" [1]; this conviction gave rise to "witch-hunts", which triggered bloody riots.

In Italy, the "contagionist" thesis prevailed, and the doctors present in the Health Magistracies recommended sanitary cordons and quarantine everywhere. The most sagacious magistrates drew upon both theories in order to implement those measures that they believed to be beneficial to public health: sanitary cordons and quarantine on the one hand; the removal of refuse,

cleansing of houses and propaganda on personal hygiene on the other [1].

Cholera came to Genoa in August 1835, despite the fact that the health authorities of the Kingdom of Sardinia had begun to implement interventions in 1831. These concerned regulations on trade and travel and the diffusion of rules and instructions on health and prevention among the population.

By the summer of 1835, the disease had reached Vienna and was approaching the borders of Savoy [22]; on July 18, a Higher Health Council, together with Provincial Councils, was established, in order to protect the kingdom's states from the disease. This council was charged with drafting public health regulations and trade restrictions and setting up quarantine.

The institution of the Health Magistrates was also maintained, whose tasks included communicating the orders and regulations deemed necessary against cholera. The measures and actions implemented by the Health Magistrate roughly retraced and repeated the Model that had already been tried and verified during the plague of 1579 and 1656-1657: public health officers were deployed to guard the coasts; the city gates were garrisoned *etc.* [23].

In Turin, a "Committee of Doctors for the Study, Prevention and Treatment of Cholera" was created, whose orders were to be carried out by the entire population. The first preventive measures of a "contagionist" nature were implemented: sanitary cordons were established in border areas, regulations were issued on quarantine and the transport of people, animals and goods, and sanctions were imposed in the event of violations [24]. Humans and transported goods have always been considered the main vectors of contagious diseases. Thus, in the case of cholera too, all those regulations that characterized attempts to contain the *17th century* plagues were reintroduced: *"those institutions and practices were rediscovered in the 19th century during the cholera epidemic and constituted the basis of the modern development of healthcare organization"* [5, 25].

News of the disease and its spread caused general concern, and reawakened a whole range of fears that were thought to have been overcome during the 18th century: fear of food, of death, of other people, of doctors and medicine - irrational fears, superstitions and beliefs dating back to the *ancien régime;* it was even believed that diseases were the result of sin.

Thus, people again invoked divine intervention; forms of popular devotion were revived, such as processions and collective prayers addressed to sacred images. Moreover, great importance was once again attributed to atmospheric factors, as people discerned a link between cholera mortality and adverse weather conditions.

The population asked for cannon to be fired and bonfires to be lit, in order to move and purify the air. The wealthiest individuals abandoned the cities and took refuge in their country houses or in areas that were not affected by the disease.

This sudden change in everyday habits interrupted trade and reduced work activities. It also led to the suspension of social relationships, reactions of anger or apathy, and even the rejection of reality; some were also prompted to overindulge in food and alcohol.

As most cases of cholera were ascribed to an unhealthy diet, health authorities urged people to eat with moderation and pay careful attention to the state of conservation of meat and the ripeness of fruit. Such regulations and calls for moderation elicited contrasting reactions; some people drastically reduced their food intake, while others defied the authorities, believing that an abundance of food and drink would enable them to recover their strength and keep disease at bay [14].

In this setting, any hint of gastrointestinal problems triggered terror: not only terror of the disease itself, but also fear of letting the authorities know, since this entailed isolation at home or transfer to hospital, a dreaded environment.

The fear of other people, who were seen as potential vectors of disease transmission, was heightened by the movement of the population from the countryside to the cities in search of food, shelter and care, as often occurred during epidemics and famines; this "forced urbanization" aroused resentment and rekindled the fear of others, who were regarded as intruders. Thus, the measures implemented during previous epidemics of the plague were revived; the city authorities banned vagabonds, itinerant entertainers and prostitutes in an attempt to contain the spread of the disease by isolating the city [14].

The "bill of health" was reintroduced, which was an indispensable document for those who wanted to travel; anyone found traveling with a false or expired bill was taken to the so-called "observation houses" [14].

Contagion was also facilitated by the fact that people did not seek medical attention promptly, but only when their symptoms were already very advanced and the disease was often incurable; this exacerbated public distrust of doctors, and many people turned to charlatans and faith-healers. Moreover, the disease was often left to run its course, especially if the patients were elderly or children.

In addition, as medical treatment was very expensive, natural and practical remedies were often preferred to medicines. Indeed, medical remedies were far from efficacious or innovative, being still tied to traditional practices such as bloodletting and phlebotomy, or ineffective medicines.

In the very rare cases of cure, it was believed that the physician's art had played no role.

"In many cases the most fearsome enemy was not so much cholera but the lack of assistance" [14]. Indeed, the desertion of healthcare personnel was frequent, owing to fear of the disease and its rapid spread. Treatment at the patient's home, when requested, was almost identical to that administered in hospital: *elderberry, zinc pills, enemas, linseed oil, olive oil, massage of the feet and stomach with hot cloths, baths in warm water, the application of leeches, drinking abundant water, mustard poultices, peach, cedar and alkermes tonics, rum, cinchona infusions and decoctions of chamomile, cinnamon and lemon balm, laudanum,*

lemon, vermifuges, anti-emetics, infusions of lime, wine, pine and malaga.

Every doctor proposed his own remedy, which was often different from that of other doctors, in a desperate bid to find a miracle cure for cholera. However, all such attempts ended in failure [14].

Most of the fears connected with cholera would be unfounded today. At that time, however, medical practice was somewhat backward, being still tied to ancient paradigms.

Indeed, only later would major breakthroughs be made, such as *Filippo Pacini's* discovery in 1854 of the presence in the intestines of cholera victims of millions of bacteria, which he named *Vibrio cholerae* (Fig. 1), or John Snow's discovery of the correlation between cholera and polluted water during the 1854-55 epidemic in London (Fig. 2), or the work of Robert Koch (1843-1910) (Fig. 3), who isolated and cultivated the *Vibrio cholerae* responsible for the disease in 1882.

The names of these three individuals are also associated with several fundamental discoveries in the history of science and medicine: the first is credited with the discovery of tactile nerve endings, now known as Pacinian corpuscles; the second is closely associated with advances in anesthesiology, having experimentally investigated and established the appropriate dosage between ether and chloroform; the third is primarily remembered for the discovery of the tuberculosis bacillus in 1882, which earned him the Nobel Prize in Physiology or Medicine in 1905.

Furthermore, a cholera vaccine was first developed in 1892 by Waldemar Haffkine (1860-1930) (Fig. 4), who conducted a trial of it in India in 1893; he is also known for having developed a plague vaccine in 1897.

However, these discoveries would only acquire meaning in the light of the germ theory put forward by Louis Pasteur (1822-1895) (Fig. 5) and the consequent bacteriological revolution [26].

A further aspect of interest in relation to communication concerns the use made of the content it conveyed, particularly in light of the fact that contemporary medical information was inherently unreliable due to the limited knowledge of a disease that was, at the time, still largely unknown [14]. It is possible to identify a political and economic purpose underlying the use of circulating information, for instance to target rival state entities, as occurred with Genoa at various points in history. In this regard, the quarantine regulations imposed on arrivals from Livorno from 1749 onward may be interpreted in the context of the peace treaties between the Tuscan

Fig. 1. Filippo Pacini (1812-1883) - [Public domain Wikipedia commons.

Fig. 2. John Snow (1813-1858) - [Public domain Wikipedia commons].

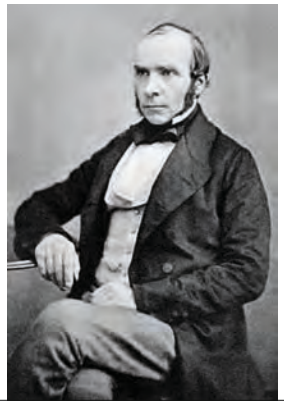

Fig. 3. Heinrich Hermann Robert Koch (1843-1910) - [Public domain Wikipedia commons.

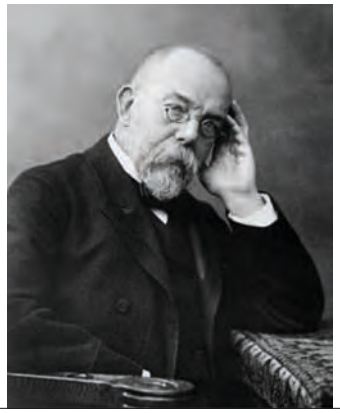

Fig. 4. Waldemar Haffkine (1860-1930) - [Public domain Wikipedia commons.

Fig. 5. Louis Pasteur (1822-1895) - [Public domain Wikipedia commons.

city and the Berber regencies, which were consistently regarded as a threat to public health [27, 28]. Similarly, the ban measures enforced by Florence against Genoa in 1652, following the spread of plague in Sardinia and its presumed presence in Genoese Corsica, can be understood within this framework [6]. In the context of 19th cholera, such an application of information was observed primarily in the Kingdom of the Two Sicilies, where information was used to incite the early anti-Bourbon uprisings during the transitional period between the two halves of the century [1, 20, 29].

Historical sources also reveal situations in which communication practices targeted more limited and individual groups. Instructions were disseminated to encourage the removal of beggars, the poor, and foreigners from cities as a preventive measure, based on the assumption that these minority groups were disruptive elements and facilitators of disease propagation [1, 6, 10].

The situation in Genoa and the city's precious archival sources

As mentioned above, the cause of the disease was ascribed to dietary disorders, exposure to the cold and the fear of the disease itself, which were unpredictable everyday factors.

With regard to Genoa, important archival documentation can be found in: *"Resoconto del colera a Sampierdarena tra il 24 agosto e il 24 ottobre 1835" (Report on cholera in Sampierdarena between August 24th and October 24th 1835);* "*Specchio dei colerosi tra il 22 agosto e il 22 settembre nel comune di Recco" (The picture of cholera patients between August 22nd and September 22nd in the municipality of Recco);* "*Quadro dei colerosi di Nervi" (Nervi's cholera sufferers);* "*Quadro dei colerosi di Quinto" (Quinto's cholera sufferers)* and "*Quadro dei colerosi di Cornigliano" (Cornigliano's cholera sufferers)* [30].

These documents report the name, surname, age, symptoms, presumed causes of the disease and occupations of the infected persons or victims.

The occupations comprised: vendors, blacksmiths, greengrocers, dyers, washerwomen, carpenters, domestic servants, boatmen, tavern keepers, health inspectors, porters, sailors, the children of sailors, fishermen, spinners, farmers, innkeepers, waiters, cheesemongers, shopkeepers and cobblers.

These are obviously professions that involve contact with other people, with materials that can easily harbor miasmas and dirt, and with damp environments.

For this reason, it was believed that these features predisposed people to cholera, and this reinforced the erroneous conviction that crowded and climatically unsuitable environments facilitated contagion, in addition to a low social status, which entailed an inadequate diet, scant hygiene in homes and workplaces and poor personal hygiene.

What the authorities lacked, however, was the awareness of a precise connection with contaminated water. This led to very generic conclusions involving a whole range of possible causes of the disease. Indeed, the traditional *Galenic-miasmatic paradigm* persisted. This close connection with tradition emerges clearly from the extensive production of information brochures.

Between October 1831 and March 1832, the Royal Printing House in Turin published the *Leggi e Provvedimenti di Sanità per gli Stati di Terraferma di S. M. Il Re di Sardegna* (Laws and Health Provisions for the Mainland States of His Majesty the King of Sardinia), a text of 19 chapters which was sent to the provinces and then reprinted and distributed to all pharmacies, which were instructed to keep it carefully [31].

The main purpose of this campaign of communication was to educate the public regarding the alleged methods of avoiding or treating cholera. In addition, however, it was also aimed at supporting and comforting the population, in order to counteract the fear, spread by state, ecclesiastical and health authorities. The instructions contained in the above-mentioned text were proposed and subsequently re-proposed in a series of pamphlets issued by the Royal Printing House in Turin from 1831 onwards, and later collected organically in the *Preservativo del Cholera* [32], which was printed in 1835.

The text strongly recommended an adequate standard of living, respect for the rules of domestic and personal hygiene and the avoidance of insidious pleasures.

- Regarding homes: occupants were instructed to remove all sources of dampness, especially stagnant water; to maintain a certain distance from wells; to keep land clear and drain puddles; not to live in recently built houses, as these were damp; to use fireplaces frequently, so as to prevent dampness; to dispose of rubbish away from inhabited areas; to clean rooms, especially kitchens; to open windows for at least half an hour to change the air; to purify the air by lighting fires; not to keep coal indoors; to keep chimneys clean, so as to ensure air exchange; and to clean latrines.
- Regarding individuals: it was important to wash the face and hands and, in the event of contact with a sick person, to use vinegar and calcium chloride [33]; to

change and wash clothes often; to keep clean clothes in the open air; to wear heavy clothes in cold weather *etc*.
The importance of moderation in food, in terms of both quantity and quality, was emphasized; unripe fruit, stale fish, legumes, chestnuts and mushrooms were deemed unhealthy, as they are difficult to digest, while rice, meat and potatoes were highly recommended; fatty condiments containing garlic or onion were to be avoided.
Concerning beverages, spring water was recommended; wine was to be drunk with moderation, and mixing different types of wine was to be avoided.
Light meals were suggested, such as broth, boiled meat, a little ripe fruit and watered down wine. Foods that were difficult to digest, such as pork, salty and fatty meat and condiments, were to be avoided; fish and cheese were to be consumed with moderation, and fruit and vegetables eaten only when properly ripe.
Close attention to diet was underlined in the bulletins on the sick with regard to the alleged causes of the disease: disorders of the dietary regime, abuse of new wine, consumption of unripe fruit, mushrooms, peaches or onions, as well as reactions such as hysteria and fear [34].
The importance of physical exercise, walking, and solidarity towards those infected was also emphasized. Prompt assistance for cholera sufferers was also essential: when the first symptoms appeared, the person was to go to bed immediately, to be kept warm with woolen blankets and to be fed hot *polenta* made with cornmeal or bran flour; in addition, the stomach, hands and feet were to be sprayed with mustard, and herbal infusions such as sage, chamomile, peppermint or lemon balm were to be drunk.
Vinegar was to be kept on hand for washing purposes, as was calcium chloride to disinfect the room and clothes; the patient was to be kept warm with the aid of hot bricks or bags of hot ash, given rice to eat and olive oil to drink, to prevent vomiting. Hot baths were also recommended.
This long and detailed list of preventive measures and treatment methods demonstrates that ignorance of the etiology of the disease played a determining role in rendering the action of the health authorities ineffective - a concept that applied just as much to cholera in the 19th century as it had to the plague in the 17th [35].

Conclusion

Epidemics, like wars and famines, are a constant feature of human history: the most feared of the Horsemen of the Apocalypse, an evocative biblical image that characterizes the late Middle Ages and the modern age.
This image is applicable not only to the 16th century [36], but also to the plague that broke out during the Peloponnesian Wars, to the epidemics of smallpox and measles in the Roman Empire, to the Justinian plague, which is considered the "first great pandemic" [2], up to the disastrous return of the plague in Europe in 1347 and to the subsequent epidemics of *Cholera Morbus* in the 19th century [37]. Clearly, these historical periods were constantly riven by epidemic upheavals that had "profound repercussions on the socio-economic and political-institutional scenario, as well as on the mentality and behavior of contemporaries" [38].
The appearance of a new and unknown evil has always triggered measures and reactions characterized by ignorance and fear, altering the social order despite governments' frequently ineffective efforts to tackle the situation. Fear and irrationality in popular reactions are also a key to understanding the development of such dramatic events: dynamics such as non-observance of regulations, refusal to submit to authority and attempts to escape from reality *etc.*
Phenomena of this type were recorded both in the 17th century and, with regard to cholera, in the 19th.
In Genoa, for example, cases of theft of materials by armed guards occurred and porters charged with transporting the sick sometimes refused to do their job [32] *etc*. It should also be noted that economic considerations frequently hindered institutional action, resulting in the need to "sacrifice public health to the economy" [7].
When it first appeared, cholera had a devastating impact; it spread at lightning speed, mainly affected the working class, was most lethal in subjects aged over 40/50 years, and carried a mortality rate of just under 50% (as shown by the Genoese health bulletins issued between 1835 and 1837) [34, 39].
On the basis of these data, cholera appears to have been less insidious than the previous epidemics of the plague; however, the historical and cultural context must also be taken into account.
Between the 14th and 18th centuries, the plague was considered to be the most fearsome evil of all, while during the 19th century one of the most feared diseases was cholera.
In conclusion, it is clear that all the elements analyzed unite the past and the present. Indeed, we can discern many analogies between the arrival of an unknown evil two centuries ago and the 2020 COVID pandemic [40].

- When *COVID-19* arrived in Italy, the first measures to be implemented concerned the reduction of gatherings and the limitation of movements and individual contacts.
- Subsequently, self-certification was introduced to authorize travel.
  In this regard, if we used the expressions "sanitary cordons", "general quarantine" and "bill of health", we would connect worlds that, albeit centuries apart, are united by reactions and behaviors resulting from traumatic and emergency events.
- These analogies can also be discerned in the work of doctors, in the care of patients and in the fear of hospitals, which were once again seen as hotbeds of infection – a return to the ancient view of the hospital as the "antechamber of hell" [6].

- The figure of the surgeon of yesteryear, wearing a bird-beak mask and a waxed gown, is similar to that of the modern-day doctor endowed with personal protective equipment, in that the evil enemy sometimes manages to overcome these barriers and strike the individual committed to saving the patient [41].
- During the COVID-19 pandemic, at least in its initial phase, patient care also encountered difficulties, owing to lack of knowledge of the disease itself [42]. Consequently, therapy was to some extent experimental.
- With regard to the circulation of information, between the early modern period and the 19th century it was evidently slower, and constrained in content by the limited knowledge available on the subject. Today, and in the context of the COVID-19 pandemic, this phenomenon has been exponentially accelerated by the web and social media, which in turn constitute an additional source of risk in the form of misinformation.

  Misinformation represents a major challenge for contemporary society, contributing to distorted judgments and decision-making processes in critical domains such as public health crises, and often exerting a persistent influence on reasoning even after it has been corrected. Its dissemination is greatly facilitated by channels such as AI and social networks [43, 44], where the rapid and large-scale spread of false information constitutes a global risk. Several approaches have been proposed to identify and mitigate these threats, including deep learning–based methods, prebunking interventions, and reactive debunking strategies; nevertheless, countering misinformation remains a challenge of considerable complexity [42, 45, 46, 47].

These similarities, however, may be somewhat misleading. Indeed, modern medical science soon found a way to immunize the population against COVID-19, while Alexandre-Émile-John Yersin (1863-1943) isolated the *Yersinia Pestis* bacillus only in 1894 [48, 49], more than half a millennium after the plague reached Messina from Caffa in 1347.

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Authors' contributions

FD: conceived the study; FD & MM: designed the study; drafted the manuscript; performed a search of the literature; revised the manuscript; conceptualization and methodology; investigation and data curation; original draft preparation; review; editing. All authors have read and approved the latest version of the paper for publication.

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Correspondence: Mariano Martini, Via Pastore 1, 16132 Genoa, Italy. E-mail: mariano.martini@unige.it

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History of medicine and ethics

In memory of Ryan White, the boy with haemophilia who showed the world the other side of AIDS Lest We Forget...

MARIANO MARTINI[1,2,3], DAVIDE ORSINI[4]
[1] Department of Health Sciences, University of Genoa, Italy; [2] Interuniversity Research Center on Influenza and Other Transmissible Infections (CIRI-IT), Genoa, Italy; [3] UNESCO Chair "Anthropology of Health - Biosphere and Healing System", University of Genoa, Genova, Italy; [4] Department of Life Sciences, Health and Health Professions, Link Campus University - Rome, Italy

Keywords

History of hemophilia • History of HIV • AIDS • Stigma • Ryan White • David Kirby

Summary

In the 1980s, AIDS triggered a huge wave of fear, as always happens when unknown, deadly diseases emerge. The fact that gay men were among the first to be infected with HIV and to manifest the disease prompted public opinion to link the infection to behaviours that were, at least at that time, transgressive and therefore unacceptable and shameful. AIDS sufferers were therefore exposed to discrimination from the outset.
The case of young Ryan White prompted much-needed reflection in the mid-1980s. Born with a severe form of haemophilia, Ryan contracted AIDS through the therapeutic administration of an infected blood product. This demonstrated that AIDS was not a disease that affected only homosexuals and drug users; it could strike anyone.
Through the story of Ryan White, an "innocent victim" of AIDS, the authors highlight the changes that occurred between the 1980s and 1990s, and which led civil society – as well as researchers – to modify its perception of the disease.
This was no easy process, since discrimination and stigma have deep roots, exerting a cascading effect that is very difficult to counteract, and which sometimes proves even more harmful than the disease itself.

Introduction

In 1984, Ryan White was a teenager living in Kokomo, Indiana (USA). Born in 1971, Ryan suffered from a severe form of haemophilia A, but despite his potentially fatal disease, he tried to live his life as normally as possible, supported by his mother, Jeanne. To control his disease, Ryan underwent the administration of coagulation factor VIII, a clotting agent made from plasma collected from donors and used to treat episodes of bleeding in haemophiliacs.

The history of haemophilia: great victories and a tragic "blind spot"

The first description which we may say perhaps to mention to "haemophilia" are from the end of the 18th century when we can find various reports of families in which males suffered abnormally prolonged post-traumatic bleeding [1]: the anonymous obituarist of Isaac Zoll, writing in 1791 [2], Consbruch in 1793 and 1810, Rave in 1796 [3], and the "Haemophilia" was first described in 1803 by the American physician John Conrad Otto (1774-1844) [4] (Fig. 1).
He described an inheritable bleeding disorder in several families where only males born from unaffected mothers were affected [5]. He then called them the "bleeders.

Conrad published the results of his studies on a predisposition to haemorrhage in some families in *An Account of an Hemorrhagic Disposition in certain Families* [6].
He understood the main characteristic of haemophilia, *i.e.*

Fig. 1. John Conrad Otto (1774-1844) - (Public domain - Wikipedia commons).

that males tend to inherit the disease, while females are generally healthy carriers. This is because haemophilia is an X-linked inherited disease. Indeed, males have only one X chromosome; therefore, if they inherit a defective copy of this chromosome, they will always have the disease. As females have two X chromosomes, they usually have a healthy copy that compensates for the defective one; they are therefore either healthy carriers or affected by mild forms of the disease.

These accounts began to define a clinical syndrome on which the 19th century developed an extensive literature. The german physician and psychiatrist Christian Friedrich Nasse (1778-1851) (Fig. 2) was the first to publish the genetic description of "hemophilia" in "Nasse's Law", a dictum formulated by him in 1820 where he states that haemophilia is transmitted entirely by unaffected females to their sons [7, 8]. He states*: "women of bleeding families, although they marry men from normal families, carry the disease over from their own fathers to their children, and yet never suffer from the disease themselves"*. Not a hypothesis, not a conjecture, not a theory, but a full-blown law! [9].

In the historical evolution of this disease, different terms were used: *haemorrhoea, idiosyncrasia haemorrhagica, haematophilia, bleeding disease, hereditary haemorrhagic diathesis*, but the name then used and the current name *"haemophilia"* (the word was derived from the Greek words haima (blood) and phila (love or tendency), with the full term being haemorrhaphilia or "love of bleeding") arises only in 1828 [1].

"Hemophilia", as a term, was in fact first documented in 1828 by Johann Lukas Schönlein (1793-1864) (Fig. 3) a German naturalist and professor of medicine with his student Friedrich Hopff in his doctoral dissertation at the University of Zurich (Switzerland) which described the condition as "On hemophilia, or the hereditary predisposition to fatal bleeding". Schönlein was the physician also known for being the first who published the name "tuberculosis" (German: Tuberkulose) in 1832 [10]; before Schönlein's designation, tuberculosis had been called "consumption" [11].

However, historical evidence of the disease is much older. According to some scholars, Hippocrates of Kos (460 BC-post 377 BC) described a case of anomalous blood coagulation in a wounded soldier.

"Haemophilia" was acknowledged in ancient times; the Babylonian Talmud, one of the sacred texts of Judaism (a collection of Jewish rabbinical writings from the second century AD), affirmed that male babies should not be circumcised provided two brothers had already died owing to excessive bleeding from the procedure [12]; the disease is mentioned about a woman who had lost her first two sons from circumcision: *"If a woman has her first son circumcised and he dies as a result, and she then has her second son circumcised and he also dies, she should not have her third son circumcised, since the deaths of the first two prompt the presumption that this woman's sons die because of circumcision"* [13].

Similarly, in the year 1000, the Arab physician Abulcasis (Abū l-Qāsim Khalaf ibn ʿAbbās al-Zahrāwī, 936-1036), who is acknowledged by historians to be the "father of surgery", wrote a treatise entitled *al-Tasrif*, in which he described a disease that can certainly be identified as haemophilia. Albucasis, described a family with males who died from bleeding after trivial injury [14].

It was, however, only in the 20th century that fundamental discoveries were made that would enable haemophilia to be treated.

In 1952, the case of a patient named Stephen Christmas (1947-1993) led to the identification of two types of haemophilia (A and B), which are caused by the lack or deficiency of coagulation factors VIII and IX, respectively.

Again in the 1950s, the British researcher Ethel Bidwell (1919-2003), in the laboratory directed by Robert Macfarlane in Oxford, succeeded in

Fig. 2. Christian Friedrich Nasse (1778-1851) - (Public domain - Wikipedia commons).

Fig. 3. Johann Lukas Schönlein (1793-1864) - (Public domain - Wikipedia commons).

producing factor VIII in a concentrated form that could be administered to patients. Nevertheless, the availability of factor VIII remained limited by the fact that the preparation, which was made to order for each patient, could not be stored.

A few years later, however, in 1964, the American physiologist Judith Graham Pool (1919-1975) noticed that, on thawing previously frozen plasma, a sediment called cryoprecipitate was formed, and that this was extremely rich in factor VIII. Cryoprecipitation decisively changed haemophilia patients' lives and life expectancy, which at the beginning of the 1960s did not exceed 30 years; it even allowed them to undergo surgical operations that had hitherto been absolutely impossible.

However, the greatest advance in treatment stemmed from DNA studies and the cloning of the factor VIII gene in 1982 and the factor IX gene in 1984, which, in the late 1980s, enabled recombinant F VIII and subsequently F IX to be produced industrially [15].

The most recent studies in gene therapy involve the use of a modified virus, which does not cause disease, to insert a copy of the patient's missing gene which codes for the coagulation factor [16, 17].

In this process, which opened up the possibility of a cure for haemophilia, there remained, however, a short period of time, a sort of "blind spot", in which the therapeutic replacement of factors VIII and IX, obtained mainly from the plasma of healthy donors, was not supported by the tests needed in order to avoid contamination by infectious diseases.

Consequently, between the 1980s and the early 1990s, tens of thousands of people worldwide were infected by HIV and hepatitis B and C viruses through infected blood products.

A particularly significant portion of these were haemophiliacs. Indeed, according to data from the Hemophilia Federation of America (HFA), "in the 1980s, approximately 90% of patients with severe hemophilia were infected with HIV, and almost all patients with hemophilia who used factor products before 1988 were infected with hepatitis C virus (HCV)" [18]. One of these patients was Ryan White.

The global perception starts to change: not all AIDS victims are gay or drug abusers

In the mid-1980s, epidemiologists began to hypothesize that AIDS might also be spread through blood products. This had serious implications for haemophiliacs who periodically received concentrates produced from large batches (pools) of plasma, much of which had been collected in the late 1970s and early 1980s, before the first cases of HIV infection had even been detected. This was exactly how Ryan White contracted AIDS – through the administration of contaminated blood products to treat his haemophilia.

Throughout the summer and autumn of 1984, Ryan was ill, plagued by stomach cramps, diarrhoea and exhaustion. In December of that year, he was admitted to the local hospital in Kokomo, where he was diagnosed with antibiotic-resistant pneumonia in both lungs. He was then transferred to Riley Hospital for Children in Indianapolis, where doctors began to suspect that Ryan had contracted *Pneumocystis carinii* pneumonia (PCP) from contaminated factor VIII.

In those years, the diagnosis of *Pneumocystis carinii* pneumonia (PCP) meant that the patient had AIDS. A biopsy revealed that Ryan had indeed contracted PCP, confirming the most dreaded diagnosis at the time: AIDS.

Despite this, Ryan was determined to live his life like any other 13-year-old. "Let's pretend I haven't got it", he told his mother, asking to return to school as soon as his condition improved.

"*Ryan White just wanted to go back to school. In much the same way that he had handled hemophilia, Ryan vowed not to let his AIDS diagnosis spoil his otherwise 'normal' childhood. A key component of living like a 'normal kid', Ryan's deeply held wish, was to attend school and socialize with friends and acquaintances"* [19].

But on July 27, 1985, officials of the Western School Corporation (WSC) in Russiaville, Indiana, prohibited Ryan from attending classes because of his illness, so as to ensure the safety of other students. Their decision suddenly shattered Ryan's dream of returning to normality despite his illness.

Two days earlier, on July 25, the American actor Rock Hudson (1925-1990), who was hospitalized following a collapse in Paris, where he had gone to undergo experimental treatments at the American Hospital and the Institut Pasteur, had his staff issue a press release in which he officially announced that he was suffering from AIDS [20].

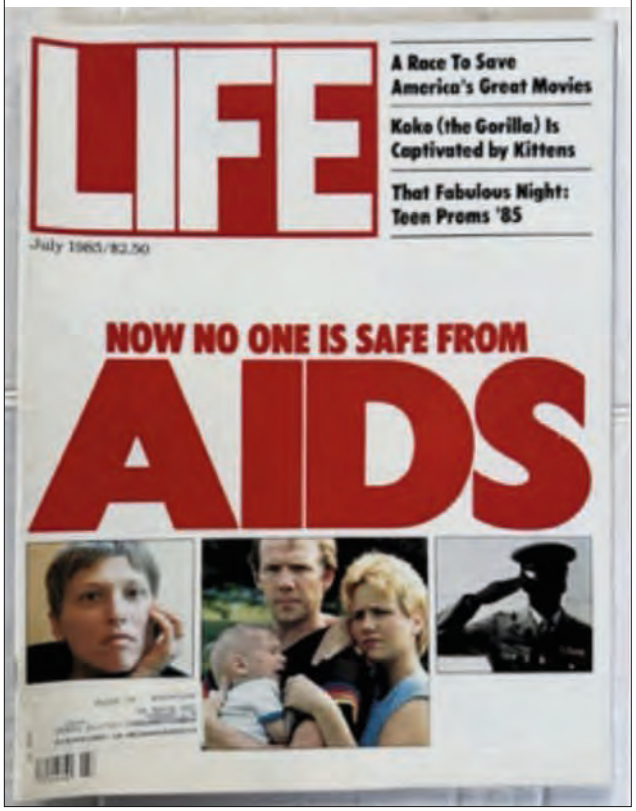
The two pieces of news had a profound impact on civil society. People's beliefs regarding AIDS were largely called into question; it was not a disease that exclusively affected promiscuous homosexuals and drug users. Life magazine headlined: "Now no one is safe from AIDS", above a photograph of a seemingly worried white, heterosexual family (Fig. 4).

The young man who fought against the stigma of AIDS

The White family began a strenuous legal battle to uphold Ryan's right to attend school, bringing the AIDS issue into the national spotlight. In the spring of 1986, Ryan was granted the right to attend in-person classes. The media gave the case ample coverage and Ryan became one of the most well-known people in the United States, the face that raised awareness of the tragedy of AIDS, an "innocent victim" of a medical error.

With his readmission to school, the issue seemed to have been resolved. And yet, on the day of his return to class, two-fifths of the school's students were absent; a group of parents had even set up an alternative school in an old American Legion Hall, so as to stop their children from coming into contact with Ryan. Thus, Ryan became engaged in a new battle, alongside his fight against the disease: the fight against the discrimination and stigma that afflicted AIDS.

Fig. 4. The cover of Life magazine, July 1985 (Public Domain).



Ryan's battle to attend school also forced American society to confront widespread prejudices regarding the AIDS epidemic; this white, heterosexual, middle-class teenager from the American Midwest debunked the idea that AIDS affected only "deviant" groups.

He began appearing on the evening news and on the covers of popular magazines, thereby publicizing his story. Many prominent figures in the world of music and sport wanted to meet him and support him in his struggle. He was interviewed on ABC's "Good Morning America" programme [21] and took part in a charity event for the newly formed American Foundation for AIDS Research (amfAR) (Fig.5).

But the stigma hit hard, prompting people to focus on the concepts of "guilt" and "innocence" that imbued the social representation of the AIDS crisis; if Ryan was the innocent victim, then homosexuals and drug users, the outcasts of society, were the culprits [22]. Indeed, as Ryan's story grabbed national headlines, the media increasingly accused gay men and drug addicts of contaminating American society. As for Ryan himself, however, he never denigrated gays or blamed them for his illness.

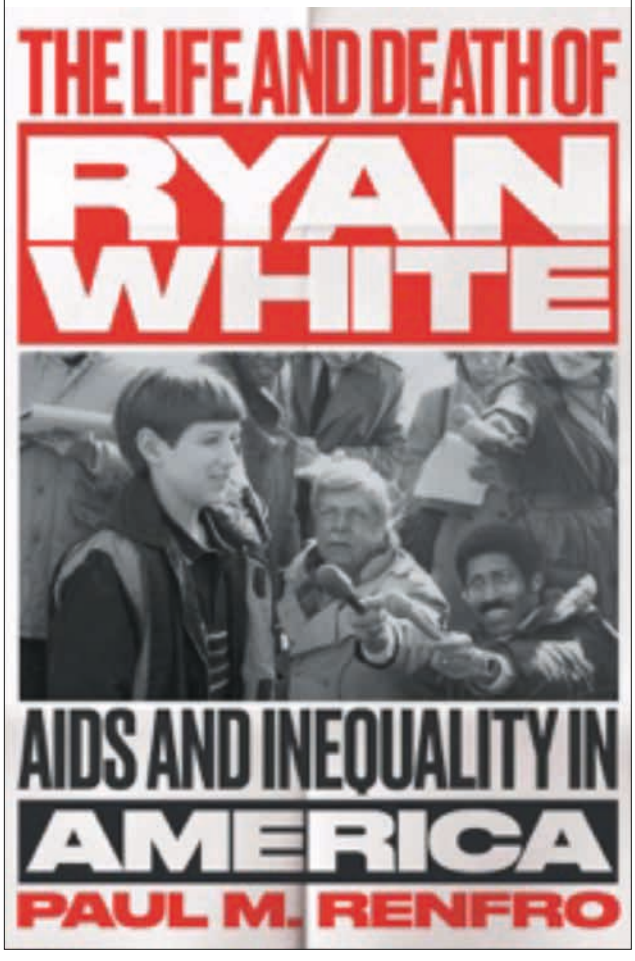
"In addition, during HIV's first decade, intense fear and stigma led to new HIV-specific criminal laws. In the name of public health, criminal laws were passed in more than 35 states that punished behaviors that might transmit HIV; states without HIV-specific laws used general criminal laws to accomplish the same end" [23]. People with AIDS were isolated from their families and friends; the stigma placed on them became a phenomenon of enormous proportions. In this context, Ryan White's testimony provided a glimmer of light and hope in an absolutely bleak landscape. His short life became a manifesto for the fight against the stigmatization of people with AIDS.

Similarly, the last days of life of another young AIDS patient, David Kirby (1957-1990), who was homosexual and a gay rights activist, made a fundamental contribution to the fight against discrimination and marginalization of those suffering from the so-called gay plague.

In November 1990, Life magazine published a photograph of Kirby on his deathbed, while his father hugged him lovingly. Therese Frare, at the time a student at Ohio University, immortalized the last moments of David Kirby, surrounded by his family, in what Life called "The Photo That Changed the Face of AIDS" [24].

Kirby's parents accepted not only their son's sexual identity, but also his illness, thus demonstrating how a true family could stay close to a terminally ill HIV-positive person: an extremely rare occurrence at the time. The publication of this photograph shocked the United States, but above all it sparked reflection, prompting many people to seek information and to take action.

Fig. 5. The cover of the book "The Life and Death of Ryan White: AIDS and Inequality in America" by Paul M. Renfro, showing the young Ryan White (Public Domain).



David Kirby died on May 5, 1990, at the age of just 32 years. Only a month earlier, on April 8, Ryan White had also died.

Ryan White's story did not end with his death

Ryan's death was perceived as a national tragedy. His funeral was a media event; CNN broadcast the ceremony live, and all three major American television networks showed footage of it [25]. His coffin was carried by Los Angeles Raiders' "defensive end" Howie Long, singer Elton John and television host Phil Donahue [26]. Among the more than 1,500 people who attended his funeral were First Lady Barbara Bush and Michael Jackson, who sat next to Ryan's mother, Jeanne White. The corpse lay in an open coffin at the entrance to the church – in stark contrast to the quiet, sparsely attended ceremonies that usually marked the funerals of AIDS victims.

Ryan's life, albeit brief, contributed to raising awareness of AIDS and, above all, to the realisation that this disease was not necessarily the of certain lifestyles.

Thus, Ryan's case helped to fuel a political debate that would prompt the federal government to allocate the funds needed to fight HIV infection and to approve an act that would bear Ryan's name. Indeed, shortly after Ryan's death, the United States Congress passed the Ryan White Care Act to support care for AIDS sufferers who did not have adequate health insurance or other resources. Signed by President George Bush Sr. on August 18, 1990, the act allocated $882 million in AIDS funds for 1991 and $4.5 billion in federal grants through 1995. This act was reconfirmed in 1996, 2000, 2006 and 2009, and is known today as the Ryan White Treatment Extension Act of 2009. The Ryan White programme constituted the US federal government's largest and most comprehensive commitment to improving the quality and availability of care for medically disadvantaged individuals and families affected by HIV.

Conclusion

Ryan White, in his short life – he died at the age of 19, having lived with the disease for years, despite the doctors' diagnosis in 1984 having been much more severe, granting him only 6 months to live – forced American society to confront AIDS, about which little or nothing was known at the time and which was associated exclusively with homosexuality. With his active testimony, he accompanied people in a profound reflection on their prejudices about the AIDS epidemic and those affected by this pathology, attempting to break down all forms of stigma [27].

White, along with many others, helped to raise public awareness of AIDS, a key factor in changing social perceptions and in promoting disease prevention. Thanks to Ryan, but also to many activists for patients' rights, HIV infection became a focus of research, and today AIDS is a preventable and treatable disease.

However, much remains to be done in terms of education, so that young people will not lower their guard and will take care to prevent any possibility of contagion. In this regard, WHO data indicate that 1.3 million [1.0-1.7 million] people contracted HIV in 2024 [28]. A great effort is also required to ensure that no one is ever stigmatized on account of a disease [29, 30]. Indeed, stigmatization has been shown to have a negative impact on HIV prevention, on individuals' decisions to undergo testing and to access health services, and on the healthcare management of people living with HIV [31]. "Ending the AIDS epidemic by 2030 will require addressing stigma more systematically and on a larger scale than current efforts" [32].

In this regard, it is necessary not only to strive to change society, but also to petition for laws that protect people and do not criminalise HIV and to make people understand the dangers of certain behaviours rather than simply prohibiting and sanctioning those behaviours [33].

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Authors' contributions

MM: conceived the study; DO: designed the study; DO & MM drafted the manuscript; performed a search of the literature; revised the manuscript; conceptualization and methodology; investigation and data curation; original draft preparation; review; editing. All authors have read and approved the latest version of the paper for publication.

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Correspondence: Mariano Martini, Via Pastore 1, 16132 Genoa, Italy. E-mail: mariano.martini@unige.it

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History of medicine and ethics

Black Death of 1348 in Florence and SARS-CoV-2 (COVID-19) in the 650th anniversary of the death of the writer Giovanni Boccaccio (1313-1375)

MARIANO MARTINI[1], FRANCESCO BALDANZI[2], DONATELLA LIPPI[2]
[1] Department of Health Sciences, University of Genoa, Italy; [2] Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy

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Black Death • Plague • Infectious diseases • Giovanni Boccaccio • Marsilio Ficino • SARS-CoV-2 (COVID-19) • Florence

Summary

The 650th anniversary of the death of the Tuscan writer Giovanni Boccaccio (1313-1375) provides an opportunity to reread some pages of his masterpiece, the Decameron, from a historical-medical perspective. In this work, Boccaccio gives an account of the "Black Death", a devastating pandemic of bubonic plague, which reached Europe, Messina (Sicily), from Asia Minor in September of 1347. The plague travelled along the commercial route taken by Genoese sailors returning from their strategic trading posts at Kaffa on the Crimean Peninsula, which was under siege by the Mongols. The framework, the cage that encloses the 100 short stories that comprise Boccaccio's work, is the starting point for a novelistic reinterpretation. On an unspecified summer day in 1348, the plague broke out in Florence, Italy. In a few years, the terrible "Black Death" decimated the population of Europe. The city of Florence was shocked by the aggressiveness of the disease and by the collapse of the most basic norms of respect and civil coexistence. On the 650th anniversary of Boccaccio's death, the authors of this short article commemorate this great writer, his work and, in particular, the historical, social and public health responses to this massive pandemic. The Black Death shared some similar features with the recent COVID-19 pandemic: from the initial difficulties and misunderstandings to the adoption of public safety and prevention measures, such as quarantine, and the lasting impact on society after the event had passed. The similarities between Boccaccio's description and what we experienced during the COVID-19 era regard also other aspects of public health aspects.

Introduction

The 650th anniversary of the death of the Tuscan writer Giovanni Boccaccio (1313-1375) (Fig. 1) provides an opportunity to reread some pages of his masterpiece, the *Decameron*, from a historical-medical perspective.

In 1348, the "Black Death" broke out in Florence, (Italy) (Fig. 2); the city was shocked by the virulence of the disease and the dissolution of the most basic norms of civil coexistence.

The plague served Boccaccio as a prologue to his literary masterpiece, describing the moral misery and death that reigned in human society.

Seven young women and three young men met in the Dominican church of Santa Maria Novella in Florence and, at the suggestion of one of them, decided to move from the city to the countryside, in the hope of escaping contagion – although the plague did not spare the countryside either – and with the stated aim of living honestly, far from the moral decay that reigned supreme in Florence.

Over the course of two weeks, each member of the group took a turn at being king or queen over the others, deciding how to spend the day and establishing the theme of the stories that will be told in turn each day. These narrative spans ten days of the two weeks, hence the title of the book, "Decameron" or "Ten Days"; in all, 100 tales are told.

Although remembered by most people as a repertoire of comical and licentious situations, the Decameron seeks

Fig. 1. Giovanni Boccaccio, affresco, 1450, Galleria degli Uffizi, Firenze. [Public domain. Wikipedia commons].

Fig. 2. The Plague in Florence in 1348. Luigi Sabatelli engraving of the edition he edited of the Decameron. [Public domain. Wikipedia commons].

to convey a profoundly serious message, an invitation to a serene and courageous view of life, far from ignoring moral and religious values, but without surrendering to fideism and moralism. It therefore indicates a way to celebrate and exalt human vitality and assert the ability to adapt in the face of adversity, such as the plague that struck Florence in 1348, which forms the backdrop to the work.

It is a work that extols intelligence (ingenuity) and cunning as effective and useful means of mastering fortune, which is seen as an unpredictable factor in earthly life.

Through his 100 short stories, the author, the writer Giovanni Boccaccio explores the complexity of man and his nature, addressing themes such as love (both carnal and spiritual), pranks, religious hypocrisy and the transformation of contemporary society, while also highlighting the virtues of the mercantile world and social satire.

The Decameron is also a tribute to the power of literature and the art of storytelling as a means of exploring and understanding the human soul.

Black death

The opening page of the first day of the *Decameron* focuses on three thematic themes:

- the description of the plague in Florence in 1348;
- the gathering of the joyful company of ten young people in the church of Santa Maria Novella;
- their refuge in a villa in the countryside to escape the contagion [1].

Boccaccio provides a very lively description of the plague, hypothesizing its origin from the East and examining the various possible causes, ranging from divine punishment to the influence of the stars:

I say, then, that the years of the beatific incarnation of the Son of God had reached the tale of one thousand three hundred and forty-eight, when in the illustrious city of Florence, the fairest of all the cities of Italy, there made its appearance that deadly pestilence, which, whether disseminated by the influence of the celestial bodies, or sent upon us mortals by God in His just wrath by way of retribution for our iniquities, had had its origin some years before in the East, whence, after destroying an innumerable multitude of living beings, it had propagated itself without respite from place to place, and so, calamitously, had spread into the West.

In Florence, despite all that human wisdom and forethought could devise to avert it, as the cleansing of the city from many impurities by officials appointed for the purpose, the refusal of entrance to all sick folk, and the adoption of many precautions for the preservation of health; despite also humble supplications addressed to God, and often repeated both in public procession and otherwise, by the devout; towards the beginning of the spring of the said year the doleful effects of the pestilence began to be horribly apparent by symptoms that shewed as if miraculous [2].

Boccaccio then describes the symptoms of the disease, which in the East manifested itself with abundant nosebleeds, while in Florence black buboes appeared on the bodies of plague victims.

The buboes could vary in size, but initially they were concentrated in correspondence with the lymph node stations: armpits and groin.

Not such were they as in the East, where an issue of blood from the nose was a manifest sign of inevitable death; but in men and women alike it first betrayed itself by the emergence of certain tumours in the groin or the armpits, some of which grew as large as a common apple, others as an egg, some more, some less, which the common folk called gavoccioli. [011] *From the two said parts of the body this deadly gavocciolo soon began to propagate and spread itself in all directions indifferently; after which the form of the malady began to change, black spots or livid making their appearance in many cases on the arm or the thigh or elsewhere, now few and large, now minute and numerous.* [012] *And as the gavocciolo had been and still was an infallible token of approaching death, such also were these spots on whomsoever they shewed themselves.*

The disease could be transmitted from human to human but it could also be transmitted by objects and could also affect animals.

Moreover, the virulence of the pest was the greater by reason that intercourse was apt to convey it from the sick to the whole, just as fire devours things dry or greasy when they are brought close to it. [015] *Nay, the evil went yet further, for not merely by speech or association with the sick was the malady communicated to the healthy with consequent peril of common death; but any that touched the clothes of the sick or aught else that had been touched or used by them, seemed thereby to contract the disease.*

I say, then, that such was the energy of the contagion of the said pestilence, that it was not merely propagated from man to man, but, what is much more startling, it was frequently observed, that things which had belonged to one sick or dead of the disease, if touched by some other living creature, not of the human species, were

the occasion, not merely of sickening, but of an almost instantaneous death.

Doctors were completely helpless, and there was no effective medicine: the only possible solution was to flee. Boccaccio emphasizes that during the emergency, charlatans proliferated, facilitated by the fact that many doctors had left. Thus, useless, if not harmful, remedies were administered [3].

Some again, the most sound, perhaps, in judgment, as they were also the most harsh in temper, of all, affirmed that there was no medicine for the disease superior or equal in efficacy to flight; following which prescription a multitude of men and women, negligent of all but themselves, deserted their city, their houses, their estates, their kinsfolk, their goods, and went into voluntary exile, or migrated to the country parts, as if God in visiting men with this pestilence in requital of their iniquities would not pursue them with His wrath wherever they might be, but intended the destruction of such alone as remained within the circuit of the walls of the city; or deeming, perchance, that it was now time for all to flee from it, and that its last hour was come [4].

The rites of death were completely disregarded: funerary rituals were no longer carried out as usual and burials were carried out in great haste, often by throwing the bodies into mass graves, covering them with quicklime to prevent animals from digging them up [5].

Nor, for all their number, were their obsequies honoured by either tears or lights or crowds of mourners; rather, it was come to this, that a dead man was then of no more account than a dead goat would be to-day… As consecrated ground there was not in extent sufficient to provide tombs for the vast multitude of corpses which day and night, and almost every hour, were brought in eager haste to the churches for interment, least of all, if ancient custom were to be observed and a separate resting-place assigned to each, they dug, for each graveyard, as soon as it was full, a huge trench, in which they laid the corpses as they arrived by hundreds at a time, piling them up as merchandise is stowed in the hold of a ship, tier upon tier, each covered with a little earth, until the trench would hold no more.

The city became frighteningly silent, as the daily noises of the markets, the shops, and the people crowding the streets fell silent.

The consequence was the complete blockage of trade, commerce, and any other activity, so much so that the citizens became impoverished and, exhausted by hunger, also fell ill for other reasons.

Wherefore, they too, like the citizens, abandoned all rule of life, all habit of industry, all counsel of prudence; nay, one and all, as if expecting each day to be their last, not merely ceased to aid Nature to yield her fruit in due season of their beasts and their lands and their past labours, but left no means unused, which ingenuity could devise, to waste their accumulated store; [045] *denying shelter to their oxen, asses, sheep, goats, pigs, fowls, nay, even to their dogs, man's most faithful companions, and driving them out into the fields to roam at large amid the unsheaved, nay, unreaped corn.*

The comparison

A few years later, another Tuscan writer, Marsilio Ficino (1433-1499) (Fig. 3), a philosopher and physician, wrote a text in the vernacular dedicated to his fellow citizens, offering suggestions on how to escape the plague [6].

Ficino was then living outside the city, on the Careggi hill, at Villa Le Fontanelle, which had been given to him by Cosimo the Elder so that he could translate Plato's texts in peace.

Ficino, perhaps wrote his book because he felt guilty for living in a privileged situation, compared to the population exposed to the risk of disease [7].

He had a very different approach from Boccaccio: the text includes a chapter on the natural origins of the plague, described as a general phenomenon that corrupted nature before attacking the health of individuals, providing opinions from various sources, always taking into account astrological changes and the resulting poisoning of the air and water [8].

This is followed by a list of the disease's symptoms and how to recognize the progression of the infection [9].

A series of suggestions for preventing and treating the plague is then provided, often including recipes for medicines that could be obtained from a pharmacist or doctor, or prepared at home.

Ficino offered suggestions tailored to the recipient's wealth, with remedies proportionate to their resources [10].

Plague was considered a sort of poison, an all-encompassing phenomenon that corrupted the surrounding nature before it attacked the health of individuals.

Ficino believed that plague originated in the air under specific natural conditions and was transmitted through contact between individuals.

Those who cared for the sick were most at risk of contracting the disease, and Ficino devoted an entire chapter to describing the precautions that could be taken to avoid contagion during contact with the sick.

If you ask me how this poison enters, I answer: through

Fig. 3. Portrait of Marsilio Ficino (1433-1499) - [Public domain. Wikipedia commons].

all the pores of the body, especially the most open ones, the mouth and nose…Walls, iron, and wood hold it for a year... wool is nourishment for this poison...Therefore, you should not eat or drink from poison vessels or touch anything that they have touched [11].
Avoid conversations, and when you do converse, stay at least two arm's lengths away from your companion, in an open space, and if you are suspicious, at least six arm's lengths away, and make sure the wind doesn't blow from him toward you.
The table and the bed, and narrow places and many winds together, are very dangerous.
Not everyone was susceptible to the disease, even though they were exposed to the risk, maybe alluding to *healthy carriers*:
…don't be surprised if a man sometimes catches this vapor and isn't offended by it, but offends others… It's like red-hot iron…: it ignites and consumes the tow and straw, but isn't consumed
Ficino was strongly influenced by Galenic medicine and gave great importance to lifestyle, nutrition, evacuations and recommended tranquility and moderation, which would have guaranteed the mainteinance of a good humoural balance.
The most common advice to avoid the plague was always to flee, summed up by the exhortation "*Cito, longe, tardi*" – flee quickly, go far away and return late.
Although Ficino's primary motivation for writing the *Consiglio...* was compassion for his fellow Tuscans, the work was written for a more professional audience, including barber-surgeons, bathhouse staff, midwives, and pharmacists.
Preventive measures – bloodletting, purges, and enemas – could not be applied by the untrained: many of the surgical remedies – punctures, cauterizations, leeches, and cuppings – could only be performed by experts.
Treatment included the traditional theriac and plague pills: for the poor who had little money for expensive medicines to prevent the plague, he recommended "*pieces of toasted bread, soaked in vinegar with a little rue, eaten with raw onion and accompanied by good wine*."
Likewise, for those caring for the sick, he recommended the use of emeralds, to be held in the mouth, worn, or drink powdered; the poor, who could not afford emeralds, would have to make do with radishes *"...to dry the blood and counteract the poison*."
Those who cared for the sick were the most likely to be infected by the disease and Ficino dedicates a whole chapter to describe precautions that may be taken so as to avoid infection while in contact with the sick.
Beware of stuffy air… Keep your whole body well washed. Fumigate your home often with good odors, and likewise your clothing... Wash your mouth, face, and hands often with vinegar. …Use moderate exercise in a spacious place…I advise anyone who is very careful about touching things brought from diseased places…
The room of the sick... let the air be exhaled and removed, but let sheets soaked in vinegar be stretched around the bed and sprinke vinegar down the walls and throughout the room.
Ficino understood that there is a risk of multiple infections and called for caution:
Let no one say that he who is once freed from the disease is free forever… Even this year, in the month of September, I freed a woman from the disease. Then, being as healthy as any other person, she conversed with some infected people and after 18 days she became ill again and died, not having the medicine in time.

Conclusion

The recent SARS-CoV-2 and the Black Death are completely different diseases, one caused by a virus and the other by bacteria [12]: SARS-CoV-2 (causing COVID-19) is a viral infection, while Plague is a bacterial disease [13]. However, the Black Death shared some similar features with COVID-19 pandemic: from the initial difficulties and misunderstandings to the adoption of public safety and prevention measures, the lasting impact on society after the event had passed.
The historical and societal responses to the COVID-19 pandemic and the Black Death (a major plague pandemic) have shown some similarities, particularly in the initial lack of understanding,, the mischievous and indiscernible nature of disease, the helplessness of medical treatments, the recommendation to avoid physuical contacts with infected people, and prevention initiatives of public health measures like quarantine...
Reading the first pages of the Decameron offers food for thought regarding the spread of the Black Death in Florence of 1348. Indeed, Boccaccio's narrative is that of a man of letters, a witness to the devastation of the city and its values.
The similarities between Boccaccio's description and what we experienced during the COVID-19 era are evident: the Eastern origin of the disease, its novelty, the lack of treatment, the need for isolation, unceremonious burials and economic instability.
By contrast, Marsilio Ficino (1433-1499), an Italian scholar and Catholic priest who was one of the most influential humanist philosophers of the early Italian Renaissance, offered a more detached interpretation of the disease; he adopted a medical approach and a perspective that focused on public health aspects, such as preventive measures, safety precautions, the importance of isolation and quarantine, territorial control, *etc.*
Furthermore, Marsilio Ficino clearly advocated the proactive aspect: distancing, frequent hand-washing [14], the risk of reinfection, and the modes of contagion – all of which denote the modernity, attentiveness and foresight of public health at that time.
Later, during the Hong Kong epidemic in 1894, Alexander Yersin (1863-1943) identified the bacterial agent that causes the plague, and which bears his name, *Yersinia pestis*. However, we can say that 650 years earlier Boccaccio had described significant essential features of the disease, paving the way to understanding

how major epidemics affect humanity and what impact they may have in subsequent periods, not least from an economic and social standpoint.

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Authors' contributions

DL: conceived the study; DL & FB: designed the study; DL, FB and MM drafted the manuscript, performed a search of the literature, revised the manuscript; DL and FB: methodology; FB: investigation and data curation; DL, FB and MM: review; MM: editing. All authors have read and approved the latest version of the paper for publication.

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Correspondence: Mariano Martini, Via Pastore 1, 16132 Genoa, Italy. E-mail: mariano.martini@unige.it

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INFECTIOUS DISEASE

Pneumococcal Vaccination of Adults in Italy: What Strategies?

ELVIRA MASSARO[1], GIOVANNI GABUTTI[2]
[1] ASL3 Healthcare System of the Liguria Region, Genoa, Italy; [2] Italian Society of Hygiene, Preventive Medicine, and Public Health (SItI), Cogorno (Ge), Italy; Adult Immunization Board (AIB)

Keywords

Pneumococcal Vaccination • *Streptococcus pneumoniae* • Invasive Pneumococcal Disease • Epidemiological Surveillance

Summary

S. pneumoniae has been classified by the World Health Organization (WHO) as one of the 12 priority pathogens with the greatest global health impact. Although many individuals (approximately 20–30% of adults and nearly 40–50% of children) may carry the bacterium asymptomatically, certain groups are considered at higher risk of disease (non-invasive illnesses and invasive diseases). These include young children, the elderly and individuals who are immunocompromised or affected by pre-existing medical conditions.

Italian surveillance data show a significant increase in Invasive Pneumococcal Disease (IPD) incidence in 2023 in comparison with 2021 and 2022, rising from 0.84 cases per 100,000 population in 2021 to 3.02 in 2023. The highest rates were observed in children under 1 year of age [10.41/100,000 (2023)] and in adults aged 65 and over (7.45/100,000 in 2023 compared with 2.11 in 2021 and 4.49 in 2022).

Surveillance systems and epidemiological studies on the global distribution of the different pneumococcal serotypes associated with disease continue to be essential to determining which serotypes to include in new vaccines, in order to produce preparations capable of preventing an increasing number of cases, hospitalizations, sequelae and deaths.

A milestone in pneumococcal vaccination was the development of conjugate vaccines (PCVs), which started in the 2000s. The first PCV, which covered seven serotypes (PCV7: 4, 6B, 9V, 14, 18C, 19F, and 23F), was introduced in Italy in 2005 for the pediatric population. The introduction of this vaccination strategy leading to a significant reduction in disease among children and an overall decline in the pneumococcal disease burden across all age-groups. However, an increase in disease caused by serotypes not included in PCV7 was observed. This phenomenon, named serotype replacement, led to the development of higher-valency conjugate vaccines. In 2010, the 13-valent pneumococcal vaccine (PCV13) and 10-valent pneumococcal vaccine (PCV10) were approved. However, the phenomenon of serotype replacement continued to be observed, and consequently, the need for broader-spectrum vaccines remained a public health priority.

In 2021 and 2022 PCV15 (serotypes: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F) and PCV20 (serotypes: 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F and 33F) were authorized for immunization in individuals aged ≥18 years, respectively. In March 2025, the use of a new 21-valent pneumococcal vaccine was approved (serotypes: 3, 6A, 7F, 19A, 22F, 33F, 8, 10A, 11A, 12F, 9N, 17F, 20, 15A, 15C, 16F, 23A, 23B, 24F, 31 and 35B) and it included some serotypes particularly aggressive or emerging.

Maximizing the effectiveness of a vaccination program in combating diseases related to S. pneumoniae is based on the integration of three key elements: epidemiological need, immunological need and vaccine compliance.

From an epidemiological perspective, the 2023 specific data analysis reveals that, out of 1,783 cases, 734 involved individuals over the age of 64 (41.2%). The estimated global coverage with the PCV20 vaccine would be 63.6%, while with the PCV21 vaccine it would be 76.4%. The specific analysis of the most recent available data (1st half of 2024) reveals that a total of 1,152 cases were reported, 58.4% of which occurred in individuals over 64. If only the data referring to subjects over the age of 64 are analyzed, the estimated coverage becomes 72.1% for PCV20 and 79.2% for PCV21.

From an immunological standpoint, the vaccine of choice should induce an immune response that is at least non-inferior to the comparator, and ideally, more robust and long-lasting.

Regarding compliance, all possible strategies must be activated in order to raise public awareness of the risks of pneumococcal disease and the benefits of vaccination, so as to increase coverage rates.

A thorough analysis of epidemiological and clinical data, combined with an assessment of the economic and social impact, is crucial to guiding vaccination policies and supporting efficient decision-making in order to protect the health of the entire population.

Introduction

Streptococcus pneumoniae (*S. pneumoniae*), a Gram-positive bacterium, causes a wide spectrum of diseases, ranging from non-invasive illnesses such as bronchitis, non-bacteremic pneumonia, sinusitis and otitis media, to invasive diseases, including bacteremia, septicemia, osteomyelitis, pneumonia and meningitis [1].

S. pneumoniae is able to colonize the nasopharynx, resulting in a carrier state, which involves approximately 20–30% of adults and nearly 40–50% of children [2].

Among its essential structural components, phosphorylcholine – part of the bacterial cell wall – plays a key role in the colonization of the upper respiratory tract, owing to its ability to bind specific receptors on human epithelial cells [3, 4].

Under normal conditions, colonization does not progress to clinically apparent disease. Progression to invasive disease requires the local activation of proinflammatory mediators, such as interleukin-1 (IL-1) and tumor necrosis factor (TNF) [5]. This inflammatory response induces both quantitative and qualitative changes in the receptors present on epithelial and endothelial cells. Choline in the bacterial cell wall has a high affinity for the platelet-activating factor receptor, whose expression is increased during inflammation [6]. Interaction with this receptor facilitates bacterial internalization and promotes transcellular passage across epithelial and vascular barriers, allowing *S. pneumoniae* to invade deeper tissues [7].

Another key factor in the pathogenesis of pneumococcal disease is pneumolysin, a cytotoxin capable of forming pores in eukaryotic cell membranes and interfering with complement activation, thereby contributing to immune evasion and tissue damage [6, 7].

Although many individuals may carry the bacterium asymptomatically, certain groups are considered at higher risk of disease. These include young children, the elderly and individuals who are immunocompromised or affected by pre-existing medical conditions. Among these, diabetes mellitus, chronic lung disease, liver disease, chronic kidney disease and sickle cell anemia are major risk factors. Recent studies have also identified additional predisposing conditions, such as sarcoidosis, inflammatory polyarthropathies, systemic connective tissue diseases and various neurological disorders, highlighting the complexity of individual susceptibility profiles [8]. Furthermore, concurrent viral infections can predispose individuals to invasive pneumococcal disease [9]. Other contextual and behavioral factors – such as the winter season, tobacco smoking and chronic alcohol consumption – also constitute risk factors for the development of invasive pneumococcal disease [8].

To date, the polysaccharide capsule surrounding the cell wall is widely recognized as the main virulence factor of *S. pneumoniae*. The structural composition of the capsule enables the bacterium to evade opsonization and phagocytosis [10]. Analysis of the capsule's polysaccharides has led to the identification of over 100 different *S. pneumoniae* serotypes. However, it is important to note that only a subset of these serotypes is responsible for the majority of invasive clinical cases [11]. Disease-causing serotypes differ not only in their structural characteristics but also in their associated disease severity, lethality, invasiveness, antibiotic susceptibility and distribution across age-groups and geographic regions [12, 13].

The Burden of *Streptococcus pneumoniae* Disease in Adults: A Major Public Health Concern

Despite significant progress in diagnostic and therapeutic pathways, infections caused by *S. pneumoniae* remain associated with high morbidity and mortality rates, particularly among vulnerable populations such as children, the elderly and individuals with compromised immune systems [14]. Indeed, *S. pneumoniae* has been classified by the World Health Organization (WHO) as one of the 12 priority pathogens with the greatest global health impact [3].

In 2021, *S. pneumoniae* was responsible for the majority of lower respiratory tract infection (LRTI)-related cases and deaths (excluding SARS-CoV-2), with an estimated 97 million cases and 505,000 deaths globally. Of these, the largest number occurred in children under the age of 5 years, and in adults over 70 years old [15, 16].

According to data from the European Centre for Disease Prevention and Control (ECDC), in 2022 the incidence rate of invasive pneumococcal disease (IPD) in Europe was 5.11 cases per 100,000 population, with the highest rates being observed in individuals over 64 years of age and in children under 4 years (13.42 and 12.49 cases per 100,000 population, respectively). Clinically, the most common presentations were bacteremic pneumonia (41.2%) and septicemia (37.7%), followed by meningitis (13.8%). Overall case fatality rates were 17.1% among those over 65 and 10.9% among individuals aged 45–64 [17].

Italian surveillance data show a significant increase in IPD incidence in 2023 in comparison with 2021 and 2022, rising from 0.84 cases per 100,000 population in 2021 (500 cases) to 3.02 in 2023 (1,783 cases). The highest rates were observed in children under 1 year of age [10.41/100,000 (2023), exceeding the pre-pandemic value of 6.50 in 2019] and in adults aged 65 and over (7.45/100,000 in 2023 compared with 2.11 in 2021 and 4.49 in 2022). This increase was probably attributable, at least in part, to improved diagnostic techniques and growing awareness of IPD in Public Health Surveillance. Most notifications occurred during the winter months, confirming the established seasonal pattern. The most frequently reported clinical manifestations were sepsis and bacteremia (37–55% of cases), followed by pneumonia associated with sepsis/bacteremia (25-36%) and meningitis, with or without sepsis/bacteremia (18-25%) [15]. The interim report for the first six months of 2024 cited a total of 1,152 IPD cases, 673 of which occurred in individuals over 64 years of age [18].

S. pneumoniae infections, especially in the elderly, are often responsible for a large number of community-acquired pneumonia (CAP) cases, making them the leading cause of hospital admissions among individuals aged > 65 years – approximately 2,000 admissions per 100,000 per year in the developed countries [19]. Moreover, beyond the disease burden directly caused by the infection, pneumococcal CAP in the elderly is frequently complicated by cardiovascular events, which further increase its clinical, economic and social impact [14, 20, 21].

In high-income countries, *S. pneumoniae* remains responsible for up to 50% of CAP cases, with in-hospital mortality reaching as high as 40% among older adults [22].

In Italy, CAP has a significant clinical and economic impact, with a hospitalization rate of 31.8% among adults, and *S. pneumoniae* remains the main etiological agent [23]. A large study conducted in four Italian regions between 2017 and 2020 found that, among 1,155 individuals aged ≥ 65 years hospitalized for CAP, 13.1% had an infection caused by *S. pneumoniae*. The most frequently detected serotypes were: 3 (2.0%), 8 (1.7%), 22F (0.8%), 11A (0.7%) and 9N (0.6%). Moreover, the study showed that highly invasive serotypes (1, 5, 7F and 8) accounted for 2.1% of cases. Serotypes included in the conjugate vaccines PCV15 and PCV20 were present in 4.4% and 7.5%, respectively, of CAP cases [24].

Serotype 3 plays a significant role in clinical manifestations and is associated with more severe disease [22, 25]. In recent years, this serotype has become one of the most commonly identified causes of interstitial lung disease in most Western countries [24, 26]. Its increased circulation is probably due to several factors: the current conjugate pneumococcal vaccines (PCVs) for adults appear to have limited efficacy against this serotype, whose polysaccharide capsule is thicker and lacks a covalent bond to the peptidoglycan layer. This characteristic renders the capsule more resistant to immune attack, as it reduces opsonophagocytic killing, thereby facilitating persistence and transmission.

Surveillance Systems: The Importance of Continuous Monitoring

Communicable diseases continue to constitute a public health priority, owing to their significant clinical, economic and epidemiological impact. In this context, epidemiological and laboratory surveillance plays a central role, as it allows the systematic and integrated collection of essential data that can guide public health decision-making, support efforts to combat respiratory infections and aid the development of new vaccines. It also plays a key role in both global and local health security. By definition, infectious disease surveillance involves the continuous and systematic collection of information regarding the distribution of diseases and associated risk factors, as well as the analysis of temporal, spatial and demographic trends, with the aim of informing effective prevention and control measures [27].

Recently, the World Health Organization (WHO), through the publication of the *Global Strategy on Comprehensive Vaccine-Preventable Disease Surveillance (2021–2030)*, has emphasized the need to develop more comprehensive and integrated national and regional surveillance systems capable of monitoring the full spectrum of the infectious diseases that are most relevant in various geographical contexts. This integrated approach not only supports efforts to achieve the elimination and eradication goals set out in the *Immunization Agenda 2030*, but also constitutes an essential tool for strengthening vaccination programs [28].

In the United States, following the release of the report *Addressing Emerging Infectious Disease Threats: A Prevention Strategy for the United States* [29], the Emerging Infections Program (EIP) was established a network of state health departments coordinated by the Centers for Disease Control and Prevention (CDC). The aim of this network is to detect emerging pathogens, conduct research based on laboratory and epidemiological data, and implement projects supporting public health protection and prevention efforts [30].

In 1995, the Active Bacterial Core Surveillance (ABCs) system was launched – a surveillance network created under the CDC's EIP to monitor and estimate the burden of invasive bacterial infections of public health relevance [31]. Initially composed of four sites (California, Connecticut, Oregon and Minnesota), the ABCs network expanded in 2003 to include Georgia, Maryland, New York, Tennessee, Colorado and New Mexico, thus comprising a total of 10 sites. The network ensures case monitoring through the systematic verification of clinical and laboratory data in collaboration with the CDC, state health departments and universities [32].

The need to establish an active surveillance network arose alongside the development of the 13-valent PCV, as it was crucial to have a system capable of determining baseline IPD rates, monitoring circulating serotypes and assessing vaccine effectiveness. Indeed, evidence gathered through the ABCs network revealed a significant reduction in IPD incidence in children, due to the introduction of the 7-valent PCV (PCV7), as well as in adults, due to herd protection. However, it also showed an increase in cases caused by *S. pneumoniae* serotypes not included in the commercial vaccines [31].

In Europe, the first *S. pneumoniae* surveillance systems date back to the 1990s, when the growing availability of vaccines – initially polysaccharide-based and later conjugate vaccines – highlighted the need for standardized data on disease incidence and serotype distribution, in order to measure vaccine impact and guide immunization strategies. With the introduction of the PCV7 conjugate vaccine, several European countries established dedicated surveillance systems or strengthened existing ones.

The ECDC implemented the TESSy surveillance, which was designed for the collection, analysis and sharing of epidemiological data across the European Union and the European Economic Area. This system integrates demographic, clinical and laboratory data, enabling time-trend analyses of cases and comparisons between member states, with the aims of monitoring incidence, evaluating the impact of vaccination programs, identifying emerging trends and supporting evidence-based policy decisions.

In Italy, a surveillance system for Invasive Bacterial Diseases (MIB), coordinated by the Istituto Superiore di Sanità (ISS), has been in place since 2007. The aim of this surveillance is to monitor the temporal and spatial trends of these diseases, describe the frequency of cases

by pathogen (*Neisseria meningitidis*, *S. pneumoniae* and *Haemophilus influenzae*) and serotype, and estimate the proportion of cases preventable through vaccination, in order to improve prevention and control strategies [15].

Pneumococcal Vaccines: Epidemiological Evolution, Serotype Variation and New Opportunities

Surveillance systems and epidemiological studies on the global distribution of the different pneumococcal serotypes associated with disease continue to be essential to determining which serotypes to include in new vaccines, in order to produce preparations capable of preventing an increasing number of cases, hospitalizations, sequelae and deaths [33].

The development of the first generation of pneumococcal polysaccharide vaccines using purified capsular polysaccharides dates back to the 1950s. The non-conjugate polysaccharide vaccines elicit a short-lived immune response, with a significant decline in immunity 6–24 months after vaccination. Indeed, these vaccines primarily induce a B cell-mediated immune response without involving T cells [34-36].

The first second-generation pneumococcal polysaccharide vaccine was the 14-valent PPSV14, licensed in the United States in 1977. It was later superseded by PPSV23, which contains the serotypes most commonly associated with invasive pneumococcal disease (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F) [35]. PPSV23 is indicated for active immunization from 2 years of age, is administered in a single dose and is used sequentially after a conjugate vaccine, with revaccination being possible after five years [37].

A milestone in pneumococcal vaccination was the development of conjugate vaccines (PCVs), which started in the 2000s. These vaccines are based on mechanisms similar to those of conjugated Hib vaccines, which used carrier proteins such as diphtheria toxoid (PRP-D), meningococcal outer membrane protein (PRP-OMP) and tetanus toxoid (PRP-T) [34]. The covalent conjugation of capsular polysaccharides with a carrier protein has been shown to elicit a T cell–dependent adaptive immune response and induce B memory cells, resulting in immunological memory. This antigenic shift renders these vaccines much more immunogenic in both adults and infants [38, 39].

The first PCV, which covered seven serotypes (PCV7: 4, 6B, 9V, 14, 18C, 19F, and 23F), was introduced in the United States in 2000 and in Europe in 2001. In Italy, vaccination with PCV7 was included in the National Immunization Prevention Plan (PNPV) in 2005 for the pediatric population [40].

The introduction of pediatric vaccination with PCV7 effectively generated long-lasting immunity in vaccinated infants and reduced nasopharyngeal carriage of the seven most virulent *S. pneumoniae* serotypes – leading to a significant reduction in disease among children and an overall decline in the pneumococcal disease burden across all age-groups [39, 41, 42].

In parallel with the reduction in IPD cases caused by vaccine-targeted serotypes, however, an increase in disease caused by serotypes not included in PCV7 was observed [43]. This phenomenon, named serotype replacement, *i.e.* a relative increase in cases of disease due to serotypes not included in the commercially available vaccine, led to the development of higher-valency conjugate vaccines. In 2010, the 13-valent pneumococcal conjugate vaccine (PCV13) was approved. In addition to the serotypes in PCV7, it covers serotypes 1, 3, 5, 6A, 7F and 19A. Initially indicated only for children, it was later approved for adults over 50 years of age [44]. Around the same time, a 10-valent conjugate vaccine was also approved for the pediatric population [45].

In high-income countries, the introduction of PCV10 and PCV13 conjugate vaccines has led to two significant trends: on one hand, a considerable decrease in invasive and non-invasive disease caused by vaccine-included serotypes; on the other, the phenomenon of serotype replacement [35]. This epidemiological phenomenon has generated the need to develop conjugate vaccines that contain an ever-greater number of serotypes, in order to broaden protection against pneumococcal disease.

In 2021, the European Medicines Agency (EMA) authorized PCV15, a conjugated and adsorbed polysaccharide vaccine containing the serotypes: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F. Initially used for the active immunization of adults aged ≥18 years, in October 2022 it was also authorized for use in individuals from six weeks of age. For those over 18 years, a single dose is administered, and it is important to note that the product's Summary of Product Characteristics (SmPC) indicates co-administration with the seasonal quadrivalent (inactivated, split virion) influenza vaccine, thus providing an important contribution to vaccination strategies [46].

In February 2022, in Europe (in May 2022 in Italy), the 20-valent conjugated adsorbed vaccine (serotypes: 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F and 33F) was authorized for immunization in individuals aged ≥18 years. Later, PCV20 also obtained authorization for pediatric use (March 2024) according to a 3 + 1 schedule. In adults and the elderly, PCV20 may be co-administered with the seasonal influenza vaccine [47].

The systematic review by Teixeira et al. examined 118 studies published between 2010 and 2022 in 33 European countries, and showed that the serotypes covered only by PCV20 (8, 10A, 11A, 12F, 15B, 22F and 33F) have become increasingly prevalent among adults since the introduction of PCV13, causing both invasive and non-invasive pneumococcal disease [12].

A recent cost-effectiveness study used a Markov model to evaluate the implementation of PCV20 in the Italian adult vaccination strategy. Assuming vaccination of 100% of cohorts aged 65 to 74 years, immunization with PCV20, in comparison with PCV13, proved to

be dominant (lower cost and a better health outcome), yielding an estimated reduction of 1,208 deaths; 1,171 cases of bacteremia (excluding meningitis); 227 cases of meningitis; 9,845 hospitalized cases of non-bacteremic pneumonia, and 21,058 non-hospitalized cases; the total gain was of 6,581.6 life-years and 4,734.0 QALYs (Quality Adjusted Life Year). Comparison with PCV15 showed an ICER (Incremental Cost-Effectiveness Ratio) of €66 per life-year gained and €91 per QALY. The authors concluded that vaccination of the elderly population with PCV20 was a sustainable and efficient investment [48].

In March 2025, in Europe and subsequently in Italy (May 2025), the use of a new 21-valent pneumococcal conjugate polysaccharide vaccine, conjugated to the CRM197 carrier protein, was approved [49]. The vaccine protects against 21 serotypes (3, 6A, 7F, 19A, 22F, 33F, 8, 10A, 11A, 12F, 9N, 17F, 20, 15A, 15C, 16F, 23A, 23B, 24F, 31 and 35B), some of which are particularly aggressive or emerging. Administered in a single dose, it is indicated for active immunization against invasive disease and pulmonary infection caused by *S. pneumoniae* in individuals aged 18 years or older.

Clinical trials conducted in adults have evaluated its effectiveness against invasive pneumococcal disease and pulmonary infection, as well as its immunogenicity. The double-blind, randomized STRIDE 3 trial included pneumococcal vaccine-naïve adults aged 18 years and older, with or without stable chronic medical conditions [50]. Participants were divided into two cohorts: the first included individuals aged 50 and older, who were randomized 1:1 to receive either PCV21 or PCV20. The second cohort comprised participants aged 18 to 49 years, randomized 2:1.

Serotype-specific opsonophagocytic activity (OPA) and IgG responses were measured on Day 1 and Day 30 post-vaccination. PCV21 displayed non-inferior OPA levels in comparison with PCV20 for the ten shared serotypes and met superiority criteria for 10 of the 11 serotypes included only in PCV21 (with the exception of serotype 15C). Although superiority was not reached for 15C, robust immune responses were observed. Additionally, PCV21 elicited a cross-reactive immune response to serotype 15B, probably due to structural similarity between 15B and 15C. PCV21 was generally well tolerated, with a safety profile similar to PCV20, and showed a greater response toward serotypes 3 and 8. Furthermore, the most commonly reported adverse events were mild and short-lasting (less than 3 days) pain at the injection site and headache [50].

In another Phase III randomized controlled trial (STRIDE-6), the safety, tolerability and immunogenicity of the PCV21 were evaluated in adults aged 50 years and older. The study included 717 previously vaccinated adults, who were divided into three cohorts on the basis of their prior vaccination history:

Cohort 1: individuals previously vaccinated with PPSV23, randomized 2:1 to receive PCV21 or PCV15.

Cohort 2: individuals previously vaccinated with PCV13, randomized 2:1 to receive PCV21 or PPSV23.

Cohort 3: individuals with mixed vaccination history received open-label PCV21.

Immunogenicity was assessed 30 days post-vaccination in terms of geometric mean titers (GMTs) of OPA and geometric mean concentrations (GMCs) of IgG for all serotypes included in V116. Safety was monitored by recording the proportion of participants reporting adverse events.

PCV21 was found to be immunogenic against all 21 serotypes included, with immune responses generally comparable to those elicited by the other vaccines used in the study. Thirty days after vaccination, OPA GMTs against shared serotypes were generally similar between PCV21 and PCV15 (Cohort 1), and between PCV15 and PPSV23 (Cohort 2). The most frequently reported adverse events were injection site pain and fatigue, usually mild to moderate in intensity and lasting no longer than 3 days [51].

It is also noteworthy that PCV21 includes emerging and hard-to-control serotypes, including 9N, 15C, 16F, 17F, 20A, 23A, 23B, 24F, 31 and 35B. Notably, serotype 15C is capable of eliciting a cross-reactive immune response against the deOAc15B polysaccharide, owing to structural similarity, thereby providing protection against serotype 15B.

Table I provides a summary of the evolution of pneumococcal vaccines.

Figure 1 illustrates the evolution of third-generation pneumococcal vaccines.

Pneumococcal Vaccination of Adults in Italy: Where Do We Stand?

Recent demographic projections for Italy indicate an ongoing transition marked by progressive population aging. Indeed, it is estimated that, by 2050, individuals aged 65 and over will constitute 34.6% of the total population, compared with the current 24.3% [52]. In this context, it is clear that Public Health must pay particular attention to this population group, in order to implement vaccination programs capable of reducing the disease burden due to preventable infectious illnesses.

With regard to invasive pneumococcal disease (IPD) in Italy, among adults over the age of 64, the incidence increased in 2023, reaching 7.45 cases per 100,000 inhabitants, compared with 2.11 in 2021 and 4.49 in 2022 [15].

Pneumococcal vaccination with conjugate vaccines for adults and the elderly began to be offered in 2015 in certain Italian Regions, with a gradual rollout. The 2017-2019 PNPV recommended free pneumococcal vaccination for all individuals aged ≥65 years; this consisted of the administration of PCV13, followed, after at least two months, by a dose of 23-valent polysaccharide vaccine (PPSV23) in a sequential schedule. Vaccination was also recommended for all individuals at higher risk of severe pneumococcal infections and complications due to specific clinical conditions or chronic comorbidities [53].

The 2023–2025 PNPV reinforces previous

Tab. I. Pneumococcal vaccines: the evolution.

FIRST GENERATION
1911: whole-cell vaccine
1930: vaccine serotypes combined with live attenuated bacteria
Mid-1930s: multivalent vaccines containing partially purified capsular material
Late 1940s: multivalent polysaccharide vaccines
Early 1950s: first generation of pneumococcal polysaccharide vaccines introduced into the market
SECOND GENERATION
Unconjugated polysaccharide vaccines
1977: 14-valent vaccine approved in the USA
1983: 23-valent vaccine (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 11F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F) approved in the USA
Conjugated polysaccharide vaccines
2000: 7-valent vaccine (PCV-7) (4, 6B, 9V, 14, 18C, 19F, 23F) approved in the USA and shortly afterwards in Europe (2001)
THIRD GENERATION
Conjugated polysaccharide vaccines with expanded antigenic coverage
2009-2010: approval of the 10-valent vaccine (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F) and the 13-valent vaccine (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F)
December 2021 (European approval) - March 2021 (Italian approval): 15-valent vaccine (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F) approved for adults ≥ 18 years.
February 2022 (European approval) - May 2022 (Italian approval): 20-valent vaccine for individuals ≥18 years.
March 2025 (European approval) - May 2025 (Italian approval): 21-valent vaccine (3, 6A, 7F, 19A, 22F, 33F, 8, 10A, 11A, 12F, 9N, 17F, 20, 15A, 15C, 16F, 23A, 23B, 24F, 31 and 35B) approved for individuals aged ≥ 18 years.

Fig. 1. Evolution of third-generation pneumococcal vaccine.

* For PCV21, a cross-reactive immune response was observed *versus* serotype 15B; this was elicited by serotype 15C, which is structurally similar to serotype 15B.

recommendations, reaffirming the need to ensure free pneumococcal vaccination for the cohort of 65-year-olds and for frail patients of any age [54]. It should be noted that the right to free vaccination is maintained for life.

Regarding at-risk adults and older individuals, vaccination with a single dose of PCV is recommended starting from the cohort of 65-year-olds. The offer should eventually be supplemented with a sequential vaccination schedule (PCV/PPSV) depending on the type of PCV used.

For these categories, a minimum coverage target of 75% and an optimal target of 95% has been established, in line with the standards already defined for other adult vaccinations. The stated objective is to harmonize vaccination uptake across the country, reduce regional inequalities and ensure adequate protection for the most vulnerable segments of the population [54].

A cross-sectional study conducted as part of the OBVIOUS project and published in 2024 analyzed pneumococcal vaccination coverage in Italy and the barriers limiting uptake. Conducted in 2022 on a representative sample of adults, the survey revealed that coverage among high-risk adults remained unsatisfactory: only 39.5% of eligible individuals had been vaccinated, with even lower rates among those aged ≥65 years (33.7%). Slightly higher rates were recorded among patients with chronic conditions such as diabetes, cardiovascular or respiratory diseases, but coverage still fell well below the ≥75% target set by the national program [55].

Another retrospective study, published in 2024 and conducted in the Province of Viterbo (Lazio Region, Italy), investigated the rate of completion of the sequential pneumococcal vaccination schedule among 65-year-olds. Coverage was extremely low, with only 2.32% of individuals completing the schedule within two years of turning 65, reaching a peak of just 3.27% in 2020 [56].

Finally, a study conducted during the 2023–2024 vaccination season at the geriatric outpatient clinic of the University of Palermo involved 76 frail elderly patients, who were primarily affected by cognitive or endocrine disorders such as diabetes and osteoporosis. The aim was to assess the feasibility and impact of a proactive vaccination strategy by directly offering influenza and pneumococcal vaccines at the clinic. Vaccination

coverage proved encouraging: 46.05% of patients received only the pneumococcal vaccine, 28.95% received both vaccines (influenza + pneumococcus), and 25% received only the influenza vaccine [57].
However, it is important to note that the available data on pneumococcal vaccination coverage in adults and the elderly come only from local or regional studies, making it difficult to assess whether the coverage targets set by the PNPV and the Essential Levels of Care (LEA) have been achieved.

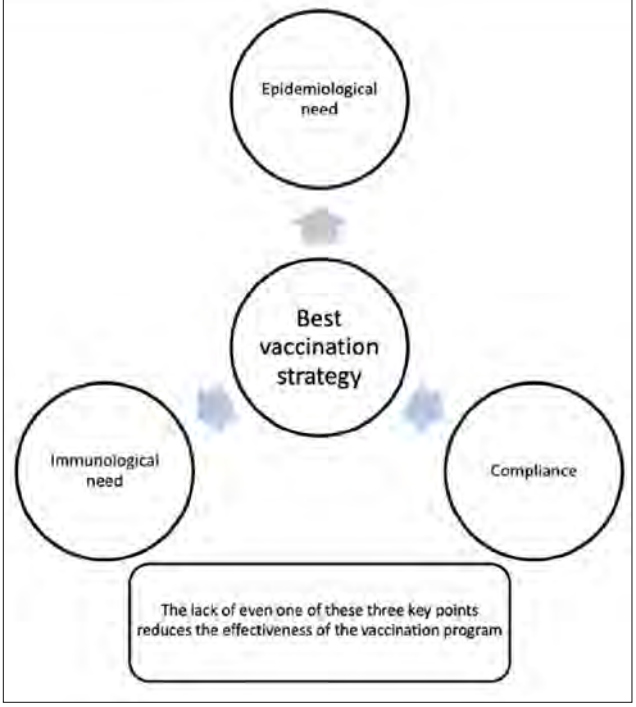
Key Elements for Choosing the Best Vaccination Strategy

Maximizing the effectiveness of a vaccination program in combating diseases related to *S. pneumoniae* is based on the integration of three key elements (Fig. 2):
- Epidemiological need,
- Immunological need,
- Vaccine compliance.

Epidemiological Need

The concept of epidemiological need is fundamental to defining vaccination strategies, as it is linked to ensuring that a vaccine effectively addresses the needs of a given population at a specific point in time, taking into account continuously evolving demographic characteristics. In the case of pneumococcus, the high antigenic variability (over 100 serotypes identified), the dynamics of serotype replacement induced by the selective pressures of conjugate vaccines, and the heterogeneity of the population groups affected require continuous surveillance and regular updating of preventive strategies [11-13, 58]. Over the years, serotype replacement has profoundly changed the epidemiology of IPD and CAP, particularly in the adult and elderly populations [58].
In the United States, after the introduction of PCV13, the incidence of IPD cases caused by vaccine serotypes in adults sharply decreased, displaying a 70% reduction in those aged ≥65 years. However, since 2014, no further reductions have been recorded, and during the 2018–2020 period, serotypes covered by PCV20 and PCV21 accounted for 54% and 85% of IPD cases in the elderly, respectively. In Canada, the most prevalent serotype among individuals aged ≥65 years in 2022 was serotype 3 (13.3%), followed by 22F (9.9%) and 9N (6.7%), with PCV20 coverage at 58.5% [59].
According to data from the ECDC, in 2022, cases due to serotypes not included in PCV13 showed higher incidence rates in individuals aged >64 years and children under 4 years old than in other population groups, with rates of 4.32 and 4.66 per 100,000 inhabitants, respectively [17]. In recent years, European epidemiological surveillance has revealed that certain serotypes continue to play a predominant role in causing invasive disease and CAP [12]. In particular, serotype 3 remains one of the main causes of IPD and CAP in adults and the elderly [60].
Data from various European and North American contexts report a considerable portion of cases caused by serotype 3 (between 12% and 19%) in subjects aged over 50 [12]. A systematic review analyzed data from primary studies conducted between 1984 and 2020 in order to gather information on the distribution of serotypes involved in pneumococcal pneumonia in adults and the elderly, while also considering the vaccination strategies in place during the studies. In all the publications, serotype 3 was the most common (11.9% of total isolates), with a growing percentage with increasing age (18.9% in those over 50). The authors reported that the prevalence of serotype 3 remained high even after the introduction of PCV10/PCV13 vaccination [60].
The persistence of this serotype, even though it was included in earlier-generation conjugate vaccines (PCV13), may be explained by its particular ability to evade the antibody response, a feature which contributes to its greater invasiveness and clinical severity, with significantly higher fatality rates than those of other serotypes [61].
At the same time, serotypes 22F and 33F have shown increasing epidemiological importance, emerging as frequent causes of invasive disease in adults. Indeed, a 2023 systematic review documented that serotype 22F accounted for approximately 6-7% of IPD cases not covered by PCV13 in adults, ranking among the most common serotypes alongside 8, 12F and 19A [62]. These findings are consistent with observations from European surveillance systems, which confirm the rising incidence of 22F and, to a lesser extent, 33F as causal agents of IPD in individuals aged ≥65 years [62].
In Italy, the ISS reported that in 2023, 58% of IPD cases

Fig. 2. Key elements for choosing the best vaccination strategy.



Tab. II. Serotypes identified in cases of invasive pneumococcal disease reported to the Italian MIB surveillance system that are common to both PCV20 and PCV21 vaccines [15, 18].

Serotype	2021	2022	2023	2024 (1st semester)	Total
3	41	171	336	183	731
6A	1	3	3	4	11
7F	2	5	8	7	22
8	52	137	191	118	498
10A	9	18	31	13	71
11A	8	18	29	13	68
12F	3	1	10	16	30
15B*	5	6	14	14	39
19A	11	43	57	42	153
22F	5	13	51	74	143
33F	0	4	9	9	22
Total	137	419	739	493	**1788**

* Serotype included in PCV20. For PCV21, a cross-reactive immune response was observed; this was elicited by serotype 15C, which is structurally similar to serotype 15B.

Tab. III. Serotypes identified in cases of invasive pneumococcal disease reported to the Italian MIB surveillance system that are exclusive to PCV20 [15, 18].

Serotype	2021	2022	2023	2024 (1st semester)	Total
1	4	2	8	7	21
4	2	2	8	6	18
5	1	1	1	0	3
6B	1	4	3	0	8
9V	1	1	3	1	6
14	5	15	17	22	59
18C	0	0	2	3	5
19F	7	21	34	18	80
23F	0	2	6	7	15
Total	21	48	82	64	**215**

Tab. IV. Serotypes identified in cases of invasive pneumococcal disease reported to the Italian MIB surveillance system that are exclusive to PCV21 [15, 18].

Serotypes	2021	2022	2023	2024 (1st semester)	Total
9N	7	21	42	19	89
15A	8	13	30	9	60
15C	1	1	11	16	19
16F	2	3	3	5	13
17F	1	6	8	1	16
20	5	4	9	9	27
23A	13	22	30	31	96
23B	7	24	29	15	75
24F	1	10	22	6	39
31	2	8	13	19	42
35B	0	3	11	3	17
Total	47	115	208	123	**493**

were covered by PCV20, compared with only 40% covered by PCV13. Among subjects aged ≥65, serotype 8 was the most frequent (15% of isolates), followed by 3, 22F and 33F. This indicates a mismatch between the vaccine used and the actual burden of disease [15].

An analysis of the data from the Surveillance System for Invasive Bacterial Diseases for the period 2021–2024 (first half) reveals the most frequently detected serotypes and allows us to compare them with recent conjugate vaccine formulations currently available for the adult/elderly population (PCV20 and PCV21).

Table II lists the *S. pneumoniae* serotypes detected by invasive bacterial disease surveillance in Italy during 2021–2024 (first half) [15, 18] that are common to both PCV20 and PCV21 vaccines.

As shown in Table II, a significant proportion of cases could potentially be prevented through the use of one of the latest-generation vaccines.

Surveillance data from 2021–2024 (first half) prompt further considerations.

Tables III and IV report the cases that could potentially be prevented by the exclusive use of PCV20 and PCV21, respectively.

As shown in Table IV, the new PCV21 vaccine has been specifically developed to include emerging serotypes of significant epidemiological and clinical relevance.

The 2023 specific analysis reveals that, out of 1,783 cases, 734 involved individuals over the age of 64 (41.2%). The estimated coverage with the PCV20 vaccine would be 63.6%, while with the PCV21 vaccine it would be 76.4%.

The specific analysis of the most recent available data on invasive disease cases (1st half of 2024) reveals that a total of 1,152 cases were reported, 58.4% of which occurred in individuals over 64. If only the data referring to subjects over the age of 64 are analyzed, the estimated coverage becomes 68.1% for PCV20 and 78.7% for PCV21.

The epidemiological need is conditioned not only by the age of the population but also by its vulnerability. Patients with immunodeficiencies, asplenia, HIV, or those who have undergone solid organ or hematopoietic transplants have a risk of invasive pneumococcal disease (IPD) that is 5 to 20 times higher than that of the general population [63]. Indeed, 30-day mortality in cases of pneumococcal bacteremia among immunocompromised patients can exceed 25%, as opposed to 10–15% in the general population [64]. The 2023-2025 National Immunization Plan (PNPV) therefore explicitly includes vulnerable individuals among the priority groups for vaccination, regardless of age, setting a minimum coverage target of 75% [54]. This measure addresses a clear epidemiological need to protect the groups at highest risk, in whom the expected benefit is greatest in terms of reducing hospitalizations and mortality. In summary, the persistence of serotype 3 and the emergence of new serotypes highlight the importance of ongoing epidemiological surveillance and the continuous updating of vaccination strategies. The inclusion of emerging serotypes in next-generation vaccines is a crucial step in further reducing the burden of pneumococcal disease among adults and the elderly – populations that are particularly vulnerable to this disease and its complications.

Immunological Need

Immunogenicity constitutes the second pillar underpinning efforts to achieve "better protection". The vaccine of choice must induce an antibody response that is at least non-inferior to that of the reference comparator, thereby ensuring a comparable or superior efficacy profile across the age-groups and risk categories targeted by the vaccination program.

PCVs (pneumococcal conjugate vaccines) were developed to overcome the limitations of purified capsular polysaccharides, which elicit a T-cell–independent immune response that is poorly effective in young children and incapable of generating immunological memory [65]. The addition of a protein carrier (*e.g.,* CRM197, a non-toxic mutant of diphtheria toxin) converts the polysaccharide antigen into a T-cell–dependent immunogen that is capable of stimulating helper T cells, generating memory B cells and ensuring a stronger anamnestic response. This mechanism enhances long-lasting protection and reduces nasopharyngeal carriage, leading to herd immunity [66].

The introduction of PCV13 in children, and later also in the adult/elderly population, marked a turning point. However, as cases of IPD caused by vaccine-included serotypes declined, an increase in disease caused by non-vaccine serotypes was observed.

Another phenomenon emerged during the PCV13 vaccination campaigns; protection against serotype 3 proved to be suboptimal, with immunity waning over time. Several studies have documented lower antibody titers and lesser clinical effectiveness against this serotype, which remains a leading cause of CAP and invasive pneumococcal disease (IPD) in adults [24]. These findings have highlighted two critical aspects of immunogenicity; it must be evaluated not only in quantitative terms (antibody titers), but also in qualitative terms (opsonophagocytic activity and duration of protection).

The main correlate of protection against IPD is OPA (opsonophagocytic activity), which measures the ability of antibodies to mediate phagocytosis and bacterial killing. OPA titers ≥1:8 are generally considered protective, although the exact threshold may vary by serotype [67]. Capsular IgG antibodies (measured by enzyme-linked immunosorbent assay - ELISA) are useful, but not always predictive of protection. For example, serotype 3 can induce high IgG levels with low opsonophagocytic activity, which explains the suboptimal protection observed [68].

The two most recent conjugate vaccines currently available for the adult/elderly population (PCV21 and PCV20) meet the non-inferiority criteria for shared serotypes (*vs*. PCV13) and display superiority for the additional ones — reinforcing the rationale for their adoption. It should be noted, however, that in the non-inferiority study of PCV20 vs PPSV23, PCV20 did not meet the non-inferiority criterion for serotype 8 [47].

Compliance Need

The parameter associated with adherence to the vaccination program plays a crucial role.

To achieve a significant public health benefit, it is essential to reach and maintain vaccination coverage levels in line with the targets set by the National Immunization Plan, *i.e.* 75% or higher in adults and the elderly.

With regard to pneumococcal vaccination, "compliance" goes beyond individual adherence to recommendations: it is a key element of Public Health. Indeed, it reflects the system's ability to translate epidemiological needs and the immunological potential of vaccines into real, sufficiently high coverage rates capable of generating a collective impact. Compliance is therefore not only a responsibility of individual citizens but also of health institutions, which must ensure that vaccination pathways are accessible, free of charge and actively promoted.

In this context, strategic planning must include multiple actions implemented through a multidimensional approach. Desirable measures include:

- Integrating vaccination pathways into both primary care and specialist care settings;
- Strengthening the active role of general practitioners and medical specialists;
- Launching information campaigns to raise public awareness of pneumococcal risks and the benefits of vaccination, also by enlisting the support of patient associations;
- Enhancing training programs for healthcare professionals;
- Improving digital systems for tracking vaccination coverage.

In summary, adequate professional training, proper public awareness, efficient local health service organization, and continuous monitoring of coverage rates are key means of ensuring broad and equitable protection.

These efforts will help reduce the clinical, social and economic burden of pneumococcal diseases, especially in the context of Italy's aging population.

Conclusions

Infections caused by *Streptococcus pneumoniae* constitute a significant public health challenge both globally and locally, as they are associated with a substantial burden of morbidity and mortality in the general population – particularly among young children and the elderly.

Patients over the age of 65 are especially vulnerable to pneumococcal diseases, owing to age-related changes in the immune system and a higher prevalence of chronic conditions. Therefore, they are a primary target for vaccination programs.

The emergence of serotypes that are poorly covered by current vaccines, combined with the significant incidence and severity of disease, calls for a reassessment of the adequacy of existing vaccination strategies, especially in adults. A dynamic vaccination strategy is required – one that can adapt to serotype replacement, a

phenomenon driven by the very vaccination campaigns themselves [69].

From an epidemiological perspective, it is essential that the vaccine of choice provides broad and optimal protection against the serotypes most responsible for disease in the target population, in alignment with surveillance data.

From an immunological standpoint, the vaccine chioce should induce an immune response that is at least non-inferior to the comparator, and ideally, more robust and long-lasting.

Regarding compliance, all possible strategies must be activated in order to raise public awareness of the risks of pneumococcal disease and the benefits of vaccination, so as to increase coverage rates.

The absence of even one of the three above-mentioned pillars – epidemiological need, immunological strength and compliance – reduces the overall impact of the vaccination strategy and may have consequences both on the incidence of pneumococcal diseases and on the associated economic and social burden.

A thorough analysis of epidemiological and clinical data, combined with an assessment of the economic and social impact, is crucial to guiding vaccination policies and supporting efficient decision-making in order to protect the health of the entire population. An additional factor that makes the strengthening of vaccination campaigns even more urgent is the fight against antimicrobial resistance. Indeed, a major contributor to the significant burden of pneumococcal disease is growing resistance to the commonly used antibiotic therapies – such as beta-lactams and macrolides – with resistance rates exceeding 20% in Southern Europe [70-72].

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Conflict of Interest statement

The authors declare that they have no conflicts of interest in relation to this manuscript.

Authors' contributions

The authors contributed equally to the entire drafting of the manuscript.

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Correspondence: Elvira Massaro, MD, ASL3 Healthcare System of the Liguria Region, Genoa, Italy. E-mail: elvira.massaro@edu.unige.it.

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Errata

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Non communicable diseases

Why do middle-aged adults use or avoid health services? A study of social and demographic determinants

SEYED ABBAS HOSEINALIPOUR[1], MARYAM FARHADIAN[2,3], AKRAM KARIMI-SHAHANJARINI[1,4]
[1] Department of Public Health, School of Public Health, Hamadan University of Medical Sciences, Hamadan, Iran;
[2] Department of Biostatistics, School of Public Health, University of Medical Sciences, Hamadan, Iran;
[3] Research Center for Health Sciences, Institute of Health Sciences and Technologies, Hamadan University of Medical Sciences, Hamadan, Iran; [4] Social Determinants of Health Research Center, Institute of Health Sciences and Technologies, Hamadan University of Medical Sciences, Hamadan, Iran

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SEYED ABBAS HOSEINALIPOUR[1], MARYAM FARHADIAN[2,3], AKRAM KARIMI-SHAHANJARINI[4,5]
[1] Student Research Center, Hamadan University of Medical Sciences, Hamadan, Iran;
[2] Department of Biostatistics, School of Public Health, University of Medical Sciences, Hamadan, Iran;
[3] Research Center for Health Sciences, Institute of Health Sciences and Technologies, Hamadan University of Medical Sciences, Hamadan, Iran; [4] Department of Public Health, School of Public Health, Hamadan University of Medical Sciences, Hamadan, Iran;
[5] Social Determinants of Health Research Center, Institute of Health Sciences and Technologies, Hamadan University of Medical Sciences, Hamadan, Iran


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