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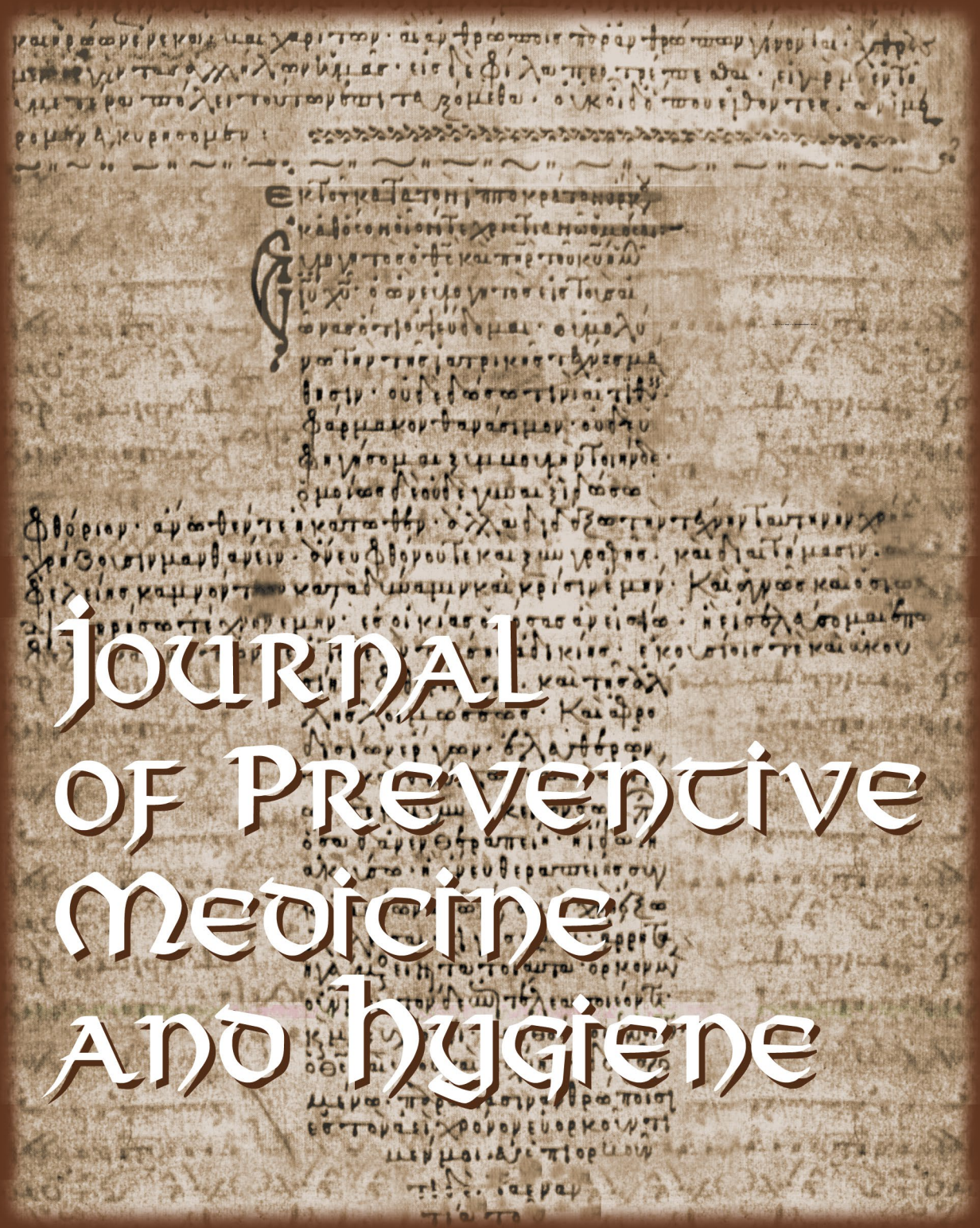

The original document of Hippocrates' oath

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CONTENTS

Short article

Paediatric activities and adherence to vaccinations during the COVID-19 epidemic period in Tuscany, Italy: a survey of paediatricians

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Keywords

Paediatric vaccination coverage • Adherence • COVID-19 pandemic • Paediatricians • Survey • Italy

Summary

Introduction. *The global COVID-19 pandemic is placing a heavy burden on health services. One result could be a general reduction in routine vaccination activities. In Tuscany (Central Italy), paediatricians (in agreement with the regional health service) administer and register paediatric vaccinations of their patients. The aim of the present study was to evaluate the impact of the COVID-19 epidemic on paediatric vaccinations administered by Tuscan paediatricians, as a proxy of adherence to vaccinations during this epidemic period.*
Methods. *Four hundred members of the Tuscany section of the Italian Federation of Paediatricians (FIMP) were invited to participate in a semi-structured online survey.*
Results. *During the COVID-19 pandemic, almost all (98.2%) of the 223 respondents reported a general decline in outpatient paediatric visits; 65.8% reported a more than 60% reduction (144 answers) in comparison with the situation before the COVID-19 pandemic. A total of 208 paediatricians (93.3%) continued to vaccinate in the period considered: 66/208 (31.7%) reported a reduction in parents' compliance with mandatory vaccination (hexavalent and MMRV vaccines), and 88/208 (42.3%) reported a reduction in compliance with non-mandatory vaccinations. Almost all paediatricians declared having taken preventive actions to counter the spread of SARS-CoV-2.*
Discussion and conclusions. *Although the majority of Tuscan paediatricians continued to vaccinate during the lock-down, some parents decided to postpone their children's scheduled vaccinations, mainly owing to fears concerning the safety of access to health services. When Italian immunization coverage data on the first months of 2020 become available, it will be possible to assess the real impact of the COVID-19 pandemic on paediatric vaccinations. It is crucial to continue vaccinating against preventable infectious diseases in order to avoid other possible epidemic outbreaks. The pandemic must not be seen as an obstacle to compliance with the vaccination schedule, but rather as an excellent opportunity to underline the importance of all recommended vaccinations.*

Introduction

Coronavirus disease (COVID-19) is an acute respiratory disease caused by a newly discovered coronavirus called SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2). On March 11, the WHO Director-General declared COVID-19 a pandemic, since over 118,000 cases had been reported globally in 114 countries and 4,291 people had died [1]. The first outbreak occurred in Wuhan (China), where several cases of pneumonia of unknown origin had alarmed the local authorities [2, 3]. Within a few months, the high communicability of SARS-CoV-2 had determined a state of emergency in numerous countries.
In Italy, after confirmation of the first two cases of infection in a couple of Chinese tourists from Wuhan (31 January 2020), the outbreak began in the northern regions, the first indigenous case being discovered in the province of Lodi, in Lombardy (21 February 2020) [4]. Initially, the epidemic mainly affected Lombardy, Veneto and Emilia Romagna, and then spread nationwide. In Tuscany, the epidemic spread more slowly than in the most seriously affected regions of Italy, and recent estimates indicate 10,121 total cases and 1,055 deaths (data updated to 3 June 2020) [5]. To curb the spread of SARS-CoV-2, an initial nationwide lock-down phase started on 11 March 2020, with the suspension of production, commercial activities and non-essential services; whenever possible, so-called "smart working" was encouraged in both the public and private sectors [6]. Given the downward epidemiological trend following the adoption of these measures, a 'phase 2' started on 4 May with the gradual re-opening of some production facilities and work activities [7].
The COVID-19 pandemic has severely affected global health services, placing an enormous burden on healthcare systems [8]. In this context, it is important not to overlook the value of some public health preventive interventions which cannot be postponed, such as vaccinations. In Italy, public health services provide vaccinations free of charge, in accordance with the 2017-2019 National Immunization Plan (NIP) [9]. In Tuscany, central Italy, paediatricians administer and register paediatric vaccinations of their patients, in agreement with the regional health service.

The aim of the present study was to evaluate the impact of the COVID-19 epidemic on paediatric vaccinations administered by paediatricians in Tuscany, as a proxy of adherence to vaccinations during this epidemic period.

Methods

Four hundred members of the Tuscany section of the Italian Federation of Paediatricians (FIMP), corresponding to almost 90% of the paediatricians affiliated to the regional health service, were invited to fill out a semi-structured online questionnaire (accessible via an embedded URL link or by scanning a QR code). Data regarding the period 11 March-4 May 2020 (first phase of Italian lockdown) were collected. The deadline for returning completed questionnaires was 31 May.

Respondents were asked to answer 14 questions plus an open-ended question. The research instrument, which was specifically designed to gather information from paediatricians, was divided into some sections: participants' characteristics, access to outpatient paediatric clinics, behaviour of paediatricians and adherence of parents to paediatric vaccinations, the last section measured the preventive actions put in place to counter the spread of SARS-CoV-2. Participants were informed that the questionnaire was anonymous and would take around 10 minutes to complete.

Results

Participant characteristics

A total of 400 paediatricians from the Tuscany-FIMP were invited to fill out the online questionnaire: 223 did so, yielding an overall response rate of 55.7%. The answers received came from all ten provinces of Tuscany: 46.2% from the Local Health Unit (LHU) of Central Tuscany (Florence, Pistoia and Prato), 24.2% from the LHU of South-East Tuscany (Arezzo, Grosseto and Siena) and 29.6% from the LHU of North-West Tuscany (Livorno, Lucca, Massa-Carrara, Pisa). The greatest number of questionnaires filled in came from Florence (31.4%), followed by Pisa (9.9%) and Siena (9.9%).

Access to outpatient paediatric clinics

Almost all the paediatricians surveyed (98.2%) reported a general decline in outpatient paediatric visits during the COVID-19 epidemic period. Figure 1 shows their perception of access to their clinics; 65.8% reported a more than 60% reduction (144 answers) in comparison with the situation before the COVID-19 pandemic.

Activities and behaviour of paediatricians and uptake of vaccinations

A total of 208 respondents (93.3%) continued to vaccinate in the period considered, while 15 (7%) answered that they had suspended vaccinations. Of the 208 who continued to vaccinate, 66 (31.7%) reported a reduction in the compliance of parents with mandatory vaccination (hexavalent and MMRV vaccines), and 88 (42.3%) reported a reduction in adherence to non-mandatory vaccinations, in comparison with the pre-epidemic period.

Most of the 66 paediatricians who had noticed a reduced uptake of mandatory vaccination reported relatively low percentages of reduction (under 30%) in comparison with the pre-epidemic period. Concerning the uptake of non-mandatory vaccinations, a more homogeneous distribution was observed among the 10 percentage ranges considered, as shown in Figure 2.

Of the 208 paediatricians who continued to vaccinate, 37 (17.8% of the sample analysed) stated that they had administrated only the first scheduled doses of the vac-

Fig. 1. Paediatricians' perception of the reduction in access to their outpatient clinics.

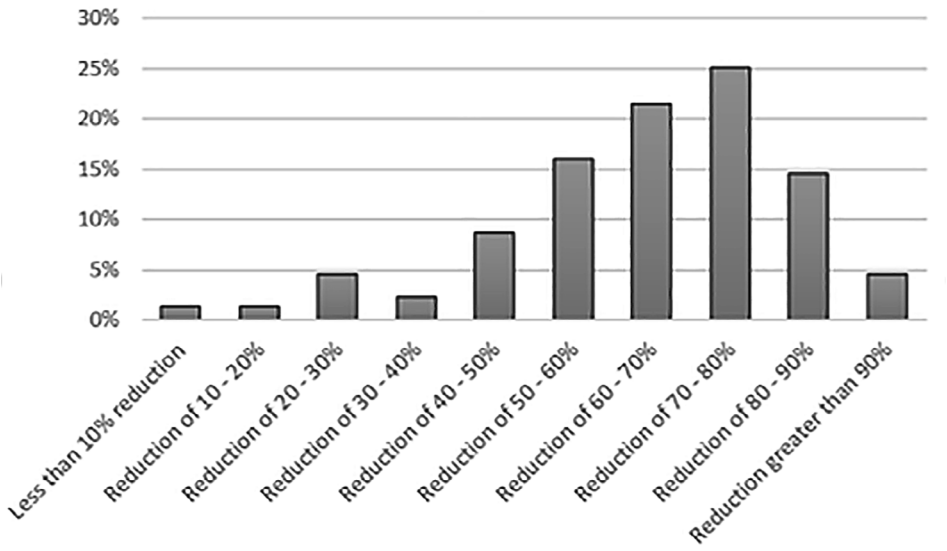
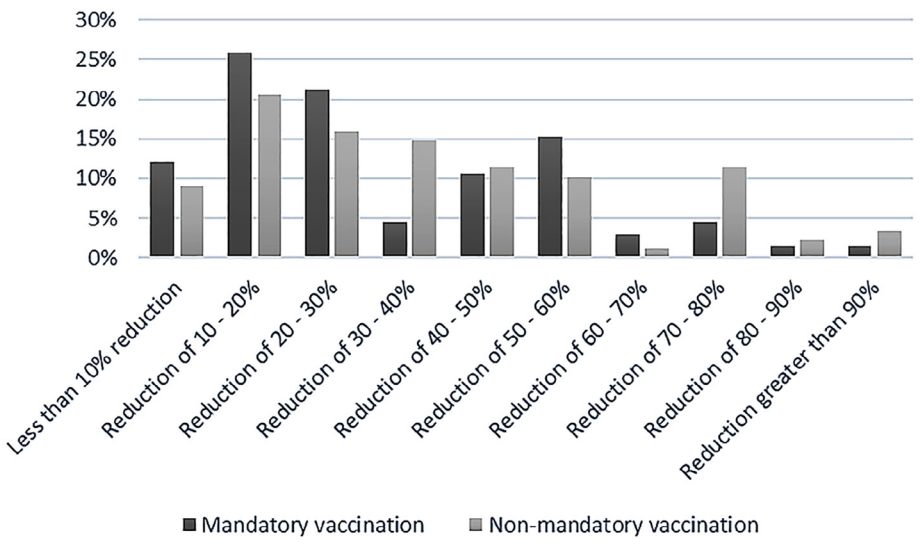


Fig. 2. Paediatricians reporting a reduction in adherence to mandatory and non-mandatory vaccinations.



cines, while the majority (82.2%) reported administering all the scheduled vaccine doses.
Moreover, 99% and 93.3% of the vaccinating paediatricians did not recommend postponing mandatory and non-mandatory vaccinations, respectively.

Preventive actions taken to counter the spread of SARS-CoV-2

To limit the spread of SARS-CoV-2, 223 paediatricians declared that they had taken several preventive actions; specifically, they reported providing hand-sanitizing gels in waiting rooms and common areas (98.2%), scheduling visits to limit crowding in waiting rooms (98.2%), carrying out environmental sanitation (92.4%), implementing physical distancing measures in waiting rooms (87.4%) and other measures, as reported in Table I.

Discussion

Updated data on vaccination coverage in all the Italian Regions during the pandemic COVID-19 are not yet available; therefore, we cannot assess the impact of the COVID-19 pandemic on the uptake of vaccination among Italian infants.
In the USA, preliminary vaccination coverage data have been analysed by Bramer et al. [10], who used Michigan Care Improvement Registry (MCIR) data in order to evaluate the status of vaccinations of multiple cohorts of children (between 1 and 24 months) and to compare the period May 2016-May 2019 and the period January-April 2020. According to their study, vaccination coverage decreased in all age-cohorts, except for birth-dose hepatitis B coverage, which is typically administered in the hospital setting. For example, in the cohort of children aged 5 months, coverage by all recommended vaccines (doses: 2 HepB, 2 Rota, 2 DTaP, 2 Hib, 2 PCV, 2 IPV) declined from approximately two thirds during 2016-2019 (66.6%, 67.4%, 67.3%, 67.9%, respectively) to less than half (49.7%) in May 2020.
In addition, the Centers for Disease Control and Prevention (CDC) published data showing that from mid-March to mid-April 2020, doctors in the Vaccines for Children program (VFC) ordered 2.5 million fewer doses of vaccines and 250,000 fewer doses of measles-containing vaccines, compared with the same period in 2019 [11]. The decline in routine paediatric vaccine ordering and in the doses administered might indicate that US children and their communities will face an increased risk of outbreaks of vaccine-preventable diseases (VPDs) in the future. With national data showing immunization rates for all ages dipping to dangerously low levels, the American Academy of Pediatrics (AAP) has launched a campaign to urge parents to schedule visits to their paediatricians for vaccinations and health check-ups.
As reported by WHO guidelines, the disruption of immunization services, even for brief periods, will result in increased numbers of susceptible individuals, raising the risks of an upsurge in outbreak-prone VPDs [12]. The reduction of vaccination coverage could cause an increase in morbidity and mortality, especially in the age-groups most at risk, such as young children or the elderly. Consequently, in the future, a greater burden could be placed on health systems already sorely afflicted by the COVID-19 pandemic.

Tab. I. Preventive actions taken to counter the spread of Sars-Cov-2 during paediatric outpatients visits.

Preventive actions	n (%)
Scheduling visits	219 (98.2)
Hand sanitizing gel	219 (98.2)
Environmental sanitation	206 (92.4)
Physical distancing measures	195 (87.4)
Limitation of the daily number of visits	135 (60.5)
Distribution of gloves and masks	85 (38.1)

Examples from previous large epidemics (e.g. diphtheria in the former Soviet Union in 1990-1996 and in Venezuela in 2017-2018) show that, when vaccination coverage falls or vaccinations are disrupted, cases of infectious diseases that have apparently disappeared can quickly re-emerge [13-14].

In order to avoid shrinkage of the vaccine offer and to limit the risk of SARS-CoV-2 transmission during vaccination activities, the WHO has drafted a detailed guideline indicating the correct hygiene rules to respect and the importance of primary courses of vaccinations (such as measles, rubella, pertussis, poliomyelitis).

As reported in our study, many families have preferred to postpone the mandatory and non-mandatory vaccination sessions scheduled for their children, which has resulted in a general decline in outpatient paediatric visits in comparison with the situation before the COVID-19 pandemic. Moreover, the few paediatricians (7%) who decided to temporarily suspend vaccination undermined vaccination uptake. The main reasons for lower adherence to vaccination lie not only in the social restrictions imposed, but also in the fear of contagion. Indeed, parents' concerns about potentially exposing their healthy children to COVID-19 during clinic visits might have greatly contributed to the observed decrease.

As shown by the above data, it is crucial to convince parents of the importance of protecting their children against serious VPDs by means of public health interventions, even during a pandemic period. One of the most useful ways to do this is to provide them with correct and effective information on the importance and safety of vaccinations. Given the current relaxation of the social distancing measures and quarantine policies adopted in Italy, children who are not protected by vaccines could be more vulnerable to VPDs, such as measles, as social contacts are resumed.

With regard to the possible risk of contagion during paediatric outpatient visits, the strategies for administering vaccinations need to be modified in order to ensure safety. Some such modifications are: reducing the number of people in waiting rooms, asking patients to stay outside the facility until they are called, scheduling visits, using personal protective equipment, marking out personal spaces, and adopting specific hygiene measures and physical distancing procedures.

It will be crucial to organize programs for the recovery of vaccinations missed during the COVID-19 pandemic as soon as possible. This will necessitate verifying the current vaccination coverage status of target groups, tracking unvaccinated children by means of active calls, and planning the supply of an adequate number of doses. Additional vaccination sessions should also be organised in order to reach susceptible children.

A possible bias of our results may lie in the selection of the sample. Indeed, in Tuscany, unlike other Italian Regions, almost all paediatricians are personally and directly involved in immunization activities and are particularly sensitive to this issue, as is revealed by the fact that the majority of them continued to vaccinate during the lock-down. However, paediatricians in Tuscany also reported a general reduction in parents' compliance with vaccinations. Although our data cannot be immediately generalized to the entire country, our survey is, to our knowledge, the only preliminary available indicator of a possible falling trend in immunization coverage during the COVID-19 epidemic period in Italy. When the Italian vaccination coverage data for the first months of 2020 become available, it will be interesting to compare our regional data with those recorded in other Regions, and to assess the real impact of the COVID-19 pandemic on the uptake of paediatric vaccinations.

Conclusions

In conclusion, despite the difficulties of the health services in managing the current COVID-19 emergency, we hope that adequate communication strategies will soon be put in place in order to reduce concerns about vaccinations and to redress the decline in vaccination coverage that occurred during the months of lock-down. In addition, new evidence is emerging on the possible positive effects of some vaccinations on the COVID-19 pandemic: cross-protective antibodies against measles could provide indirect protection against SARS-CoV-2 [15]. The pandemic must not be seen as an obstacle to compliance with the vaccination schedule, but rather as an opportunity to further stress the importance of all recommended vaccinations.

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Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

Conceptualization and design, SB, AB. and PB; methodology, SB, AB, GG, and BG; acquisition of data, GG, BG and VF; formal analysis and interpretation of data, SB, AB, GG, BG; writing - Original Draft, SB, AB, GG, BG. and BZ; writing - Review & Editing, SB, AB and PB; supervision and Project Administration, S.B. and A.B. All authors have read and agreed to the submitted version of the manuscript.

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ORIGINAL ARTICLE

Changing epidemiology of SARS-CoV in the context of COVID-19 pandemic

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Keywords

COVID-19 • SARS-CoV • Changing epidemiology • Evolution

Summary

SARS-CoV-2 is a new form of β-coronavirus that has been recently discovered and is responsible for COVID 19 pandemic. The earliest infection can be traced back to Wuhan, China. From there it has spread all over the world. Keeping in view the above perspective, an attempt is made in order to find out the epidemiological pattern of COVID 19 pandemic, if any, in different geo-climatological regions of the world in terms of case incidence and mortality. This study is also an endeavor to review and analyze the gradual changes of the genetic makeup of SARS-CoV from evolutionary and epidemiological perspectives. The raw data of COVID-19 cases and death incidences were collected from the World Health Organization (WHO) website from the time period: 1st April to 6th April, 2020. The data that are utilized here for general and Case fatality rate (CFR) based analysis. Western pacific region, European region and Americas have the greatest number of infected cases ($P < 0.001$); whereas deaths have been found to be significantly higher in Europe ($P < 0.001$). Total number of confirmed cases and deaths in south-east Asia are comparatively lower ($P < 0.001$). Case fatality rate (CFR) has also found significant for European region. SARS-CoV-2 is considered to be a strain of SARS-CoV that has a high rate of pathogenicity and transmissibility. Result indicated that the European region has been affected mostly for both cases and death incidences. The novel mutations in SARS-CoV-2 possibly increase the virus infectivity. Genetic heterogeneity of this virus within the human population might originate as the representatives of naturally selected virus quasispecies. In this context, the presence of the asymptomatic individuals could be a significant concern for SARS-CoV-2 epidemiology. Further studies are required to understand its genetic evolution and epidemiological significance.

Introduction

Coronavirus (CoV) is a positive single stranded RNA virus which causes a respiratory tract infection in human [1]. Earlier in 2002 and 2012, the emergence of severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV) and Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV) have attracted the researchers to explore the epidemic potential [1] of these viruses. A newly discovered β-coronavirus led to the occurrence of a number of pneumonia cases in Wuhan, China, in December 2019. Initially (on 12 January 2020), it was given the name, the 2019-novel coronavirus (2019-nCoV) by the World Health Organisation (WHO). Later, the disease was officially renamed as coronavirus disease 2019 (COVID-19) by WHO. The new coronavirus was termed as SARS-CoV-2 by the *Coronavirus Study Group (CSG) of the International Committee*, on 11 February 2020 [2]. The SARS-CoV-2 also develops an upper respiratory tract infection much alike its earlier ancestor SARS-CoV, however, the recent pandemic due to this novel mutated SARS-CoV-2 virus infection created a critical pandemic situation throughout the globe [3]. Until now, different researches are being performed to understand the infection severity and virus transmissibility of novel SARS-CoV-2. Keeping in view the above perspective, an attempt is made in order to find out the epidemiological pattern of COVID-19 pandemic, if any in different geo-climatological regions of the world in terms of case incidence and mortality. In addition, this study is also an endeavor to review and analyze the gradual changes of the genetic makeup of SARS-CoV from evolutionary and epidemiological perspectives.

Coronavirus (CoV) and its characteristics

Coronaviruses are non-segmented, enveloped and positive sense single-stranded RNA virus genomes. They have a size ranging from 26 to 32 kilobases. The virion consists of a nucleocapsid composed of genomic RNA and phosphorylated nucleocapsid (N) protein, covered by two different types of spike proteins: the hemagglutinin-esterase (HE) (found in some CoVs) and the spike glycoprotein trimmer (S) (found in all CoVs). The S protein in the virus envelop consists of the membrane (M) protein and the envelope (E) protein [2]. The α, β, γ and δ coronaviruses are the four genera into which the coronavirus subfamily is genotypically and serologically divided [4]. Gastroenteritis in animals and respiratory illness in humans are caused by α-coronaviruses and β-coronaviruses. The two deadly and extremely pathogenic β-coronaviruses and 2002 SARS-CoV and the 2012 MERS-CoV, cause severe respiratory diseases in humans. HCoV-NL63 and HCoV-229E, the α-coronaviruses and HCoV-OC43 and HKU1,

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the β-coronaviruses, are the four human coronaviruses that cause mild upper respiratory syndromes in immunocompetent hosts, though severe infections can be caused by few of them in infants, young children, elderly people and immune-compromised individuals [5-7]. The majority COVID-19 infection remains asymptomatic or mild. The non-SARS like CoVs are responsible for upper respiratory tract (20%) infections in adult individuals. However, these non-SARS like CoVs are often associated with severe acute respiratory illness (SARI) in elderly people and immunosuppressed individuals [8]. All human coronaviruses are considered to have an animal origin, according to the recent sequence databases. Among them, SARS-CoV, MERS-CoV, SADS, HCoV-NL63 and HCoV-229E are recognized to have an origin in bats, while HCoV-OC43 and HKU1 are considered to have an origin in rodents [5]. The zoonotic transmission of virus from natural hosts to humans may certainly be carried out by domestic animals that portray an important part as intermediate hosts. These domestic animals can also be infected by spillover of the diseases caused by bat-borne or closely related coronaviruses [5, 9, 10]. The SARS-CoV-2 is also considered to have a zoonotic origin and has a close genetic resemblance to the bat coronaviruses that suggests it has emerged as a bat-borne virus [11, 12]. Additionally, introduction to humans is also thought to be brought about by pangolin that serves as an intermediate animal reservoir [13]. Several dogs and cats (domestic cats and a tiger) have tested positive to COVID-19 virus following close contact with infected humans [14].

SARS-CoV-2 and COVID-19

On 11 February 2020, the *International Committee of Taxonomy of Viruses* (ICTV) announced that, the differences between 2019-nCoV and the virus strain from the 2003 SARS outbreak were not enough to declare them to be separate viral species; as per the rules that calculate hierarchical relationships among different coronaviruses on the basis of five conserved nucleic acid sequences. Hence, 2019-nCoV was identified as a Severe Acute Respiratory Syndrome-related Coronavirus. Taxonomically, SARS-CoV-2 was thus declared to be a strain of SARS-CoV-2 [15] which is responsible for COVID-19. The genome of the coronaviruses is seen to contain variable numbers (6-11) of open reading frames (ORFs) [11]. 16 non-structural proteins (NSP) are encoded by two-thirds of viral RNA located in the first ORF. The spike (S) glycoprotein, small envelope (E) protein, matrix (M) protein, nucleocapsid (N) protein and many accessory proteins are encoded by the viral genome that play an important role in the host innate immune response [2, 5]. Certain degree of similarity has been found in the S-glycoprotein gene and receptor-binding domain (RBD) of SARS-CoV-2 and SARS-CoV. This explains the capability of direct human transmission of SARS-CoV-2 [5]. High infectious capability of SARS-CoV-2 is attributed by novel mutations in their non-structural proteins. Two predominant evolvement types of SARS-CoV-2 include the L type (~70%) and the S type (~30%) strains. The L type strains have derived from the S type and are more aggressive and contagious, evolutionarily [16].

Aspects of SARS-CoV-2 infection

SARS-CoV uses ACE2 as its cellular receptor, which is found in the lower respiratory tracts of humans. It has also been confirmed that SARS-CoV-2 also uses the same cellular receptor, ACE2, to gain entry into the host cells. The S-glycoprotein on the surface of the coronavirus can attach to ACE2 on the surface of the human cells [2, 12]. Among all the known β-coronaviruses, SARS-CoV-2 is distinct because of the presence of two of the most important genomic factors that increase the pathogenicity and transmissibility of the virus (Fig. 1):

1. *polybasic furin cleavage site and O-linked glycans*: A polybasic cleavage site is present at the junction of S1 and S2, the two spike subunits, in SARS-CoV-2. Thus, furin and other proteases can carry out effective cleavage, which in turn plays a major role in establishing viral infectivity and host range;
2. *mutations in the receptor binding domain* (RBD) of SARS-CoV-2. The most flexible part of the coronavirus genome is the RBD in the spike protein. The RBD of SARS-CoV-2 binds with high affinity to the ACE2 of humans, ferrets, cats and other species with high receptor homology [17, 18].

Materials and methods

The raw data of COVID-19 cases and death incidences were collected from the World Health Organization (WHO) website [19]. Data that are utilized here for analysis were taken from the time period: 1st April to 6th April, 2020. These were initially arranged in groups according to different geo-climatic regions. Then the case fatality rate (CFR) is calculated by the following way:

$$\text{Number of death incidence/ total number of case incidence} * 100\%$$

Statistical differences between standard error of the means (SEM) of the studied groups were assessed using one-way analysis of variance (ANOVA) followed by suitable post-hoc test (i.e. Bonferroni test). Level of statistical significance is expressed through the P-value: $P < 0.001$, $P < 0.01$ and $P < 0.05$.

Results

It can be seen from Figure 2, that Western Pacific region, European region and Americas have the greatest number of infected cases ($P < 0.001$); whereas deaths have been found to be significantly higher in Europe ($P < 0.001$). On the other hand, the total number of confirmed cases and deaths in South-Eastern Asia are comparatively

Fig. 1. Major structural characters of SARS-CoV-2 [17].

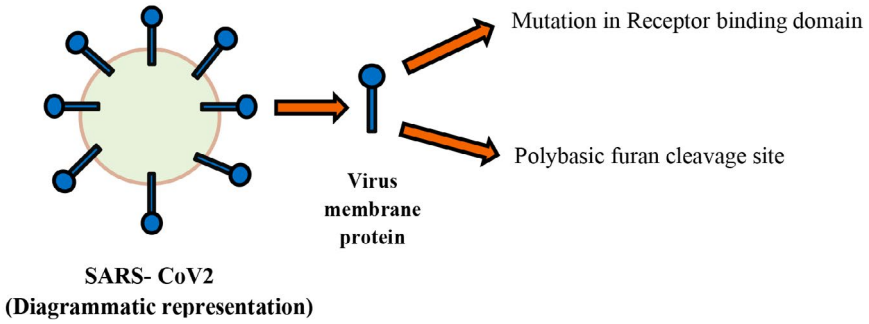
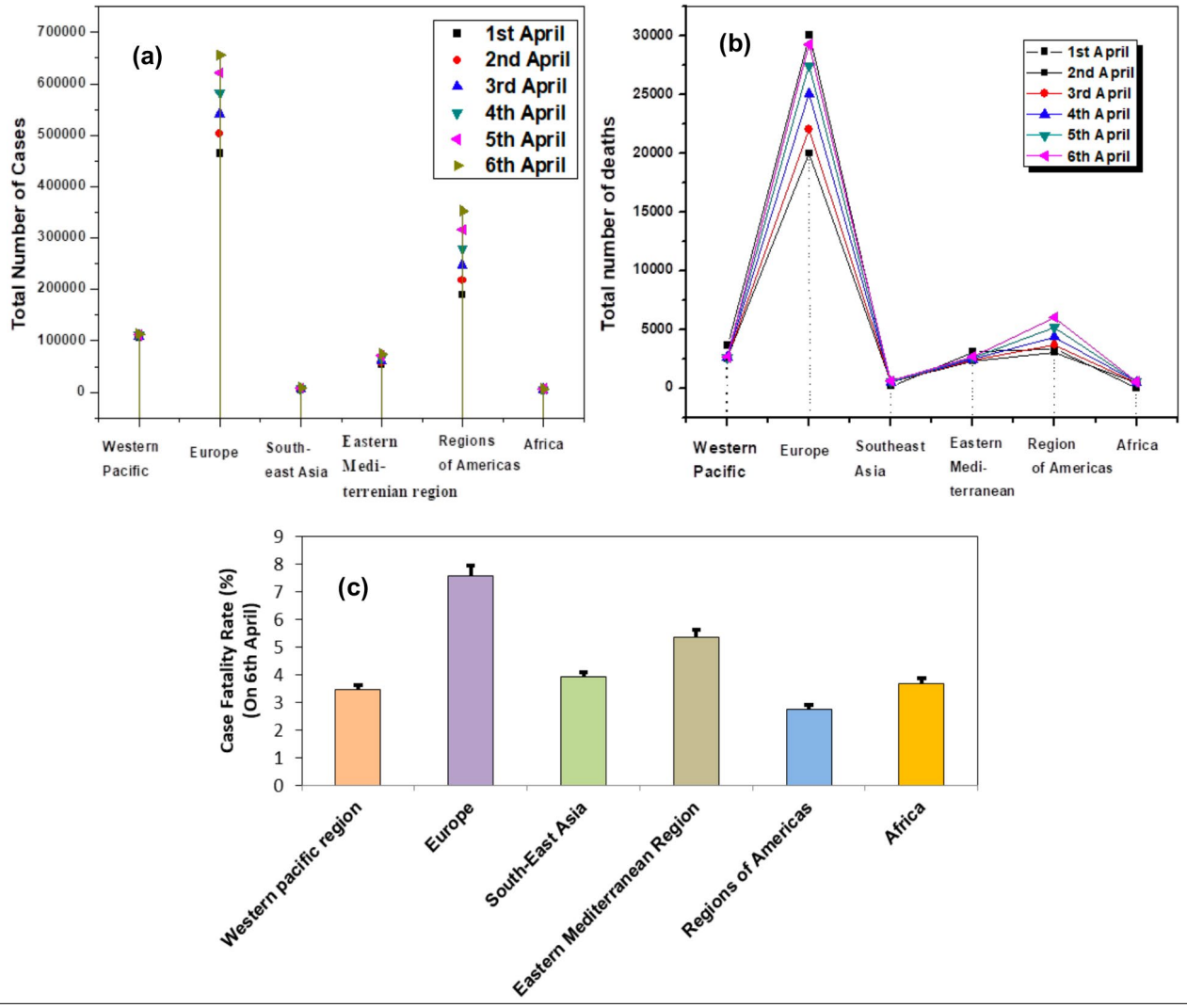


Fig. 2. Effect of COVID-19 on human population. A) total number of confirmed COVID 19 cases; B) total number of deaths in different regions within the globe from 1st to 6th April, 2020; C) Case Fatality Rate (%) of COVID-19 on 6th April, 2020. Bars indicate percentage of statistical errors of the CFR data [19].



lower than that of Europe and America ($P < 0.001$) [19] (Fig. 2). Case fatality rate (CFR) was also found to be significant for European region. Hence, it has been clearly seen that the European region have been affected mostly ($P < 0.001$) with respect to the number of cases and deaths. This disease severity might be linked to the genetic uniqueness of the mutated SARS-CoV-2.

Discussion

Epidemiological study from the result section indicates COVID-19 cases and deaths are significant in both European and American region. This global pandemic situation due to COVID-19 is caused by SARS-CoV-2, which is a new form of β-coronavirus that has

Tab. I. COVID-19 cases comparison between different geographical regions (from 1st to 6th April 2020) [19].

Geographical regions	COVID-19 cases	Affected age groups
Western Pacific and Europe	Significant in Europe (P < 0.001)	50-80 years
Western Pacific and Southeast Asia	Significant in Western Pacific (P < 0.01)	
Western Pacific and Regions of Americas	Significant in region of Americas (P < 0.001)	
Western Pacific and Africa	Significant in Western Pacific (P < 0.001)	
Europe and South East Asia, Region of Americas, Eastern Mediterranean, Africa	Significant in Europe (P < 0.001)	
Region of Americas and Southeast Asia, Africa, Eastern Mediterranean	Significant in region of Americas (P < 0.001)	

Tab. II. Comparison of death incidences due to COVID-19 between different geographical regions (from 1st to 6th April 2020) [19].

Geographical regions	Deaths due to COVID-19	Mostly affected age group
Europe and Western Pacific, South East Asia, Region of Americas, Eastern Mediterranean, Africa	Significant in Europe (P < 0.001)	Over 60 years
South East Asia and region of Americas	Significant in region of Americas (P < 0.05)	
Region of Americas and Africa	Significant in region of Americas (P < 0.05)	

been recently discovered. SARS-CoV-2 is considered to be a strain of SARS-CoV that has a high rate of pathogenicity and transmissibility. European countries have been affected severely (cases and deaths) by the virus than the other regions (Tabs. I, II). The highest death rate has been found significant between 50-80 years of age [19] (Tab. II). The mutation in the receptor binding domain and the polybasic furin cleavage site on the spike protein might be the major contributor of the significant infectivity and transmissibility to the virus. However, research indicated that different transition type of point mutation causes the virus heterogeneity in different geographical regions [20]. These ultimately affect the virus infectivity. Interestingly, the individuals over 60 years are developing severe pneumonia [21]. This might be due to the genetic structure of the virus which affects the low immunity of elderly individuals. However, different immune-pathological factors can also play a role in this. The exact process of affecting the immune system by SARS-CoV-2 is still unclear, however it can be said that virus like SARS-CoV after entering into human body is recognized by different receptors (like Toll Like Receptor [TLR], Pattern Recognition Receptor [PRR]) and induces response like expression of inflammatory factors, synthesis of type I interferon. In this context, it is relevant to mention that SARS-CoV has the ability to bypass this strong immunological barrier through the activity of its N protein. This supports the high infectivity of the virus [21].

The significant cases and deaths found throughout the different geo-climatic regions (i.e. Western Pacific, Europe, America, Eastern Mediterranean, South East Asia) due to SARS-CoV-2 is potentially caused by mutational changes in the virus genome. The novel mutations in SARS-CoV-2 possibly increase the virus infectivity through the introduction of unique mutations in their RNA genome. It has been found that there are ninetythree mutations are present in the entire genome of SARS-CoV-2. Among them, 42 missense mutations are found within the non-structural and structural protein of the virus. In addition, 29 and 8 missense mutations were located in the ORF1ab polyprotein region and spike protein [22]. However, the mutation in the receptor binding domain and the polybasic furin cleavage site on the spike protein might be the major contributor of the significant infectivity and transmissibility to the virus.

The significant cases of COVID-19 throughout different climatic regions possibly indicate the SARS-CoV-2 RNA genome fitness. In this context, virus quasispecies might play a significant role in virus heterogeneity. It has been stated that, RNA virus quasispecies could successfully bypass host immune system and its response; which might further increase the genetic diversity of the virus [23, 24]. This viral RNAs of the quasispecies from naturally "fit" RNA virus population will increase the potential risk of infection and disease severity [23], which could ultimately affect the known face and nature of SARS-CoV epidemiology.

The high CFR and case incidences in European and American regions indicate the disease severity of COVID-19. This disease severity could also be attributed to antibody-dependent enhancement phenomenon (ADE). ADE is caused by non-neutralizing antiviral proteins that facilitate virus entry into the host cells, causing enhanced infectivity in the cells [25]. In case of ADE, a high-affinity memory B cell, specific for a particular virus (For eg, Virus A), is preferentially activated by a new serotype of the virus (For eg, Virus A1), to produce antibodies that bind ineffectively to this new serotype. The presence of these ineffective antibodies inhibits activation of naive B cells that could produce more effective antibodies against the new serotype. This causes a reduced immune response against the new serotype and increases the potential for serious infection. This condition has already been reported in case of other RNA viruses like Dengue virus. Four antigenically different serotypes of dengue virus (1-4) exist. Infection with one serotype leads to the production of neutralizing homotypic IgG antibodies that provide lifelong immunity against that particular serotype. The phenomenon of ADE is seen when a different serotype of the dengue virus infects a person within months or

years of the first infection by a serotype different from the currently infecting one. In such cases, the clinical manifestations of the secondary infection are much more severe than the primary infection [26]. Study indicated that coronavirus like HCoV NL63 has been circulating in human population for centuries and this virus and SARS-CoV-2 are possible serotypes which are using similar mechanism for the cell entry [4, 27], thus this ADE phenomenon might play an important role in increasing the SARS-CoV-2 infectivity and disease severity leading to COVID-19 pandemic.

In the context of disease severity and epidemiological complexity, the asymptomatic cases have the notable importance. Recent research indicated that 1-2% of the cases in the Chinese population during COVID-19 were asymptomatic [28]. It has been documented that, as of February 11, 2020, there were 72, 314 cases probably involves the asymptomatic individuals [29]. These asymptomatic cases are associated with mild COVID-19 symptoms. The development of a significant viral load within the asymptomatic human individual could further facilitate the virus transmission and thereby complicate the disease situation. Thus, in depth study is required to understand the behavior and role of asymptomatic cases in COVID-19 pandemic.

On the other hand, the higher COVID-19 death incidences were often associated with the complex response of human immune system. It has been found that patients with COVID-19 are often associated with cytokine storm syndrome. This is a systemic inflammatory response of the innate immune system in response to a bacterial/viral infection which can lead to multi organ failure [21, 30]. Research indicated that one of the reasons of the significant mortality in COVID-19 is hyper-inflammation and lung injury which might be caused from the "cytokine storm" effect [30]. This observation can be correlated with the fact that, COVID-19 causes notable mortality to elder groups throughout the world as elder people are much more prone to respiratory inflammatory problems which could ultimately lead to lung injury. The high case incidence of COVID-19 in western part of world (i.e. Europe and America) compared to the South East Asia and Western Pacific indicates that the temperature might play a significant role in CoV infection. Research demonstrated that SARS-CoV2 is notably stable in low temperature like 4ºC [31]. This observation can be correlated with the prevalence of COVID-19 cases and deaths in the temperate regions of Europe. However, the tropical regions like south-east Asia have also shown notable COVID-19 cases, which left the further possibility of research in this direction.

Conclusions

COVID-19 has become a pandemic, which leads to the death of large individuals of the entire population of Earth. SARS-CoV-2 is a novel virus which harbors significant genetic mutations that are completely new to the innate immune system of the human population. Thus, this virus was capable of affecting a large section of the human populations. Western pacific region, European region and Americas have the greatest number of infected cases. European region has been affected mostly for both cases and death incidences. SARS-CoV-2 is the highly contagious representative of coronavirus that contains mutated genomic content. This mutation might play a key role in the directional selection of this group of viruses in their evolution. The recent researches of virus heterogeneity across the continents probably indicate the probable existence and role of viral quasispecies, shaping and facilitating the natural selection of the coronavirus and thereby facilitate further emergence as a novel mutated virus which can adapt to the different eco-climatic regions. This can be supported by recent research where different subtypes of the virus have been found responsible for the infection. The presence of the asymptomatic individuals could further be a significant concern for SARS-CoV-2 epidemiology. As the asymptomatic person will act as a carrier for the virus, determination and isolation of the symptomatic patients will not be helpful to manage this present epidemic. Thus, sustained testing for the virus infection is recommended largely by the scientific community. On the other hand, asymptomatic carriers could play a notable role as a "mixing pot" for the virus subtypes and thus might develop different viral strain within the human body. RNA virus infections involve an "amplification host" which amplifies the virus. These asymptomatic SARS-CoV carriers could possibly act as both, "amplifying host" and "mixing pot" and may create a more complex epidemiological situation. However, more studies are required in this direction to prove this hypothesis. Undoubtedly, SARS-CoV-2 is a virus with altered genetic makeup and this introduces a selection pressure to the human immune system. Hence, over a period of time, herd immunity can become an important phenomenon to reduce the severity of the virus. However, this will be a time-dependent phenomenon. On the other hand, the continuous genetic mapping is required which will elaborate the understanding of the virus "mutation spectrum" that will further facilitate the development of a vaccine. Further studies with deep genomic sequencing and identification of mutations are required to understand the evolving faces of SARS-CoV and its epidemiological significance.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

Conceptualization: PB and SB; methodology: PB; data analysis, interpretation and representation: PB; preparation of initial draft of manuscript: PB; editing: PB, SB, SP; Supervision: PB.

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ORIGINAL ARTICLE

Safe Villages during the 1918-1919 influenza pandemic in Spain and Portugal

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Keywords

1918 influenza pandemic • Spanish flu • Prevention of infectious diseases • Safe Village • Covid-19

Summary

The 1918-1919 influenza pandemic had a significantly different impact on mortality rates in Spanish and Portuguese provinces and cities. In this study, several small villages have been identified which were not affected at all by the Spanish influenza pandemic. These all shared a number of features in common: their villages were very small, comprising only a few hundred inhabitants; they were located in mountainous regions, with very poor transport infrastructure; and they were self-sufficient and capable of fulfilling their basic alimentary needs. Their inhabitants were conscious of the problem and acted together, effectively isolating themselves from surrounding villages. Since these villagers managed to avoid direct contact with ill people from other municipalities, the flu was not transmitted and the pandemic did not arise in their villages.

In this paper, it is proposed that the human habitability spaces that meet these characteristics, I call them "Safe Villages" or "Shelter Village". Knowledge of the circumstances in which the 1918-1919 flu pandemic developed and of the means employed to resist it can help us to take relevant measures when faced with future pandemics.

Introduction

The Iberian Peninsula, composed by Spain, Portugal, Andorra and Gibraltar, is the most occidental of the southern European peninsulas. Its strategic location between Europe and Africa and between the Atlantic Ocean to the West and the Mediterranean Sea to its East converted it, during the First World War, into one of the epicenters of the 1918-1919 influenza pandemic. The so-called "Spanish Flu", which is considered by Taubenberger and Morens, to be "the mother of all pandemics" [1], has been the object of a plethora of studies in recent years [2].

Its centenary has also been important for the emergence of interesting reflections about the pandemic, such as the works of Martini, Gazzaniaga, Bragazzi and Barberis Barberis [3], and also Taubenberger, Kash and Morens Morens [4]. According to the estimates of various authors, such as Patterson and Pyle [5], Johnson and Mueller [6] and Phillips and Killingray [7], this pandemic caused between 40 and 50 million deaths worldwide. Associated with the First World War, this pandemic was much more mortal than the War itself which according to Morrow [8], produced 10 million victims. Of all the soldiers who died during the War, it is estimated that around 13 per cent died due to a variety of diseases and not due to war wounds.

During the spring of 1918, a widespread, but low-mortality flu epidemic appeared in the Northern hemisphere. In Western Europe, which had been enduring the Great War, this epidemic was particularly virulent in Madrid (Spain), a city which had around 600,000 inhabitants, half of which came down with the flu [9]. This very serious episode which took place during the months of May and June, prompted international Media to call the event the "Spanish influenza" [10], starting with The Times newspaper on June 2, 1918. During the development of the pandemic, the differences in excess mortality between some Spanish provinces and others were very evident, as has been demonstrated by Chowell et al. [11]. Together with studies dealing with cultural and social factors [12], there are other partial studies about the capital [13], provinces [14] or recapitulations [15]. Good research about Portugal [16] and Andorra [17] has also been published. In continental Europe, differences in mortality rates among countries in the north and south have been quantified by Ansart et al. [18], who estimated that the mortality rate for the whole continent was 11 per 1,000 people. In the Mediterranean countries, the gross mortality rate varied from 10.6 per 1,000 inhabitants reported by Tognotti [19] for Italy, to 12 per 1,000 as reported by Echeverri [20] for Spain.

Studies which dealt with medieval epidemics, principally with the the Black Death, such as those by Naphy and Spicer [21] or that of Benedictow [22], insist on the complete absence, in those eras, of effective preventative measures to stop the expansion of the epidemics and to treat patients effectively. The web page of the London Science Museum, when referring to "The Black Death and early public health measures" [23], states the well-known Latin saying "*cito, longe, tarde*" or "*cito, longe fugeas et tarde redeas*" ("Leave quickly, go far away and

come back slowly"), as the only preventative measure in the face of these pathologies. Historians consider that these epidemics of past centuries presented common denominators, such as their gradual expansion, and their extension to all the cities and villages, even to the smallest ones; that the population density was not a conditioning factor in their development; and that the presence of health infrastructures was a *sine qua non* condition to halt their expansion.

However, as I will show here, these characteristics were not all present in the case of the Spanish flu pandemic. In fact, I have identified some villages which, despite being located within the focus of epidemic diffusion, did not present evidence of the presence of the pandemic. In this study, I present the hypothesis that there existed the human habitability spaces which were "resistant" to flu pandemic infection during the 1918-1919 period. I refer to these localities, which shared a number of features in common, as "Safe Villages" or "Shelter Villages".

This is a concept which is different to that of the maritime quarantines on the South Pacific islands [24], or in general, in small, insular nations [25]. Some researchers, such as Shanks, Brundage, Hussell, Wilson and Kippen have studied the effect of the 1918-1921 flu pandemic on populations in Pacific islands. These studies [26] provide an accurate analysis and an extensive bibliography about the subject [27]. Some Atlantic islands such as the Canary Islands [11] or Puerto Rico [27] could also be considered to be "Safe Islands" on the basis of similarities which they present with the villages studied in the present work.

Methods

The method employed here is based on field work, i.e. the direct identification of all those who died for any reason, and in particular, due to flu and respiratory system diseases, in many of the villages of the provinces of Biscay, Gipuzkoa and Navarre, located in the north of the Iberian Peninsula, bordering with France. Mortality data were obtained from church and civil archives, having identified the date, age, sex and cause of death of inhabitants around 1918. I also used other sources, such as articles, books and published studies that served to complete the information.

Results

Within the Iberian Peninsula, I identified four small villages which were unaffected by the Spanish flu pandemic and in which there was no increase in mortality during 1918-1919. One of these is located to the north of Portugal, as reported in a doctoral thesis which was defended in 1921. The other three are located in villages in the Autonomous Community of the Basque Country and in the Autonomous Community of Navarre, situated in the border region between Spain and France [28].

Amieiro

The Alijó municipality, situated in the Vila Real district in the north of Portugal, has an extension of 297 km^2 and in 1900 had a population of 19,914 inhabitants. Nowadays, it has a population of 14,300 inhabitants. It is divided into 19 small population nuclei *(freguerías)* dispersed over a wide area. Very near to the Tua river, which separates it from the Branganza district, I can find the small village of Amieiro, made up of around 40 houses grouped together thus forming an isolated village nucleus and isolated/removed from the principal transportation routes.

When the Spanish flu began to affect the neighboring municipality of San Mamede de Ribatua and eventually arrived at Alijó, "the inhabitants of this small village got together and decided to isolate themselves, and not permit the slightest contact with people from other localities. To this end, they set up lookouts on the outskirts of the village which were manned day and night, and forbade the entrance or exit of anyone. In the evenings, they lit bonfires on the roads and in big houses using pine and eucalyptus branches, and kept them going during the night, and thus managed to scare off '*a malina*' ('the bad'), so that it did not enter the village" [29].

In Amieiro, there was not a single case of flu in 1918 and 1919, and no one died due to this disease. In the previous 1889-1890 flu pandemic, the same strict isolation measures were also taken to avoid any contact with neighbors from other villages. In a similar manner, they also managed to avoid deaths or sicknesses due to the Russian flu pandemic.

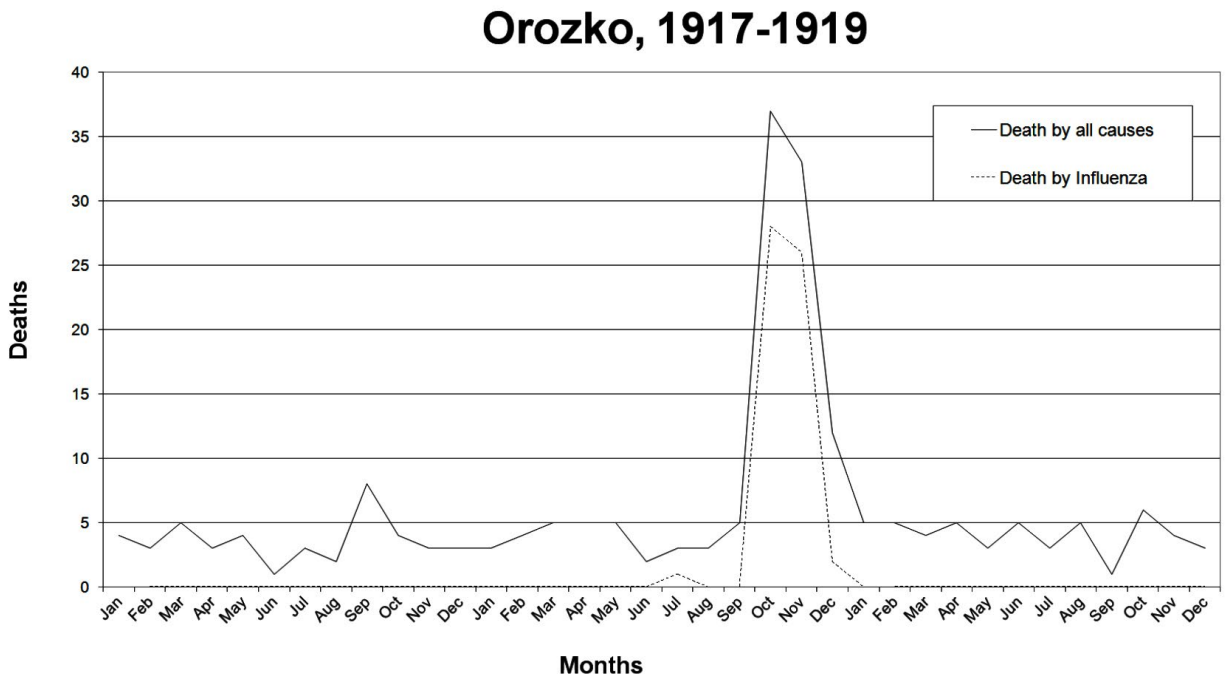
Urigoiti (Orozko, Biscay)

Orozko is a large municipality, with around 102 km^2, located in the mountainside of Gorbea, the highest mountain of the Autonomous Community of the Basque Country. It had a population of 3,109 inhabitants in the year 1900, 2,840 in 1920 and today this is around 2,800. The most important economic activities are farming and those related to forestry. The population is distributed in the principal nucleus, Zubiaur, and around various rural neighborhoods, with the most distant one being Urigoiti. This latter village is made up of 20 houses located around the parish church of San Lorenzo. The neighborhood is isolated, and is situated at the end of a road in the Gorbea mountainside.

In 1917, the mortality rate for all causes of death in the whole municipality of Orozko was 15.1 per 1,000 inhabitants. In 1918, this rose to 41.2. This substantial rise in mortality which occurred particularly in the months of October and November was due to the Spanish flu pandemic. In 1919, this mortality rate dropped to 17.2. I can deduct from these data that excess mortality due to the Spanish flu pandemic in this municipality was 26.1 per 1,000 inhabitants. The distribution of the number of deaths per month is shown in Figure 1.

Whereas in this municipality, between the months of October and November 1918, 2.5 per cent of

Fig. 1. Number of deaths due to all causes and to flu between January 1917 and December 1919 in the Orozko municipality (Bizkaia, Spain).



inhabitants died due to the Spanish flu, in the Urigoiti neighborhood, there were no deaths! It is even remembered nowadays that it was believed that there were no deaths in this neighborhood due to its isolation and because its inhabitants, to prevent the disease, drank nettle (*Urtica dioica L.*) infusion [30]. In the Basque folkmedicine, massages with nettles *(plegazinoak, ortigaciones)* have been widely used for the treatment of influenza [31].

Zerain (Gipuzkoa)

Zerain is a small village in the interior of the Gipuzkoa province dedicated to Shepherd's work and agriculture. In 1900, it had a population of 552 people and by 2016 this number had dropped to 255.

According to its Parish Archive, in 1918 10 people died, the same number dying again in 1919. In 1920, the number of deaths dropped to 6. Taking into account that the population was stable during the early decades of the 20th century, the 1918 mortality rate was 18.1 per 1,000, identical to that of 1919.

Thus, in Zerain, there was no increase in mortality with respect to other years. In fact, flu was not even mentioned as the cause of death in the autumn of 1918, nor in the beginning of the following year, as occurred in other areas of the Basque Country, where on average, 12.1 people per 1,000 inhabitants died [32], the majority of whom died in October. In particular, the 10 deaths which occurred in 1918 included: a 20 year-old man who died in February of *"grippe intestinal"* (intestinal flu, a common diagnosis in those times, not always associated with the pandemic influenza); two elderly people in February due to heart failure; and one person each month during March, April, May, June, August, October and November, the majority of whom died due to pneumonia. In 1919, 10 people died: in January, a newborn due to a developmental defect and an elderly person due to senility; in March, two elderly people due to senility and heart failure; and between May and December, three due to cancer, one to tuberculosis, one to gastroenteritis, and the last one due to uremia.

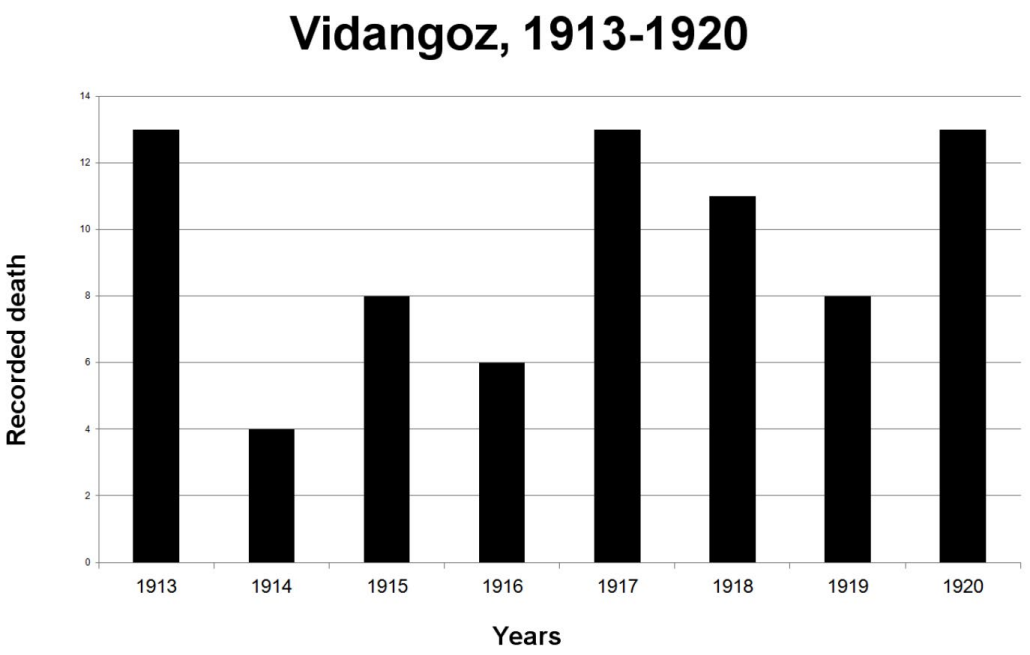
The former Director of the Bilbao Ethnographic and Historic Museum, Karmele Goñi, who was born in this village, claims that in the Autumn of 1918, during the development of the Spanish flu epidemic, the village kept itself isolated, without any communications with other nearby villages. To avoid the spread of the epidemic which was devastating other villages and to prevent it affecting them, the villagers held a religious procession which marched with the image of a saint at its head to the limit of the municipality with the neighboring village of Mutiloa. There, the religious processions of both towns met, but they did not join or mix among themselves; the neighbors of both villages maintained safe distance.

Vidángoz-Bidankoze (Navarre)

The Vidángoz-Bidankoze locality is situated in the Roncal Valley (Navarre) which is located on the southern face of the Pyrenees mountain range, (separating France and Spain). Its population at the beginning of the 20th century was 370 inhabitants (nowadays it is 95). From 1913 to 1920, an average of 9 to 10 people died each year. This means that the mortality rate due to all causes was 24.3 per 1,000 (Fig. 2).

In 1918, 11 people (6 adults and 5 children) died in this village. In January-February, an elderly person and a very young child died; in May, two newborns died, as

Fig. 2. Number of deaths due to all causes in Vidángoz-Bidankoze (Navarre, Spain) between 1913 and 1920.



well as one woman due to a postpartum infection; in July, there was a measles epidemic which killed a child and a 42 year-old adult; an elderly person also died of natural causes at 87 years of age. In October and November, two other elderly people died due to diarrhea and old age, respectively. And on 5th December, a 2 year-old girl was diagnosed with bronchopneumonia flu. The death of 8 people in 1919 was due to causes unrelated to the flu.

A news item appearing in the *Diario de Navarra* newspaper on 7th December 1918 stated that, although the Spanish flu pandemic appeared to have passed over the village of Vidángoz-Bidankoze, without affecting anyone, there were now 12 cases diagnosed with mild flu. However, only one person died, i.e. the above-mentioned girl on 5th December. She was the single victim of the pandemic in this village in the north of Navarre. Paradoxically, whereas cumulative excess mortality, presented as rates per 1,000, for the whole of Navarre, rose to 11.6 (Chowell et al.), in some villages this figure was triple, in clear contrast to that which occurred in Vidángoz-Bidankoze.

Conclusions

Here, I propose the name "Safe Village" or "Shelter Village" for these villages and others which present the same features. All of these managed to avoid the 1918-1919 flu pandemic and share the following characteristics in common:

- firstly, their geographical location is noteworthy; they are far from large communication networks, with few and difficult accesses;
- secondly, they are located in mountainous regions, either in mountainsides or in the high regions of mountain chains, and are far from large cities and middle-sized villages;
- the third feature is the large extension of these municipalities, which comprise hundreds of square kilometers in some cases;
- the population density of these small villages is very low. The villages are very small, with only a few hundred inhabitants who live in houses which are low-storey, extensive and with much space around them. Thus, in all cases, they form low density population nuclei;
- they did not have health infrastructures, such as sewerage and water treatment plants. Neither did they have regulated, controlled drinking water sources, but rather they drank from traditional fountains and springs;
- they were economically self-sufficient and produced the basic foods necessary to maintain nutritional autonomy for long periods of time;
- sociologically, they were villages whose inhabitants faced up to the problem, acted together and implemented measures to resolve the problem. This social and political consensus allowed the civil authorities (in the case of Amieiro) and the religious authorities (in the case of Zerain) to align themselves with this objective and they were able to agree on measures which achieved the absolute isolation of the neighbors of these villages with respect to the inhabitants of neighboring villages;
- since there was no contact with sick people from other villages, there was no transmission of the virus. Neither was there, at least in the cases examined here, transmission by air of the virus.

One hundred years later, in Europe at the beginning of the 21st century, it would be unrealistic to try to imitate the conditions of isolation achieved by the neighbors of these villages. However, it would be judicious to keep in mind

these experiences for when, in a not too distant future and faced with an event of epidemic emergency, it would be necessary to reproduce the model of these "Save Villages" which allowed their inhabitants to protect themselves from the terrible flu pandemic of 1918-1919, and, as I have seen in one case, of that of 1889-1890.

Thus, if I want to have a precise and accurate knowledge of what happened during the Spanish flu pandemic, it is essential to identify the facts, study them in detail, name them and adequately conceptualize them. The multidisciplinary approach provides richer and more varied research results. Other disciplines such as sociology, anthropology and ethnography can also contribute to a better understanding of past pandemics and to preparing ourselves better for those which are still to come.

In addition, the pandemics of the future, when they occur, give us surprises in their evolution and in the measures taken to contain them. In January 2020 the epidemic of covid-19, caused by the coronavirus SARS-CoV-2, appeared in the Chinese city of Wuhan, forced the authorities of this country to decree the quarantine of its entire population (11 millions of inhabitants [33]). In mid-February, the population in quarantine in cities and provinces of central China reached 60 millions of inhabitants. Quarantines were also applied in northern Italy [34], Iran, on cruise ships [35], hotels and other parts and places of the world. I have never seen in the history of medicine such high numbers of people in quarantine.

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Conflict of interest statement

The author declares no conflict of interest.

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Review

Tuberculosis: a timeless challenge for medicine

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Keywords

Tuberculosis • History • Infectious disease • *Mycobacterium tuberculosis* • Antibiotic Era

Summary

This overview shows how tuberculosis has represented and still represents a continuous challenge for Medicine. Starting from the dawn of medicine, when tuberculosis was called "phthisis" by Hippocrates, passing through the discovery of the tubercles and the creation of the word "tuberculosis", following the application of the anatomo-clinical method, until the discovery of a microscopic enemy: Mycobacterium tuberculosis. The progressive discovery of the pathological basis of tuberculosis has allowed to devise important therapeutic strategies in Pre-Antibiotic and Post-Antibiotic Era. In particular, "antibiotic therapy" had to be the end of the challenge between man and tuberculosis. However it was only an illusion. Despite progress in care and prevention, tuberculosis remains one of the world's leading causes of ill-health and the first cause of death from infectious disease. Nowadays, the drug resistance, individuals with immune deficiencies, the ageing and globalization are just some of the causes responsible for the increasing of the challenge between man and tuberculosis.

Tuberculosis in the history of infectious diseases

History of Medicine is not a discipline destined to culturally enrich only those who work in the health sector. All historians know very well how some medical events have influenced the course of history. In particular, infectious diseases, being interconnected with geo-political, social, economic and war-related issues, have an important historical significance [1]. Some of the classic examples are the plague epidemics that occurred in the 6th, 14th and 17th centuries [2], syphilis considered as the disease imported from the new world [3], the pandemic Spanish influence of 1918 [4] and now the pandemic SARS-CoV-2 (COVID-19).

The diseases listed above have dramatically marked the history of humanity, with events that can be clearly defined with a start date and an end date, except for the COVID-19 which is still ongoing now. Other pathologies, such as malaria [5, 6] and schistosomiasis [7], have taken root as endemic diseases and they have been timeless enemies for some peoples.

Tuberculosis (TB) is an ancient scourge. It has plagued humankind throughout known history and human prehistory. It has surged in great epidemics and then regressed, thus acting like other infectious diseases, but with a time scale that challenges accepted explanations for epidemic cycles. *Mycobacterium tuberculosis* may have killed more persons than any other microbial pathogen [8].

The coexistence of man and tuberculosis: historical and social aspects

Modern strains of *Mycobacterium tuberculosis* appear to have originated from a common ancestor about 15,000-20,000 years ago [9, 10].

The first tuberculosis infections are demonstrated in the most ancient civilizations. Tuberculosis in Egypt has been documented more than 5,000 years ago.

Skeletal abnormalities associated with tuberculosis, including characteristic Pott's deformities, have been found in Egyptian mummies (confirmed by DNA analysis in mummified tissues) and are clearly depicted in early Egyptian art.

Tuberculosis is clearly noted in the Biblical books of Deuteronomy and Leviticus, however, using the ancient Hebrew word "schachepheth" [8].

In the collective imagination, people living in a condition of socio-economic decay become ill with tuberculosis; this association could have been decisive to create the "Pulcinella" character, a stereotype of the poor peasant.

"Pulcinella", mainly known in the English-speaking world as "Mr Punch", is a character from the Italian *Commedia dell'Arte,* whose origins can be traced back to protagonists of Roman Atellan comedy (e.g. Maccus or Bucco), whose grotesque appearances closely resemble the 16th century Neapolitan mask.

This character, as we know him today, originated in Naples (city sadly known for tuberculosis epidemics), most likely representing a poor and hungry, ready to steal food even at the cost of cheating and lying [11, 12].

This character may well be analyzed in an ethnological and anthropological fashion, with his distinctive physical appearance being exaggeratedly hook-nosed, back-humped, and with a paunch/ lumbar lordosis. A similar spinal deformation may be caused by tuberculosis in its form known as Pott's disease, the most widespread tubercular osteo-articular presentation, capable of affecting every segment of the rachis, albeit more commonly the lowermost section of the thoracic column and the lumbar tract [12].

Traditional puppets with social and somatic characteristics similar to those of "Pulcinella", a poor peasant with a hump, are present in the folklore of different European states.

Ancient Medicine: when tuberculosis was called phthisis

In the history of medicine, tuberculosis is well suited to study the epistemological path of medical thought, from its origins to the present day.
Tuberculosis was well known by Hippocrates, who is universally recognized as the father of medicine. He clearly recognized tuberculosis, where it was called phthisis, and understood its clinical presentation. "Phthisis makes its attacks chiefly between the age of eighteen and thirty-five," he wrote in his aphorisms, clearly recognizing the predilection of young adults for active tuberculosis [13].
"Consumption was the most considerable of the diseases which then prevailed, and the only one which proved fatal to many persons," he wrote in Book I, *Of the Epidemics* [14].
Another Greek physician who has a pivotal role in the history of medicine is Clarissimus Galen. He became physician to Roman Emperor Marcus Aurelius in 174. He wrote of tuberculosis and recommended fresh air, milk, and sea voyages for its treatment, but the disease does not have prominence in his medical texts [8].

The anatomical revolution in the history of tuberculosis

With the beginning of the Middle Ages, scientific progress stopped, even in the medical field. Hippocratic and Galenic knowledge was studied and applied to clinic in a dogmatic manner, being considered absolute truths.
Although starting from the 14th century, Mondino de Liuzzi (1275-1326) began to verify on cadavers the notions handed down by the fathers of medicine, thus starting the experimental sciences.
It has been necessary to wait centuries before the scientific approach had a confirmation in clinical practice and thus physicians abandoned humoral theories. In the study of tuberculosis the transition from the dogmatic to the experimental approach has been particularly slow.
In the 17th century Marcello Malpighi (1628-1694) introduced the use of the microscope in anatomy.
Thanks to this instrument he was able to describe the anatomical structure of the lung [15].
In 1689 the English physician Richard Morton (1637-1698), contemporary of Malpighi, was the first to state that tubercles were always present in the lungs suffering from phthisis [16].
As the result of 900 post-mortem investigations, in 1810 Gaspar Laurent Bayle (1774-1816) described that tubercles could also be detected in organs other than the lung [17, 18].
Thanks to the incessant study of corpse René Théophile Hyacinthe Laennec (1781-1826), who was a colleague to Bayle, laid the foundation for a modern clinic understanding of tuberculosis [8, 19].
In 1819 he published a treatise that not only clearly expounded the pathology of tuberculosis unifiying the concept of the disease, whether pulmonary or extrapulmonary, but also described most of the physical signs of pulmonary disease, introducing terms to describe those findings that are still in use today [20].
In 1839 Johann Lukas Schönlein (1793-1864) coined the term "tuberculosis" replacing the terms consumption and phthisis that were used in the 17th and 18th centuries [21].

The discovery of a microscopic enemy: *Mycobacterium tuberculosis*

Although many important anatomopathological and clinical aspects of the tuberculosis were clarified, its etiopathogenesis remained unknown.
In Northern Europe tuberculosis was generally considered a heritable disease; in Southern Europe it was felt to be infectious in nature.
That tuberculosis was, indeed, infectious in nature was probably first suggested in 1720 by Benjamin Marten (c. 1690-1752), who attributed the disease to "some certain species of animalcula" [22]. The infectious nature of phthisis was demonstrated in 1865 by Jean-Antoine Villemin (1827-1892), a French military surgeon at the Army Medical School.
He formulated his hypothesis observing that tuberculosis was more frequent among soldiers who stationed for long times in barracks than among those in the field. He also highlighted how healthy army recruits coming from the countryside often became consumptive some months after the beginning of their service. He infected a rabbit with "a small amount of purulent liquid from a tuberculous cavity" removed at autopsy from an individual who had died of tuberculosis [21].
On the evening of March 24, 1882, Robert Koch (1843-1910) presented the discovery of the infectious cause of tuberculosis at the Berlin Physiological Society.
Koch summarized the importance of his findings, for which he received the 1905 Nobel Prize, in a manuscript published in the Berliner Klinische Wochenschrift shortly after his announcement: "In the future the fight against this terrible plague of mankind will deal no longer with an undetermined something, but with a tangible parasite, whose living conditions are for the most part known and can be investigated further" [23, 24].
Koch's studies on tuberculosis are a milestone in the history of medicine: they inaugurated the beginning of the reign of bacteriology in hygiene.
The social history of medicine has placed Koch's early work on tuberculosis at the outset of the bacteriological era in hygiene and public health that led to the "medicalization" of entire societies in the late 19th century.
The new bacteriologists' conception of the pathogens stripped epidemics of any political meaning, turned them into exclusive objects of scientific investigation, lending legitimacy to extended positivism based on medical expertise [25].

Tuberculosis therapy in the Pre-Antibiotic Era

Despite the fundamental diagnostic advances that occurred in the nineteenth century, therapeutic solutions for tuberculosis were still immature.
In the second half of the 19th century, it was a common conviction that specific climatic environments could contribute to cure tuberculosis. Subsequently, the most frequently prescribed remedy for pulmonary forms was a stay in a temperate climate.
In Europe, the first sanatorium was founded in 1854 by Hermann Brehmer in Germany, in Goebersdorf in Slesia, a village on the border between Poland and the Czech Republic. Brehmer stressed the therapeutic effect of the climate in the treatment of phthisis.
The sanatorium regimen planned to cure tuberculosis with Galenic principles of hygiene: isolation, fresh air, exercise and good nutrition.
Eminent physicians supported these remedy for the treatment of the most serious forms of the disease for a few decades [26].
People suffering from tuberculosis became often ill also because of their socio-economic conditions. The correct lifestyle offered in sanatoriums could help patients to rehabilitate themselves and find the strength necessary to defeat the disease. Furthermore, the isolation of tuberculosis carriers protected the population from infection.
These two functions were the only medical goals that could be hoped for from a sanatorium. The seriously ill were unlikely to benefit from staying in the sanatorium [8, 27].
For this reason, in the first half of the 20th century, numerous preventoria were opened.
They had a preventive function: they housed healthy children potentially at risk of infection. In these facilities the guests had the opportunity to respect the main hygienic rules and to feed themselves correctly, as in the sanatorium, keeping themselves healthy [28, 29].
The second therapeutic strategy for the treatment of tuberculosis was the therapeutic pneumothorax. The first successful therapeutic pneumothorax was induced by F.H. Ramadge in London in 1834; he reported complete healing of his patient. Carlo Forlanini (1847-1918) is remembered as the inventor of artificial pneumothorax for treatment of pulmonary tuberculosis. He carefully documented his results with artificial pneumothorax in 1894, and thereafter the procedure became widely used [30]. It is probable that pneumothorax was a useful therapy, primarily because it often resulted in cavity closure and sputum conversion to negative. In 1913 and 1914, Forlanini, thanks to his discovery, was on the shortlist of the Nobel Committee and thus one of the prime candidates for the prestigious prize [31].
However, there are no controlled studies of its efficacy – it is difficult to know how one could design such trials – and one must rely on reviews of series of treated patients [8].
In 1890 Robert Koch developed tuberculin, a glycerine extract of the tubercle bacilli, as a remedy for tuberculosis, but reductions in deaths did not meet those expected of the treatment [25]. However, thanks to the studies of Koch, the tuberculin skin test has been developed and are still used in the diagnosis of tuberculosis.
In 1900 Albert Calmette and Camille Guérin began their research for an antituberculosis vaccine at the Pasteur Institute in Lille and, in 1921, the time was ripe for a trial of the vaccine, called Bacille Calmette-Guérin (BCG), in man.
Vaccines have changed the history of many infectious diseases, the most illuminating example is the eradication of smallpox. BCG has not had the same luck.
Although the efficacy of the BCG vaccine continues to be controversial, live attenuated BCG is still the only vaccine in use for the prevention of tuberculosis in humans [32].

Antibiotics: turning point in the fight against tuberculosis

The optimism brought by Koch's discovery had no significant consequences in medical practice for over 60 years.
The first truly effective anti-tuberculosis drug arrived in 1943: streptomycin, isolated in the laboratory of Selman Waksman at Rutgers University. In November 1944, a patient with tuberculosis received streptomycin and was declared healed from the disease.
Other cases of successful treatment soon followed [33, 34].
Streptomycin was among the first antibiotic molecules on the market. Again, we find that tuberculosis has been involved in an epochal shift in the history of medicine: the advent of the antibiotic era.
The British Medical Research Council conducted the first large-scale clinical trial of streptomycin in 1948 [35].
This study, said to be the world's first published drug trial that involved the randomization of participants, set the methodologic standard for modern randomized controlled trials. In 1951, isonicotinic acid hydrazide (isoniazid) was tested, followed by the development of pyrazinamide (1952), cycloserine (1952), ethionamide (1956), rifampin (1957), and ethambutol (1962) [34].
The introduction of antibiotics in a short time has radically changed medical practice.
This change can be documented in the medical literature intended for the general practitioner. For example, in Italy the Anton Spartaco Roversi's Manual of Medicine was a consultation pocket book that tried to give an comprehensive overview about medical practice in order to provide a useful bed-side tool for generations of Italian physicians.
In its first editions (1940 and 1944) tuberculosis was finely explained in a systematic manner in every possible manifestation within the chapters divided by organ "With the arrival of effective antibiotic therapies, in the subsequent editions of the book (1954 and 1967) there has been a drastic drop in the number of pages devoted to tuberculosis and its manifestations, indicating a decreased finding of extrapulmonary complications of the disease, and therefore a decreased interest for the general practitioner" [36].
Optimism that tuberculosis would soon be eliminated was not restricted to wealthy countries. At the 1978 International Conference on Primary Health Care in Alma-Ata (now

called Almaty), Kazakhstan, delegates from around the world endorsed the goal of "health for all by the year 2000." The eradication of smallpox had been announced the previous year, and the future of international public health looked promising to many who were gathered there. But it was not to be.

Tuberculosis therapy in the Post-Antibiotic Era

The enthusiasm for the success of anti-tuberculosis drug therapy stifled the alarm bells that did start to ring around the limits of antibiotic therapy.
Studies on tuberculosis in the 1950s anticipated a problem of great relevance today, anti-antibiotic resistance. Once again, tuberculosis is the protagonist in an epochal change in medicine: the post-antibiotic era.
The first national drug-resistance survey in the world, which involved 974 clinical isolates cultured from newly diagnosed cases of tuberculosis in Britain (1955-1956), showed strains that were resistant to streptomycin (2.5%), para-aminosalicylic acid (2.6%), and isoniazid (1.3%) [34].
Tuberculosis, whether caused by drug-susceptible or drug-resistant strains, rarely made even medical headlines, in part because its importance as a cause of death continued to decline in areas in which headlines are written. In such settings, where many of the social determinants of tuberculosis - extreme poverty, severe malnutrition, and overcrowded living conditions - became the exception rather than the norm, some public health experts declared that "virtual elimination of the disease as a public health problem" was in sight [37].

Currently, what are the challenges that tuberculosis offers to us?

Despite progress in care and prevention, tuberculosis remains one of the world's leading causes of ill-health and death and the top cause of death from an infectious disease globally [38]. The fight against drug resistance is only a tile of an always changing mosaic that needs constant attention and innovation in therapeutic strategies [39, 40].
Globalization is improving circulation of people, goods, but also of microbial agents which may find favorable habitats. Individuals with immune deficiencies represent an ever-increasing population at higher risk of contracting tuberculosis. Co-infection with HIV is also a new scenario where doctors have to fight tuberculosis [41].
At last, we must remember that ageing makes people particularly fragile versus tuberculosis, since it decreases the efficiency of the immune system and increases difficulty in tolerating side effects of anti-tuberculosis drugs, sometimes lethal [42, 43].
As often happens in the management of infectious diseases, only comprehensive approaches that aim to tackle down social determinants of tuberculosis, coupled with scientific progress in diagnostic and therapeutic management of patients with tuberculosis, may allow to eradicate this disease in heavily affected countries [44].

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

EA designed the study. EA and MM conceived the study; EA and MM drafted the manuscript, revised the manuscript and performed a search of the literature. All authors critically revised the manuscript. All authors have read and approved the latest version of the paper for publication.

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Case report

Endoneural abscess of common popliteal nerve as first clinical manifestation of leprosy: the first reported case in history in a low-incidence country

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Keywords

History • Leprosy • Neuropathy • Nerve abscess • Epineurotomy

Summary

A migrant from Palestine came to our attention for weakness of dorsiflexion of the left foot and hypoesthesia of the homolateral common peroneal nerve territory. Skin biopsies from skin lesions in the hypoesthetic area were not diagnostic. Radiological investigation showed focal nerve enlargement with a possible focal lesion. At this time, and given the uncertainty of the diagnosis, we had to choose between medical therapy with steroid and a surgical exploration of the nerve. We decided for the latter option. Intraoperatively, we found a focal round enlargement of the nerve. Epineurotomy was performed at that level, revealing a round caseous granulomatous mass that was excised. Microbiological examination revealed presence of Mycobacterium Leprae allowing diagnosis of leprosy. Medical therapy was then started, leading to resolution of clinical symptoms. Endoneural lepromatous abscesses are uncommon lesions that should be suspected in patients presenting with peripheral nerve dysfunction with anamnesis of travel in leprosy endemic regions or contacts with people from endemic regions with or even without skin lesions. Detection of endoneural abscesses is of critical importance because prompt surgical excision in conjunction with medical therapy leads to improvement of symptoms and permits correct diagnosis. In times of large human migrations from leprosy endemic areas, knowledge of this uncommon presentation of leprosy and its management will help lead to the best management of these patients.

Introduction

Although leprosy is one of the oldest infectious diseases in human history, it is still responsible for great morbidity and mortality [1]. In fact, more than 175,000 patients were on treatment for leprosy in 2015 [2].
In 2016, the World Health Organization (WHO) reported more than 200 000 new cases of leprosy worldwide [3]. In Italy, a low-endemic country for leprosy, only 20 cases occurred between 2016 and 2017 [4]. Most of patients acquired leprosy outside Italy with main risk factors being long stay or coming from endemic areas [5].
Due to patient's genetic variations and *Mycobacterium leprae* different tropism for skin and peripheral nerve tissue, leprosy clinical manifestations can be insidious and hard to diagnose [6].
Moreover, in European countries, where the incidence of leprosy is low and mainly due to migrants from endemic Regions, the lack of disease's awareness can delay the diagnosis [7].
Entrapment neuropathy is a common manifestation of leprosy and may benefit from decompressive surgery by means of neurolysis and epineurotomy [8]. The Neurosurgery Unit of Policlinico San Martino Hospital in Genoa, Italy refers to one of the three 'National Hansen Disease centers' and to the only Italian third level diagnostic laboratory for Hansen Disease. At our Institution, we have performed neurosurgical decompression procedures for leprosy peripheral neuropathy in 22 patients in the last 10 years (2,2 cases per year), 14 of these in the last 5 years thus revealing a moderate increase tendency. All of these were 'imported' cases, defined by a positive anamnesis for travelling to or from endemic areas.
The aim of this case-report is to communicate a rare first clinical manifestation of leprosy, naming endoneural abscess of a peripheral (common popliteal) nerve.

Materials and methods

We are presenting the case of a patient that was treated for a leprosy abscess of a peripheral nerve at the Unit of Neurosurgery of Policlinico San Martino Hospital, Ligurian region, Italy. We have retrospectively reviewed and reported clinical data, radiological exams, anatomopathology records and subsequent follow-up documentation.

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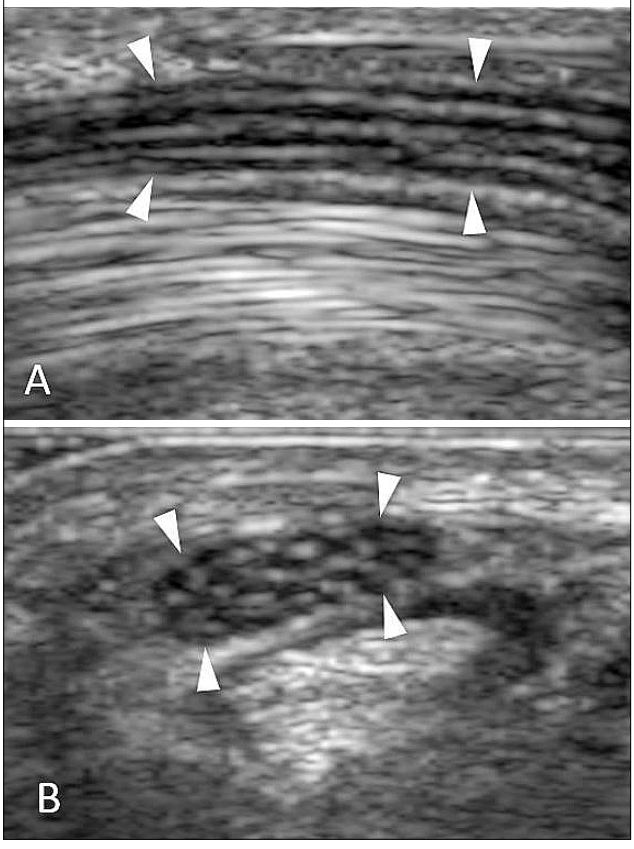
Case report

A 24 years old male Palestinian immigrant came to medical attention for dorsiflexion weakness of the left foot (graded 2 according to the Medical Research Council Manual Muscle Testing scale) [9] and hypoesthesia of the ipsilateral common peroneal nerve territory. No other strength deficits and no other hypoesthetic lesions were present. Skin lesions were present at first admission.
Biopsies were performed on the skin lesions, but histologic exam was not diagnostic, showing only non-specific chronic granulomatous dermatitis with focal neurotropism. Skin-smear examination was not performed because leprosy was initially not suspected.
Blood tests revealed only unspecific inflammation without other anomalies able to help the diagnosis.
Electroneurography (ENG) was then performed on lower limb nerves, showing reduction of evoked response amplitude in the right deep peroneal nerve (DPN) and absence of response in the left DPN. This result was consistent with a bilateral asymmetric peripheral neuropathy, more severe on the left lower limb, where clinical symptoms could be observed.
In suspicion of a neural entrapment, echography of the ischiatic nerve was then performed revealing on the left side a predominantly focal large dimensional increase of the left common peroneal nerve (67,6 mm^2) from the lateral femoral condyle to the peroneal neck (Fig. 1).

Fig. 1. A) echographic appearance of left common peroneal nerve showing enlargement in longitudinal view (outlined by white triangles); B) echographic appearance of left common peroneal nerve showing enlargement in transversal view (outlined by white triangles).

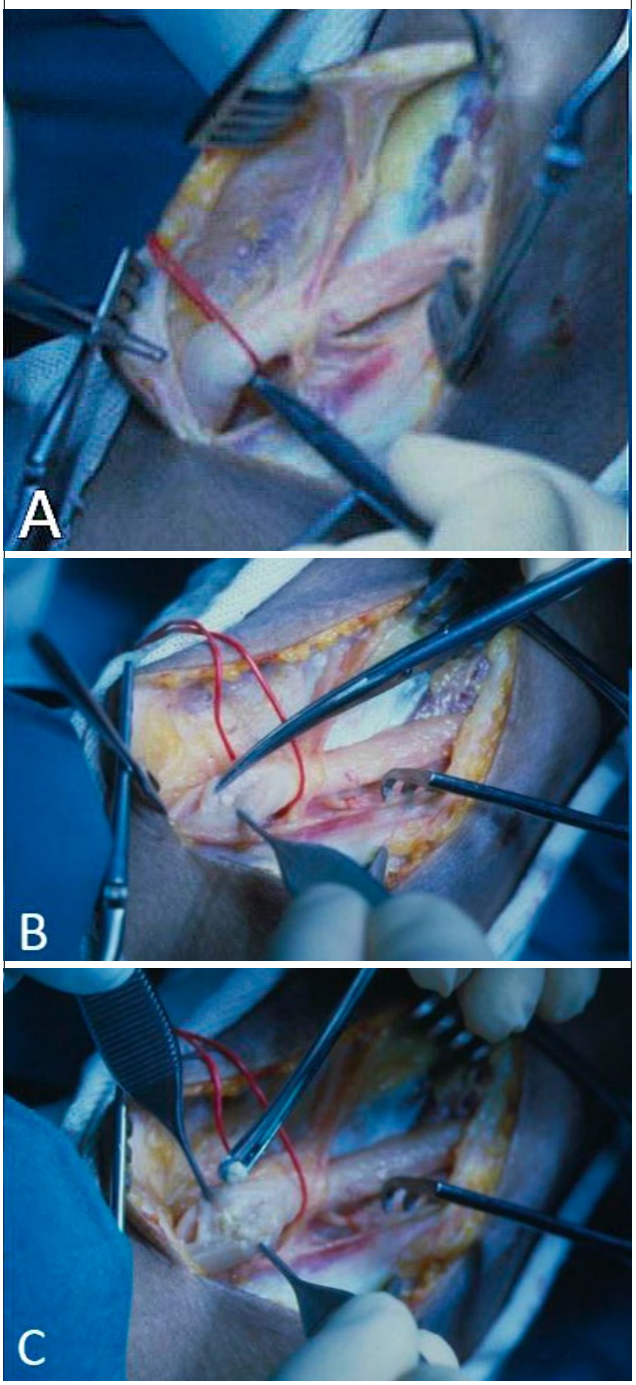


Echographic structure in that nerve tract was subverted and inhomogeneous and Doppler appearance was hypovascular. Ischiatic nerve on right side showed a normal ecographic appearance.
Magnetic Resonance Imaging (MRI) was then performed to better investigate the focal nerve enlargement seen at echography. It showed enlargement and inhomogeneity of the common peroneal nerve, all the way from its origin from the ischiatic nerve until its bifurcation into superficial and deep peroneal nerves. At the level of this bifurcation the MRI showed a focal area of signal alteration with a liquid core and a thin wall.
Electromiography (EMG) showed a severe peripheric neurogenic lesion at tibialis anterior muscle, possible signs of peripheric neurogenic lesion at left gastrocnemius muscle and no involvement of other muscles. This finding was consistent with the presence of the liquid-core lesion seen at the MRI.
We repeated echography that did not show variations from the previous exam and was not able to clearly detect the lesion seen at MRI.
Thus, while the clinical picture and the echography could not rule out an entrapment neuropathy at the peroneal capitol, the MRI clearly showed a focal lesion. We had to choose between aspecific conservative medical treatment with steroids and explorative surgery. We decided for the latter option.
After isolation of the common peroneal nerve, just before its bifurcation we observed a focal round enlargement (Fig. 2). Epineurotomy was performed at that level, revealing a round caseous granulomatous mass that was excised (Fig. 2). Microbiological examination revealed presence of Mycobacterium Leprae allowing diagnosis of leprosy. Appropriate medical therapy was then started.
Follow up echography was repeated 18 months after treatment, showing significant volume reduction of common peroneal nerve (29,3 mm^2, down from the initial 67,6 mm^2). Clinical symptoms resolved after surgery.

Discussion

Neuropathy is a trivial manifestation of leprosy disease that needs prompt diagnosis and treatment to allow relief of symptoms [10]. Leprosy neuropathy may present as an entrapment neuropathy that, even lacking high-level evidence, may benefit from surgery and concomitant corticosteroid therapy [11].
Less frequently than entrapment neuropathy, peripheral lepromatous nerve abscesses can occur. While these lesions have been described in endemic countries [12], to the best of our knowledge this is the first case reported from a non-endemic country.
It is useful to notice how a surgical operation may represent not only a therapeutic procedure but also an important diagnostic tool when the diagnosis is not clearly defined, and when the correct diagnosis is initially mistaken [6].

Fig. 2. A) exposition of common peroneal nerve with evidence of focal round enlargement; B) epineurotomy and exposition of endoneural abscess; C) excision of endoneural abscess.



A precise diagnosis is of critical importance to plan the correct surgical procedure. External neurolysis, which is viable in cases of entrapment neuropathy [4] may not lead to symptoms relief if there is an underlying endoneural abscess that conversely will be best treated with epineurotomy and surgical excision. Echography, MRI and neurophysiological investigations are useful tools that permit to achieve the correct diagnosis of the underlying lesion [13].
Echographic appearance of endoneural leprosy abscesses is usually characterized by focal hypoechogenicity, fascicular pattern disorganization, marked focal thickening with sometimes a predominantly anechoic roundish lesion inside the nerve [14].
MRI is useful in detecting leprosy nerve abscesses. MRI appearance is characterized by a peripherally enhancing lesion, T1 hypointense and T2 hyperintense, inside a T2 hyperintense nerve, expression of inflammation [15].
Lack of knowledge of such a leprosy neuropathy presentation may lead to delay in diagnosis and treatment, with subsequent loss of chance of clinical improvement. Delay in diagnosis has been reported in developed western countries that account for a very small number of cases per year [16].

Conclusions

Knowledge of this uncommon presentation of leprosy will gain increasing importance in the near future. In times of large human migrations from leprosy endemic countries, this condition that physicians from leprosy low incidence countries may have only anedoctically seen, will be more and more frequently encountered.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

SG and AB conceived the study, AB and NR drafted the manuscript; SG, PA and PF revised the manuscript. AB and NR reviewed the literature. CM provided radiological images. All authors critically revised the manuscript. All authors have read and approved the latest version of the manuscript.

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ORIGINAL ARTICLE

Invasive meningococcal disease in Italy: from analysis of national data to an evidence-based vaccination strategy

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Keywords

Invasive meningococcal diseases • Epidemiology • Surveillance system • Anti-meningococcal vaccination strategies

Summary

Introduction. *Invasive meningococcal disease (IMD) is one of the most severe vaccine-preventable disease not yet under control. In Italy, although different anti-meningococcal vaccines are available, their offer among regions is heterogeneous. The aim of this study is to describe the epidemiology of IMD in Italy based on analysis of national surveillance data for 2011-2017 to optimize the vaccination strategy.*

Methods. *IMD surveillance data from the Italian National Health Institute were analysed. Microsoft Excel was used to present trend analysis, stratifying by age and serogroups.*

Results. *In Italy, during the period 2011-2017, the incidence of IMD increased from 0.25 cases/100,000 inhabitants in 2011 to 0.33 cases/100,000 in 2017. Most cases after 2012 were caused by non-B serogroups. The number of cases in subjects aged 25-64 years increased steadily after 2012 (36 cases in 2011, 79 in 2017), mostly due to non-B serogroups, representing more than 65% of cases in those aged 25+ years.*

Conclusions. *In the period from 2011 to 2017, the incidence of IMDs increased in Italy. The increase, probably due also to a better surveillance, highlights the importance of the disease in the adult population and the high level of circulation of non-B serogroups in particular after 2012. Our analysis supports an anti-meningococcal vaccination plan in Italy that should include the highest number of preventable serogroups and be aimed at vaccinating a wider population through a multicohort strategy.*

Introduction

Invasive Bacterial Infection (IBI) caused by *Neisseria meningitidis (N. meningitidis)*, commonly known as Invasive Meningococcal Disease (IMD) or meningococcal disease, is one of the most severe vaccine-preventable disease [1]. *N. meningitidis* is a gram-negative diplococcus often detected in the human nasopharynx of asymptomatic carriers (especially adolescents). It only infects humans; there is no animal reservoir [1-5]. Occasionally, it invades normally sterile sites (e.g. bloodstream, brain and cerebrospinal fluid) causing diseases with a variety of non-specific clinical presentations, including meningitis (the most common disease caused by *N. meningitidis*) and sepsis [1, 6]. Disease progress is usually acute and severe, requiring comprehensive treatment in hospital, and even when the disease is diagnosed early and adequate treatment is started, between 10% and 15% of patients die, and up to 60% have long-term sequelae [1, 6-11].

Epidemiology of IMD

The incidence of IMD is generally low with regional differences. The incidence ranges from less than 1 case per 100,000 in North America and Europe to 10-1000 cases per 100,000 during epidemic years in Africa [12, 13]. In 30 European Union (EU)/European Economic Area (EEA) countries, there were 3,221 confirmed cases of IMD in 2017 with 282 deaths reported [14], and the overall notification rate (NR) was 0.6 per 100,000 persons, the same as in 2016 and 2015, after a decreasing trend observed in the previous years [14, 15].

N. meningitidis disease-causing serogroups are identified according to the antigenic structure of the polysaccharide capsule; essentially six serogroups (A, B, C, W, Y and, rarely, X) are responsible for human disease [16]. The distribution of the serogroups varies worldwide and within the same region, changing rapidly due to an epidemic or slowly over time because of secular trends, the emergence of hypervirulent clones, new vaccination strategies, the changing state of population immunity, and environmental and behavioural risk factors [12, 16-18]. Moreover,

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capsular switch from one serogroup to another may occur [12, 18-22]. In Europe, despite a decreasing trend in serogroups B and C (in particular in countries that introduced meningococcal vaccination) and an increasing trend in serogroups W and Y, serogroup B continues to be the main cause of IMD [14, 15]. Specifically, during 2017, most of the 2,979 cases of IMD reported with a known serogroup belonged to serogroup B (51%), followed by W, C and Y (17%, 16% and 12%, respectively) [14].

Furthermore, the incidence of meningococcal disease varies according to the age group considered. In Europe, the highest incidence occurs in young children (NR of 8.2 confirmed cases per 100,000 in children less than 1 year of age, and 2.5 per 100,000 population in those aged 1-4 years), with a second disease peak among adolescents and young adults (15-24 years old; rate of 1 per 100,000 population) [14]. IMD risk is increased in crowded situations associated with mass gatherings, life in close quarters (e.g. military barracks, college dorms), or travel to hyper-endemic regions [23]. However, even a single case of meningitis, especially in children, can trigger the so-called emotional epidemiology, which evokes memories of past pandemics and makes the disease feared [24, 25].

The prevalence of each meningococcal serogroup varies according to age. In the EU/EEA countries, serogroup B caused the highest proportion of cases in all age groups less than 65 years and accounted for 70% of IMD cases in children less than 5 years of age. Serogroup C was most prominent in 25-49-year-olds, but rare among those aged less than 24 years, especially in countries that introduced a universal infant or toddler vaccination programme [14]. Serogroups W and Y were high in those aged 65 years and greater, causing 30% and 26%, respectively, of IMD cases in these age groups [13]. Moreover, a threefold increase in serogroup W was observed between 2013 and 2017 (from 0.03 to 0.10 per 100,000), most pronounced among young children and adults, probably due to the rapid epidemic expansion of a single clone from the United Kingdom to several other EU member states [26-28].

There is potential for underestimation of cases of IMD as a result of underreporting of notification involving surveillance systems [29-34]. The available data are usually derived from passive surveillance systems that provide varying estimates throughout Europe and worldwide [14, 31, 35, 36].

Anti-meningococcal vaccines and vaccination strategies

Different anti-meningococcal vaccines for primary prevention (routine immunization) of IMD and in response to outbreaks (prompt reactive vaccination) are available: monovalent vaccines against serogroup A, B (protein-based vaccine [MenB]) and C (conjugate vaccine [MenC]) and quadrivalent vaccines, mainly conjugated, against serogroups A, C, W, Y (MenACWY) [37]. To date, no universal vaccine against meningococcal disease exists. Vaccination strategies adopted throughout the world are heterogeneous, usually based on local epidemiologic data and environmental circumstances within a region or country. Considering the rapid and severe clinical evolution of IMD, relative ease of transmission, and unpredictability of IMD outbreaks and epidemiology, protection can best be achieved by initiating proactive rather than reactive vaccination strategies [38]. The Italian National Immunization Prevention Plan (Piano Nazionale Prevenzione Vaccinale [PNPV]) recommends different meningococcal vaccines with different age schedules. [39]. In particular, MenB vaccination is recommended for all infants, followed by one dose of MenC conjugate vaccine (or the conjugate MenACWY vaccine, according to regional evaluation) in the 13th-15th month and by the conjugate MenACWY vaccine at 12-18 years, in previously vaccinated or unvaccinated adolescents [39]. Moreover, the PNPV recommends anti-meningococcal vaccination regardless of age for people at an increased risk of developing the disease, such as those with some pathological conditions (e.g. hemoglobinopathies, asplenia, congenital or acquired immunodepression, type 1 diabetes, etc.), and their caregivers, and for all travellers to countries in the sub-Saharan belt or on a pilgrimage to Makkah al-Mukarramah [39]. At regional level, these recommendations are implemented as minimal offer, with the possibility of adding more cohorts, creating a heterogeneous offer.

Aim

The aim of the study is to describe and reinterpret as a whole the Italian epidemiological IMD data from 2011 to 2017. This will help to evaluate serogroup- and age-specific trends in order to provide a clear analysis that can be helpful to develop evidence based future Italian IMD prevention strategies.

Methods

Data sources

Data from Italian surveillance reports on vaccine-preventable invasive bacterial diseases (VP-IBDs) provided by the National Institute of Health (Istituto Superiore di Sanità [ISS]) for 2011-2017 were analysed [40, 41].

Italian Surveillance of IMD

In line with other EU/EEA countries [14], VP-IBDs caused by *N. meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* are included in an enhanced national surveillance system. In Italy, it is coordinated by the ISS and has been active since 2007 [42]. This system requires that all forms of IBI from pathogens for which there is a vaccine available are reported by clinicians and laboratory staff in hospitals to local health authorities, regions and, finally, to the ISS [42]. Moreover, isolates are sent for further microbiological and molecular analysis to Regional Reference Laboratories or to the National Reference Laboratory at the ISS [42].

The surveillance system collects demographic characteristics of each patient (personal information such as name, surname and date of birth, city of residence, nationality, presence of risk factors, potential hospitalization, outcome and sequelae, state of vaccination, etc.) and data regarding the agent causing the disease (e.g. species, serotype/serogroup, etc.) using microbiological or molecular methods [42]. Microbiological characterization also includes an assessment of antibiotic sensitivity, important for detecting the circulation of antibiotic-resistant strains used in therapy and chemoprophylaxis. In addition, emerging and virulent strains can be highlighted by molecular typing, giving the opportunity to reconstruct the transmission chain in case of outbreaks [43].

Data selection and analysis

Data from the latest consolidated IMD surveillance reports were used [40, 41]. It was decided not to use the surveillance data from 2018 because they are not consolidated yet. Data on notified cases of IMD for 2011-2017 are originally disaggregated in different reports. The data were reorganized and grouped to be analysed and critically interpreted. Based on data availability, stratifications by age group (0-12 months, 1-4, 5-9, 10-14, 15-24, 25-64, > 64 years) and serogroup were carried out. Microsoft Excel 2013 was used for trend analysis.

Results

In Italy, during the study period, the overall NR trend for meningococcal disease increased from 0.25 cases per 100,000 persons in 2011 to 0.33 in 2017 (Fig. 1) [40, 41].

IMD by serogroup

Looking at the overall number of cases by serogroup during the period analysed, it was not possible to distinguish a homogeneous trend for serogroup B, whereas the overall number of cases caused by ACWY serogroups increased during the period (Fig. 2). Of the total number of cases of IMD notified, the percentage of cases without a notified serogroup decreased from 2013 when these cases where 56 (32.6% of the total) to 37 (16.3%) in 2016 and 19 (9.6%) in 2017 (Supplementary Tab. I). Looking at the individual serogroups, serogroups B and C were the most prevalent meningococci in Italy (Fig. 3). Serogroup B showed a decreasing trend between 2011 and 2015, before increasing again over the last 2 years, representing the absolute and relative majority of IMD cases in 2017. An increase in serogroup C was reported in 2015 and 2016, causing more than 40% of cases and becoming the most frequent serogroup each year. Serogroups W and Y also increased over the years, representing almost 7% and 19% of typed cases in 2017, respectively. During the analysis period, six cases of IMD caused by serogroup X were reported. Detailed information on cases of IMD is given in Supplementary Table I.

IMDs by age

The age-specific incidence rate was higher in children less than 1 year of age (NR of at least 3.20 confirmed cases per 100,000 population per year in 2013), followed by 1-4-year-olds, with another smaller peak in 15-24-year-olds in 2011, 2012 and 2015-2017 (Tab. I). In the age group 25-64 years, an increase in the absolute number of cases was seen achieving a peak in 2016 with 83 cases and 79 in 2017.

IMD by age groups and serogroups

Serogroup B had the highest prevalence in the paediatric population less than 5 years of age, nevertheless serogroups W and Y cases increased over the period (Fig. 4). In the age-groups 5-9 and 10-14 years there was a decrease in cases by serogroup B compared with the other

Fig. 1. Notification rate of cases of invasive meningococcal disease per 100,000 population by year, 2011-2017.

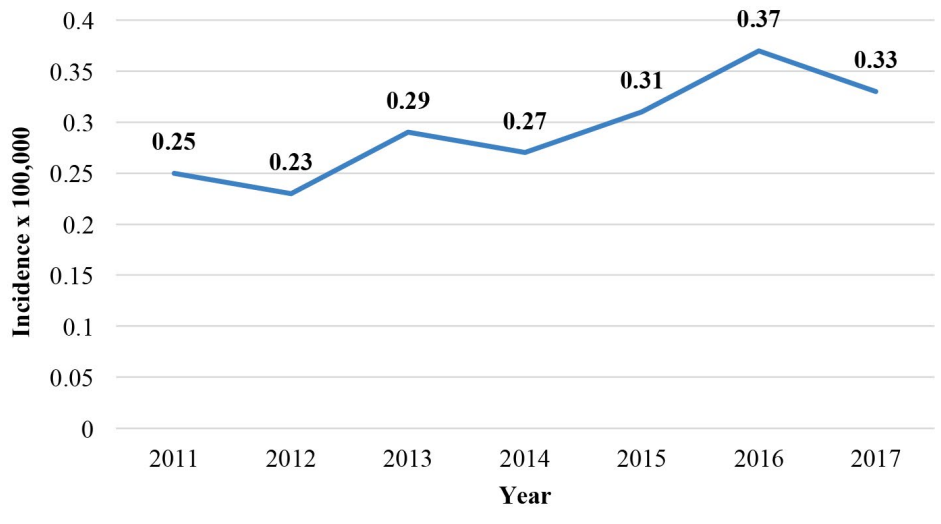


Fig. 2. Absolute number of cases for serogroup B versus ACWY versus X + unnotified serogroup, 2011-2017.

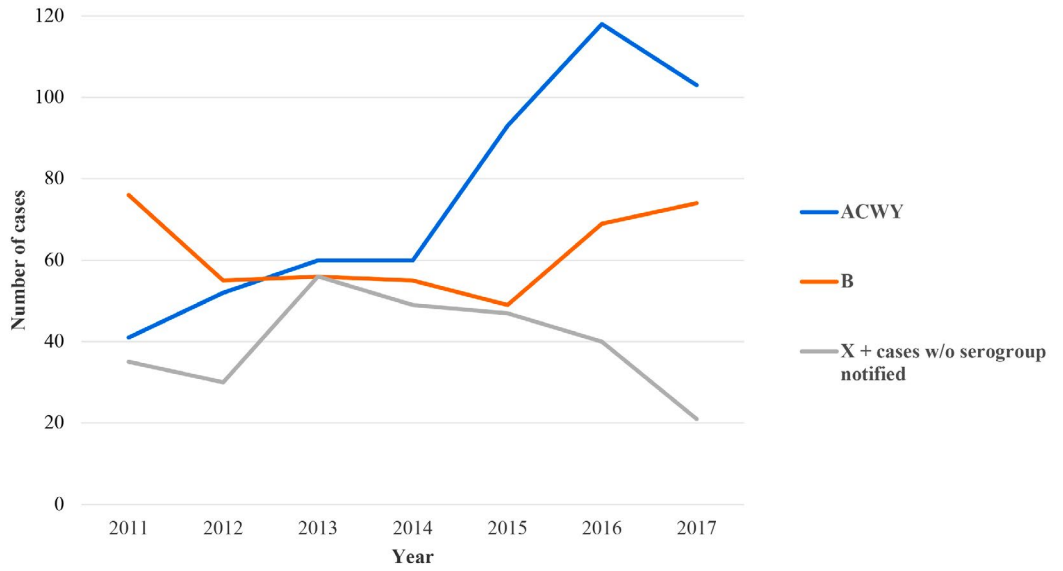
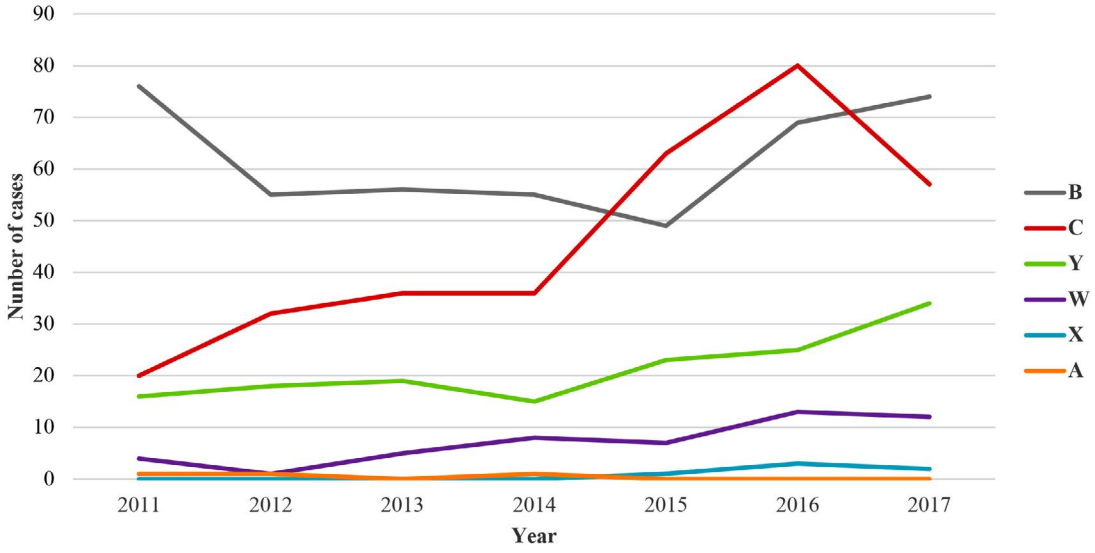


Fig. 3. Trends for the absolute number of cases for each typed serogroup, 2011-2017.



age groups. In the same age-group a relative increase in the number of cases from serogroups C, W and Y was observed. In adolescents (15-24 years), most of the cases were caused by serogroups B and C in the study period (with a serogroup C outbreak recorded in 2015/2016 and a fluctuating trend of serogroup B), while serogroup Y increased reaching 27% of the overall typed cases in 2017. In older age groups (25+ years), cases of IMD caused by non-B serogroups were predominant (except for 2011); among these, most cases were attributed to serogroup C, representing at least 44% of the total during the last 5 years. In adults and the elderly (25+ years), a substantial prevalence of serogroups Y and W was also registered (28% in 2011, 23% in 2012, 23% in 2013, 21% in 2014, 25% in 2015, 13% in 2016, 25% in 2017). Focusing on the period from 2015 to 2017 (Fig. 5, Supplementary Fig. 1 and 2), in those aged 0-12 months, the prevalence of serogroup B was always more than 55% of the typed serogroups, increasing over time (58% of cases in 2015, 72% in 2016 and 85% in 2017). Among those aged 1-4 years, serogroup B decreased from 70% in 2015 to 50% in 2017, serogroup C increased in 2016 to 40%, returning in 2017 to the level seen in 2011-2014, whereas almost 17% of the typed cases during 2017 were serogroup Y. Among those aged 15-24 years, serogroup C was the most frequently typed in 2015 and in 2016, whereas in 2017, serogroup B prevailed, representing more than half of the serogroups typed (52%), followed by serogroup Y (27%). In adults and the elderly, serogroup C was the predominant serogroup notified each year (56% and 40% of cases in 2015, 56% and 48% in 2016, 48% and 39% in 2017, respectively), followed by serogroups B, Y and W.

Tab. I. Absolute number, percentage of cases of invasive meningococcal disease and incidence rate (per 100,000 population) of IMD by age group and year, Italy, 2011-2017.

	Year																				
	2011			2012			2013			2014			2015			2016			2017		
Age group	N	%	Incidence	N	%	Incidence	N	%	Incidence	N	%	Incidence	N	%	Incidence	N	%	Incidence	N	%	Incidence
0-12 months	18	11.8%	3.24	17	12.4%	3.20	21	12.2%	4.01	21	12.8%	4.13	22	11.7%	4.43	22	9.7%	4.59	15	7.6%	3.21
1-4 years	23	15.1%	1.00	25	18.3%	1.13	27	15.7%	1.22	25	15.2%	1.13	18	9.5%	0.83	22	9.7%	1.05	19	9.6%	0.93
5-9 years	19	12.5%	0.67	13	9.5%	0.47	11	6.4%	0.39	11	6.7%	0.38	7	3.7%	0.24	16	7.1%	0.56	13	6.5%	0.46
10-14 years	11	7.2%	0.39	8	5.8%	0.29	13	7.6%	0.46	15	9.1%	0.53	10	5.3%	0.35	9	4.0%	0.32	12	6.1%	0.42
15-24 years	32	21.1%	0.53	22	16.1%	0.37	26	15.1%	0.44	18	10.9%	0.30	39	20.6%	0.66	51	22.5%	0.86	35	17.7%	0.59
25-64 years	36	23.7%	0.11	34	24.8%	0.10	51	29.6%	0.16	53	32.3%	0.16	68	36.0%	0.20	83	36.6%	0.25	79	39.9%	0.24
> 64 years	13	8.6%	0.11	18	13.1%	0.15	23	13.4%	0.18	21	12.8%	0.16	25	13.2%	0.19	24	10.6%	0.18	25	12.6%	0.18
Total	152	100%	0.25	137	100%	0.23	172	100%	0.29	164	100%	0.27	189	100%	0.31	227	100%	0.37	198	100%	0.33

Discussion

Incidence and surveillance of IMD in Italy

Italy has shown a lower incidence of IMD compared with the EU/EEA countries overall (NR, 0.6 per 100,000 population during the lasts 3 years) [14]. Nevertheless, in the period 2011-2017, the incidence of IMD has increased from 0.25 cases per 100,000 inhabitants to 0.33 [40, 41]. One reason that could explain the increase in IMDs is the peak of cases recorded in Tuscany in 2015 and 2016, especially in adolescents and young adults [40, 43-45] and in Liguria in 2016 and 2017 [40, 41]. Moreover, there have also been improvements in the laboratory diagnosis confirmation system, both at regional and national level [33]. For example, in Tuscany during 2015, real-time polymerase chain reaction (PCR), a more sensitive, rapid and accurate laboratory diagnostic test [33], was made available to all hospitals by a regional law [46], reducing the underestimation of IMD [29] and consequently improving the accuracy of the surveillance system and differentiating IBIs [29, 33, 47]. These methods contributed to a reduction in the percentage of cases of IBI with an unidentified cause [40] and, specifically, of IMD, for which the number of cases without a notified serogroup decreased during the study period [40]. This was confirmed by a data comparison between the number of cases of IBD identified from Italian Hospital Discharge Records and those notified to the Surveillance System reported from 2007 to 2016, which showed increasing concordance between the two institutional in-

Fig. 4. Number of cases of invasive meningococcal disease by age groups and serogroups, 2011-2017.

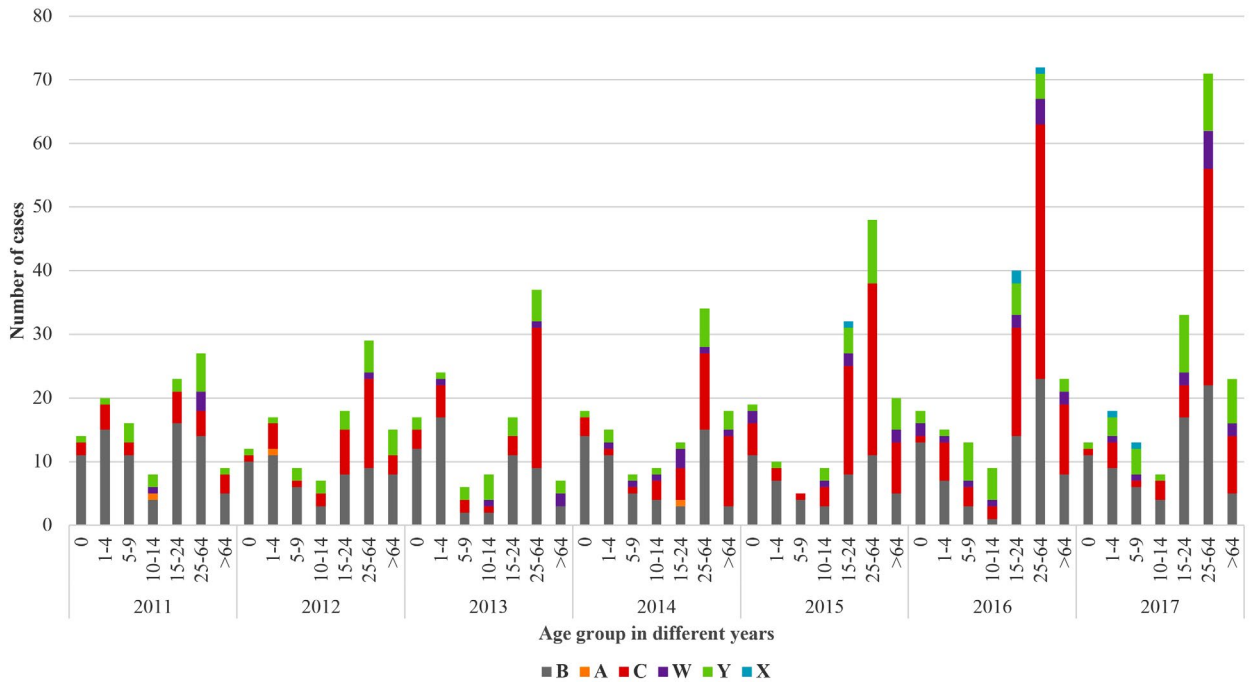
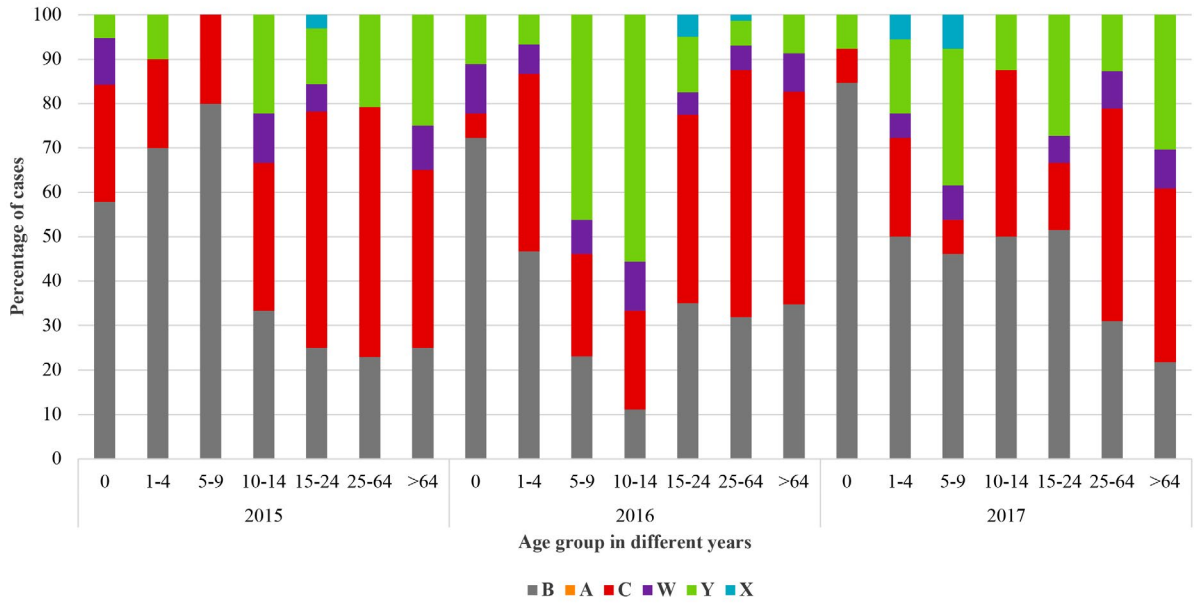


Fig. 5. Proportion of cases by serogroups and age groups, Italy, 2015-2017.



formation systems for VP-IBD [30]. However, despite the improvements, the surveillance system still fails to identify every case of IMD and underreporting is still present [30, 40, 41].

IMD SEROGROUPS

In Italy, during 2011-2017, serogroup B was overall the predominant *N. meningitidis* serogroup, as observed in other EU/EEA countries [14-16]. Nevertheless, the overall number of cases caused by non-B serogroups, increased during the study period. In particular, an increase in cases of IMD related to serogroups Y and W was described [40, 41, 48], whereas serogroup C was almost s from 2012 to 2014, increasing in 2015 and 2016 [40, 43-45]. This epidemiological evidence, as well as the possibility of capsular switch from one serogroup to another [12, 18-22], should lead the national decision makers to boost the use of the MenACWY vaccine instead of MenC in the next PNPV, as already done in Emilia-Romagna [49], Apulia [50] and Sicily [51, 52] and recently implemented in other countries [53, 54], to ensure more comprehensive protection.

IMD BY AGE GROUPS

The age distribution of IMD cases in Italy is similar to the general distribution within the EU/EEA countries [14], with the highest peak incidence in infants and young children and a second peak among adolescents and young adults [40, 41]. Nevertheless, during the study period, the number of cases of IMD notified annually for the 25-64-year-old age group highlights the importance of the disease in the adult population. Moreover, during the last 3 years analysed (2015-2017), an overall increase in the absolute number of cases in adults was seen, especially caused by non-B serogroups. Thus, an effective immunization strategy with a vaccine covering a higher range of serogroups should be implemented in a wider population.

Conclusions

In Italy, since 2011 there has been an increasing number of cases and increased attention given to meningococcal disease [40, 41], although underreporting to the national surveillance system and underestimation of the number of cases of IMD is still present [29, 30]. The data showed that serogroup B is still the most relevant causative agent, but other vaccine-preventable serogroups (e.g. serogroups C, Y and W) have almost reached the same importance [40, 41]. Moreover, although IMD is often considered to be a disease affecting children, the number of cases among older age groups is high and increasing [40, 41].

It is essential to continue to enhance the surveillance systems, improving complete reporting of data to adequately monitor the epidemiology of IMD and to design the most effective public health action plan to tackle the disease. For example, after the peak in the number of cases of serogroup C in 2015, [40, 43-45] the Tuscany Region carried out extraordinary public health measures, including active free-of-charge offer of the MenACWY vaccine to all teenagers (up to 20 years of age) and adults (up to 45 years) living in the areas at greatest risk and an extra dose of MenC conjugate vaccine at 6 years of age [46, 55]. Indeed, during the outbreak, cases of IMD were reported in previously vaccinated children and adults. Most of these cases were in individuals who were vaccinated more than 2 years before developing the disease, indicating a rapid loss of protection that suggested the implementation of a booster dose [56].

A vaccination strategy against meningococcal disease should protect against all possible pathogenetic *N. men-*

ingitidis serogroups. Indeed the Italian PNPV has included the possibility to switch to quadrivalent vaccination instead of monovalent vaccine against serogroup C with the aim of enhancing coverage in adolescents and high-risk adults [39]. As a result, some Italian regions, such as Emilia-Romagna [49], Sicily [51] and Apulia [50], have switched to quadrivalent vaccination and added an additional age cohort to their calendar. Furthermore, consensus among several national scientific societies has led to the development of the "Calendario per la Vita 2019" in which they suggest switching to quadrivalent vaccination, the addition of another age cohort with a boost between 6 and 9 years old and a broader range of high-risk adults compared with the PNPV [39, 57]. Nevertheless, looking at the epidemiologic data, those more than 24 years of age are an important target population [40, 41] that is not fully addressed with the PNPV. In our opinion a possible strategy to consider is a boost (or a first anti-meningococcal vaccination) during the 10-year periodic recall for vaccination against diphtheria, tetanus, and pertussis already in use [39]. Further analysis should be done to better understand the best preventive strategy.

The emergency of Covid-19 pandemic is catalysing everyone's attention and preventive measures, such as vaccinations, for other infections are at risk of being overshadowed. But when community life and the vivacity of interhuman relationships will resume fully, we will need to be prepared for the recirculation of meningococci and other pathogens in the population. Therefore, recommended vaccinations should continue to be administered and the recommendation to ensure a wider and adequate vaccination coverage for meningococcal disease appears even more important.

IMD is a rare but severe vaccine-preventable disease that has garnered great public attention due to its seriousness and unpredictability as well as the long-term impact of sequelae. The key role of public health is to go beyond the emotional epidemiology and have a broader view of the disease and its consequences, as well as monitor serogroups, trends and outbreaks and strengthen methodological evidence-based tools for decision-making processes, public health policies, planning of health care services and intervention measures, including immunization.

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Conflicts of interest statement

SI, LB, SP and GCL work for Sanofi Pasteur Italia. The other authors declare no conflict of interest.

Authors' contributions

Conceptualization: SI, LB, AT, CA, PB, PC, MC, SE, GG, GI, PLL, FV, SP and GCL; methodology: SI, LB and AT; acquisition of data: SI, LB, AT and GCL; formal analysis: SI, LB and AT; interpretation of data: SI, LB, AT, CA, PB, PC, MC, SE, GG, GI, PLL, FV, SP and GCL; writing - original draft: SI, LB, AT and SP; writing - review and editing: SI, LB, AT, CA, PB, PC, MC, SE, GG, GI, PLL, FV, SP and GCL; supervision: GCL; project administration: GCL. All authors have read and agreed to the submitted version of the manuscript.

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Supplementary data

Tab. SI. Cases of invasive meningococcal disease according to serogroup and year, Italy, 2011-2017.

	Year														Overall (2011-17)	
	2011		2012		2013		2014		2015		2016		2017			
	N	% Out of the total typed	N	% Out of the total typed	N	% Out of the total typed	N	% Out of the total typed	N	% Out of the total typed	N	% Out of the total typed	N	% Out of the total typed	N	% Out of the total typed
Serogroup																
A	1	0.9%	1	0.9%	0	0.0%	1	0.9%	0	0.0%	0	0.0%	0	0.0%	3	0.3%
B	76	65.0%	55	51.4%	56	48.3%	55	47.8%	49	34.3%	69	36.3%	74	41.3%	434	44.9%
C	20	17.1%	32	29.9%	36	31.0%	36	31.3%	63	44.1%	80	42.1%	57	31.9%	324	33.5%
W	4	3.4%	1	0.9%	5	4.3%	8	7.0%	7	4.9%	13	6.8%	12	6.7%	50	5.2%
X	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.7%	3	1.6%	2	1.1%	6	0.6%
Y	16	13.7%	18	16.8%	19	16.4%	15	13.0%	23	16.1%	25	13.2%	34	19.0%	150	15.5%
IMD with serogroup notified	117		107		116		115		143		190		179		967	
IMD without serogroup notified	35		30		56		49		46		37		19		272	
Total IMD notified	152		137		172		164		189		227		198		1,239	
% of the total IMD with serogroup notified	77.0%		78.1%		67.4%		70.1%		75.7%		83.7%		90.4%		78.0%	

IMD: invasive meningococcal disease.

Fig. S1. Proportion of cases in subjects ≥ 15 years divided for serogroup B versus ACWY versus X, 2015-2017.

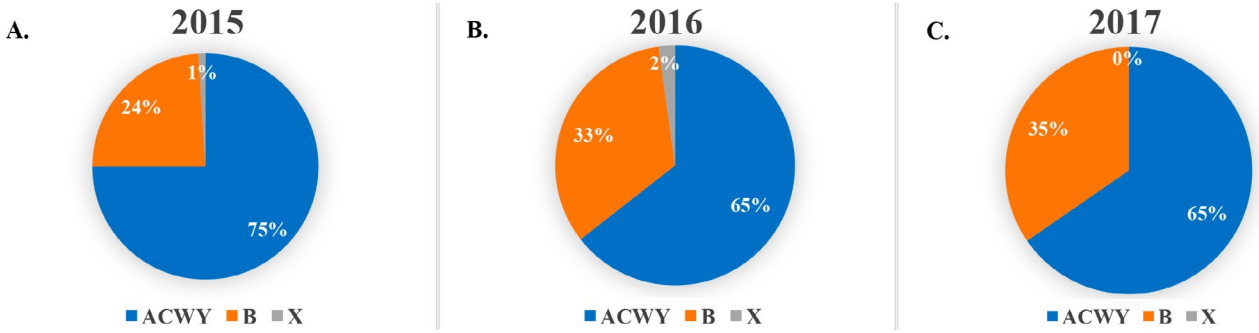
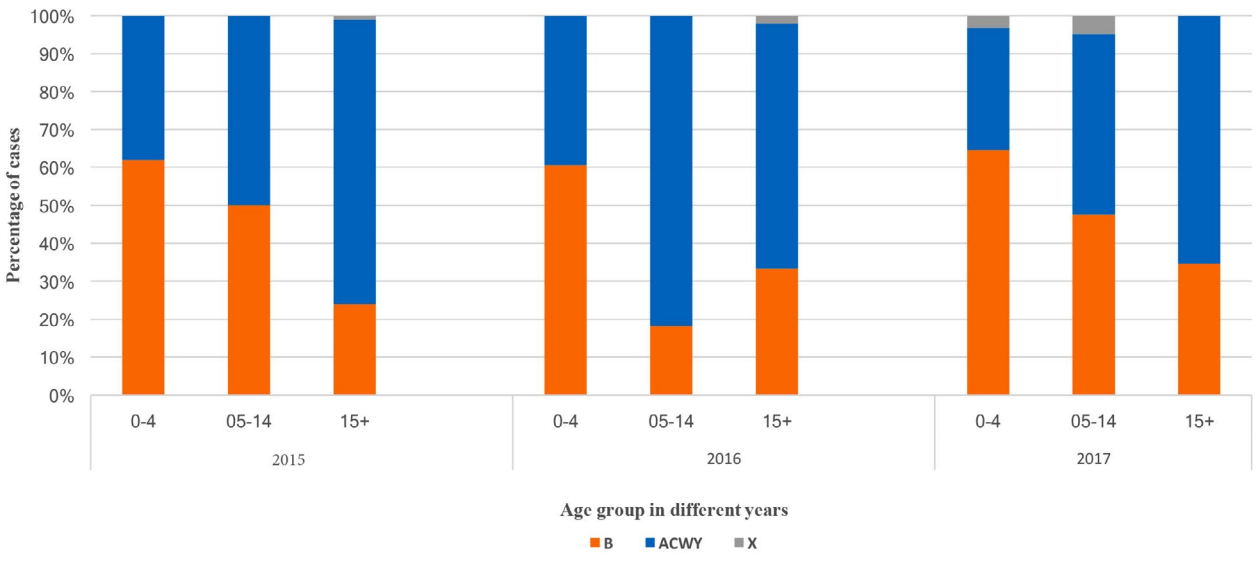


Fig. S2. Proportion of cases for serogroup B versus ACWY versus X and age groups, 2015-2017.



ORIGINAL ARTICLE

Bacterial invasive infections in a neonatal intensive care unit: a 13 years microbiological report from an Italian tertiary care centre

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Keywords

NICU • Invasive infections • Colonization • *Staphylococcus aureus*

Summary

Introduction. *To evaluate the aetiology of neonatal invasive diseases (positive cultures from blood or cerebrospinal fluid, CSF) due to bacteria other than coagulase-negative staphylococci in a large tertiary care centre and compare with results of surveillance cultures.*
Methods. *Retrospective analysis of microbiological data of children admitted in neonatal intensive care unit (NICU) of a large tertiary care centre from 2005 to 2018.*
Results. *230 bacterial strains, 223 from blood and 7 from CSF, respectively, were detected as cause of invasive infections, while 152 were detected in surveillance cultures. Methicillin-susceptible Staphylococcus aureus (MSSA) was the most frequently isolated pathogen both in invasive infections (18%) and colonizations (23%) followed by Escherichia coli (16% on invasive disease and 20% of colonizations). Other common bacteria include Enterococcus faecalis and Streptococcus agalactiae for invasive disease and methicillin-resistant Staphylococcus aureus in colonizations. Invasive infection was due to a pathogen detected in surveillance cultures in 33% of cases. In more than 50% of invasive diseases the identified pathogen was not present in surveillance cultures.*
Conclusions. *The high percentage of invasive infections due to bacteria not previously identified in surveillance cultures raises doubts about the efficiency of this procedure and highlights the need to search for alternative infection sources. This finding and the high prevalence of invasive infections due to nosocomial pathogens such as Staphylococcus aureus could be the result of horizontal transmission between patients through the hands of health care professionals, emphasizing once again the importance of applying stringent hand hygiene procedures and isolation standards.*

Introduction

Invasive infections are a leading cause of morbidity and mortality in pre-term infants with wide differences between countries [1]. Despite the lack of a consensual definition for neonatal sepsis, this clinical condition is usually considered in the presence of a positive culture from blood or cerebrospinal fluid [2], associated with different clinical signs or symptoms, that might be non-specific. Initial symptoms might be few and could include apnoea or tachypnoea or temperature variations. Later on, signs of poor perfusion (as pallor and/or mottled skin) associated with tachycardia or bradycardia may appear. Respiratory symptoms include apnoea, distress or cyanosis. On the neurological side irritability or lethargy could be frequently seen [3].
Neonatal sepsis is traditionally divided in early onset (occurring in the first 72 hours of life) and late onset (occurring after 72 hours) with different pathogens involved. The most common agents associated with early-onset neonatal sepsis are *Streptococcus agalactiae* (group B streptococci, GBS) and *Escherichia coli*. Both are pathogens that typically colonize the maternal genitourinary tract and may infect the newborn whether in utero or during delivery. *Listeria monocytogenes* and non-typeable *Haemophilus influenzae* have also been implicated in early-onset neonatal sepsis, although less frequently [4]. Late onset sepsis recognise a higher prevalence of Gram-positive bacteria (*Staphylococcus aureus* and coagulase-negative staphylococci, CoNS) as a result of postnatal exposure to healthcare: contacts with hospital staff, contaminated devices (mainly central catheters in preterm infants) and parents [3, 5].
The aim of this study was to report microbiology of invasive infections and colonizations by bacteria other than common skin contaminants in patients admitted in a neonatal intensive care unit (NICU).

Materials and methods

Istituto Giannina Gaslini, Genoa, Italy, is a children's care hospital in northern Italy serving as local paediatric hospital for the Genoa area and also representing a tertiary care centre for the whole Italy and many foreign countries. According to the Italian law, to be defined as "third level", paediatric and neonatological functional units must have no less than 1000 births/year, a catchment area of at least 5000 births/year and accept births that require any kind of assistance including intensive care.

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Microbiological data from patients admitted in NICU, from January 2005 to October 2018 were anonymously extracted from the Laboratory of Microbiology database, according to Istituto Gaslini data protection policy based on European Union Data Protection Rules (https://ec.europa.eu/commission/priorities/justice-and-fundamental-rights/data-protection/2018-reform-eu-data-protection-rules_en). As a consequence, demographic and clinical data could not be retrieved, but only data on ward of admission and site of isolation were available.

In the NICU the surveillance cultures protocol calls for nasal, pharyngeal and rectal swab, and tracheal aspirates in those who are invasively ventilated [6] to detect potentially pathogens, including carbapenem-resistant enterobacteria [7]. These cultures are performed at time of 1st admission and then repeated weekly. For the purpose of the present study in case of multiple isolations of the same pathogen in a single patient only the first one isolation was considered. In case of clinical suspicion of invasive disease blood cultures and cultures from clinically relevant sites, included cerebrospinal fluid (CSF) are performed. Invasive infections were defined by isolation of pathogens from blood or cerebrospinal fluid diagnosed in presence of a positive blood or CSF culture.

Blood or CSF cultures yielding CoNS were excluded from the analysis since the lack of clinical data on patients implied the impossibility to define a real infection (invasive or localized) rather than a bacterial contamination.

Statistical analysis

Categorical variables were reported as proportions (percentages, %), while continuous variables were described in terms of median and inter quartile range (1st and 3rd quartile, IQR) because of their non-normal distribution. The epidemiology of bloodstream infections and colonizations was analysed by calculating the rate of episodes, i.e. the number of invasive infections or first episode of colonization observed in one year divided by the total number of admissions in the same period and expressed as episodes/1,000 admissions. The evaluation of changes in rates during the study period were performed with the Pearson's correlation coefficient (r) that is a measure of linear association between two variables. To test whether the association between year and isolation rates was merely apparent and might have arisen by chance we used the t test in the following equation: $t = r\sqrt{[(\text{number of observations} - 2 \text{ degrees of freedom})/(1-r2)]}$. The t value was compared with specific tables of two-tailed distribution, and a $P \leq 0.05$ was considered as significant [8]. Calculations of r and t coefficients were performed by means of Microsoft Excel 365 for Windows (Microsoft Corporation 2019).

Results

During the study period 230 bacterial strains fulfilled our inclusion criteria: 223 from blood and 7 from CSF, detected in 198 patients. A total of 152 strains were detected in surveillance cultures in 61 patients.

Table I reports on absolute numbers and proportions of different pathogens causing invasive infections or colonizations. Methicillin-susceptible *Staphylococcus aureus* (MSSA) was the commonest isolated pathogen in invasive infections (17.8%) followed by *Escherichia coli* (16.5%), *Enterococcus faecalis* (14.8%) and *Streptococcus agalactiae* (10%). Among Gram-negatives causing disease carbapenem resistance was observed in 1 *Pseudomonas aeruginosa* strain, but in no case of invasive infection due to *Enterobacteriales*.

MSSA was the most frequently identified pathogen (23.2%) also in case of colonization, followed by *Escherichia coli* (19,9%) and methicillin-resistant *Staphylococcus aureus* (MRSA) (11.3%). None of Gram-negatives colonizing patients resulted carbapenem resistant.

A total of 76 strains (33% of those observed in invasive diseases) were detected both in blood and surveillance cultures: for 56 bloodstream infection followed colonization detection after a median of 7 days (IQR 2.5-21.5), while for other 20 (8.6%) blood and surveillance cultures resulted positive on the same day. Other 42 strains (18.3%) causing invasive infections were not present among bacteria already colonizing the patient. Finally, 116 (50.0%) strains were isolated in absence of any colonization.

Table II reports the yearly rate of invasive infections during the study period and the rate of infections due to pathogens colonizing the patient.

Mean crude rate of invasive infection was 73 with a minimum of 27 and maximum of 168.7 in 2012. Mean rate of sepsis by the same pathogen from a previous colonization was 23.5 with a maximum of 40 in 2016. During the study period there was an increase in the rate of invasive infections. The analysis of possible correlations between rate of bloodstream infections or colonizations and year of observation showed t values of 0.377 and 1.72, respectively, without significant differences.

Discussion

In the present study we analysed the epidemiology of invasive bacterial infections due to pathogens other than "common" skin contaminants, in neonates admitted in NICU in a tertiary care Italian centre. A colonizing agent was the cause of 33% of invasive infections, with a median of 7 days between colonization and disease occurrence, and in less than 10% of cases the same agent was detected in blood and surveillance cultures collected on the same day. Noteworthy near 20% of diseases was due to non-colonizing microorganisms and in ½ of cases of bacteraemia it was observed in absence of any colonization. As a consequence, we could estimate that surveillance cultures detect only 1/3 of pathogens that will cause invasive disease in our NICU.

Tab. I. Bacterial prevalence in invasive infections and colonizations (n = absolute number).

Pathogen	Pathogens isolated in invasive infections (total 230)		Pathogens isolated in surveillance cultures (total 152)		Concomitant (same day) isolations in surveillance cultures and invasive disease (total 72)	
	N	% over total positive blood or CSF cultures	N	% over total colonizations	N	% over total invasive diseases
Methicillin susceptible *Staphylococcus Aureus*	41	17.8	35	23.0	19	8.3
Escherichia coli	38	16.5	30	19.7	17	7.4
Enterococcus faecalis	34	14.8	4	2.6	1	0.4
Streptococcus agalactiae	23	10.0	4	2.6	4	1.7
Klebsiella pneumoniae	20	8.7	11	7.2	6	2.6
Methicillin resistant *Staphylococcus Aureus*	19	8.3	17	11.2	9	3.9
Klebsiella oxytoca	15	6.5	7	4.6	2	0.9
Enterobacter cloacae	11	4.8	10	6.6	3	1.3
Serratia marcescens	5	2.2	7	4.6	3	1.3
Enterobacter aerogenes	4	1.7	3	2.0	1	0.4
Enterococcus spp.	3	1.3				
Enterococcus faecium	2	0.9				
Haemophilus influenzae	2	0.9				
Listeria monocytogenes	2	0.9	1	0.7	1	0.4
Morganella morganii	2	0.9				
Citrobacter koseri	1	0.4	2	1.3	2	0.9
Citrobacter spp.	1	0.4				
Enterobacter spp.	1	0.4	1	0.7	1	0.4
Klebsiella spp	1	0.4	1	0.7	1	0.4
Proteus mirabilis	1	0.4	1	0.7	1	0.4
Pseudomonas aeruginosa	1	0.4	4	2.6		
Serratia plymuthica	1	0.4				
Stenotrophomonas maltophilia	1	0.4	4	2.6		
Streptococcus pneumoniae	1	0.4	1	0.7	1	0.4
Acinetobacter baumannii			4	2.6		
Bacillus cereus			2	1.3		
Citrobacter freundi			1	0.7		
Serratia liquefaciens			1	0.7		
Serratia spp.			1	0.7		

Tab. II. Year-on-year trend in invasive infection in NICU (n = absolute number).

	Admissions (N)	Invasive infections (N)	Rate	Invasive infections by the same pathogen previously colonizing the patient (N)	Rate
2005	67	4	59.7	1	14.9
2006	277	17	61.4	9	32.5
2007	197	11	55.8	7	35.5
2008	90	11	122.2	2	22.2
2009	234	14	59.8	5	21.4
2010	258	7	27.1	1	3.9
2011	230	14	60.9	3	13.0
2012	166	28	168.7	5	30.1
2013	191	13	68.1	4	20.9
2014	253	11	43.5	6	23.7
2015	280	15	53.6	5	17.9
2016	273	21	76.9	11	40.3
2017	312	13	41.7	6	19.2
2018	213	26	122.1	7	32.9

N: absolute number; rate: episodes/1,000 admissions.

Invasive disease can follow colonization because of barrier leak, an event related with pathophysiology of neonate (e.g. immaturity of skin and gut barriers) influenced by iatrogenic factors such as insertion and/or manipulation of devices (e.g. central venous catheters) or therapies (e.g. use of proton pump inhibitors) [9]. On the other hand, bacteremia from non-colonizing pathogens could derive from cross transmission between patients in the same ward, and the transfer may not only take place directly via healthcare workers hands, but also indirectly through contamination of the patient-unit. In departments with high-intensity care and long hospital stays such as NICUs, this problem is particularly important [10]. It is likely, but not directly provable, that this type of transmission was one of the main causes of the majority of invasive infections observed in our study. MSSA was the most commonly colonizing pathogen associated with invasive infection, and this observation is similar to that reported in other third-level centres [11, 12]. The 26% prevalence of *S. aureus* (MSSA and MRSA) infections we observed in our study is higher than that observed in other series [13, 14], but there may be differences related to local factors that could affect the results. Interestingly, we observed also a non-negligible proportion of GBS (10% of all invasive infections and 2.6% of surveillance cultures) as a cause of late infection, confirming our previous results [15]. In this case we can hypothesize a role of maternal late colonization transmitted via breast milk [15].

As regards Gram-negatives, the most frequently isolated pathogen in invasive diseases was *Escherichia coli* (16%) followed by *Klebsiella pneumoniae* (9%) and *Klebsiella oxytoca* (6%). These proportions are different to that reported in other studies [16-18], but also in this case local factors could represent the leading cause for the observed discrepancies.

Beyond the relationship between colonization and infection in a given patient, there is the problem of horizontal transmission (i.e. cross infections by healthcare workers hands). A single study sought to create a model of indirect transmission between patients through the hands of healthcare workers in a context completely different and not comparable with a NICU (adult surgery unit) [19]. Hand hygiene is the first rule to be applied in order to interrupt the chain of contamination (both of patient-unit and directly to the patients) and infection: the aforementioned study [19], clearly documented that the proportion of hand hygiene procedures adherence is inversely proportional to pathogens transmission. In a study conducted in our Institution we estimated the average number of hand hygiene procedures in different wards including NICU that showed a very high number of correct procedures [20]. In spite of this, it is likely, but not directly provable (given the limits of our methods relying solely on culture data and not molecular typing), that the majority of invasive infections observed in our study could have been due to pathogens not colonizing the patient but brought in some way by the hands of the staff, by means of a not correct approach [17].

Finally, the efficiency and role of surveillance cultures for identification of pathogens causing invasive diseases in NICU is still to be completely determined. The problem is not easy to solve since it has been proved that interventions aimed at promoting hand hygiene alone may not be sufficient to reduce the incidence of some pathogens, in particular multi-resistant ones [17]. Therefore, isolation procedures and correct hand hygiene must be implemented and constantly maintained especially in high risk wards as NICU [20].

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

MM collected data, analyzed results and drafted the manuscript. RB designed the study, collected data and reviewed the manuscript. DLM analyzed results and reviewed the manuscript. DM collected data a, analyzed results and reviewed manuscript. IB, SS, AM and CS analyzed results and reviewed the manuscript. LR designed the study and reviewed the manuscript. EC designed the study, analyzed results and reviewed the manuscript. All authors critically reviewed the manuscript and approved the final version.

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ORIGINAL ARTICLE

Laboratory-based surveillance of invasive listeriosis in Northern Italy over a fourteen-year period: epidemiological and clinical results

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Keywords

Listeria monocytogenes • Listeriosis • Surveillance

Summary

Introduction. *Invasive listeriosis is a rare foodborne disease with a significant impact on public health worldwide, because of the severity of its clinical manifestations and high fatality rate. In this study, we provide a snapshot of epidemiology of listeriosis in Lombardy Region, Northern Italy, reviewing enhanced surveillance data collected over fourteen years, after the implementation of a voluntary laboratory-based surveillance system for the referral of clinical isolates of Listeria monocytogenes to a regional reference laboratory, since 2005.*
Methods. *Invasive listeriosis cases data from 2005 to 2018 were extracted from the regional laboratory-based surveillance system database and compared with the regional mandatory notification disease system data.*
Results. *Over the fourteen-year period under study, 533 Listeria monocytogenes isolates were detected by the laboratory surveillance system, 55 of which from pregnancy-related cases. The median age of non-pregnancy-associated patients was 71 years, with 64.6% of cases observed in the elderly. Cases with underlying medical risk conditions accounted for 92.1%, and the fatality rate was 26.2%. By integrating data from the mandatory notification system and the laboratory-based surveillance system, a total of 935 cases were recorded. The collection of data through the laboratory surveillance system allowed to increase the surveillance sensitivity by 18%.*
Conclusions. *Our results documented the growing epidemiological relevance of listeriosis through the analysis of two information sources, the regional mandatory notification system and the regional laboratory-based surveillance system. The data we obtained were consistent with the literature, except for pregnancy-related cases, which are often underdiagnosed. This study highlighted the importance of laboratory-based surveillance system, which led to a significant increase in the sensitivity of the mandatory notification system.*

Introduction

Listeriosis is a foodborne illness caused by the bacterium *Listeria monocytogenes*, with a relatively low incidence of disease among the 28 European Union Member States (0.47 per 100,000 population) [1]. Nevertheless, it is of major public health concern, because of the severity of its clinical manifestations (hospitalization rate > 90%) and the high fatality rate (20-30%) [2-4], mainly among the pregnant women, neonates, elderly and immunocompromised patients [5].
In Italy, since 1990, invasive listeriosis is subjected to mandatory notification, and the notification rate in 2018 was 0.29 per 100,000 population [1]. The majority of notified listeriosis cases (55%) is reported by Lombardy Region (Northern Italy), the most populous region in Italy, with 17% of the population [6], and a notification rate of 0.70 per 100,000 population [7]. Investigation on the transmission route is complex because of the long incubation period of the invasive infection (up to 70 days), foods with a long shelf-life and the probable high number of asymptomatic infections in people exposed to the same infection vehicle [4, 8, 9]. Moreover, the contemporary exposition of several people to the same food vector may result in a succession of apparently unrelated cases [10]. Therefore, it is essential that conventional epidemiology be supported by the molecular investigation, which allow to distinguish between outbreak-related and sporadic cases, and link cases to particular food and animal sources [11]. Since 2005, Lombardy Region holds an enhanced surveillance system that involves a voluntary laboratory-based network [12]. Hospital laboratories participating in the surveillance network voluntarily send clinical isolates to the Regional Reference Laboratory (RRL), which collects clinical and epidemiological data and carries out molecular subtyping. All the *Listeria monocytogenes* isolates are sent to the ECDC Operational Contact Point for *Listeria monocytogenes*, at the National Institute of Health (Istituto Superiore di Sanità, ISS), for further typing and characterization. The present study was undertaken to describe the epidemiological and clinical results of the laboratory-based surveillance system in Lombardy Region from the beginning of the surveillance (2005) until December 2018. The aims were to make a comparison with mandatory notification system data over the same period and to assess how much laboratory-

based network has increased the sensitivity of the surveillance system in Lombardy Region.

Methods

The laboratory-based surveillance program in Lombardy Region is performed with the delivery of *Listeria monocytogenes* isolates from hospitalized clinical cases to the RRL, which routinely carries out pulsed-field gel electrophoresis (PFGE) typing and whole-genome sequencing (WGS). The isolates are sent along with a standardized report form, agreed with ISS, used to collect: i) demographic data (e.g. age, gender, province of residence); ii) clinical data (e.g. symptoms, clinical form of disease, existence of underlying conditions, outcome); and iii) microbiological data. All data of the *Listeria monocytogenes* isolates from human cases occurred in Lombardy Region between 2005 and 2018 and collected by the RRL were included in our study. In case there were two or more isolates from the same patient only the first one was included in the analysis. For the purposes of the present work, an invasive listeriosis case was defined as an isolate of *Listeria monocytogenes* from a normally sterile site. A pregnancy-related listeriosis case was defined an isolate of *Listeria monocytogenes* from clinical sample of pregnant woman or foetus, stillborn, new-born aged < 28 days. Confirmed cases with isolation of *Listeria monocytogenes* from both mother and infant were considered as single cases. In order to make a comparison with regional mandatory notification system data, all available information regarding listeriosis cases were extracted from the regional web-based database MAINF (Sistema di sorveglianza notifiche di malattie infettive), and all listeriosis cases from MAINF and RRL were cross-matched according to whether they were present or absent in each data source. The detection of the same individuals in the two sources was determined by name, sex, age and date of hospitalization or symptom onset, and a joint database was generated, in order to include all reported cases of both systems. Observed cases were defined as the sum of cases reported only in MAINF, those recorded only by RRL and those present in both surveillance systems.
The statistical analyses were performed by chi-square test, using OpenEpi software (version 3.01).

Results

A total of 533 *Listeria monocytogenes* isolates were collected by the RRL between 2005 and 2018, 55 of which from pregnancy-related infection cases (10.3%) (Tab. I). The median age of non-pregnancy-associated patients was 71 years, with 64.6% of cases observed in people older than 65 years. The prevalent clinical manifestations were sepsis (62.1%) and central nervous system infections (28.9%). Atypical and rare forms of the infection were also detected: two cases of endocarditis, two cases of endophthalmitis and a case of periprosthetic joint infection. The number of patients whose outcome was known was 267, and the fatality rate was 26.2%. Cases with underlying medical risk conditions accounted for 92.1%, including cancer (32.2%), renal failure (10.1%), hemopathies (7.8%) and diabetes (7.3%). Fourteen pregnancy-related infection cases (31.8%) resulted in foetal death, miscarriage or stillbirth.
In the same period, MAINF recorded a total of 790 notified cases (Tab. I). Sixty-eight were pregnancy-related cases (8.6%). The median age of non-pregnancy related patients was 72 years, with 67.4% of cases observed in elderly patients (≥ 65 years). Sepsis was the most common clinical manifestation (49.6%), followed by meningitis and other central nervous system infections (28.7%). Cases with known outcome were 454, and the fatality rate was equal to 24.7%. Five hundred and ninety-six notified cases (90.3%) had at least one underlying risk condition for developing listeriosis: among others, cancer (30.1%), renal failure (8.3%), diabetes (8.2%) and hemopathies (3.6%). Seventeen pregnancy-related infection cases (33.3%) resulted in foetal death, miscarriage or stillbirth.
No significant differences were found between the variables reported in Table I, based on the chi-square test.
The distribution by year of listeriosis cases from the two data sources MAINF and RRL and total observed cases by year are presented in Table II. Overall, the two sources observed a total of 935 cases over a 14-year period, with an average of 66.8 cases per year. The incidence of the observed listeriosis cases in Lombardy is included in the range 0.29 per 100,000 population (2005) - 0.97 per 100,000 population (2011), with an average of 0.68 per 100,000 population. Considering the cases reported by the two sources and the cases observed through the cross-matched data, the increasing tendency is evident, as well as the presence of two peaks, one in 2009-2011 and one in 2017 (Fig. 1).
The distribution of listeriosis cases in the twelve provinces of Lombardy is shown in Table III and Figure 2. A third of the observed cases (311 out of 935) were recorded in the province of Milan, which with over 3,000,000 inhabitants corresponds to a third of the Lombardy population. The distribution of cases is not homogeneous, the incidence varies in a wide range, from 0.21 per 100,000 inhabitants to 1.00 per 100,000 inhabitants (Fig. 2).
The collection of data through the RRL system, which identified 145 cases not notified to the MAINF system, allowed to increase the surveillance sensitivity by 18% (Tab. II). The increase in sensitivity is particularly evident in 2007 (+ 35.3%) when there were 46 cases, 34 of which reported by the official notification system and 23 by the laboratory surveillance system, with an overlap of only 11 cases. As shown in Table III, the laboratory surveillance system resulted in an increase in sensitivity not uniformly distributed in the twelve provinces and, above all, concerned two of them, Brescia and Lodi (+ 40.0% and + 47.1%, respectively).

Tab. I. RRL and MAINF databases: main features of non-pregnancy and pregnancy-related listeriosis cases occurred in Lombardy Region, 2005-2018. All variables were calculated for patients with known information.

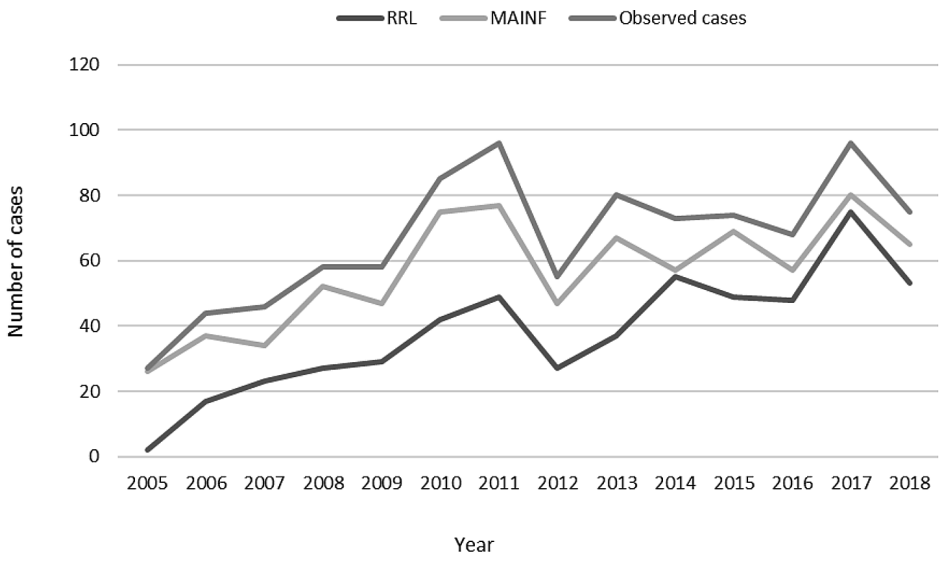
Characteristics	RRL (%)		MAINF (%)	
Number of cases	533		790	
Pregnancy-related cases	55	(10.3)	68	(8.6)
– fatality rate*	14	(31.8)	17	(33.3)
Non-pregnancy related cases	478	(89.7)	722	(91.4)
– median of age (years)	71		72	
– patients ≥ 65 years	309	(64.6)	487	(67.5)
– m:f	1.19		1.23	
– underlying condition	399	(92.1)	596	(90.3)
– fatality rate	70	(26.2)	112	(24.7)

*: no maternal fatality was recorded.

Tab. II. Listeriosis cases from two data sources (MAINF and RRL) and total observed cases by years of diagnosis.

Year	MAINF	RRL	MAINF only (A)	RRL only (B)	Both sources (C)	Observed cases (A+B+C)	B/A+C	Incidence per 100,000 population
2005	26	2	25	1	1	27	3.9%	0.29
2006	37	17	27	7	10	44	18.9%	0.46
2007	34	23	23	12	11	46	35.3%	0.48
2008	52	27	31	6	21	58	11.5%	0.60
2009	47	29	29	11	18	58	23.4%	0.60
2010	75	42	43	10	32	85	13.3%	0.87
2011	77	49	47	19	30	96	24.7%	0.97
2012	47	27	28	8	19	55	17.0%	0.57
2013	67	37	43	13	24	80	19.4%	0.82
2014	57	55	18	16	39	73	28.1%	0.72
2015	69	49	25	5	44	74	7.3%	0.74
2016	57	48	20	11	37	68	19.3%	0.68
2017	80	75	21	16	59	96	20.0%	0.96
2018	65	53	22	10	43	75	15.4%	0.75
Total	**790**	**533**	**402**	**145**	**388**	**935**	**18.4%**	**0.68**

Fig. 1. Listeriosis cases from two data sources (MAINF and RRL) and total observed cases by years of diagnosis.



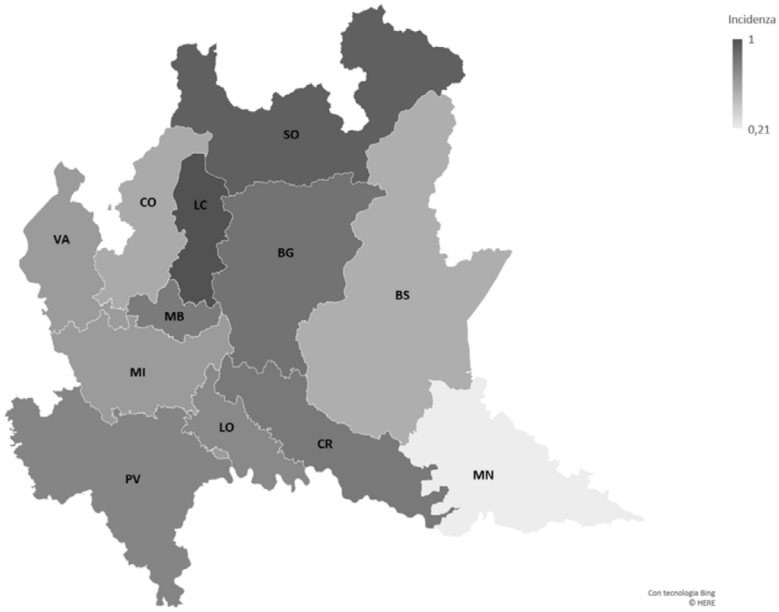
Discussion and conclusions

Although listeriosis has been included in the mandatory notification-based surveillance system in Italy since 1990, accurate data on epidemiology of this severe foodborne disease are still very limited. This study showed the results of the laboratory-based surveillance of listeriosis in Lombardy Region over the period 2005-2018, in comparison with mandatory notification system data, in order to learn more about the health impact of *Listeria monocytogenes* infections. The epidemiological scenario, without significant differences between the

Tab. III. Listeriosis cases from two data sources (MAINF and RRL) and total observed cases by Lombardy's provinces.

Province	MAINF	RRL	MAINF only (A)	RRL only (B)	Both sources (C)	Observed cases (A+B+C)	B/A+C	Incidence per 100,000 population
BG	113	77	48	12	65	125	10.6%	0.83
BS	70	66	32	28	38	98	40.0%	0.53
CO	37	24	23	10	14	47	27.0%	0.55
CR	38	8	31	1	7	39	2.6%	0.80
LC	44	15	30	1	14	45	2.3%	1.00
LO	17	19	6	8	11	25	47.1%	0.72
MN	11	2	9	0	2	11	0.0%	0.21
MI	249	197	114	62	135	311	24.9%	0.63
MB	67	59	21	13	46	80	19.4%	0.79
PV	47	30	24	7	23	54	14.9%	0.74
SO	24	0	24	0	0	24	0.0%	0.93
VA	73	36	40	3	33	76	4.1%	0.63
Tot	**790**	**533**	**402**	**145**	**388**	**935**	**18.4%**	**0.68**

Fig. 2. Geographical distribution of the mean annual incidence (cases per 100,000 population) of observed listeriosis cases in Lombardy Region during the period 2005-2018.



two sources, is consistent with the literature, except for the proportion of pregnancy-related cases, lower than reported in literature (20-43%) [13]. It is not clear if this lower frequency is real or due to underdiagnosis or underreporting of pregnancy related cases. Underdiagnosis could be more likely, considering that earlier stages miscarriage may be seldom investigated. On the other hand, the use of diagnostic tool for the detection of the pathogens in blood culture and CSF culture in non-pregnancy-related cases, mostly sepsis and meningitis in immunocompromised patients, are routinely performed [13].

As expected, the most affected age group was the elderly people [4] and, in most cases, one or more underlying immunosuppressive conditions were present. In the elderly, the most common clinical manifestation was sepsis. The fatality rate for non-pregnancy-associated cases (26.2%) was higher than that reported by the last ECDC report (15.6%), while for pregnancy-related cases the fatal outcome was observed in the 25% of cases [1]. This difference could be explained by a higher propensity to diagnose and report severe cases, with a frequently fatal outcome.

In Lombardy, the mean annual incidence of observed cases (0.68 per 100,000 population), obtained by integrating data from the two surveillance systems, was not homogeneously distributed neither in the twelve provinces (0.21 per 100,000 population - 1.0 per 100,000 population) nor in the considered years (0.29 per 100,000 population - 0.97 per 100,000 population). In particular, although no epidemic events were officially notified, a higher concentration of the number of cases in spotted areas and in certain periods was observed. More in detail, peaks in the years 2009-2011 in the provinces of Bergamo and Milan and in 2017 in the provinces of Brescia and Milan were identified. The laboratory-based surveillance allowed to identify a major listeriosis outbreak, linked to soft cheese, occurred in 2009-2011,

which went undetected by local health authorities [14]. Concerning the second peak occurred in 2017, the epidemiological investigation did not point out any link between cases, even though an outbreak was suspected.

In Europe, outbreak-related cases are apparently not frequent: in the report published in 2019 by the ECDC [1], only 158 out of 2561 cases reported in Europe (6.2%) belong to an outbreak (14 outbreaks in total). This rare outbreak identification could only be apparent and could represent the consequence of a series of difficulties deriving from the peculiar characteristics of *Listeria monocytogenes* infections. Indeed, the epidemiological investigation is often intricate because of many concurrent factors, such as the contamination of foods with long shelf lives, the long incubation period and the low attack rate of exposed people that may allow a listeriosis outbreak to occur as a succession of apparently unrelated cases [4, 10].

Laboratory-based surveillance system, introduced in Lombardy Region fifteen years ago, not only has supported the recognition of outbreaks, but has also led to a significant increase in the sensitivity of official surveillance (overall + 18% in the study period). However, it is surprising that this increase in sensitivity is included in a very wide range (+ 3.8 in 2005, year of start of RRL and, only two years later, in 2007, + 35.4%) and fluctuating over the fourteen years observed. This oscillation could be explained by hypothesizing a different sensitivity of the laboratory surveillance, which acts on a voluntary basis and which is conditioned by the difficulties in sending the isolates from the provinces distant from the RRL [12]. This difficulty does not concern MAINF, since notifications are mandatory, and the surveillance system is web-based.

Overall, our results document a not inconsiderable incidence of listeriosis, equal to 0.68 per 100,000 population if we consider all the "observed cases", 0.60 per 100,000 population and 0.40 per 100,000 population if we calculate the incidence from MAINF system and laboratory-based system, respectively. The increasing tendency in incidence, observed by both independent data sources, is probably real, as it is not possible to hypothesize – at least for the MAINF system – significant changes in the sensitivity of the surveillance over the considered period. It is also probable that the data of our Region, even referring only to the officially notified cases, have strongly contributed to the increase observed at national level, and highlighted in the latest European report, which document a significant increase in listeriosis incidence for nine European countries, including Italy, in the period 2014-2018 [1].

The explanation of this increase could be related to the progressive increase of population at risk, both for age and for other underlying conditions (e.g. diabetes, cancer), without excluding the role of the eating habits of groups characterized by situations of social hardship or ethnic groups, as already reported in the United Kingdom [15, 16].

In conclusion, having documented the growing epidemiological relevance of listeriosis through the analysis of two information sources, in order to consolidate surveillance, reduce underestimation and promote a more effective ability to suspect and recognize epidemic events, we believe that notification system should be integrated with laboratory-based system. Laboratory-based surveillance system must not be a voluntary-based channel alongside the official notification system, but the results of molecular analysis should systematically and as soon as possible be merged into the same database, in order to identify clusters of possibly related listeriosis cases and outbreaks undetected by the traditional surveillance systems. In this direction, in Italy, listeriosis surveillance has been improved since the end of 2019, with the creation of the Integrated Rapid Infectious Disease Analysis (IRIDA) Advanced Research Infrastructure for Experimentation in GenomicS (ARIES) platform [17]. IRIDA-ARIES is an open-source software set up and maintained at the ISS, which collects genomic and epidemiological data from the regional reference laboratories, in order to get real time data for timely detection of clusters of listeriosis and other foodborne diseases.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

MG, GC and SB managed the databases, analysed and interpreted the data. MG, GC, MP and ET wrote the paper. MP and ET conceived the work and led the study group. AA contributed to the conception and design of the study and critically revised the manuscript. MG, SS and DC coordinated surveillance and control activities in Lombardy Region. All authors have read and approved the final version of the manuscript.

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ORIGINAL ARTICLE

Malaria prevalence and its sociodemographic determinants in febrile children - a hospital-based study in a developing community in South-East Nigeria

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Keywords

Children • Malaria • Prevalence rate • Parasite density

Summary

Background. *Malaria remains one of the major contributors of child mortality in many developing countries in Africa. Identifying its determinants will help in prevention and prompt intervention in these settings.*
Methods. *This cross-sectional descriptive study was conducted over an eight-month period. It enrolled 382 children who were presented with fever to the children outpatient and emergency unit of a tertiary hospital in South-east Nigeria. A structured questionnaire was used to collect information on socio-demographic factors. Blood film microscopy for malaria and parasite density was done on all subjects that tested positive for malaria.*
Result. *The malaria prevalence rate was 16.7%, 26.7%, 29.9% and 46.2% in children < 5 years, 5 to < 10 years, 10 to < 15 years and 15-17 years respectively. Logistic regression analysis showed that malaria was more prevalent in older children but children under the age of 5 years were more prone to higher parasite density. Also, children of mothers with lower educational attainment, children from families of lower socio-economic class and resident in rural settings had higher likelihood of malaria infection.*
Conclusions. *Sustained improvement in strategies to prevent malaria infection is still imperative in children of all ages, especially those under 5 years, children from families of low socio-economic class and those residents in rural communities.*

Introduction

Malaria is major public health issue that has globally seen several efforts to reduce morbidity and mortality in the past years with some impressive results [1]. These achievements are as a result of increased funding, scale up of intervention measures (such as the use of long lasting insecticidal nets (LLINs), intermitent preventive treatment (IPT) for pregnant women and vector control) [1]. Africa remains the region with the highest burden of malaria in the world [1]. Nigeria bears the burden of the highest number of cases and deaths than in any other country in the world, and it accounts for 30% of under five years old-mortality and 25% of infant mortality [2]. In line with the global achievements, Nigeria has also recorded laudable strides in malaria control through integrated vector management, prompt and effective case management [2]. Despite these gains, 97% of Nigeria's population are at risk of malaria [2]. Risk factors which predisposes one to malaria include environmental, socioeconomic and interventional factors [2, 3]. A high malaria prevalence had been reported in febrile kids under five years of age [4]. Recent data have shown lower prevalence in these patients with an increasing incidence in older children [5-7]. This was alluded to several interventional activities focused on these kids under five years of age. The decreasing parasite transmission in such subjects may have lead to loss of acquired functional immunity, making them even more susceptible to malaria at an older age [8-10]. Studies have similarly shown that caregiver illiteracy, poverty and ignorance place children at higher risk of infection [11, 12]. Conversely, Nigeria Malaria Indicator Survey (NMIS) reported a higher use of malaria preventive measures in the illiterate and poor despite the fact that educated and rich people have better knowlegde of malaria causes, prevention and treatment [13]. This was attributed to the fact that malaria intervention campaigns have been carried out heavily in rural communities where a greater percentage of these illiterate and poor respondents resided [13]. This trend if incessant is worrisome because the urban, literates and rich need to be reached for effective malaria control. As such, this study sought to determine the current sociodemographic determinants of malaria in ill children visiting a tertiary hospital which offers primary, secondary and tertiary levels of care to its catchment area.

Methods

Study area and design

This is a hospital based, cross-sectional descriptive study carried out between 2nd of June 2016 and 28th of January

2017 at Nnamdi Azikiwe University Teaching Hospital (NAUTH) Nnewi, one of the two tertiary institutions in Anambra State. Nnewi is a commercial city located in Nnewi North Local Government Area. Its population is 391,227 based on 2006 census estimate [14]. The people are predominantly Igbo speaking and mainly traders and civil servants. Nnewi is located on latitude 6º 01' N of the equator and longitude 6º 55' E of the Greenwich meridian [15]. It has a mean daily temperature of 30.4ºC, and mean annual rainfall of about 2,000 cm [15]. It falls within the tropical rain forest region of Nigeria with 2 main seasons: the rainy season spanning from April to October, and the dry season spanning from November to March [15]. The Children Outpatient (CHOP) clinic of the NAUTH is not part of the general outpatient clinic of the Hospital but under the Pediatric Department. Even though NAUTH is a tertiary institution which is supposed to be a referral center, the CHOP clinic functions as a primary, secondary and tertiary care facility as many patients from the community present there for the first time without any referral.

Study population

The study population consisted of children aged 6 months to 17 years who presented with fever at the CHOP clinic and children emergency room (CHER) of the Hospital. Inclusion criteria were axillary temperature > 37.4ºC or history of fever in the preceding 48 hours, children (< 6 years) whose caregivers gave consent and/or assent if child is ≥ 6 years. Excluded from the study were children who had received a full course of artemisinin combination therapy (ACT) in the current illness or on malaria prophylaxis prior to the onset of the extant illness.

Subjects' recruitment

The minimum number of children enrolled in this study was calculated using the Cochran formula for calculation of sample size based on a confidence interval of 95% which is equivalent to a confidence coefficient of 1.96, malaria prevalence of 20% in febrile children [5] and a non-response rate of 5%. This gave a minimum sample size of 246. Hence, 382 children were recruited. Febrile children were recruited consecutively using purposive sampling method. Once consent/assent was given, the child was screened by the investigators. The screening determined who was recruited into the study, and children who fulfilled the inclusion criteria were recruited into the study. Information obtained included biodata of the subject such as age, sex, parental occupation, highest educational level of either parent and place of residence. Socioeconomic class of the subjects was grouped into low, middle and high class using Oyedeji social classification indices [16].

Measures

Axillary temperature was taken using a digital thermometer (Domotherm® Germany, 0.2˚C sensitivity). The tip of the thermometer was placed at the apex of the axilla and held in place with upper limb adducted till a beep was heard. The displayed reading, in centigrade to one decimal place was taken as the child's temperature.

Laboratory procedure

Two laboratory scientists trained and certified in malaria microscopy by WHO assisted in preparation and reading of the thick and thin blood film for malaria microscopy. All the laboratory scientists who assisted in this study were blinded to the history and examination findings of the children. Two milliliters of blood were collected from each child and put in an ethylene diamine tetra-acetic acid (EDTA) bottle, maintaining aseptic and universal safety precautions all through. A code number was assigned to each EDTA bottle. The blood collected was subjected to tests within 24 hours of collection. Two slides were prepared for each sample; each slide had a measured volume of 6µl for the thick film and 2 µl for the thin film. Three percent working Giemsa stain was prepared with stock of Giemsa staining solution and working Giemsa buffer. The thin and thick blood films were stained for 45 to 60 mins with working Giemsa stain after fixing with absolute methanol. The entire film was screened at a low magnification (10X x 40X objective lens) to detect suitable fields with even distribution of white blood cells [17]. The film was then examined using X100 oil immersion. At least 100 high power fields were examined before a thick film was said to be negative. The parasites were counted against 200 leukocytes or 500 leukocytes where less than 9 parasites were counted after counting against 200 leukocytes. Malaria parasite density was calculated using the following formula [17]:

$$\frac{\textit{Number of parasites counted} \times \textit{Total leukocyte count}}{\textit{Number of leukocytes counted}}$$

Parasite density class ≤ and > 5,000/µl was regarded as light and heavy parasitemia respectively. Thin films were examined to identify the parasite specie. The blood film was said to be positive when a concordant result was produced by the two microscopists.

Ethical clearance

Ethical clearance was obtained from the Health Research and Ethics Committee of NAUTH Nnewi with reference number NAUTH/CS/66/VOL.7/44. Informed consent was obtained from each caregiver and assent from children who were 6 years and above.

Data analysis

The data was cleaned and entered into Statistical Package for Social Sciences (SPSS) version 23 Chicago, IL for analysis. The predictor and outcome variables were categorized accordingly, and association was compared using contingency tables such as chi-square (χ^2) or Fischer's exact analysis where appropriate. The p-value was considered statistically significant at < 0.05. Logistic regression analysis was used to determine the independent effect of the predictor variables on malaria parasitemia (Tab. I).

Tab. I. Logistic regression analysis of malaria parasitemia and socio-demographic factors of children seen for febrile illnesses in the outpatient and emergency room of NAUTH.

Factors	Variables	Odd Ratio (95% Confidence Interval)			
		Crude	P-value	Adjusted†	P-value
Age (years)	Less than 5	1	--	1	--
	5 to < 10	2.04 (0.33-0.94)	**0.031**	2.10 (1.09-4.04)	**0.027**
	10 to < 15	1.93 (0.94- 3.95)	0.073	2.21 (1.02-4.40)	**0.044**
	15 to 18	4.01 (1.61-10.03)	**0.003**	4.34 (1.72-10.93)	**0.002**
Gender	Male	1	--	1	--
	Female	3.32 (0.43-1.29)	0.299	0.75 (0.43-1.10)	0.297
Maternal education	Primary or less	3.75 (1.63-8.61)	**0.002**	2.90 (0.90-4.34)	0.075
	Secondary	2.62 (1.42-4.84)	**0.002**	2.68 (1.18-6.10)	**0.019**
	Tertiary or higher	1	**--**	1	--
Socio-economic class	Low	3.33 (1.32-8.42)	**0.011**	3.57 (1.38-9.21)	**0.009**
	Middle	1.15 (0.56-2.36)	0.706	1.07 (0.51-2.22)	0.865
	High	1	--	1	--
Place of residence	Urban	1	**--**	1	--
	Rural	1.94 (1.14-3.29)	**0.015**	1.93 (1.12-3.30)	**0.017**
Sleep under LLIN	No	1	--	1	--
	Yes	0.48 (0.28-0.84)	**0.010**	0.44 (0.25-0.80)	**0.007**

†: adjusted for gender, prior use of anti-malarial and use of other malaria control measures; bold P-values are statistically significant; LLIN: long-lasting insecticide nets.

Results

Characteristics of children surveyed

A total of 494 children presented with fever in the children outpatient and emergency department during the study period. Three hundred and eighty-two (91.8%) who were enrolled were analyzed. Children under-5 years old made up over half of enrolled children with a male-female ratio of 3:2. Table II shows other clinical and demographic features of children enrolled. Malaria parasite density was light in 22.6% and heavy in the remainder of cases (77.4%).

The mean parasite density was heaviest in children under-5 years of age (349, 290 per µL) and lowest in those 15-18 years (28,366.67 per µL), P = 0.223. Correspondingly, children under-5 years of age presented with a higher mean temperature compared to older children (P = 0.541) and the mean time from fever onset to presentation to the hospital was shortest in younger children (P = 0.045) Table III shows a summary of other selected clinical parameters based on their age categories.

Malaria prevalence among surveyed children

Figure 1 shows the overall prevalence of malaria. Out of the 382 febrile children, 89 (23.3%) were positive on thick blood film microscopy. All the parasites identified were *Plasmodium falciparum* (*P. falciparum*).

Table IV shows the malaria prevalence rate among the surveyed children stratified by socio-demographic parameters of interest in this study. Of the 203 children

Tab. II. Characteristics of children seen for febrile illness at the children outpatient and emergency unit of the Nnamdi Azikiwe University Teaching Hospital Nnewi.

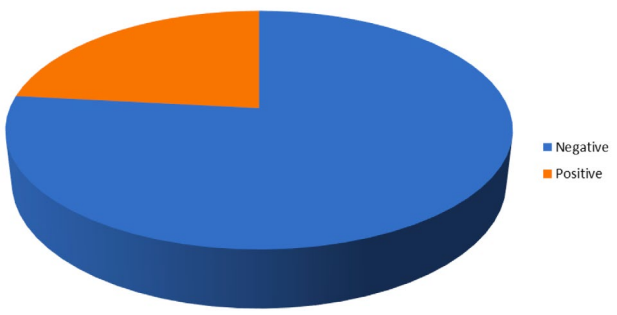
Characteristic	Variable	Number (n)	Percentage (%)
Gender (n = 382)	Male	230	60.2
	Female	152	39.8
Age (years) (n = 382)	< 5	203	53.1
	5 to < 10	86	22.5
	10 to < 15	67	17.5
	15-18	26	6.8
Place of residence (n = 382)	Urban	207	54.2
	Rural	175	45.8
Maternal education (n = 382)	Primary or less	43	11.3
	Secondary	111	29.1
	Tertiary or higher	228	59.6
Socio-economic class (n = 382)	Low	107	28.0
	Middle	148	38.7
	High	127	33.3
Malaria parasite density per µL (n = 89)	Light (< 5,000)	21	22.6
	Heavy (≥ 5,000)	68	77.4

Tab. III. Summary statistics of children seen for febrile illness at the children outpatient and emergency unit of the NAUTH stratified by age group.

Clinical parameters	N	Minimum	Maximum	Mean ± SD	ANOVA**	P-value
Age (years)						
Under-5	203	0.5	4.9	2.2 ± 1.3	158.00	**0.001**
5 to < 10	86	5.0	9.8	7.3 ± 1.4		
10 to < 15	67	10.0	14.8	12.0 ± 1.4		
15 to 18	26	15.0	17.9	16.4 ± 0.9		
Total	382	0.5	17.9	6.0 ± 4.9		
Axillary temperature						
Under-5	203	35.7	40.3	38.8 ± 0.97	0.72	0.541
5 to < 10	86	35.8	39.8	37.7 ± 1.1		
10 to < 15	67	36.0	40.2	37.8 ± 1.2		
15 to 18	26	35.8	39.3	37.4 ± 1.2		
Total	382	35.7	40.3	37.8 ± 1.0		
Fever duration						
Under-5	203	0.0	7.0	2.6 ± 2.3	2.70	**0.045**
5 to < 10	86	0.1	14.0	3.3 ± 3.2		
10 to < 15	67	0.3	14.0	3.4 ± 2.8		
15 to 18	26	1.0	21.0	5.4 ± 5.8		
Total	382	0.0	21.0	3.6 ± 3.4		
Parasite density						
Under-5	203	828	3,938,534	349,290.38	1.49	0.223
5 to < 10	86	623	525,200	58,790.17		
10 to < 15	67	1403	778,707	165,828.05		
15 to 18	26	494	112,715	28,366.67		
Total	382	494	3,938,534	189,719.19		

**: ANOVA-analysis of variance; dold values of P are statistically significant.

Fig. 1. Malaria parasitaemia.



under the age of five years evaluated, 34 had a positive malaria test giving a malaria prevalence rate of 16.7% among this age group. Children under the age of 5 years in the low socio-economic class had a significantly higher prevalence rate (32.7%) compared to those in the middle (14.6%) and high socio-economic class (5.1%); P = 0.001. There was no significant difference in malaria prevalence rate between males (20.0%) and females (12.5%) under-5 years (P = 0.156) or between those that were resident in urban (13.3%) and rural areas (21.1%, P = 0.137). For children that are 5 to < 10 years, overall malaria prevalence was 26.7%, with those living in rural areas (38.5%) having a significantly higher malaria prevalence rate compared to those living in urban areas (17.0%, P = 0.025). Furthermore, a malaria prevalence rate of 29.9% was recorded among children between 10 years to < 15 years with no significant difference when sub-categorized by gender (P = 0.677), socio-economic class (P = 0.367) or place of residence (P = 0.407). Lastly, the highest malaria prevalence rate (46.2%) was noted among children between 15-8 years. Females (55.6%), those from low socio-economic class (54.5%) and rural dwellers (54.5%) within this age category had a higher malaria prevalence rate compared to those in the corresponding categories although statistical significance was not attained, (P > 0.05).

Figure 2 shows a bar chart of malaria prevalence and parasite density by age. Kids under five years of age were found to have heavier parasite density despite the lower prevalence and reverse was found in the children aged 15 to < 18 years.

Predictors of malaria infection among children surveyed

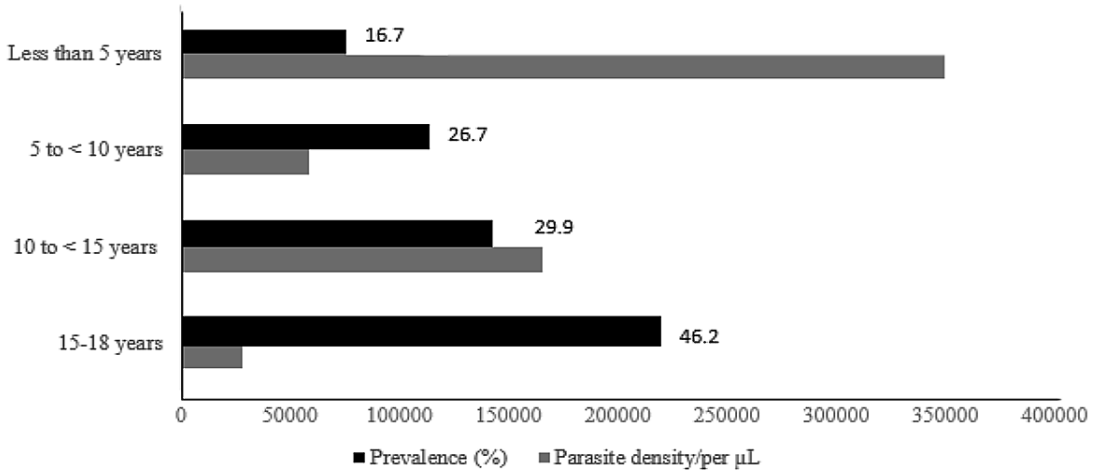
The cross-tabulation analysis of malaria parasitemia and socio-demographic factors associated with malaria infection is shown in Table V. It was noted that the age of children (P = 0.002), maternal education (P = 0.001), socio-economic class (P = 0.001), place of residence (P = 0.006) and sleeping under a long-lasting insecticide treated bed net (P = 0.001) were significantly associated with malaria prevalence in surveyed children. On adjusted binary logistic regression analysis, the risk of malaria infection increased proportionately with increasing age. It was seen that children between 5 to < 10 years [OR = 2.10; 95% CI (1.09-4.04)], those between 10 to < 15 years [OR = 2.21 95% CI (1.02-4.40)] and 15 to 18 years [OR = 4.34; 95% CI (1.72-10.93)] were 2.1, 2.2 and

Tab. IV. Prevalence rate of malaria infection among febrile children seen at the outpatient and emergency unit stratified by age and other socio-demographic factors.

Age categories (in years)	Malaria prevalence (%)									
	Sex			Socio-economic class				Place of residence		
	Male	Female	χ^2 (P)	Low	Middle	High	χ^2 (P)	Urban	Rural	χ^2 (P)
Under-5	20.0%	12.5%	2.01 (0.156)	32.7%	14.6%	5.1%	**16.12 (0.001)**	13.3%	21.1%	2.21 (0.137)
5 to <10	28.1%	24.1%	0.15 (0.697)	31.8%	31.3%	18.8%	1.67 (0.435)	17.0%	38.5%	**5.00 (0.025)**
10 to <15	31.7%	26.9%d	0.17 (0.677)	42.1%	22.7%	26.9%	2.01 (0.367)	25.0%	34.3%	0.67 (0.407)
15 to 18	41.2%	55.6%	0.49 (0.484)	54.5%	20.0%	50.0%	1.74 (0.417)	40.0%	54.5%	0.01 (0.926)
Total	25.7%	19.8%	1.79 (0.181)	(36.4%)	19.6%	16.5%	**14.74 (0.001)**	7.9%	29.7%	**7.44 (0.006)**

χ^2: chi-square value; bold value of P is statistically significant.

Fig. 2. Bar chart showing the mean prevalence and malaria parasite.



Tab. V. Cross-tabulation analysis showing association between malaria parasitemia and socio-demographic factors of febrile children presenting to NAUTH.

Socio-demographic factors	Malaria blood film			Chi-χ^2
	Negative n (%)	Positive n (%)	Total n (%)	P-value†
Age				
Less than 5 years	169 (83)	34 (17)	203	14.65
5 to < 10 years	63 (73)	23 (27)	86	**0.002**
10 to < 15 years	47 (70)	20 (30)	67	
15 to 18 years	14 (54)	12 (46)	26	
Gender				
Male	171 (74)	59 (26)	230	1.792
Female	122 (80)	30 (20)	152	0.181
Maternal education				
Primary or less	20 (46)	23 (54)	43	14.21
Secondary	61 (55)	50 (45)	111	**0.001**
Tertiary or higher	176 (77)	52 (23)	228	
Socio-economic class				
Low	68 (63)	39 (27)	107	14.74
Middle	119 (80)	29 (20)	148	**0.001**
High	106 (84)	21 (16)	127	
Place of residence				
Urban	170 (82)	37 (18)	207	7.439
Rural	123 (70)	52 (30)	175	**0.006**
Sleep under LLIN	n = 293	n = 89	n = 382	10.68
No	143 (49)	61 (69)	204 (53)	**0.001**
Yes	150 (51)	28 (31)	178 (47)	

†: Yates correction applied where applicable; bold p-value are statistically significant association; LLIN: stands long-lasting insecticide nets.

4 times more at risk of malaria infection compared to children below 5 years of age. Even though the risk of malaria infection was inversely proportional to age, the malaria parasite density showed a reverse pattern. Children under-5 years and those 5 to < 10 years had a 2.39 and 1.17 more likelihood of having heavier malaria parasite density than those that are 15-18 years old [OR = 2.39; 95% CI (0.34-16.83)] and [OR = 1.17; 95% CI (0.164-8.33)] respectively.

Similarly, the likelihood of malaria infection among children whose mothers had primary education or less were lower [OR = 0.24; 95% CI (0.08-0.78)] and those whose mother had secondary education had higher odds of malaria infection compared to children whose mother had tertiary education or higher [OR = 1.57; 95% CI (0.76-3.27)]. Also, it was noted that children from families in the lower socio-economic class had 3.57 times more likelihood of acquiring malaria infection compared to those in the high socio-economic class [OR = 3.57; 95% CI (1.38-9.21)] while the likelihood were almost similar for children in the middle and those in the high socio-economic class [OR = 1.07; 95% CI (0.51-2.22)]. Finally, children that live in the rural area had almost twice the likelihood of acquiring malaria infection compared to those that residing in urban settings, OR = 1.93 95% CI (1.12-3.30).

Discussion

The overall prevalence of malaria observed in this study suggests that malaria is still a major cause of childhood morbidity. A slightly lower prevalence of 20% was reported in the rainy season of the year 2014 at the same study site, which compares to 23.3% seen in this study [5]. This shows a near uniform transmission in the study locale. The prevalence found in this study was close to 27.7% reported in a tertiary health center in the Northern part of Nigeria during the rainy season 6 years earlier [6]. It is also comparable to 26% reported in a study conducted in a tertiary health center in the South-west region of the country, which spanned through the rainy season [18]. Comparable malaria prevalence of 29.8% and 24.3% was reported amongst hospitalized children in tertiary hospitals in Kampala and Gabon respectively, during the rainy season 5 years earlier [10, 19]. This shows that there may be a uniform transmission of malaria during the rainy season. The prevalence reported in this study which spanned through the rainy season was higher than the 14.7% recorded in a study which was conducted in the dry season in Lagos, Nigeria [20]. The differences in these prevalence rates could be due to the seasonal variation as well as geographic location. A comparatively high transmission rates in the wet season with lower prevalence in certain geographic zones of the country has been reported [13].

The prevalence of malaria significantly differed in the different age groups and is higher with increasing age. Such trends have been recently reported in both foreign and local studies [9, 10, 19, 21]. A 6-year serial cross sectional study done in Gabon and a similar study in Gambia observed that there was a shift in the prevalence of malaria from the kids under five years of age to older children [19, 21]. The lower prevalence in such patients may be due to the recorded gains in the malaria control programs which had emphasized on this anagraphic category. This reduced exposure to the parasite in such category may have led to delayed acquisition of functional immunity making them more susceptible to malaria at an older age. *P. falciparum* was the only parasite species encountered in this study which is similar to reports from other studies among hospitalized children [5, 6, 22]. This supports the fact that *P. falciparum* is the most prevalent plasmodium species in Nigeria and mostly responsible for childhood morbidity. Since this specie of malaria parasite which is known to cause significant morbidity is highly prevalent in Nigeria, it is not surprising that malaria is still a significant cause of childhood mortality in Nnewi and perhaps in Nigeria. It was observed in this study that majority of children had heavy parasitemia (parasite density ≥ 5,000/µl). This may be as a result of the fact that the study included the rainy season which is a high transmission season and also because this study focused primarily on ill children. Similar report of heavy parasitemia in the rainy season and among symptomatic patients who present to health facilities has previously been reported [18, 23]. Parasite density ranged from as low as 494/µl to as high as 3,938,534/µl in this study, demonstrating the ability of *P. falciparum* to parasitize the RBCs at different stages of maturation resulting to hyper-parasitemia. This supports the report that parasite density at all levels can lead to clinical illness [17].

It was found in this study that age of a child was an independent predictor of a child's malaria status. Children between 5 to < 10 years, those between 10 to < 15 years and 15 to 18 years were more at risk of malaria infection compared to children below 5 years of age. Similar finding was reported in other studies done in Nigeria and other African countries [10, 21, 22]. This may reflect the effects of the control measures focused on younger children which has reduced their vulnerability in the short term but probably not in the long term. This is because lack of exposure to malaria infection makes their immunity against malaria naïve. Without adequate focus of the control measures on the older children, these younger ones with naïve immunity get older with time and are exposed to the parasite, hence, making them even more vulnerable to the disease.

Also, the likelihood of malaria infection among children whose mothers had primary or lower education were lower while those whose mother had secondary education had higher likehood of malaria infection compared to children whose mother had tertiary education or higher. The surprising lower odds in mothers with primary education may be related to the fact that most malaria

prevention program in Nigeria are primarily focused on families in poor and low-income settings. Mothers are culturally the primary care givers of children in Nigeria, so if they are more educated, it would have a positive impact on their child's health. This is because they may have better knowledge of health-related matters which will impact on their prevention approaches as well as care seeking behavior. It is therefore not surprising that the socioeconomic class of the family was also significantly associated with a child's malaria parasite status as was also reported in other studies [13, 21, 22]. The likelihood of malaria infection was higher in rural dwellers as was reported in other studies [13, 21]. The higher occurrence of malaria in rural dwellers may be due to the increased agricultural activities in those areas which provide suitable platform for the breeding of mosquitoes. Kumar et al. [24] referred to areas with required environmental factors suitable for breeding of mosquitoes as hotspots and these are said to be the best target areas for malaria control activities [24]. Although anopheles mosquitoes are known to breed more in the rural areas, they have also been found to adapt to urban breeding sites over time [25]. This creates the need to also spread out the control measure to the urban areas.

Conclusions and recommendation

There was a high prevalence of malaria in the febrile children in Nnewi, with relatively higher prevalence in older children. Age, maternal education, family socioeconomic status and place of residence were independent predictors of a child's malaria status. Therefore, there is a need to maintain and strengthen malaria control policy in the kids under five years of age and extend these control measures to the older children. Malaria control measures also should be intensified especially in the rural areas and amongst families in the low SEC.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

EIN: conceptualization, design, data collection and analysis tools, wrote the manuscript with input from all the authors. IE: conceptualization, supervised the work. JCE: conceptualization, supervised the work. CDIO: performed the data analysis and wrote the result section of the work. CAN: design and data collection. OCO: design and data collection.

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ORIGINAL ARTICLE

Medical students' knowledge and attitudes regarding vaccination against measles, influenza and HPV. An international multicenter study

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Keywords

Medical students • Health care workers • Vaccination

Summary

Introduction. *Inaccurate information leads to increased scepticism concerning vaccinations among health care workers. Therefore, a proper education of medical students on vaccination is important.*
Methods. *During summer term 2015, we performed a paper-based survey to identify the knowledge and attitudes of medical students on vaccinations against measles, influenza and HPV in seven medical schools in Germany, Austria and Switzerland.*
Results. *Altogether, 3,652 questionnaires were analyzed. Knowledge of country-specific public recommendations increased significantly with the number of semesters of medical studies. Concerning the knowledge about vaccinations against measles, influenza and HPV, one third of the answers were given correctly. Again, a strong correlation between the knowledge and the semester of medical studies could be observed. The attitudes concerning vaccinations in general and especially for HCWs were highly positive.*
Conclusions. *This study provides some important arguments for the development of a comprehensive vaccination education for medical students.*

Introduction

Infectious diseases have been significantly reduced or even eradicated by vaccines and they are one of the most cost-effective prevention measures, saving millions of lives each year.
Despite the well-established benefits of immunization, lacking or omitted vaccinations remain a public concern [1]. Insufficient immunization rates are not only a problem in the public but also among health care workers (HCW) in Europe, although immunization of HCWs is a major issue for infection control in healthcare facilities [2]. Because of their contact with patients or infectious material from patients, many HCWs are at risk of vaccine preventable diseases (VPD) e.g. influenza and measles. Many institutions strongly recommend (not mandatory) vaccination for HCWs to protect them from infectious agents, but also to prevent nosocomial transmission of pathogens and its consequences [3]. Medical students already belong to health care professionals during their medical training and will be one of the main contact persons regarding vaccinations in the future.
Concerning social cognitive variables underlying the decision of HCW for getting vaccinated (or not), data show mostly similar results for vaccination in different European countries. Self-protection, patient and family members protection were reported as most important reasons for getting vaccinated. Reasons for rejecting vaccinations were fear of side effects caused by the vaccine, a low risk-perception, disbelief in the effectiveness of influenza vaccination, organizational barriers, misconceptions, and undefined negative emotions [4]. Previous studies showed that inadequate knowledge of physicians regarding vaccines and patient eligibility for vaccination reduced vaccination rates. In addition, HCWs attitudes towards vaccines directly influenced patient's decisions to accept or reject vaccinations [5-7]. Additionally, reported positive or negative experiences with vaccines prior to and during education at medical school may have an impact on future physicians' recommendations about immunizations of patients [8, 9]. Therefore, it seems crucial that medical students acquire solid knowledge of vaccination, resulting in good skills and attitude to be prepared for competent and evidence-based counseling of patients. However, empirical data on this issue are limited so far. The aim of the current survey was to evaluate on a broad basis the information status and personal attitude

towards vaccination in medical students of three different German-speaking countries.

Materials and methods

This descriptive observational study was conducted at seven medical schools in Germany, Austria and Switzerland between June 2015 and October 2015. In Germany, we included the medical schools of the Ludwig-Maximilians-University (LMU) Munich, the Technical University of Munich (TUM; main study center), the University of Duisburg-Essen, the Saarland University (Homburg/Saar) and the Technische Universität of Dresden (TUD). In Austria we involved students of the medical schools at the University of Innsbruck and the Medical University of Vienna. Switzerland was represented by the Medical School at the University of Zurich. These medical schools were chosen to include a wide range of the German-speaking area of Europe. We aimed to include as many medical students as possible. The survey was handed out to the medical students mainly after annual exams, progress tests or compulsory courses. Participants were provided orally with information concerning the purpose of the survey, anonymity and the voluntariness of participation before handing out the questionnaires. The research ethics board of the medical faculty of the Ludwig-Maximilians-University (LMU) Munich reviewed and approved the study (file number AZ 12-15; confirmation date: 08.01.2015).

As there were big differences concerning the number of evaluated questionnaires of each country, the subsequent results of the three countries were not comparable. To get as complete an impression as possible, also partly filled questionnaires were included in the evaluation.

The survey covered the topics of demographic data (8 items), general vaccination related questions (2 items), and knowledge about vaccinations against measles, influenza and against HPV (5 items each). These diseases /vaccines were chosen, because measles should be eradicated by 2020, influenza vaccination is a major issue in HCW and HPV is a comparable new vaccine. We were asking for different attitudes towards vaccinations in general (3 items), vaccinations against measles (5 items), vaccinations against influenza (2 items) and vaccinations against HPV (3 items). The questions concerning knowledge about vaccinations were answered with "yes/no/I don't know". The attitude regarding vaccinations was rated with "I agree/ I disagree/ I don't know". The participants were advised not to guess. For detailed information the questionnaire can be found as supplemental material.

The statistical analysis was performed by IBM SPSS Statistics 24 (version 2016) and GraphPad Prism 6. Sociodemographic data, students'knowledge and attitude were presented by descriptive statistics (percent [%], means [M] and standard deviations [SD]). To analyze different influences on student's knowledge we performed statistical hypothesis testing (t-tests [p-value < 0.05]), as well as a multiple regression analysis (regression coefficient [r] and commonality [h^2]).

Results

Demographic data

During the survey period, 19,521 medical students were enrolled at the participating universities, of whom 7,617 students (39.0%) could be reached after annual final exams, progress tests or compulsory courses.

Finally, 3,671 questionnaires could be evaluated. 2,015 (54.9%) of the evaluated questionnaires came from German medical schools, 1,160 (31.6%) from Austria and 496 (13.5%) from Switzerland. The participants were mainly 20-25 years old (n = 2.980; 81.2%), female (n = 2,204; 60.0%) thus representing the overall majority of female students in medical schools. Most of the participants were in their 6th semester of medical studies (n = 584; 15.9%) (Tab. I).

Knowledge about vaccinations

Concerning their knowledge, students were asked about their awareness of the country-specific public recommendations for HCW. 2,405 participants (65.5%) stated, they would not know these recommendations. However, we could observe a strong correlation between knowledge and progress of years of study. While only 65 students (16.3%) in their first semester stated to be aware of the country-specific public recommendations concerning vaccinations for HCWs, 73 students (64.0%) in the 11th semester and 43 students (62.0%) in the 12t^{h} semester of their studies confirmed this statement (Fig. 1).

Furthermore, we asked five questions concerning the immunization against measles, as well as five questions concerning the immunization against influenza, respectively HPV (15 items in total; see online supplement).

On average, the participants were able to answer 1.66 of these five questions about measles correctly. Also 1.60 of the five questions concerning influenza and 1.81 of the questions concerning HPV were answered correctly on average. In absolute numbers, 3,439 students were able to give at least one correct answer concerning measles. 3,380 students were able to give at least one correct answer concerning influenza and 3,395 students were able to give one or more correct answers concerning HPV.

We observed a strong correlation between the knowledge and the semester of medical studies. As students in their first semester were able to give 2.6 correct answers on average (n = 360; SD = 2.585), medical students in their 10th semester gave 7.7 correct answers on average (n = 355; SD = 2,869; Fig. 2).

A significant correlation between former training for health care profession, such as medical technical assistant, emergency medical technician, a certified training in outpatient-service or education in nursing care, and the knowledge about vaccinations could not be observed (p = 0.227).

Tab. I. Demographic data of participants showing age, gender, semester and former medical training of students in Munich, Homburg, Dresden, Essen, Vienna, Zurich, Innsbruck.

	Age in years				Sex			Semester of medical studies		Former training for health care profession	
	20-25	26-31	> 31	Total	Female	Male	Total	Mean	Standard deviation	No	Yes
Munich LMU/Essen	808	255	36	1099	688	404	1092	6,96	1,99	838	241
Munich TUM/Homburg	426	78	22	526	339	182	521	7,38	1,42	451	72
Vienna	307	57	3	367	190	178	368	6,88	3,43	251	116
Dresden	254	121	9	384	240	150	390	6,24	3,79	264	123
Zurich	449	37	6	492	312	184	496	5,65	3,35	478	10
Innsbruck	736	39	9	784	435	357	792	3,61	2,59	585	198

Fig. 1. Correlation between the self-reported knowledge about country-specific public recommendations concerning vaccinations for HCWs and semester of medical studies ($p < 0.001$, $h^2 = .061$).

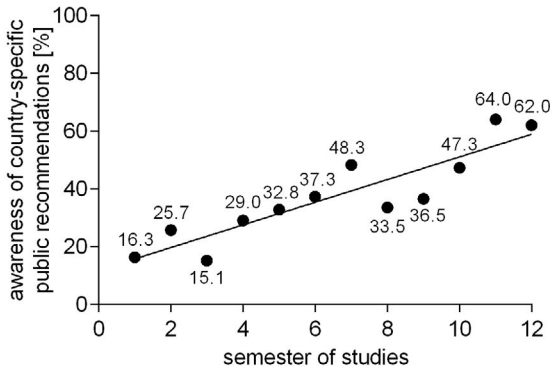
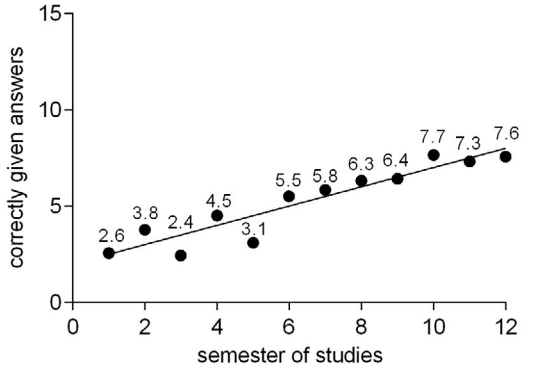


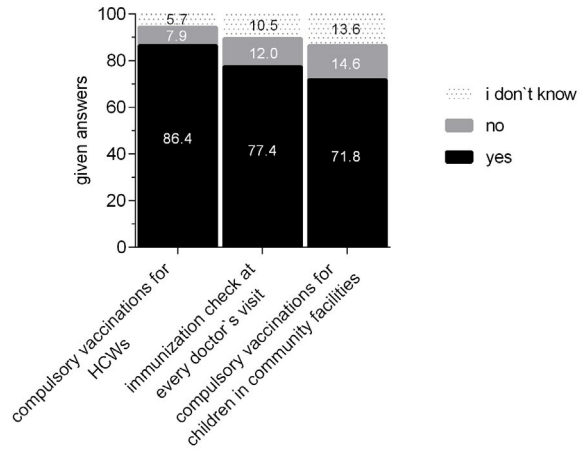
Fig. 2. Correlation of number of semesters and knowledge about vaccinations, mean values of correct given answers are indicated ($r = 0.503$; $p < 0.001$; $n = 3161$).



Attitudes towards vaccinations

Concerning HCWs, most of the participants would support more strict regulations for prevention of infectious diseases. 3.172 students (86.4%) agreed, that compulsory vaccinations should be introduced for HCWs in hospitals, ambulatory settings and midwifery practices. 2,841 participants (77.4%) approved that every doctor`s visit should be used to check the immunization status of a patient, as well as 2,636 students (71.8%) stated that vaccinations should be compulsory for children who are going to visit public community facilities like day care centers or kindergartens (Fig. 3).

Fig. 3. Attitudes towards immunization of HCWs, general public and children in community facilities.



When we asked our participants for possible obstacles to influenza vaccinations for HCW, "ineffective protection" was named in 1,725 cases (47.0%), and 1,376 participants (37.5%) mentioned "fear of side effects". The statements "the vaccination makes me sick" and "I am not at risk" were checked in 870 (23.7%) and 855 (23.3%) of all questionnaires, respectively.

Discussion

Vaccination is an important issue within primary prevention measures, especially for HCWs. Our survey of medical student`s knowledge and attitudes towards vaccination revealed several important findings. First, the knowledge among medical students about vaccinations especially against measles, influenza and HPV is poor in the analyzed German-speaking countries. In addition, the attitude of medical students towards vaccinations of HCWs and the general public was very positive.

Although immunization rates and the acceptance of vaccinations seem to be higher in medical students than in students of other subjects, immunization rates and knowledge about vaccinations are still insufficient among medical students in many European countries.

For example, more than 10% of the medical students at the Technische Universität Dresden did not even know their immunization status [10]. In Frankfurt (Germany), only 46.4% of the medical students knew that there was a general recommendation for HCW to receive the influenza vaccination and only 76.8% of the students stated to have received two measles vaccinations. Overall, two thirds of the students were "very much in favor of vaccinations" or "completely in favor of vaccinations" and estimated the probability for unvaccinated HCWs to acquire an occupationally associated infectious disease to be "quite high" or "very high" [11].
Another cross-sectional survey with 711 students studying a range of subjects in Dresden (Germany) showed a high acceptance regarding vaccination against measles. Actual self-reported vaccination rates were lower; only 65.5% of medical students and 25.3%-39.4% of other student groups reported complete vaccination against measles. Of the students, 12.6%-45% did not know their vaccination status. Consequently, vaccination acceptance did not correlate with vaccination behaviour [12].
These results are not surprising, as teaching of vaccination topics for medical students in Germany is still not part of a compulsory curriculum [13, 14].
Combined with our findings about the lack of knowledge among many students due to a missing vaccination education, these results suggest the probable receptivity of medical students to educational interventions related to immunizations [15]. Efforts to standardize immunization training for medical students as part of their curriculum would most likely benefit from reinforcement by the development of immunization core competencies [14].

Limitations of the study

We did not define a mandatory setting for the cooperating medical schools. Therefore, an unspecific bias is always possible. Some students were invited to participate during a compulsory course, other students at the end of a progress test or final exam. These different settings could have influenced the answers given. In addition, a selection bias is likely favoring those students who were present on the occasions where questionnaires were distributed. We did not match the time points of filling out the questionnaire and acquiring the vaccination-associated learning content with each other. Therefore, differences between the medical schools may also be attributed to curricular heterogeneity. Furthermore, the teaching methods and curricula in those countries might differ, which may in turn influence the knowledge level. Bias associated with self-report questionnaires is quite common and can potentially influence the outcome. Additionally, there might be other variables which might influence students` knowledge and attitudes which could not be taken in to consideration in this study.

Conclusions

To date and to our knowledge, no study comprehensively examines knowledge and attitudes of medical students in different German-speaking countries. Therefore, we performed a baseline survey to identify basic knowledge and attitudes of medical students especially concerning measles, influenza and HPV in seven different medical schools in Germany, Austria and Switzerland.
The results of the survey demonstrate the impact of current medical school curricula towards knowledge about vaccinations among medical students of the compared faculties. The survey also provides valuable information about medical student exposure to preventive medicine practices and their associations towards attitudes concerning vaccination. These findings may result in the creation of an educational tool for better training of medical students.
It is tempting to speculate that medical students positively view vaccinations, and they would probably be receptive to more education and training related to vaccines. Further studies should extend the survey to other medical school populations and explore the development of an educational intervention to address the identified knowledge gaps and boost student confidence about vaccines. We also suggest that medical institutions should consider standardizing a set of core competencies for immunization for all European medical students.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

LS and HR coordinated the data collection and evaluation, they equally contributed to the manuscript. MB and P.O.B evaluated the data. JB, BG, BH, AL, HR, KV, AK and UW collected the data at the respective study center, and supported data evaluation as well as the development of the manuscript itself. LS, HR, P.O.B and JS were responsible for the study design and the development of the questionnaire.

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ORIGINAL ARTICLE

Predictive factors for nutritional behavior among pregnant women attending antenatal care clinic in 6th of October City

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Keywords

Pregnancy • Nutrition • Life-style behavior • Eating habits • Antenatal care

Summary

Background. *Good maternal nutrition during pregnancy is important to ensure health for both the mother and the foetus. This study aimed to assess nutritional knowledge and behavior among a group of Egyptian pregnant women in addition to identify the factors influencing both their nutritional knowledge and behavior.*
Methods. *This comparative cross sectional study included 300 pregnant women attending the antenatal care clinics in 6th of October University private hospital and El-Hussary primary health care (PHC) unit. The data was collected through a modified nutritional survey that was translated from Spanish to Arabic and revised by language experts for clarity.*
Results. *Almost all of the women attending the private hospital were university educated while about half of the women attending the PHC unit were graduated from technical education. In general, the level of knowledge about food requirements of both groups was satisfactory good; however, neither of them fulfilled the WHO recommendations of food intake during pregnancy or the optimum number of meals per day. The mean of random blood glucose was higher among the women attending the PHC unit; the BMI, mid arm circumference and subcutaneous fat were higher among the same group as well. In regard to fulfilling the WHO recommended servings per day, only starch and fat items were fulfilled by both groups, whereas the other three items (vegetables, fruits and dairy products) were merely included in the diets of both groups.*
Conclusions. *Healthy behavior among pregnant women in both group were influenced by their educational level, occupation as well as their pre-gestational BMI. Those were the only three significant predictive factors, where women with higher education showed an active lifestyle. In addition, women starting with normal BMI before pregnancy had better healthy behaviours including the choice of healthy diets.*

Introduction

Maternal under-nutrition, including macro- and micronutrient deficiencies, is a significant public health problem in many developing countries [1]. Malnutrition in pregnancy not only has an ill effect on the newborn, but also impairs the mother's owns health. When the pregnant woman's diet does not supply the required nutrients for her needs and for those of the fetus, the fetal requirements are met by withdrawing these from the tissues of the pregnant mother. This tissue depletion weakens the mother and increases the probability of serious complications [2]. Thus, good maternal nutrition during pregnancy is important to ensure health for the mother and the growing fetus. This presupposes a diet with sufficient energy, with a variety of nutrients, minerals, and vitamins, and the mother's avoidance of toxins and contaminants [3].

Poor quality diet during pregnancy has been found to be associated with maternal excess weight gain, pre-eclampsia, preterm birth or even miscarriage. In addition, excess weight gain and imbalanced diet, particularly among obese women during pregnancy have been identified as risk factors for abnormal glucose tolerance [4].

Poor infant outcomes have also been linked with poor maternal nutrition. These include inadequate development, low birth weight and an increased risk of developing chronic diseases later in life adult diseases proposed to have a fetal origin, and linked with nutrition during pregnancy, include cardiovascular diseases, diabetes and issues associated with bone mass formation [4].

Women's knowledge, attitudes, and practices concerning nutritional issues related to pregnancy vary depending on level of education, age, and social class [5]. In Egypt, most of the women take their knowledge from neighbors and this makes an environment of misconceptions and myths [6]. That is why the long standing unfinished agenda of under nutrition in developing countries now co-exists with a different type of malnutrition-obesity. Egypt like other developing countries is battling with this double burden of malnutrition [7].

WHO has issued a new series of recommendations to improve the quality of antenatal care in order to reduce risk of still births and pregnancy complications and give women a positive pregnancy experience, one

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of its core contents is the nutrient needs in pregnancy with special enforcement on the application of these recommendations in the developing countries and among poor communities [8].

Few studies have explored factors related to maternal nutrition and weight gain during pregnancy, including barriers and cultural beliefs as drivers of food consumption [9]. Consequently, the lack of published data in this area raises the need for studying the nutritional behavior among Egyptian pregnant women. No previous study in Egypt (according to literature) investigated the possible predictive factors for Nutrition among pregnant women.

Aim of the study

To assess nutritional knowledge and behavior among a group of Egyptian pregnant women in addition to identify the factors influencing their nutritional knowledge and behavior.

Methods

A comparative cross-sectional study was carried out in 6th of October City in two settings:

- Family Medicine Unit (El-Hussary PHC Unit) a public clinic in 6th of October City;
- University Private Hospital Clinic (October 6th Private University Hospital Clinic).

Data Collection took 3 months from January to April 2017, and the total number of the study population was 300 pregnant women in reproductive age.

Convenient sample was drawn from both public and private clinics.

Sample size was calculated using PASS® version 11 Program [10], setting the confidence level at 95%, the margin of error at 0.05, and the power (1-β) at 0.8. Assuming that the distribution response is 50% among study population, taking in consideration 20% drop out rate, the needed sample size was 300 pregnant women.

Firstly, approval from the Research Ethical Committee Board (Faculty of Medicine, Ain Shams University) was obtained. Thereafter, administrative approval from the Directors of El-Hussary Family Medicine Unit and Private Hospital Clinic have been taken. Questionnaire used was anonymous and confidentially of data was assured.

Data was collected through a modified valid interview nutritional survey questionnaire [11]. It was translated from Spanish to Arabic and revised by language experts for clarity and absence of misinterpretation.

A pilot study was conducted on 15% of the sample size (n = 45), to identify the clarity of the questions and test its validity and reliability where some modifications were made based on participants' feedback. Instrument reliability was tested, where Cronbach's alpha was more than 0.7 for all items.

1. Interview questionnaire to assess nutrition knowledge and dieting behavior during pregnancy. Main components items were:
   - general characteristics (personal, obstetric data);
   - general health status for the mother;
   - current dietary habits;
   - food frequency;
   - knowledge regarding nutrition needs during pregnancy (energy intake - nutrients supplementation);
   - optimal nutrition items in the WHO 2016 antenatal care guidelines [8].
2. Nutritional assessment:
   - anthropometric measures: height, current pregnant women weight, body mass index (BMI), Mid Upper Arm Circumference (MUAC), triceps subcutaneous fat;
   - laboratory analysis measures: hemoglobin level by gm/dl and random blood sugar.

Statistical analysis

First, the following descriptive analysis was done: frequency, percentages, mean and standard deviation (SD). Thereafter, a comparison was done using Student t-test for quantitative variables and Fisher exact test for qualitative variables. The adjusted predictive factors were obtained by logistic regression analysis. All variables in the interview questionnaire were considered as possible candidates for the final model. P values lower than 0.05 are considered statistically significant**.** Data was collected and statistically analyzed using SPSS package for windows (Statistical Package for Social Science) program version 20, IBM Inc, 2011.

Results

The present study was conducted among a total of 300 pregnant women attending the Family Medicine Unit (El-Hussary unit) in 6th October City, and university private hospital clinic (October 6 University). Educational level and age in years were studied and shown in Table I. The mean age of the sample from the private hospital was 26.96 ± 3.937, most of them (99.3%) were university educated, while that for the sample from the PHC unit was 26.80 ± 5.684 where nearly half of them were graduated from technical education (skills diploma) and about third of them were illiterate (27.3%). Current pregnancy details – including gestational age, number of foetuses and gravidity – as well as the obstetric history of the participating mothers were studied during their antenatal care visits and are shown in Table II. There was a statistically significant difference between numbers of foetuses in both groups. Almost all of the women in both the private hospital and the PHC unit had a single fetus, 92.7% and 98.0% respectively. Less than half of the studied women in the private hospital were pregnant with their first pregnancy (47.3%) while in PHC unit group it was third of the participants (33.3%). There was a statistically significant relation between both groups and proximity between pregnancies, gravidity, past history of low birth weight and number of children with P values of 0.001, 0.001, 0.009 and 0.000 respectively. Gestational age and number of miscarriages

in both groups were not statistically significant with p values of 0.081 and 0.281 respectively.

Anthropometric measurements [current weight, preconceptional weight, height, BMI, MUAC and triceps subcutaneous fat] of both groups were studied along with the laboratory results of random blood sugar and hemoglobin levels (Tab. III). There was a statistical significance between height, BMI, mid arm circumference and haemoglobin level in both groups as the P values were 0.000, 0.024, 0.000 and 0.000 respectively. Women attending the private hospital showed a slightly less pregestational weight, current weight, BMI and MUAC in comparison with women attending the PHC unit. Triceps subcutaneous fat measuring was statistically insignificant. There was a statistically significant relationship between random blood glucose in different groups as the mean of random blood glucose among women in the private hospital group was 91.70 ± 22.110 and that of the PHC unit group was significantly higher (93.88 ± 24.021); the data calculated was taken from only 293 participants.

Regarding dietary habits nearly half (44%) of the private hospital participants have three meals per day and regularly have breakfast as well while nearly 72% of the participating women in the PHC unit were taking two meals per day and regularly had their breakfast. More than half of the studied women (60%) in the private hospital had regular multivitamins intake, while only about one third (36.7%) of the studied women attending the PHC unit did. More than half of the group from the private hospital (63%) were taking regular iron supplements during their pregnancy, while just about one third (35.3%) of the women in the PHC unit did the same.

There was a statistical insignificance differnece between both groups regarding the consumption of food rich in prebioticis with p value of 0.11. As per the use of butter, about three quarters (76.7%) of the studied women from the private hospital denied using it compared to 94.7% of the women attending the PHC unit. Almost all of the women from both groups reported using sun flower oil in their diet.

Table IV shows that nearly half (45.3%) of the studied women in the private hospital had the right knowledge of daily carbohydrates requirements, compared with only 10% of the women in the PHC unit group did. Moreover, more than three quarters (78%) of those in private hospital had the right knowledge about daily requirement of vegetables and fruits, whereas only about half (56%) of those in the PHC unit had this

Tab. I. General characteristics of studied women during their antenatal care visits.

Variable/ Category		Groups of study		Statistical test	P-value
		Private hospital (n = 150)	PHC unit (n =150)		
Educational level	Illiterate	-	41 (27.3%)	X^2= 293.027	0.000
	Primary	-	26 (17.3%)		
	Preparatory	-	17 (11.3%)		
	Diplom	-	62 (41.3%)		
	Secondary	1 (0.7%)	3 (2.0%)		
	University	149 (99.3%)	1 (0.7%)		
Age in years		26,96 ± 3,937	26.80 ± 5.684	t = 0.283	0.777

Tab. II. Current pregnancy and obstetric history of studied women during their antenatal care visits.

Variable/ Category		Groups of study		Statistical test	P-value
		Private hospital (n = 150)	PHC unit (n =150)		
Fetus	Single	139 (92.7%)	147 (98.0%)	X^2 4.795	0.029
	Twin	11 (7.3%)	3 (2.0%)		
Duration between current and previous pregnancy	Less than a year	1 (0.7%)	4 (2.7%)	X^2 17.238	0.001
	More than a year	71 (47.3%)	69 (46.0%)		
	Exactly a year	7 (4.7%)	27 (18.0%)		
	No previous pregnancies	71 (47.3%)	50 (33.3%)		
Gravidity	First	71 (47.3%)	50 (33.3%)	X^2 24.562	0.001
	Second	37 (24.7%)	25 (16.7%)		
	Third	17 (11.3%)	37 (24.7%)		
	Forth	16 (10.7%)	11 (7.3%)		
	Fifth	5 (3.3%)	16 (10.7%)		
	Sixth	3 (2.0%)	5 (3.3%)		
	Seventh	1 (0.7%)	3 (2.0%)		
	Eighth	0 (0%)	3 (2.0%)		
Past history of low birth weight	Yes	9 (6.0%)	23 (15.3%)	X^2 6.856	0.009
	No	141 (94.0%)	127 (84.7%)		
Gestational age by weeks		20.07 ± 9.826	22.14 ± 10.699	t = -1.748	0.081
Number of children		0.71 ± 0.965	1.33 ± 1.364	t = -4.544	0.000
Number of miscarriages		1.63 ± 1.087	1.38 ± 8.61	t = 1.086	0.281

Tab. III. The anthropometric measurements and laboratory measurement of pregnant women during antenatal care visits.

Groups of study	Private hospital (n = 150) mean ± SD	PHC unit (n =150) mean ± SD	Statistical test	P-value
Current weight in kg	77.6 ± 13.9	79.7± 12.9	t = -1.329	0.185
Height in cm	162.3 ± 5.3	159.8 ± 6.2	t = 3.680	0.000
Height in meters	1.6±.05	1.6 ±.06	t = 3.680	0.000
BMI	26.9 ± 4.6	28.1± 4.3	t = -2.275	0.024
Mid Upper Arm Circumference	28.2 ± 3.5	29.6 ± 3.5	t = -3.591	0.000
Triceps S.C. fat	21.9 ± 5.5	22.26 ± 5.7	t = -0.584	0.560
Hemoglobin level by gm [a]	11.309 ± 1.07	10.7 ± 1.08	t = 4.077	0.000
Random blood sugar [b]	91.7 ± 22.1	93.8 ± 24.02	t = -0.804	0.422
Preconceptional weight	70.8 ± 12.3	71.8 ± 12.4	t = -0.706	0.481
Weight groups	Under weight	3 (2.0%)	1 (.7%)	X^2 = 4.880
	Normal	51 (34.0%)	37 (24.7%)	
	Over weight	54 (36.0%)	68 (45.3%)	
	Obese	42 (28.0%)	44 (29.3%)	

[a]: data calculated with a sample size of n = 289; [b]: data calculated from a sample of n = 293.

Tab. IV. Knowledge of daily requirements from each food group according to WHO Recommendations for antenatal care.

Variable / Knowledge		Groups of study		Total	Chi-square test	P-value
		Private hospital (n = 150)	PHC unit (n = 150)			
Daily requirements of carbohydrates	Right knowledge	68 (45.3%)	15 (10.0%)	83 (27.7%)	52.347	0.000
	Wrong knowledge	82 (54.7%)	135 (90.0%)	217 (72.3%)		
Daily requirement of vegetables and fruits group	Right knowledge	117 (78.0%)	84 (56.0%)	201 (67.0%)	20.130	0.000
	Wrong knowledge	33 (22.0%)	66 (44.0%)	99 (33%)		
Daily requirement of milk and dairy products group	Right knowledge	117 (78.0%)	106 (70.7%)	223 (74.3%)	8.114	0.044
	Wrong knowledge	33 (22.0%)	44 (29.3%)	77 (25.7%)		
Daily requirement to meat group	Right knowledge	126 (84.0%)	108 (72.0%)	234 (78,0%)	6.755	0.080
	Wrong knowledge	24 (16.1%)	42 (28.8%)	66 (22%)		
Daily requirements of fat group	Right knowledge	99 (66.0%)	67 (44.7%)	166 (55,3%)	17.947	0.000
	Wrong knowledge	51 (34.1%)	83 (55.3%)	134 (44.6%)		

knowledge. Similarly, more than three quarters (78%) of the women in the private hospital and 70.7% of those attending the PHC unit had right knowledge about the daily requirement of milk and dairy products. About two thirds of participating women from the private hospital had the right knowledge of the daily requirements of fat compared with 44.7% of the PHC unit group. Nearly all groups showed statistical difference except meat group (p value = 0.080).

In general, the level of knowledge about food requirements of both groups was satisfactory good especially for daily requirements of meat group and milk groups, then vegetables and fruits, then fat, then carbohydrates groups, however, they failed to fulfill the daily requirements completely. After contrasting our results to the WHO antenatal care guidelines, it is shown in both groups that for food group in carbohydrate and fat only; and there was statistical significance in starch and meat groups with p values of 0.013 and 0.006 respectively. Neither of the two studied groups fulfilled WHO requirements concerning the number of servings of vegetables, fruits and dairy products (Tabs. V, VI).

Generally, women who fulfilled three items of WHO requirements were 8% in the private hospital group and in the PHC unit (0.7%). Taking into consideration that the consumption of starch and fats group were exceeding the recommended amount by WHO, as the consumption of starch was 12.2 and that of the fat group was 9.

As shown in Tables V and VI, only a small number of factors could show a promise in predicting or influencing maternal diet; and education wasn't one of them. There was statistically significant difference in educational level and weight group in both groups as the p values were 0.008 and 0.000 (Tab. VI). Among women who were university graduates, 8% fulfilled three items and 83.3% fulfilled two items. Dietary habits and knowledge of daily requirements according to the WHO antenatal guidelines were also studied as predictive factors. The right knowledge of daily requirements of five food groups shows a statistical difference. About 7% of the sample size fulfilled three items from the carbohydrate group; while from the meat group, only 5.1% fulfilled three items. Vegetables and fruits group showed 4.5% regarding fulfilling 3 items, the least percentage of women (4%) fulfilled three items of WHO antenatal care recommendations from milk and dairy products group.

Discussion

This study included 300 pregnant women attending 6th of October private hospital and El-Hussary PHC unit for antenatal care. We assessed their sociodemographic

Tab. V. Proposed predictive factors for nutritional behavior among pregnant women attending ante natal care clinic regarding sociodemographic and maternal history.

Variable	Category	Fulfilling one item	Fulfilling two items	Fulfilling three items	Total	P-value
Educational level	Illiterate	4 (9.8%)	36 (87.8%)	1 (2.4%)	41 (100%)	0.008
	School graduated	4 (3.7%)	105 (96.3%)	0 (0.0%)	109 (100%)	
	University graduated	13 (8.7%)	125 (83.3%)	12 (8.0%)	150 (100%)	
Occupation	Professional worker*	5(7.2%)	65 (81.2%)	8(11.6%)	69(100%)	0.019
	Technical worker**	4(6.5%)	56(90.3%)	2(3.2%)	62(100%)	
	House wife	12(7.1%)	145(91.1%)	3(1.8%)	169(100%)	
Gravidity	First	11 (9.1%)	104 (86%)	6 (5%)	121 (100%)	0.361
	Second	6 (9.7%)	53 (85.5%)	3 (4.8%)	62 (100%)	
	≥ third	4 (3.4%)	109 (93.2%)	4 (3.4%)	117 (100%)	
Chronic diseases (n = 56)	Yes	4 (19.0%)	50 (18.8%)	2 (15.4%)	56 (18.7%)	0.953
Past history of low birth weight	Yes	1 (4.8%)	29 (10.9%)	2 (15.4%)	32 (10.7%)	0.581
	No	20 (95.2%)	237 (89.1%)	11 (84.6%)	268 (89.3%)	
Duration between current, previous pregnancy	Less than a year	0 (0.0%)	5 (1.9%)	0 (0.0%)	5 (1.7%)	0.611
	More than a year	10 (47.6%)	125 (47.0%)	5 (38.5%)	140 (46.7%)	
	Exactly a year	0 (0.0%)	32 (12.0%)	2 (15.4%)	34 (11.3%)	
Weight groups	Underweight	3 (75.0%)	1 (25.0%)	0 (0.0%)	4 (100.0%)	0.000
	Normal weight	11 (12.5%)	72 (81.8%)	5 (5.7%)	88 (100.0%)	
	Overweight	4 (3.3%)	112 (91.8%)	6 (4.9%)	122 (100.0%)	
	Obese	3 (3.5%)	81 (94.2%)	2 (2.3%)	86 (100.0%)	

*: professional worker: (Doctor, Teacher, Computer office, Lawyer, Engineer, Employed, Manager); **: technical worker: (Nurse, Technician Laboratory, Vender, Coiffeur).

Tab. VI. Proposed predictive factors for nutritional behaviour among pregnant women attending antenatal care clinic regarding dietary habits and knowledge of daily requirements.

Variable			Category	Fulfilling one item	Fulfilling two items	Fulfilling three items	Total	P- value
Dietary habits	Having breakfast		Regularly	8 (4.6%)	157 (90.2%)	9 (5.2%)	174 (100.0%)	0.272
			Infrequent	10 (11.8%)	72 (84.7%)	3 (3.5%)	85 (100.0%)	
			Rarely	3 (7.3%)	37 (90.2%)	1 (2.4%)	41 (100.0%)	
	Consumption of milk and milk products		Yes	15 (7.3%)	181 (88.3%)	9 (4.4%)	205 (100.0%)	0.947
			No	6 (6.3%)	85 (89.5%)	4 (4.2%)	95 (100.0%)	
	Consumption of fruits		Yes	20 (7.5%)	235 (87.7%)	13 (4.9%)	268 (100.0%)	0.274
			No	1 (3.1%)	31 (96.9%)	0 (0.0%)	32 (100.0%)	
	Consumption of eggs		Yes	16 (7.2%)	199 (89.2%)	8 (3.6%)	223 (100.0%)	0.553
			No	5 (6.5%)	67 (87.0%)	5 (6.5%)	77 (100.0%)	
	Consumption of meat		Yes	16 (7.1%)	198 (88.0%)	11 (4.9%)	225 (100.0%)	0.704
			No	5 (6.7%)	68 (90.7%)	2 (2.7%)	75 (100.0%)	
	Consumption of vegetables		Yes	18 (6.4%)	250 (89.0%)	13 (4.6%)	281 (100.0%)	0.206
			No	3 (15.8%)	16 (84.2%)	0 (0.0%)	19 (100.0%)	
	Consumption of processed meat		Yes	7 (10.8%)	54 (83.1%)	4 (6.2%)	65 (100.0%)	0.271
			No	14 (6.0%)	212 (90.2%)	9 (3.8%)	235 (100.0%)	
	Consumption of fish		Yes	20 (7.4%)	239 (88.2%)	12 (4.4%)	271 (100.0%)	0.702
			No	1 (3.4%)	27 (93.1%)	1 (3.4%)	29 (100.0%)	
	Fat	Unsaturated	Yes	20 (6.9%)	260 (89.3%)	11 (3.8%)	291 (100%)	0.023
			No	1 (11.1%)	6 (66.7%)	2 (22.2%)	9 (100%)	
		Saturated	Yes	10 (6.8%)	129 (87.2%)	9 (6.1%)	148 (100%)	0.340
			No	11 (7.2%)	127 (90.1%)	4 (2.6%)	152 (100%)	
Supplement	Take supplement of multivitamins		Yes	12 (8.3%)	125 (86.2%)	8 (5.5%)	145 (100.0%)	0.416
			No	9 (5.8%)	141 (91.0%)	5 (3.2%)	155 (100.0%)	
	Take iron supplement		Yes	12 (8.1%)	129 (87.2%)	7 (4.7%)	148 (100.0%)	0.707
			No	9 (5.9%)	137 (90.1%)	6 (3.9%)	152 (100.0%)	
Right knowledge of daily requirements of	Carbohydrates			6 (7.2%)	71 (85.5%)	6 (7.2%)	83 (100.0%)	0.626
	Milk and dairy products group			16 (7.2%)	198 (88.8%)	9 (4.0%)	223 (100.0%)	0.983
	Vegetables and fruits group			16 (8.0%)	176 (87.6%)	9 (4.5%)	201 (100.0%)	0.904
	Fat group			11 (6.6%)	145 (87.3%)	10 (6.0%)	166 (100.0%)	0.424
	Meat group			17 (7.3%)	205 (87.6%)	12 (5.1%)	234 (100.0%)	0.146

features, nutritional status, and life style behaviours. Our main aim was to assess nutritional knowledge and behavior among a group of Egyptian pregnant women in addition to identify the factors influencing their nutritional knowledge and behavior. Our results, however, didn't show much difference between the two groups in terms of dietary habits, but indicated the predictive factors for identifying their behaviours.

Educational level and socioeconomic status have been proven to affect maternal and child health [12, 13]. Since a higher level of education means a better understanding of the nutritional needs and healthy habits during pregnancy [14], we have already anticipated that the group of women from the private hospital would have better behaviours and better nutritional status as almost all of them had a higher education as opposed to the group from El-Hussary PHC where only 7% completed their higher education. Thus, it can be inferred that the group of women from the PHCU would be more subjected to the present adverse health effects.

Differences between anthropometric variables were noted. The mean current BMI for both groups was above normal ranges (overweight), however, the BMI of the PHC unit group was higher than that of the other one. This can be attributed to the marked educational difference and socioeconomic status between the two groups where a lower educational level was proven to be associated with a higher BMI [14, 15]. Moreover, the PHC unit group showed a higher pre-gestational weight in comparison with the private hospital group, but there has not been any statistical evidence on the differences between both groups regarding weight gain during the pregnancy.

Mid upper arm circumference was another statistically significant anthropometric measurement during pregnancy, especially to indicate the potentiality of LBW infants rather than a measurement for obesity. A cut-off value of < 23 cm was recommended in African population to consider pregnant women for a feeding program [16]. By contrasting this data to our results, we found that the mean MUAC of both groups was above cut-off values.

Women attending El-Hussary PHC unit reported worse self-perceived health, where 24% of them considered their health as weak. This assessment of course is subjective and it was contradicted by the later obtained results as both groups presented similar health patterns and food intake.

Regarding lifestyle habits, both groups showed similar results in smoking assessment. About 4% of each group kept smoking during pregnancy. This is against the known data about the relation between sociodemographic factors and maternal smoking where lower socioeconomic status and lower educational levels are associated with lower rates of smoking cessation during pregnancy [17]. Nevertheless, it is important to state the cultural difference in Egypt and the possibility of active denial for the fear of shaming. A sedentary lifestyle in general (adjusted by the number of sleeping hours, TV watching, and physical activity) was more pronounced in the PHC unit group. This is in accordance with the previously stated higher BMI in this particular group, where several studies were published stating that lower physical activity during pregnancy was associated with higher BMI [18, 19].

Eventually, regarding the intake of supplements, it was as speculated by previous papers, the women attending the private hospital were more compliant to their supplements specially Iron and multivitamins. The PHC unit group's poor compliance could be attributed to less resources and less education as shown by one study conducted on Finnish pregnant women proving that there is a positive correlation between educational levels and supplement intake [20].

Different studies were carried out to assess the maternal adherence to the recommended diet during pregnancy. Similar results to ours showed that mothers ate less fruits and vegetables and had inadequate calcium intake either through diet or through supplements [21]. In contrast, a study carried out in Canada showed that women had adequate calcium and vegetables intake, while they lack the recommended amounts of cereals, fat and starch [22]. However, these data are from different countries and comparing different recommendations thus they can't be comparable to each other.

In 2014, misinformation and poor maternal knowledge about healthy diet in Egypt were studied by the Maternal and Child Health Investigation Program. The study indicated that there was a gap between the knowledge of the mothers about harmful foods during pregnancy and the actual amounts of food consumed [23]. In our study, this was shown in both populations, where neither of them fulfilled the WHO recommendations of food intake during pregnancy or the optimum number of meals per day. Less than half of the women attending the private hospital had three or more meals per day, and about 27% of the PHC unit group did. In regard to fulfilling the WHO recommended servings per day, only starch and fat items were fulfilled by both groups, whereas the other three items were merely included in the diets of both groups.

To our knowledge there hasn't been any studies assessing the predictive factors of dietary habits during pregnancy. But in general, a number of studies assessing the relation between education and diet found out that the higher the education the better the diet and the lower the weight of the mother [14, 16, 23]. However, this hasn't been the case here, since a small number of factors could show a promise in predicting or influencing maternal diet and education wasn't one of them. These factors are current pregnancy weight and parity, with the latter having a lower statistical significance. This was determined by comparing the results of the consumption of 5 main food items (fat, starch, fruits and vegetables, milk and dairy products, meat and beans) to the WHO recommended portions during pregnancy. None of the two groups of women could fulfil the 5 items or even 4 items, and assessment was done based on the fulfilment of one, two or three items. Regarding weight, a positive correlation

was observed, as the BMI increases, the number of women fulfilling two items of the 5-groups increases.
The main limitation of our current study is that it is a cross sectional study (just one setting interview) which gives us less information about studied women. However, the fact that this sampling protocol has been applied before in previous studies should support the validity of this investigation to some extent. Another shortcoming is that the dietary intakes assessed in the study all depended on recalls depending on the retrospective memory of the subject. This is a very subjective method for assessing nutrition, but this was compensated by the presence of other validated factors in the nutritional survey such as the anthropometric measurements as well as the dietary intakes and the food frequency questionnaire. One more thing that should be taken into consideration is the possible denial and under-reporting of unhealthy habits especially among obese females which are more afraid of the judgment. This problem couldn't be solved under the circumstances of this investigation as it needs more targeted questionnaires and family visits.

Conclusions

In conclusion, Healthy behavior among pregnant women in both groups was influenced by their educational level, occupation as well as their pre-gestational BMI. Those were the only three significant predictive factors, where women with higher education showed an active lifestyle. In addition, women starting with normal BMI before pregnancy had better healthy behaviours including the choice of healthy diets. Both groups of women ate food rich in starch, carbohydrates and fats while ignoring other groups to some extent.

Recommendations

1. Counselling is recommended to be done during antenatal care visit to assess nutritional intake during pregnancy.
2. The role of family physician should be reinforced in the antenatal care clinics, giving the right health education modified according to the educational level of the mothers, their occupation and their BMI.
3. Food production authorities are recommended to supply pregnant women with fortified products (containing the lacking supplements and proteins) that are low in cost and easy to reach.
4. Nutritional care programs should be updated for pregnant women adjusting to the differences in educational level and occupation differences among women.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

DAN field work supervision, analysis strategy and design, data management, data analysis and interpretation of results, decision making on content and paper write-up and revision of final draft. HSE field work supervision, analysis strategy and design, data management, data analysis and interpretation of results, decision making on content and paper write-up and revision of final draft. EAS field work supervision, analysis strategy and design, data management, data analysis and interpretation of results, decision making on content and paper write-up and revision of final draft. MFA field work supervision, analysis strategy and design, data management, data analysis and interpretation of results, decision making on content and paper write-up and revision of final draft.

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ORIGINAL ARTICLE

Effect of integrated health promotion intervention and follow up on health issues (clothing way, food habits, urinary habits, sexual behavior habits) related to urinary tract infection among pregnant women. A randomized, clinical trial

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Keywords

Consulting • Urinary tract infection • Pregnant women • Follow-up

Summary

Introduction. *Urinary tract infection, as an important health element is associated with the risk of many problems in pregnancy and support consulting is effective factor in reducing the problem. Aim of this study is to evaluate the impacts of integrated intervention on life style (clothing way, food habits, urinary habits, sexual behavior habits) Related to Urinary Tract Infection Among Pregnant women.*

Method. *This interventional used pretest- posttest design with the control group study was performed on 130 healthy pregnant women. The samples were divided randomly into two groups of 65 people. The first group received two sessions of 45 to 60 minutes Psychoeducational counseling, four telephone follow-up support and training pamphlets and the control group received routine education. The relevant questionnaires were completed by both groups before the intervention and a month later. The data were analyzed with Spss V.22 software.*

Results. *Comparing within the groups it was shown that the variables were increased in the experimental group after consulting compared to the conditions before consulting ($P < 0.001$), however, no increasing was found in the average variables before consulting and after it. Moreover, comparing the variables in two experimental and control groups significant statistical difference was found in different studied areas after consulting ($P < 0.0001$).*

Conclusions. *Psychological counseling and phone follow-up are effective in improving the knowledge, attitude, and performance of pregnant women in preventing the urinary infection Therefor it is recommended these trends to be considered as training programs in order to increase capacity and primary prevention of pregnant women.*

Introduction

Urinary tract infection is a common clinical problem, including urinary tract infections, bladder and kidney infections that asymptomatic bacteriuria is among other common cases [1, 2]. The prevalence of urinary tract infection in women is considered as an important element of public health [3]. Prevalence of urinary tract infections in pregnant women is 1-3% which is 5-10% in pregnancy and 20-40% leads to symptomatic infection if untreated, moreover, 25% of women are affected by urinary tract infection annually and each year 7 million people refer to physicians to evaluate the infection or its symptoms. More than 40-50% of women experience the symptomatic urinary tract infection at least once during their life, and its prevalence is 4 times in girls than boys [4].

According to the global estimations, 150 million people suffer from urinary tract infection annually [5, 6]. The prevalence of urinary tract infections in developing countries is 20% [7]. The prevalence is 12.4% in Iran and it is different in different cities [8-10]. Asymptomatic bacteriuria is a continuous and active proliferation of bacteria in the urinary tract without causing symptoms which is significantly important since it has no clinical symptoms. Particularly in pregnant women, physiological and anatomical changes in the urinary tract, as well as immune system changes during pregnancy increase the prevalence of asymptomatic bacteriuria and in some cases, it leads to symptomatic urinary tract infection resulting in serious danger to the mother and fetus [1, 2]. In addition to these changes, some parameters such as age, sex, socioeconomic status, parity, pregnancy, sickle cell anemia, manipulation of the urinary tract, pregnancy age, and frequency of sexual intercourse in the week are effective in increasing the prevalence of asymptomatic bacteriuria [11]. The disease can cause high blood pressure, pre-eclampsia, anemia, amnionitis, maternal mortality, preterm delivery, stillbirth, sepsis, and B streptococcal infection and low birth weight that

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the mortality rate of these infants is 11% higher than that of babies with normal weights [8, 12-15].
Children born from mothers infected with pyelonephritis are affected by impaired psychomotor development. Studies show that in children who are born preterm with low birth weight, IQ scores are lower and nervous disorders are higher [14] Some studies have shown that antimicrobial therapy of urinary tract infection does not reduce maternal and fetal complications rather it imposes a heavy cost on society [16-18]. It is estimated that the annual cost of 7 million infections in young women is over a billion dollars in the United States [4].
Urinary tract infection screening at the beginning of pregnancy is considered as the standard care actions in prenatal care that is possible through counseling and testing [19]. In consultation with pregnant women special attention should have been paid to their age as an important factor in increasing incidence of kidney infection and by increasing each age decade 1% is added to the rate of bacteriuria [20].
According to the studies, the effective practices in preventing the urinary tract infection include clothing way, food habits, urinary habits, cleaning way and habits related to sexual behavior [21]. Hence, applying empowerment programs aimed to increase the knowledge and self-efficacy is essential for the health and life quality improvement [7]. The researchers believe that education is an essential component of all preventive behaviors [22]. Awareness and observance of hygienic behavior in any society are inevitable, therefore, individuals and communities need training the proper health behaviors to understand and to practice the appropriate points in life, to maintain the health and to avoid the diseases [15]. Healthcare and pregnancy educational counseling are resources for various issues. One of the most appropriate midwifery interventions to increase the women's awareness is counseling since its assistance the client to decide consciously and voluntarily taking into account all aspects. In other words, counseling is to study the problems deeply, that the person is encountered [23]. Considering the prevalence of urinary tract infection in pregnancy and its negative impact on the mother and fetus, educational counseling can contribute to increasing the women's awareness. Hence, this study aimed to evaluate the impacts of educational intervention on life style (clothing way, food habits, urinary habits, sexual behavior habits) related to urinary tract infections. It is hoped that the results would be an effective step to reduce the rate of urinary tract infection and thereby have a primary prevention step.

Methods

This Randomized Clinical Trial intervention used pretest-posttest design with the control group. The studied population were the first-trimester pregnant women who referred to health care centers in the southeast of Iran.
Inclusion criteria including: first trimester of pregnancy, lack of urinary tract infection experience, non-infected by diseases causing the urinary tract infection such as kidney disease, diabetes, immune deficiency, and exclusion criteria included acquiring information regarding urinary tract infections from other sources by the end of sampling in the field of urinary tract infection, infecting by urinary tract infection during the study.
The sample size was calculated as 130 people considering the confidence level of 95% and loss of 10% that were divided into two groups of 65 people.

$$\frac{\left(z_{1-\frac{\alpha}{2}}+z_{1-\beta}\right)^2(\sigma_1^2+\sigma_2^2)}{d^2} \qquad n=60$$

In this study, classified random sampling method was used. First, the samples were selected from the list of pregnant women who referred for primary care. Then, based on a classified randomizing, 10 people were determined for each group (intervention and control) through sortation from a list of pregnant women in the first trimester of pregnancy from each health center. Each group received a pre-test and it was completed by patients. Then the intervention group received education program.
The participants were informed about the procedure and were reminded that participation is voluntary. The questionnaires were completed by the participants followed by obtaining written informed consent, and after reviewing the completed questionnaires, the eligible individuals were placed in groups based on the allocation sequence. The considered individuals were divided into two groups of 65 people based on classified randomizing.

Intervention

The interventional group received 2 psychoeducational counseling sessions of 45 to 60 minutes with the interval of a week, regarding the anatomy of the urinary tract and reproductive health, nutrition and its effect on urinary tract infections, sex and its relationship with urinary tract infections and the complications of urinary tract infections during pregnancy. At the end of each session, free asking question was conducted, and at the end of the second consulting session, a pamphlet containing a summary of the expressed subjects were given to them. Then four supportive counseling sessions in frequent telephone follow-up were conducted for a month focusing on observing the trained issues. All the counselling carried out by one researcher who was expert in counselling due to her university major. Telephone follow-up was just for emphasis to review pamphlet and not any excessive information other than in-person counselling sessions. The relevant questionnaire was completed by both groups before the intervention and one month later. However, the control group received just the routine cares in health care centers.
The questionnaire was developed by the researcher. It was designed based on the use of various articles, books and experts' opinions. Then its validity and reliability

were measured. The questionnaires contain three sections.

Each questionnaire contains 64 questions consisting of three parts: part I: demographic questions, 11 questions; part II: questions regarding awareness of urinary tract infections with 8 questions; part III: attitude with 11 questions, 13 questions regarding the mental performance and 20 questions for actual performance. Scoring was based on the Likert scale.

Fourth Likert scale was used in scoring. The score was from 0 to 100, and the closer the score was to 100, a better state of attitude and performance's awareness will be shown.

Content validity was evaluated through both qualitative and quantitative methods with assisting 10 the midwifery and nursing professors.

In the qualitative study of the content, the professors were asked to provide their feedback after fulfilling the qualitative examination of the tool according to the observation of the grammatical criteria, use of the proper words, the placement of the items in their proper place and the appropriate rating. Based on those points, the corrections were made. In total, in the content validity stage, 3 questions were removed and some of the changes occurred in this section regarding the suggestion of the professors included the modifications in the structure and the wordings of the questions, the simplification of the questions, the subtraction and integration of similar questions.

Cronbach's alpha coefficient was used to determine the reliability of the questionnaire, which was performed on the people whose demographic characteristics were similar. According to the researchers, alpha values are less than 5. It is unacceptable that in this study, this value was 75%.

The data were analyzed by spss V.22 software. The significance level was 0.05.

The distribution of data in these two groups was not related to age, gestational age and the times of pregnancy. Therefore, Mann-Whitney test was used for comparison. Parametric t-test and paired one [t-test] were used to compare the other data because of their normal distribution.

Results

Both intervention and data collecting lasted for 4 months. There was no significant difference in terms of socio-demographic characteristics between the groups, and both groups were similar in terms of demographic characteristics (Tab. I).

Intra-group comparison of both intervention and control groups in terms of knowledge, attitude, performance, actual and mental health performance and actual and mental nutrition performance showed that the variables in the intervention group after consultation had a mean increase compared to the previous consultation ($P < 0.001$), however, in the control group the increase in the average variable was not shown (Tab. II). By comparing between two groups after consultation, significant statistical difference was seen in the different areas of the study ($p < 0.0001$) (Tab. III).

Discussion

Results of this present study showed that supportive and psychoeducational counseling plays quite important role in informing the people regarding urinary tract infection. Hence, by awareness of risk factors for urinary tract infections and changes in health behaviors, effective steps can be taken toward reducing the urinary tract infections, particularly in women [24]. According to Gheiasi (2017) Patient education could improve self-care behaviors in patients with heart failure [25]. The results of Moor et al. study (2008), showed not respecting some health tips regarding sexual behaviors is associated with urinary tract infection. Leydon et al (2010) also stated that the most important risk factor for recurrent urinary infection in women is the risk factor associated with health behaviors [26-28].

The readiness of community members to understand and to practice the right way of life to maintain health and to prevent the diseases require shaping behavior [29].

Understanding the seriousness of the complications and costs of urinary tract infection and its treatment plays an important role in promoting the individuals' attitude in this regard. According to researchers to adopt preventive behaviors the knowledge regarding a disease is not enough, rather the mindset and attitude play an important role in preventive action [30].

Emiru (2013), concluded that the women believe that urinary tract infection causes maternal and fetal complications in addition to the imposed costs, and they request for counseling programs for preventing UTI. Regarding the attitude of women toward the infection, Shih et al. (2006) stated in their study that theories of health education in the field of health promotion, knowledge and attitude of people toward the health risk factors, changes in behavior during various stages of planning, implementing and evaluating a program are effective for women with urinary tract infection [30, 31].

Mazor-Dray (2009), in his research, achieved an increased knowledge and practice of pregnant women after training consultation. Recommendations on the detailed plan for training consultation was the framework of this study. In this study, it is recommended to focus on the increased awareness and performance of the pregnant women regarding the urinary tract infection. Moreover, this study also showed the ability of pregnant women in their care [8, 31, 32].

Health mental function associated with urinary tract infection of women in this study, showed significant statistical difference in the intervention group compared the control group, that it is consistent with the study of Jalali et al. (2014), they found that training based on the planned behavior, result in improved performance in

Tab. I. Comparison of demographic variables in the intervention and control groups.

Variable		Control	Intervention	Statistical test results
Age		27/07 ± 5/17	26/8 ± 5/28	Mann-Whitney p = 0.62
Pregnancy age		10.09 ± 2.2	10.44 ± 2.37	Mann-Whitney p = 0.29
Parity		1.68 ± 0.91	2.35 ± 1.38	Mann-Whitney p = 0.07
Education of wife	High school	17 (26.2)	25 (38.5)	X^2 = 2.25 P = 0.32
	Diploma	36 (55.4)	30 (46.2)	
	Academic	12 (18.5)	10 (15.4)	
Education of husband	High school	31 (47.7)	20 (30.8)	X^2 = 3.39 P = 0.11
	Diploma	28 (31.1)	38 (58.5)	
	Academic	6 (9.3)	7 (10.8)	
Occupation of wife	Housewife	59 (90.8)	53 (81.5)	Chi^2 = 2.25 P = 0.12
	Employee	6 (9.3)	12 (18.5)	
Occupation of husband	Employee	6(9.2)	6 (9.2)	X^2 = 0.17 P = 0.98
	Working	20 (30.86)	22 (33.8)	
	Free	27 (41.5)	25 (38.5)	
	Etc.	12 (18.5)	12 (18.5)	

Tab. II. Comparison the difference between the variables of awareness, attitude, mental and actual health performance, mental and actual nutrition performance before and after the consultation in intervention and control groups (in group).

Group	Time	Variables	Awareness	Attitude	Mental health performance	Actual health performance	Mental nutrition performance	Actual nutrition performance
Intervention	Before	Mean	48.6	52.2	60.7	62.83	57.9	49.23
		SD	12.2	16.6	12.63	10	20.92	14.61
	After	Mean	78.9	80.2	80.15	81.53	85.12	77.23
		SD	8.4	10.3	10.67	9.62	14.6	12.68
	Statistical test results		t = 23.7 P < 0/001	Z = -6.9 P < 0.0001	Z = -6.9 P < 0.0001	Z = -6.7 P < 0.0001	Z = -6.7 P < 0.00001	t = -12.6 P < 0.0001
	Before	Mean	41.7	45.8	41.48	48.37	48.37	49.8
		SD	12.3	12.48	19.12	24.32	24.32	14.8
	After	Mean	42.1	47.9	49.28	51.96	51.9	50.25
		SD	13.5	13.56	13.1	25.91	25.91	15.32
	Statistical test results		Z = -1.3 P = 0.1	Zv-3.2 P = 0.1	Z = -3.2 P = 0.1	Z = -1.34 P = 0.17	Z = -1.34 P = 0.17	Z = -1.06 P = 0.28

Tab. III. Comparison the difference between the scores of awareness, attitude, mental and actual health performance, mental and actual nutrition performance variables after the consultation in intervention and control groups (out-group).

Variable	Mean ± standard deviation		Z	P-value
	Intervention group	Control group		
Awareness	30.36 ± 10.27	0.38 ± 1.36	-10.25	< 0/0001
Attitude	28.18 ± 15.6	2.09 ± 5.14	-9.25	< 0/0001
Mental health performance	19.43 ± 14.36	0.87 ± 3.64	-7.53	< 0/0001
Mental nutrition performance	27.17 ± 20.1	3.5 ± 12.5	-7.8	< 0/0001
Actual health performance	18.7 ± 10.3	0.5 ± 3.03	-9.2	< 0/0001
Actual nutrition performance	28 ± 18.7	0.4 ± 3	-8.3	< 0/0001

preventing the urinary tract infections, it is likely that training-supportive consultation could have resulted in improved performance in increasing the awareness and the impact on people's attitude [4].

In general, a person's behavior and performance occur followed by the intention or function in the mind and without the intention, no behavior will happen. In present study, significant differences were found in mean maternal mental function compared to healthy habits associated with urinary tract infection before and after the intervention that this finding likely reflects the impact of the designed counseling program. Korb, in his study, in 2018 concluded that intervention on pregnant women regarding the urinary tract infection increases their knowledge, attitude, and self-care of that is consistent with the result of this present study

in regard with awareness, attitude and performance. Hashemi Parast in his study, in 2013 concluded that causes of Urinary Tract Infections are a low level of knowledge, attitudes, self-efficacy, and performance in this regard, which refers to the need for interventional programs that confirm the results of this present study in all three areas [33, 34]. The limitations of the study were telephone interviews and due to time and space constraints, it was not possible to have classes for the spouse or other influencer on pregnant women behavior.

Conclusions

The results of present study showed the improvement in knowledge, attitude and mental and real performance of the pregnant women followed by psychoeducational counselling and telephone follow-up. It is being suggested that holding training classes on the preventive behaviors of the urinary tract infection in the premarital counseling classes, health centers, universities, clinics and even schools will be effective as well; counseling should be used in order to change the attitudes and the behavior of women to the prevention of the urinary tract infections during pregnancy.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

SY and KA designed the work and drafted the manuscript. SY and KA had prepared counselling package. BT and SY had full access to all of the data and take responsibility for the integrity of the data. YJ take responsibility for accuracy of the data analysis. All authors read and approved the final manuscript.

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ORIGINAL ARTICLE

Diffusion of the Italian social media campaign against smoking on a social network and YouTube

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Keywords

Health prevention campaign • Tobacco smoke • Ministry of Health • Social media

Summary

Introduction. *Recently, the Italian Ministry of Health developed a health prevention campaign against tobacco smoking entitled "Ma che sei scemo? Il fumo fammale" (Are you stupid? Smoking is bad). The aim of this study was to evaluate the diffusion of the ministerial campaign by analyzing data from two web platforms, Facebook and YouTube.*

Method. *The study evaluated the dissemination of the campaign using the number of users reached, interactions and the interaction index (interactions/users reached) on the web platform Facebook and YouTube. A qualitative analysis of the text comments left by the users was also carried out.*

Result. *The average number of interactions on Facebook was 6,087 and 400 for YouTube while the total views were 356,967 for Facebook and 174,763 for YouTube. The interaction index was very low for both platforms, between 0 and 1%. A total number of 156 comments were obtained on Facebook and 37 on YouTube, most of which were negative, or comments not related to the campaign.*

Conclusions. *The Italian campaign had low diffusion on the web platforms investigated. Evidence-based public health interventions can play a central role in the prevention field but must be based on elements of scientific effectiveness. Further research should analyze the effects of social media campaigns on direct health related outcomes.*

Introduction

Tobacco is responsible for the death of about six million people every year and is the leading cause of preventable diseases [1]. Nevertheless, tobacco use remains a widespread and accepted behaviour and Italy records among the highest smoking prevalence in Europe [2]. The Italian behavioural risk factor surveillance system (PASSI) reported that 26% of the population aged between 18 and 69 years were smokers between 2014 and 2017 [3]. Conversely the survey among young people, Health Behaviour in School-aged Children (HBSC), showed that 13.8% of 15-year-old boys and 13.3% of girls smoked every day in 2014 [4].

Smoking is a well-known preventable risk factor for the development of many chronic diseases: cardio and cerebrovascular diseases, chronic obstructive pulmonary disease, osteoporosis, and many cancer types as lung, trachea, bronchi, larynx, oral cavity and esophagus [5]. Smoking during pregnancy increases the risk of having underweight babies, premature births, and sudden infant deaths. Second-hand smoke is also very dangerous especially for children, pregnant women and elderly people.

Many prevention media campaigns for tobacco cessation have been implemented [6] and are recognized as effective strategies to change smoking attitudes and behaviours [7] . The health preventive messages can be spread through different communication channels as television, radio, newspapers, billboards and posters [8]. Moreover, the social media as social networks, YouTube and blogs are used to reach a larger number of people and in particular young ones. Social media are increasingly integrated into programs and campaigns aimed at raising public awareness on specific health issues or to promote healthy behaviour. Numerous public health campaigns used them such as the seasonal flu vaccination campaign of the Center for Disease Control (CDC) [9], the national "Truth campaign" against tobacco use and the programs against HIV infection [10, 11]. These means of communication can spread health messages in an economic and efficient manner; the national anti-smoking campaign "The Tips from Former Smokers" by CDC, for example, was both cost-effective and improved smoking related health outcomes [12].

In Italy several campaigns have been carried out by the Italian Ministry of Health, as "sFreccia contro il fumo" (2013) (Whizz against the smoke) [13], and "Il fumo uccide: difenditi" (2009) (Smoking kills: defend yourself) [14]. The last one was "Ma che sei scemo? Il fumo fammale" (2015) (Are you stupid? Smoking is bad) [15], which aimed to increase awareness about the health consequences of smoking, in particular to protect children, pregnant women and elderly from second-hand smoke exposure. The objective of this study was to evaluate the diffusion of the Italian social media campaign "Ma che sei scemo? Il fumo fammale", through the number of views and interactions on the web platforms Facebook and Youtube.

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Material and methods

Study design and the media campaign

The campaign "Ma che sei scemo? Il fumo fammale" (Are you stupid? Smoking is bad) was launched by the Italian Ministry of Health in 2015. It was weekly published on the landing page "www.macheseiscemo.it" (today no longer accessible*) and on the Facebook page thus creating a mini web series [16]. For the dissemination of the spots, Facebook Advertising channel used YouTube to which is directly linked. It was also broadcast on the national television channels such as Canale5, Italia1, Rete4, La7, Deejay TV, Real Time, DMAX and on the main national and local radio stations.

The campaign included four video spots lasting 30" and aimed at different targets. It was conceived to be an innovative, social media campaign combining the anti-smoking message with other preventive messages.

- Video 1 - pregnant women. The video showed the risks and consequences of smoking among pregnant women (premature birth, retardation in mental and physical development, spontaneous abortion) [17].
- Video 2 - women who smoke. The spot focused on some consequences of tobacco use as skin ageing, teeth spot and hair weakening. Furthermore, the video promoted safe driving and suggested not to take photos while driving [18].
- Video 3 - effects of second-hand smoke on children. The video showed the negative effects of second-hand smoke on children, as respiratory and pulmonary infections or asthma attack. The spot combined the communication against smoking with a message of protection and respect of animals [19].
- Video 4 - prevention of smoking for young people. The video showed the effects of smoking on young' health as reduction of life expectancy, increase of mortality, damage for fertility and higher risk of impotence. Moreover, it combined the tobacco message with the prevention of road accidents, encouraging safe driving and the use of the helmet [20].

The testimonial, the popular ironic actor Nino Frassica, was chosen after a focus group. He repeated the expression "Ma che sei scemo? Il fumo fammale" (Are you stupid? Smoking is bad) using surreal gestures and mimics. The actor was considered credible and trustworthy for social communication.

Study design and outcome measures: dissemination and impact

The research is a study of evaluation of the impact of a preventive mass media campaign on a social network and internet. The outcome measures were decided based on the narrative revision of Bardus et al. [10] where results were reported as statistics of access to the web pages as number of visitors, registered users, followers. This research evaluated the diffusion of the media campaign using the number views and interactions ("likes", "comments", "shares") on the dedicated web platforms. Data were described using frequencies and percentages to describe outcomes of dissemination on Facebook and YouTube. The virality of the campaign's contents was evaluated with the interaction index. It was inspired to the engagement rate of Socialbakers, the social media analytics campaign, which weighs the interactions generated by posts ("likes", "comments", "shares") on the number of fans of a page or post. In this study, the webpage of the campaign was temporary, so we considered more important to compare the number of interactions ("likes", "comments", "shares") to the reached users (views) instead of the number of fans. Consequently, the page interaction rate, or interaction index, was calculated as the interactions generated by the posts (likes + comments + shares) / users reached. As far as concern the qualitative evaluation, the comments were described by frequencies and percentages. We considered the following answers:

- negative comments: expression of disapproval of the campaign as ineffective, offensive or lack of sharing of contents;
- positive comments: approval of the video;
- share to other users: signaling the video to other users;
- support for the anti-smoking message: lack of explicit approval of the campaign, but positive opinion about the anti-smoking message;
- support for the testimonial;
- comments not related to the campaign.

Results

The results of the quantitative analysis are reported in Tables I and II. A total number of 356,967 views and 6,087 interactions were recorded on Facebook. The interactions were respectively like (2,232), comments (108) and share (3,747). Most like and views were registered for the first video "Non me lo far ripetere più: il fumo fammale" (prevention message for pregnant women) followed by the fourth "Chi fuma è scemo, ma anche chi va in giro senza casco" (prevention of smoking for young people). As far as concern the comments, the second and fourth video gained 26% and 30%, more than half per cent of comments by users. The interaction index was higher for the second video (1.7%), although overall it was critically low with a mean of 1.2%. As far as concern YouTube a total number of 174,763 views and 400 interactions were obtained. The interactions were respectively likes (324), comments (31) and shares (45). The most visited video was the fourth "chi fuma è scemo, chi non indossa il casco anche" with 35% likes, 35% comments and 51% share. Consequently, it registered the highest interaction index of 0.3%. The second video gained the most views (34%). The interaction index was very low also for YouTube with a mean of 0.22%.

From a qualitative point of view, 13% of comments left by users on Facebook were of approval of the campaign, 31% negative comments, 18% share of the video and 25% gave comments not related to the campaign. The qualitative results of Facebook are shown in Table III. The qualitative results for Youtube, were 14% positive comments, 32% of negative comments, 13% of support for the message transmitted and 22% of inconsistent comments. The results for YouTube are shown in Table IV.

Tab. I. Quantitative results on Facebook.

Title of video	Like	Comments	Share	Views	N. interactions*	Interaction rate**
Video 1 "non me lo far ripetere più: il fumo fammale"	719 (32%)	26 (24%)	1,600 (43%)	173,000 (48%)	2,345 (38%)	0.013 (1,3%)
Video 2 "chi fuma è scemo, ma anche chi si fa i selfie alla guida"	468 (21%)	28 (26%)	734 (19%)	73,217 (20%)	1,230 (20%)	0.017 (1,7%)
Video 3 "chi fuma è scemo, ma anche chi non rispetta gli animali"	362 (16%)	22 (20%)	730 (19%)	111,577 (31%)	1,114 (18%)	0.009 (0,9%)
Video 4 "chi fuma è scemo, ma anche chi va in giro senza casco	683 (31%)	32 (30%)	683 (18%)	154,873 (43%)	1,398 (23%)	0.009 (0,9%)
Total	2,232 (100%)	108 (100%)	3,747 (100%)	356,967 (100%)	6,087 (100%)	0.012 (1.2%)

*: number of interactions (likes + comments + shares); **: interaction index: number of interactios/reached users.

Tab. II. Quantitative results on Youtube.

Title of video	Like	Comments	Share	Views	N. interactions*	Interaction rate**
Video 1 "Il fumo fammale (con due emme perché fa molto male)."	59 (18%)	4 (13%)	12 (27%)	50,678 (29%)	75 (19%)	0.001 (0,14%)
Video 2 "chi fuma è scemo, ma anche chi si fa i selfie alla guida"	79 (24%)	8 (26%)	7 (16%)	59,177 (34%)	94 (23%)	0.0015 (0.15%)
Video 3 "chi fuma è scemo, ma anche chi non rispetta gli animali"	73 (22%)	8 (26%)	3 (7%)	26,100 (15%)	84 (21%)	0.003 (0.3%)
Video 4 "chi fuma è scemo, chi non indossa il casco…anche"	113 (35%)	11 (35%)	23 (51%)	38,808 (22%)	147 (37%)	0.003 (0.3%)
Total	324 (100%)	31 (100%)	45 (100%)	174,763 (100%)	400 (100%)	0.006 (0.22%)

*: number of interactions (likes + comments + shares); **: interaction index: number of interactios/reached users.

Tab. III. Qualitative results obtained on Facebook.

N. comments	Video 1	Video 2	Video 3	Video 4	Total
Negative comments: expression of disapproval of the campaign as ineffective, offensive or lack of sharing of contents	17 (30%)	8 (31%)	3 (14%)	12 (54%)	40 (31%)
Positive comments: approval of the video or of the anti-smoking message	2 (3%)	5 (19%)	3 (14%)	6 (27%)	16 (13%)
Share to other users	20 (35%)	3 (11%)	0	0	23 (18%)
Support for the anti-smoking message	8 (14%)	0	4 (19%)	2 (9%)	14 (11%)
Support of the testimonial	2 (3%)	0	0	0	2 (2%)
Comments not related to the campaign	8 (14%)	10 (38%)	11 (52%)	2 (9%)	31 (25%)
Total	57 (100%)	26 (100%)	21 (100%)	22 (100%)	126 (100%)

Tab. IV. Qualitative results obtained on Youtube.

N. comments	Video 1	Video 2	Video 3	Video 4	Total
Negative comments: expression of disapproval of the campaign as ineffective, offensive or lack of sharing of contents	4 (33%)	1 (14%)	2 (66%)	5 (33%)	12 (32%)
Positive comments: approval of the video or of the anti-smoking message	1 (8%)	2 (28%)	0	2 (13%)	5 (14%)
Share to other users	0	0	0	0	0
Support for the anti-smoking message	2 (16%)	1 (14%)	1 (33%)	1 (6%)	5 (13%)
Support of the testimonial	1 (8%)	0	0	0	1 (3%)
Comments not related to the campaign	4 (33%)	3 (43%)	0	7 (47)	14 (38%)
Total	12 (100%)	7 (100%)	3 (100%)	15 (100%)	37 (100%)

Discussion

The national campaign "Ma che sei scemo? Il fumo fammale " had the aim to be a viral mean of information against smoking. Conversely, the dissemination was low, the number of users reached was small if compared to the numerosity of Italian young people and to the general population [21]. The interaction index was also very low considering the potentiality of the social networks and internet to reach many users. The qualitative results were few and not encouraging. Although it is not possible to compare the diffusion of this campaign to similar health

education programs as other outcomes of evaluation were used [10].

The findings of this study indicate that some characteristics of the media campaign were not effective for the viral spread and different reasons may be involved. The Italian media campaign used an ironic and popular approach; however, the contents may have been simplistic and the linguistic register was not serious. Considering the single elements of the media campaign, we can begin talking about the slogan which might have resulted ineffective or rather offensive, in fact, the smokers were called "silly". Smoking uptake is a voluntary behaviour, usually occurs during adolescence under the influence of peer pressure and can be considered a wrong choice for health. However, over time, smoking becomes a physical and psychological dependence and to stop can be very difficult for heavy smokers. Consequently, the catchphrase may be not an effective and strategic slogan to encourage smoking cessation, while its use may be more appropriate to prevent the onset of smoking habits among young people. As far as concern the tone, which is the general positive or negative attitude of a message, the study of Allen et al. [22] suggests that advertisements with a negative emotional connotation have a greater impact on young people than positive or neutral messages. This is in line with the studies of Biener et al. [23, 24]: the campaigns that generate negative feelings as sadness and fear are more effective than those that arouse positive emotions. Also, the study of Lee et al. [25] indicates that elements for effective media campaigns are the negative emotional reinforcement, the communication of harmfulness of smoking and the change of social norm.

As regards the testimonial Nino Frassica, the actor, wore a red and shiny dress and used an ironic style. The study of Allen et al. [22] underlines that young people are more likely to be impressed and think about advertising with intense and surprising style and images. Although we believe that the Italian campaign may have resulted as not enough impressive both for the aspects of production and style

Concerning the content of mass media campaigns, several reviews highlighted that negative messages about smoking, like health consequences of tobacco use, can be effective; although the effectiveness of negative messages was not compared with that of the positive ones [26-28]. Conversely Stead et al. [29] in their review concluded that there is insufficient evidence that a message about smoking is more effective than other messages. The review concluded that the reasons for smoking are complex and that negative messages against tobacco may not be the sole and final solution. Jepson et al. [26] highlighted that the addictive impact of nicotine is rarely mentioned in the context of antismoking messages while the fight against dependence is a crucial aspect to stop smoking.

Another aspect that influences the effectiveness is the intensity and duration of the mass campaigns [23, 29]. Carson et al. [30] underlined that anti-smoking campaigns need to use repetitive messages and to be broadcast over time. The review of Richardson et al. [31] showed that the exposure to anti-tobacco messages over time discourages smoking initiation and increases negative attitudes towards tobacco. Several studies showed that long term interventions broadcast on multiple channels are associated with better health outcomes [30, 32, 33]

Conversely, the campaign "Ma che sei scemo? Il fumo fammale was not transmitted for long time or repetitively, this is other aspect that could explain why the diffusion was very low.

Finally, this research is innovative because it tried to measure the diffusion of an education campaign on the social media and make a qualitative evaluation of the Italian campaign.

More studies and reviews on the effectiveness of new-media campaigns, including digital and social media, are needed. In addition, it could be useful to study the specific contribution of mass media campaigns as part of multicomponent community interventions considering the synergic role of public health interventions [29].

Conclusions

Evidence-based public education campaigns can play a central role to counteract tobacco use particularly among youth and young adults. Although evidence-based features and elements of the viral marketing science should be considered in order to make health messages viral and effective [34]. Further research should analyze the effects of Italian media campaigns on direct outcomes as on smoking attitude and behaviour.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

Conceptualization: GLT and AM; methodology: GLT, VDE and AM; software: GLT and AM; formal analysis: GLT; investigation: GLT, VDE, SG, AB and AM; data curation: GLT; writing - original draft preparation: GLT, VDE; writing - review and editing: GLT, VDE, SG and AB. All authors have read and agreed to the published version of the manuscript.

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ORIGINAL ARTICLE

Knowledge, attitudes and practices of primary health care providers towards oral health of preschool children in Qatar

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Keywords

Oral health promotion • Attitude of health personnel • Preventive dentistry • Health knowledge • Health care surveys • Primary health care

Summary

Objective. *Health care providers can effectively participate in oral health promotion for children in primary care setting. Currently, there are no oral health promotion programs that involve primary health care professionals in Qatar. Hence, this study was undertaken to examine the knowledge, attitudes and practices of all health professionals who work in the Well baby Clinics in the primary health centers.*

Method. *A 23-item questionnaire was distributed across 20 primary health centers. The questionnaire sought information on the demographic data of health professionals, their knowledge of oral health and their practices and attitudes towards critical oral health issues. Data were examined by Pearson Chi-squared tests or Fisher's Exact test (p = 0.05).*

Results. *The response rate of the health professionals was 67%. Only 35.7% of the 225 participants received some form of oral health training during their undergraduate programme. The participants would assess the dental problem of the child (p = 0.05) and discuss the importance of tooth brushing with the mother (p = 0.03). A significant number of respondents (p = 0.04) were unlikely to assess the children's fluoride intake. There was a significant difference in the group of participants that would examine the child's teeth (p = 0.1) and counsel the mothers on prevention of dental problems (p = 0.01). This group would also refer children to dentist at 12 months of age (p = 0.05).*

Conclusions. *Health professionals had a positive attitude towards the anticipatory guidance elements of oral health. However, the knowledge of healthcare professionals on childhood oral health is rather limited.*

Introduction

Oral health, now considered an inherent component of general health, is defined by the World Health Organization (WHO) as "a state when an individual is free of chronic oro-facial pain, oral sores or cancer, craniofacial defects such as oral clefts, gum diseases, dental decay, tooth loss or any other disorders affecting oro-dental tissues" [1]. Numerous studies have shown the association of oral health with systemic health and general well being including major chronic conditions such as obesity, cardiac diseases, diabetes and respiratory infections [2-4]. The most widely proposed mechanisms by which oral health status affects systemic heath include: a) inflammatory mechanisms: inflammation derived from host immune response against dental and/ or periodontal pathogens give rise to molecules that gain access to the circulatory system, producing systemic inflammation; b) bacterial mechanisms: bacteria and its products directly invade the tissues of the organism; c) vascular mechanisms: dental and periodontal pathogens present in the systemic circulation cause platelet aggregation and thrombus formation [5, 6]. In spite of the significance of oral health and the association with general health, it has not received the necessary attention in many regions of the world including many parts of the South-East Asia Region (SEARO), Eastern Mediterranean Region (EMRO) and Western Pacific Region (WPRO) [7]. The oral health of children, in particular, remains a concern worldwide. Early childhood caries is a major health issue and can cause distress to young children [8, 9]. Despite the acute importance of oral health, periodic dental assessment and care for children is unorganized in most countries including but not limited to Afghanistan, Philippines, Madagascar, Bolivia, Burundi, Chad, Haiti, Myanmar, Nepal, Pakistan, India, Rawanda, Senegal, Yemen and Zimbabwe [7].

Primary health care professionals including Pediatricians, play a vital role in many preventive activities for young children such as assessment of milestones and immunizations. There is mounting evidence that health care providers play a significant role not only in the systemic health but also oral health promotion for children in the primary care setting [10-12].

A recent study analyzed data derived from 195 countries between 1990 and 2015 and found that based on mortality from causes amenable to personal healthcare Qatar has the best Healthcare Access and Quality Index in the GCC (Gulf Cooperation Council) region [13]. Further, it ranked 28th in the overall list and has shown substantial progress in the quality of healthcare in the past 30 years [13]. In spite of these healthcare developments, oral

health remains a critical public concern for authorities in Qatar [14]. Several studies conducted in the Gulf Cooperation Council countries including Qatar have documented a high prevalence of dental caries in young children. These studies have strongly emphasized the necessity of community-based preventive programs and professional care that should begin during pregnancy and early childhood [15]. Routine Well Baby Clinics (WBCs) are established at all primary health centers throughout the country and they serve as vital tools to promote children's general health. Further, child care at these clinics also helps to detect and eliminate the potential health problems affecting the development, behavior and education of children. All residents of Qatar have access to these primary health centers at exceptionally subsidized cost and their children can avail services of WBCs at these centers.

Oral health services in Qatar are given considerable attention by health care planners and the dental workforce is responsible for implementing these services. However, there are no standardized oral health promotion programs involving primary health care professionals (excluding dentists) caring for children in these WBCs. The healthcare workforce in Qatar includes professionals from various countries with different educational backgrounds and diverse clinical experience. Consequently, the language barrier arising out of this diversity may hinder the participation of these professionals in health promotion regimes [16]. Furthermore, it is essential to assess the level of oral health literacy and assess if health professionals have the desired knowledge before designing such a program for oral health promotion. Hence, the aim of this study was to examine the knowledge, attitudes and practices of all health professionals including paediatricians, family physicians, general medical practitioners and nurses who work in the Well baby Clinics in the primary health centers in Qatar.

Methods

This descriptive cross-sectional study was conducted an all 20 WBCs at all primary health care centers in Qatar. The data was collected via a two-page self-completed paper-based questionnaire developed after reviewing the relevant literature (Appendix 1). A literature search was carried out by applying the key terms including and relating to oral health knowledge of health care practitioners to appropriate data sources (Medline [MeSH] via OVID, Embase via OVID, Pubmed, Cochrane Central Register of Controlled Trials and OpenSiGLE). The key words "oral health promotion", "attitude of health personnel", "preventive dentistry", "health knowledge", "health care surveys", "primary health care". The questionnaire was primarily adopted from a previous study by Lewis and co-workers (2000) [10] but was modified slightly concordant with the protocols at WBCs. The questionnaire was tested in a pilot study which preceded the main study to test the feasibility of this approach. The data from the pilot study were not included in the main study. The standardized instrument underwent reliability testing with Cronbach's alpha score of 0.79.

The questionnaire contained 3 sections and 16 items. The first section contained demographic data including details of experience and training. Also, this section included two questions about the involvement of the health practitioners with the WBC. Participants were asked to specify their profession and whether they worked in the WBC. If they were not working in the WBCs then they were asked to refrain from completing the questionnaire. Participation in the WBC thus became the sole inclusion criterion for the study. The second section sought information about the knowledge of health practitioners about oral diseases and oral health promotion approaches. This section was designed to include information regarding oral health training received by the health care provider during under graduate training, the type of oral health training; further oral health training received after graduation and their source of oral health knowledge at the time the investigation was conducted. Also, this component inquired the health care practitioners' knowledge on transmission of caries causing bacteria from mother to child [17] and if they provided oral health recommendations to their patients. The third section comprised questions about the practices and attitudes of the health practitioner towards critical oral health issues. This segment comprised questions that explored oral health practices of health care practitioners including enquiring about nocturnal bottle feeding, assessing dental problems, discussing importance of tooth brushing with mother, assessing the child's fluoride intake [18] and scrutinize the mothers 'oral health status. The respondents marked their answers as one of the following - very likely, likely, neutral, unlikely or very unlikely. Further, this section assessed the attitudes of participants towards dental examination of children, counseling mothers on prevention of dental problems, application of topical fluoride varnish [19, 20], and referral of children to dentist at 12 months of age. The participants were asked to select one of the following responses: strongly agree, agree, neutral, disagree or strongly disagree. Table I shows the dependent and independent variables used to explore the survey results.

The targeted population was health professionals working in WBCs including nurses, pediatricians, family physicians and general medical practitioners (GPs). These health professionals were employed in the primary health care centers and were not exclusively posted in WBCs, but they attended the clinic on a rotational basis, once a week per calendar month.

The participants were recruited in two phases. In the first phase 168 health professionals from all 20 health centers were approached to participate. Health professionals from only seven health centers responded and the response rate was low (53.6%). This highlighted a problem in the survey distribution method, which was delivered via email through health centre directors. The situation was amended and the surveys were re-sent individually in envelopes to the remaining 13 health centers which had not responded in the first phase. The head nurse of each of these 13 health centers was assigned the responsibility to receive the surveys via the central mail of the Primary Health Care

Tab. I. The dependent and independent variables for the survey.

Independent variables	Dependent variables
Demographic characteristics: • length of clinical experience • years of practice in the current health centre • years of working in WBCs	Knowledge: • "Caries – causing bacteria" can be transmitted from mother to child
Oral health training received: • type of oral health training received during formal education • any further oral health training received • sources of oral health knowledge	Practices: • usual clinical practice: – provide oral health recommendations • current oral health practices: – inquire about nocturnal bottle feeding – examine child's teeth – discuss tooth brushing importance with mother – assess fluoride intake – inquire about mother's dental health
	Attitudes: • assess children's dental problems in WBCS • counsel mothers on dental problems prevention in wbc • apply fluoride varnish in wbc • refer children from WBC to dentist at 12 months of age

Centers. The questionnaires were sent to the participants in sealed envelopes via the central internal mail of the Primary Health Care Centers. Sealed boxes were provided at each health centre for collection of completed questionnaires to ensure confidentiality for participants. The sealed boxes were then returned to the research office via courier.

The questionnaire data were entered into Microsoft® Excel 2003 spread sheets (Microsoft Corporation, Seattle, Washington, USA) and exported to SPSS 20.0™ for Windows® (SPSS Incorporated, Chicago, Illinois, USA). The data were analyzed and descriptive statistics and frequency tables for dependent and independent variables were prepared. Categorical data were examined by Pearson Chi-squared tests ($p = 0.05$) or Fisher's Exact test. The outcome measures (dependent variables) were the oral health knowledge of participants, and; their clinical practices and attitudes related to oral health of preschool children. The data analysis was based on determining whether the demographic characteristics of health professionals affected their knowledge, attitudes and practices towards oral health of young children.

Results

The response rate for the first phase was 53.6%, as 90 out of 168 health professionals responded to the questionnaire. However, this included the unanticipated response of 22 dental professionals. These respondents were excluded from the study as they did not meet the inclusion criteria of attending the WBCs. Moreover, their dental knowledge would differ significantly from the other participants and would induce bias in the study. Thus, a total of 68 out of 146 valid responses were obtained in the first phase. In the second phase, 190 questionnaires were distributed of which 157 health professionals responded (response rate = 82.6%). The data from both phases were pooled together in the analysis and the total number of respondents were 225 (response rate = 67.0%). There were no repeat responses as the participants from the seven health centers in the first phase were excluded in the second phase to avoid bias by "learned response".

Furthermore, some participants did not respond to all the questions in the survey. These specific questions which were left unanswered were excluded from the analysis. However, the other responses which were marked from the same participants were evaluated. Hence, not all the questions in the survey received 225 responses.

Most respondents in the study were nurses (n = 174, 77.3%) (Tab. II). The participating health professionals were in clinical practice since 8 ± 5.6 years and the mean number of years these professionals had been in the WBC was 7 ± 4.3 years. Only 35.7% of the participants received some form of oral health training during their undergraduate programme. Further, 32.9% of these participants could not remember what sort of oral health education were they imparted. After graduation, only 41 (20.1%) participants received further oral health education. Besides, a little more than half of the participants (51.7%) cited "media" as their source of general knowledge on oral health, particularly television. (Tab. III).

Many health care providers (52.8%) did not agree with the fact that caries-causing bacteria can be transmitted from mother to child [17] (Tab. III). Table IV shows the association between the type of health professional and oral health practices. Generally, the participants would assess the dental problem of the child ($p = 0.05$) and discuss the importance of tooth brushing with the mother ($p = 0.03$).

Tab. II. Distribution of occupation and years of clinical experience of responding health professionals.

Demographics	Respondents (%)
Nurses	174 (77.3)
General medical practitioners (GPs)	18 (8)
Paediatricians	23 (10.2)
Family physicians	10 (4.4)
Medical health professionals (total)	*225 (100)*
Years of clinical experience	*225 (100)*
1-5 years	26 (11.6)
6-10 years	53 (23.6)
More than 10 years	146 (64.8)

Tab. III. Distribution of responses of health professionals to oral health training and knowledge questions.

Oral health training and knowledge	Responses (%)
Oral health training received in under graduate programme	221 (100)
Yes No	79 (35.7) 142 (64.3)
Type of oral health training in under graduate qualification	79 (100)
Completed unit with several lectures Only 1-2 lectures Do not know/ cannot remember	24 (30.4) 29 (36.7) 26 (32.9)
Any further oral health training received after graduation	204 (100)
Yes No	41 (20.1) 163 (79.9)
Current sources of oral health knowledge	201 (100)
Some general knowledge from the media Read scientific articles about oral health occasionally Others	104 (51.7) 79 (39.3) 18 (8.9)
Usually give oral health recommendations	213 (100)
Yes No	166 (77.9) 47 (22.1)
Caries - causing bacteria can be transmitted from mother to child	212 (100)
True False	100 (47.2) 112 (52.8)

A significant number of respondents (p = 0.04) were unlikely to assess the children's fluoride intake [18]. Further, there was a significant difference in the group of participants that would examine the child's teeth (p = 0.01) and counsel the mothers on prevention of dental problems (p = 0.01) (Tab. V). This group would also refer children to dentist at 12 months of age (p = 0.05).

Medical professionals with more than 10 years of experience were willing to assess children's' dental problems (p = 0.05) and counsel mothers on prevention of dental problems (p = 0.04) compared to those professionals with less than 10 years of experience. Also, these individuals with more than 10 years of experience were likely to apply topical fluoride varnish for children (recommended every 3-6 months [19, 20]) (p = 0.05) and refer them to dentists at 12 months of age (p = 0.04) (Tab. VI).

Discussion

The results of this study revealed interesting insights. As far as it could be ascertained, this was the first study to assess the knowledge, attitudes and practices of primary health care providers towards oral health of preschool children in Qatar. Health professionals believed that they have an important role in oral health promotion and many were

Tab. IV. Association between type of health professional and oral health practices.

Oral health practices When attending a child patient how likely are you to	Very likely/ likely (%)	Neutral/unlikely/ very unlikely (%)	Sig. (2 - sided exact test)
Inquire about nocturnal bottle feeding			
Nurses	59 (30.7)	96 (50)	0.09
GP	7 (3.7)	11 (5.7)	
Paediatrician	10 (5.2)	5 (2.6)	
Family physician	4 (2.1)	0 (0)	
Total (n = 192)	80 (41.7)	112 (58.3)	
Assess dental problems			
Nurse	98 (47.6)	59 (28.6)	0.05
GP	11 (5.3)	6 (2.9)	
Paediatrician	13 (6.4)	10 (4.9)	
Family physician	4 (1.9)	5 (2.4)	
Total (n = 206)	126 (61.2)	80 (38.8)	
Discuss importance of tooth brushing with mother			
Nurse	114 (55.9)	40 (19.6)	0.03
GP	11 (5.4)	7 (3.4)	
Paediatrician	17 (8.3)	6 (2.9)	
Family physician	7 (3.4)	2 (1.0)	
Total (n = 204)	149 (73.0)	55 (26.9)	
Assess child's fluoride intake			
Nurse	60 (30)	91 (45.5)	0.04
GP	6 (3)	11 (5.5)	
Paediatrician	8 (4)	15 (7.5)	
Family physician	0 (0)	9 (4.5)	
Total (n = 200)	74 (37)	126 (63)	
Inquire about mother's dental health			
Nurse	76 (37.3)	78 (38.2)	0.23
GP	8 (3.9)	10 (4.9)	
Paediatrician	5 (2.5)	18 (8.8)	
Family physician	0 (0)	9 (4.4)	
Total (n = 204)	89 (43.7)	115 (56.4)	

likely to include some anticipatory guidance. The majority of participants in this study were nurses and it demonstrates their willingness to participate in health related surveys. Another possible explanation for this finding could be the fact that during the second phase of data collection the head nurse of each health centre was assigned the task of

Tab. V. Association between type of health professionals and anticipatory guidance.

Anticipatory guidance recommendations: To what extent do you agree the following should be part of well baby clinic routine care?	Strongly agree/ agree (%)	Neutral/disagree/ strongly disagree (%)	Sig. (2 - sided exact test)
Dental examination			
Nurse	134 (63.8)	27 (12.9)	0.01
GP	15 (7.1)	2 (1.0)	
Paediatrician	20 (9.5)	3 (1.4)	
Family physician	9 (4.3)	0 (0)	
Total (n = 210)	178 (84.7)	32 (15.3)	
Counseling mothers on prevention of dental problems			
Nurse	131 (61.8)	31 (14.6)	0.01
GP	17 (8.0)	1 (0.5)	
Paediatrician	20 (9.4)	3 (1.4)	
Family physician	9 (4.3)	0 (0)	
Total (n = 212)	177 (83.5)	35 (16.5)	
Applying topical fluoride varnish			
Nurse	77 (38.3)	76 (37.8)	0.37
GP	6 (3.0)	10 (5.0)	
Paediatrician	15 (7.5)	8 (4.0)	
Family Physician	4 (2.0)	5 (2.5)	
Total (n = 201)	102 (50.8)	99 (49.2)	
Referring children to dentist at 12 months of age			
Nurse	102 (51.9)	51 (24.3)	0.05
GP	10 (4.7)	8 (3.8)	
Paediatrician	13 (6.2)	10 (4.7)	
Family physician	6 (2.9)	3 (1.4)	
Total (n = 210)	138 (65.7)	72 (34.3)	

Tab. VI. Distribution of responses by medical professionals to oral health recommendations based on years of practice.

"Strongly agree" or "agree" the following to be a part of WBC routine care for children	Number of years in practice			Chi–square test
	1-5	6-10	> 10	
Assessing children's dental problems				
Nurse	20	41	96	0.05
GP	0	5	12	
Pediatrician	2	2	19	
Family physician	0	3	6	
Total (n = 206)	22	51	133	
Counseling mothers on prevention of dental problems				
Nurse	21	41	100	0.04
GP	0	6	12	
Pediatrician	2	2	19	
Family physician	0	3	6	
Total (n = 212)	23	52	137	
Applying topical fluoride varnish				
Nurse	20	39	94	0.05
GP	0	7	9	
Pediatrician	2	2	19	
Family physician	0	3	6	
Total (n = 201)	22	51	127	
Referring children to dentist at 12 months of age				
Nurse	20	41	99	0.04
GP	0	6	12	
Pediatrician	2	2	19	
Family physician	0	3	6	
Total (n = 210)	22	52	136	

receiving the questionnaires via the central mailing system. This may have prompted other subordinate nursing staff to respond to the questionnaire.

It is difficult to identify a cause-effect relationship in studies which utilize self-administered questionnaire for gathering health related information [20, 21]. Nevertheless, all efforts were made to address this issue by maximizing confidentiality during data collection. Moreover, this method of data collection has been adapted and tested previously and has demonstrated adequate reliability [10, 12].

A very small number of participants in the study had received oral health related training during their under graduate programme. Further, for a majority of them, the training only included one or two lectures on oral health. This finding reflects in the fact that more than half of the participants incorrectly responded to a basic fact on oral health that "caries-causing bacteria" can be transmitted from mother to child. Interestingly, these practitioners usually gave oral health recommendations to the parents of their preschoolers. Other studies have reported similar findings where health professionals including pediatricians have received little to no formal training on oral health education, yet, most of them provide oral health recommendations to the parents and their children [22, 23].

Health practitioners with limited knowledge of oral health should be cautious while providing oral health recommendations. Providing incorrect or improper oral health advice to parents may inadvertently cause poor oral health of children. However, there are initiatives taken in this regards and reports suggest that pediatricians and other health care professionals now receive relevant training in oral health. A study conducted on Flemish pediatricians in 2008 revealed that 71% of the participants had education on dental topics [24]. In the USA, increased attention has been given to oral health education and many pediatric boards in the country now require candidates to successfully complete an oral health education component before receiving certification [25]. In the present study, though, only 20.1% of health professionals received further oral health training after graduation. Besides, more than half of them relied on general information from media to update themselves on oral health knowledge. It is beyond the scope of this investigation to compare and contrast the different university courses across various medical specialties and sub-specialties. However, one proposition would be to include a mandatory component on oral health education by relevant medical board authorities in the form of workshops, seminars and conferences before health care practitioners can renew their practicing licenses.

A large number of practitioners assessed the dental problems of children and a significant number of them discussed the importance of tooth brushing with the mothers as well as counsel them on prevention of dental problems including those before teeth erupt. This finding was consistent across all professions including nurse, GPs, pediatricians and family physicians and is a clear indication that these professionals regard tooth brushing as one of the most critical factors essential for maintaining oral hygiene. Occasionally, both parents would attend WBCs and when present, fathers would also be given counseling. However, majority of respondents failed to inquire about the nocturnal feeding habits and about mother's dental health.

Routinely, pediatricians have taken responsibility to assess a child's fluoride intake [10]. However, in the current study, a significantly lower number of pediatricians would assess the fluoride intake of children. This finding was also reported across nurses, GPs and family physicians. Though it was not the objective of the study to explore the causes of this finding, one possible explanation for this result could be that healthcare workers may be under the presumption that children residing in Qatar consume water which has adequate amounts of fluoride [26].

Limited knowledge and lack of familiarity with oral health related issues seems to be the most important barrier to greater involvement in oral health promotion by medical professionals [22, 23, 25]. In the present study, only 35.7% of participants received some form of oral health training during their under graduate training. Furthermore, only 20.1% had received any form of oral health training after graduation. Similar figures have been reported across the world where medical professionals receive minimal to no training on oral health related subjects including countries like the United Kingdom [23], Norway [27] and Iran [28].

Also, studies from Sweden [29], Spain [30] and USA [31] have indicated that health care professionals at the primary level are inclined to provide preventive treatment but they face severe constraint in the form of limited time and resources due to an overload of curative care. These findings are concurrent with the results of the current study where health professionals were amenable to provide anticipatory guidance in the form of counseling mothers on prevention of dental problems and examining the children's oral cavity. Also, a significantly large number of professionals strongly agreed to refer children to dentist at 12 months of age. However, only half of the respondents were willing to apply topical fluoride varnish to children.

The number of years of clinical practice of health professionals had a positive impact on their inclination to provide oral health recommendations. Health professionals with more than 10 years of experience were not only willing to assess children's oral health status and counsel mothers on prevention of dental problems but also had a propensity to apply topical fluoride varnish and refer children to dentist at 12 months of age. Similar results have been observed in studies elsewhere where health providers with greater experience were more likely to engage in practice addressing the oral health of their patients [11, 32, 33]. In the present study, the mean number of years all respondents had been working in the WBCs was 7 (± 4.3) years. This reflects a reasonable experience in dealing with preschool children and explains the favorable response of these health care workers to oral health practices.

The ethnic diversity of the population in Qatar may provide some explanation for the contrasting findings of this study. The majority of the population in Qatar includes citizens from India, Nepal, Bangladesh, Philippines, Egypt, Pakistan and other south Asian and north and central African countries. The local Qataris are a minority since decades [34]. A similar diversity is reflected among professionals working in the healthcare sector where people from different

environments make up the group of healthcare providers. This diversity suggests different educational, cultural and linguistic backgrounds. It has been suggested that healthcare providers are discouraged while working with health promotion due to lack of adherence by the patients and also language difficulties. Healthcare professionals may not be inclined to discuss health promotion/ preventive regimes with patients because of these language barriers and due to paucity of adequate knowledge and information on oral health [16]. Nevertheless, it has been demonstrated that it is possible to employ staff from a wide range of specialties and different levels of education to deliver interventions targeting oral health promotion successfully [12].

The widespread neglect of oral health of preschool children in Qatar has been well documented [15]. Number of reasons have been cited for the high caries prevalence rate including high consumption of refined sugars, ineffective fluoridation policy and absence of oral health awareness among parents [15, 24]. This scenario and the findings from the current study make it imperative to introduce concrete and effective preventive programmes particularly at the Primary Health Care level. Various opportunities to deliver such programmes exist in the primary health care system and the results of this study clearly indicate that the health care providers are willing to support this cause. However, accurate oral health education and precise training of the health providers need to be undertaken to successfully execute these measures.

In spite of the straightforward methodological approach to determine the knowledge, attitudes and practices of primary health care providers, the study has certain limitations. The first phase of the study had a poor response rate and hence the questionnaires were re-sent in the second phase. Although speculative, this could imply that less participants responded in the first phase since many of them were unaware of the information sought via the survey. Regardless, resending the questionnaire to the head nurses in the second phase would have strained them to acquire more participants in the second phase who consequently may have responded to the questionnaire passively. Besides, this approach may have inadvertently introduced a bais in the study as more nurses responded in the second phase. Furthermore, no attempt was made to explain the questions to the respondents if they had any query and hence some questions were left unanswered by the participants. Nevertheless, the large sample size and the unequivocal results improve our understanding of the attitude and practices of primary health care providers.

Conclusions

Health professionals had a positive attitude towards the anticipatory guidance elements of oral health. However, the knowledge of healthcare professionals on childhood oral health is rather limited. More attention should be given to oral health education during training in pediatrics and other professions and a focused continued education plan is needed for these professionals who provide care for children to address the shortcomings in their oral health knowledge.

Significance of the study

The study explored the attitude of primary health care professionals towards oral health of children. It highlights the lack of adequate proficiency and up-to-date information of these professionals on oral health and hygiene. Further, it emphasizes that harbouring a positive attitude towards oral health is insufficient and intensive training and continuing education programmes are needed to address the issue.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

AA conceived the experiment design, performed the survey, was involved in data collection, data analayisis and interpretation; and drafted the article. MTS was involved in the study design and in composing the preliminary draft of the article. LB Messer supervised the project and provided critical revision of the article. MP contributed substantially to the design of the study and data analysis. MM supervised the project. AS provided critical revision of the article and contributed to data analaysis and interpretation and co-wrote the paper. All authors discussed the results and contributed to the final manuscript.

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Appendix 1

The Beautiful Smile Project

Health Professionals' survey

These questions aim to give some background about your type of practice and training:

1. Which type of health professional are you?	☐ Nurse ☐ General Practitioner (GP) ☐ Paediatrician ☐ Family physician ☐ Other. (Specify…….……)
2. Do you work in the Well-Baby-Clinic?	☐Yes *(please answer all the questions below to complete the questionnaire)* ☐No *(Please do not complete this questionnaire, thank you very much for your attempt)*
3. If you worked in the Well-Baby-Clinic, how long you have worked in WBC in the primary health centers in Qatar?	.....years
4. For how long you have been in practice as a health professional?	☐1-5 years ☐6-10 years ☐more than 10 years
5. In which health centre do you work? 6. For how long you worked in this health centre?	Health centre name…….. …….years
7. Did you receive any oral health training as part of your qualification course?	☐ yes *(please answer Q7)* ☐ no *(please proceed to Q9)*
8. About how many hours/ units/ lectures of oral health training did you have at your university?	☐ A complete unit with several lectures ☐ only 1-2 lecture/s ☐ None ☐ Don't know/remember
9. Have you had any oral health training since you qualified as a health professional?	☐No ☐Yes (specify……
10. What is the main source of your current oral health knowledge?	☐some general knowledge from the media ☐I read scientific articles about oral health every now and then ☐ Other (specify .....)

1

Now there are some questions about your oral health knowledge:

11. Cavity-causing bacteria can be transmitted from mother to her child	☐ True ☐ False
12. Please name three oral diseases that can affect the oral health of children?	…….. ……. …… …….
13. Do you usually make recommendations for promoting oral health when you attend a child patient?	☐ Yes ☐ No
14. If yes, can you name up to three health promotion recommendations that you may give?	…….. ……. …… …….

The next group of questions are about your usual practice in attending a child patient

15. When you examine a child how likely are you to:	Very likely				very unlikely
a. Inquire about putting the child to bed with a bottle	1	2	3	4	5
b. Examine the child's teeth for decay/cavities					
c. Counsel the parent on importance of tooth brushing	1	2	3	4	5
d. Assess the child's fluoride intake	1	2	3	4	5
e. Inquire about mother's dental health	1	2	3	4	5
	1	2	3	4	5

16. Do you agree that the following should be part of routine well-baby check-up?	**Strongly agree**				**strongly disagree**
a. Assessing dental problems during the physical examination	1	2	3	4	5
b. Counselling on prevention of dental problems	1	2	3	4	5
c. Applying fluoride varnish	1	2	3	4	5
d. Referring to the dentist at 12 months of age	1	2	3	4	5

Thank-you for your participation.

ORIGINAL ARTICLE

What explains socioeconomic inequalities in dental flossing? Cross-sectional results from the RaNCD cohort study

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Keywords

Dental flossing • Health inequalities • Concentration index • Decomposition analysis

Summary

Introduction. *The magnitude and underlying determinants of socioeconomic inequality in dental flossing are poorly understood in Iran. This study aimed to measure and decompose socioeconomic inequalities in dental flossing in Ravansar, Iran.*

Methods. *Data of 10,002 individuals aged 35-65 years who participated in the Ravansar Non- communicable Diseases (RaNCD) cohort study in Kermanshah province, western Iran, were analyzed. Based on an asset-based method, socioeconomic status (SES) was measured using principal component analysis (PCA). The concentration index and curve were employed to measure socioeconomic inequality in dental flossing. Decomposition analysis was used to estimate the contribution of each determinant to the overall inequality.*

Results. *Of 10,002 participants, 11.74% were found to practice dental floss. The normalized CI for dental flossing was 0.327 in the entire population, 0.323 in females and 0.329 in males, indicating that the use of dental floss is more concentrated among high-SES individuals. The decomposition analysis indicated that SES (50.58%) and level of education (44.90%) respectively contributed the most to this inequality. Place of residence (10.55%) and age group (2.7%) were the next main contributors, respectively.*

Conclusions. *We found a low prevalence of dental flossing among participants in RaNCD study. We also observed a relatively high degree of pro-rich inequality in dental flossing. The observed inequality was mainly explained by socioeconomic status, level of education and place of residence. Policy interventions should consider these factors to reduce inequalities in dental flossing.*

Introduction

Dental problems are major public health concerns [1] and impact negatively on the quality of life [2]. Almost all adult individuals in the world suffer from dental caries [3]. Oral and dental problems impose a substantial economic burden on individuals, households, and society as a whole [1]. Direct and indirect costs of oral diseases account for around 7% of global health expenditures, implying a high relevance for oral diseases prevention [4]. The disadvantaged bear the greatest fraction of the global burden of oral diseases [5].

It has been indicated that self-performed preventive strategies (e.g., tooth brushing and dental flossing) are cost-effective ways to improve oral health conditions [6]. Regular dental flossing can remove a large portion (i.e., up to 80%) of interdental plaque [7], which impacts both incidences of dental caries and the prevention of periodontal disease [8]. A systematic review indicated that dental flossing, in addition to tooth brushing, has a more effect on the reduction of gingivitis compared to toothbrushing alone [9]. For this reason, the American Dental Associations recommend flossing at least once a day to help remove plaque [10]. Although adherence to such oral hygiene behavior is necessary, a great proportion of individuals floss their teeth less than recommended [11].

Evidence shows that the practice of dental floss in many developing countries like Iran is still low [12]. Moreover, previous reports have indicated that the prevalence of oral and dental problems are unequally distributed across socioeconomic groups, so that individuals with lower socioeconomic status (SES) have a higher burden of dental diseases compared to those of higher SES [13-15]. Socioeconomic inequalities in oral health status have been observed in both developing and developed countries [16]. There is a limited number of studies that have assessed inequalities in oral health outcomes. Most of the existing studies in Iran have only assessed the relationship between SES and oral health status and behaviors, without measuring the extent of socioeconomic-related inequalities in this field [17]. Moreover, to the best of our knowledge, no study has been yet measured socioeconomic inequalities in the practice of dental floss as specific oral hygiene behavior. To fill this gap, this study aimed to quantify: 1) the degree of socioeconomic inequalities in dental flossing; (2) the contribution of each determinant to the measured inequality. The results

may be helpful to plan public health policies in oral health fields.

Study population and methodology study setting and sample

This was a cross-sectional analysis of the Ravansar Non-communicable Disease (RaNCD) cohort study. The RaNCD is one of the Prospective Epidemiological Research Studies in IrAN (PERSIAN) [18]. The RaNCD covers adults, aged 35 to 65 years, living in rural and urban areas of Ravansar, which is geographically located in Kermanshah province, west of Iran. The initial sample consisted of 10,086 individuals, 84 of whom were excluded due to incomplete data.

Variables

The SES of individuals was measured using an asset-based approach. The data on housing conditions (e.g. type of homeownership, the number of rooms,) infrastructure facilities (sanitation facility, source of drinking water) and ownership of a range of durable assets (e.g., car, dishwasher, television, etc.) was used to measure SES of individuals. The SES was constructed using principal component analysis (PCA) technique. The PCA generates the weight for each selected asset and then estimates a continuous index based on the sum of all weights of variables included in the PCA for each individual. The index was used to categorize individuals into five SES quintile (from poorest to richest) [19-22]. Other independent variables included age, sex, level of education, marital status and place of residence (i.e. urban and rural). Dental flossing was our dependent variable which was defined dichotomously.

Measuring inequality

Inequality in the practice of dental floss was measured using the concentration index (CI). CI is defined based on a concentration curve (CC). These measures are widely used as standard tools for assessing inequalities in health [23, 24]. The concentration curve is a graphical representation of the degree of inequality that plots the cumulative percentage of the health outcome (vertical axis) against the cumulative percentage of the population, ranked based on their rank in SES group (horizontal axis). The 45º line represents perfect equality, meaning that everyone, regardless of their SES, has precisely the same value of the health outcome variable. If the health outcome variable is concentrated among low-SES individuals, the concentration curve lies above the equality line and vice versa. The further the curve is below (above) the 45º line, the more concentrated the health outcome variable is among the high-SES individuals (low-SES individuals). The CI, which ranges between -1 and +1, equals two times the space between the concentration curve and the equality line and shows whether the outcome variable is concentrated among low- or high-SES individuals. Negative and positive values of this index respectively show that the health outcome variable is more concentrated in low- and high-SES individuals, while zero values suggest that the health outcome variable is equally distributed among the SES groups. The following formula was used to calculate the CI [23]:

$$CI = \frac{2 * cov(y_i r_i)}{\mu} \quad (1)$$

Where y_i is the health outcome variable (i.e. dental flossing); μ denotes its mean; and r_i represent the fractional rank of the ith individual in the socioeconomic distribution. As the dental flossing in this study was binary, we used Wagstaff's normalization method to measure inequality in the use of dental floss as follow:

$$CI_{normalized} = \frac{\mathrm{CI}}{1-\mu}$$

We decomposed the CI to determine the underlying causes of socioeconomic inequalities in dental flossing. According to Wagstaff for any linear additive regression model linking our health outcome variable (i.e. dental flossing), y to a set of k determinants, x_k [25]:

$$y = \alpha + \sum_k \beta_k x_k + \varepsilon \quad (2)$$

The CI for dental flossing, y, can be decomposed as follows:

$$CI = \sum_k \left(\frac{\beta_k \bar{x}_k}{\mu}\right) CI_k + GC_\varepsilon/\mu \quad (3)$$

Where $\bar{x}_k$ denotes the mean of determinant k; the CI_k is the CI for x_k; $\frac{\beta_k \bar{x}_k}{\mu}$ is the elasticity of dental flossing with respect to determinant k.

The elasticity of each determinant demonstrates the responsiveness of dental flossing to changes in the determinant. A positive elasticity means that individuals with this characteristic are more likely to practice dental floss. The GC_ε indicates the generalized CI for the error term. The first part in equation 3, $\sum_k \left(\frac{\beta_k \bar{x}_k}{\mu}\right) CI_k$, is the explained component and indicates the contribution of explanatory variables to the overall socioeconomic inequality in dental flossing. The second part of the equation, GC_ε / μ, is an unexplained (residual) component and shows the portion of the CI for dental flossing that cannot be explained by the systematic variations in the determinants across SES groups.

Wagstaff-type decomposition analysis was performed using the following formula [25]:

$$CI_{normalized} = \frac{C}{1-\mu} = \frac{\sum_k \left(\frac{\beta_k \bar{x}_k}{\mu}\right) CI_k}{1-\mu} + \frac{GC_\varepsilon/\mu}{1-\mu} \quad (4)$$

As our outcome variable was dichotomous, we used marginal effects obtained from the non- linear logit model in the decomposition analysis to estimate the contributions of the explanatory variables to the C_n. All analyses were conducted using STATA software version 14.

Results

A total of 10,002 adults with a mean age of 47.05 (SD ± 9.02) were included in the analysis, 5,259 (52.58%) of whom were women. Participants belonged to the age group of 35-44 years account for 44.07% of the sample and the majority of them was married (90.18%). Also, the illiterate participants accounted for 35.26% of the whole sample. About 11.74% of the study population practiced dental floss. The proportion of dental flossing was higher in the urban population, higher quintiles of SES, the age group of 34-45 and in participants with university degrees (Tab. I).

The normalized CI was 0.327 for dental flossing in the entire population, 0.323 in the women and 0.329 in the men. The statistically significant positive value of the shows a higher concentration of practice of dental floss among high-SES individuals (Tab. II).

The concentration curve of dental flossing lies below the line of perfect equality, meaning that the practice of dental floss is more concentrated among high-SES individuals. It indicates that there is inequality in the distribution of dental flossing favoring high-SES individuals (Fig. 1).

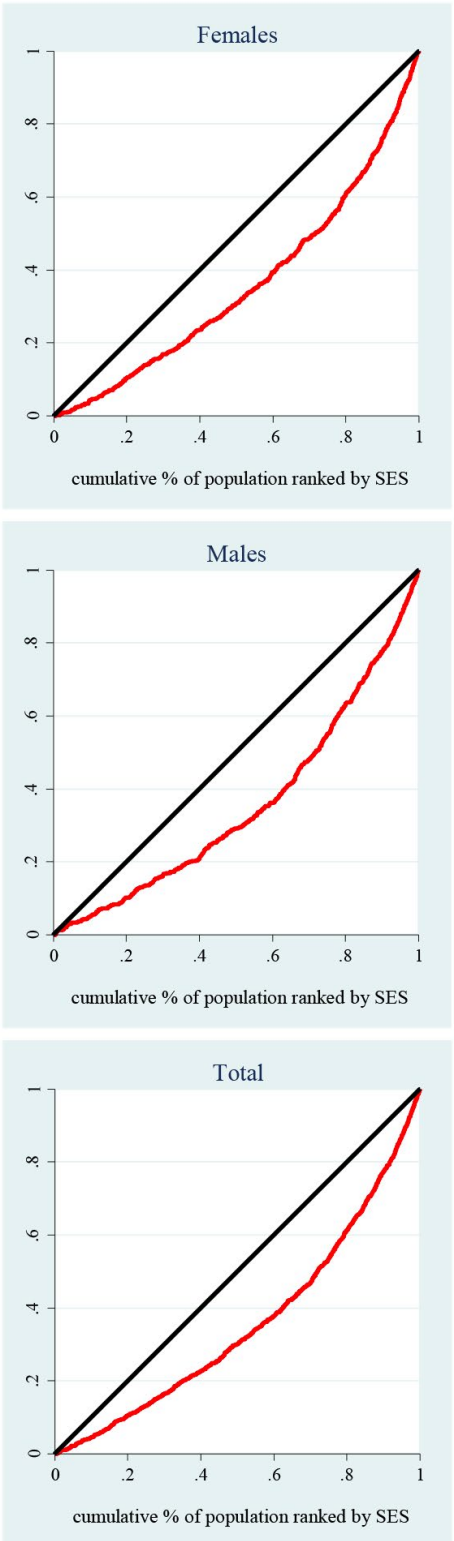
Tab. I. Prevalence of dental flossing in terms of determinant variables among cohort participants aged 35-65.

Variables	N (%)	Prevalence rate (%)
Sex		
Female	5,259 (52.58)	11.28
Male	4,743 (47.42)	12.25
Age group		
35-44	4,408 (44.07)	17.38
45-54	3,327 (33.26)	10.43
55-65	2,267 (22.67)	2.69
Marital status		
Married	9,020 (90.18)	11.87
Single/divorced/ widowed	982 (9.82)	10.49
Education		
Illiterate	4,591 (45.90)	4.77
Primary	2,616 (26.15)	10.86
Intermediate	1,064 (10.46)	17.29
Secondary	968 (9.68)	21.80
Higher	763 (7.63)	36.17
Economic status		
Poorest	2,001 (20.01)	6.20
Second poorest	2,000 (20.00)	7.10
Middle	2,003 (20.03)	8.89
Second richest	1,998 (19.98)	13.81
Richest	2,000 (20.00)	22.70
Place of residence		
Urban	5,916 (59.15)	15.53
Rural	4,086 (40.85)	6.24

Tab. II. Normalized concentration indices (95% Confidence Interval, standard error and p-value) for dental flossing.

Sample		SE	Normalized CI	95% CI	P-value
Total	10,002	0.017	0.327	0.292-0.361	0.000
Male	4,743	0.025	0.329	0.280-0.378	0.000
Female	5,259	0.024	0.323	0.275-0.372	0.000

Fig. 1. Concentration curves of dental flossing among participants of RaNCD cohort study.



The C for independent variables suggested that women and age group of 55-65 were more concentrated among the low-SES individuals. However, the married and urban participants were more concentrated among high-SES individuals. The decomposition analysis showed that SES (50.58%) and level of education (44.90%) respectively contribute the most to this inequality. The contribution of urban residence and age group in the observed inequalities was 10.55% and 2.70% respectively (Tab. III).

Discussion

In the present study, we measured and decomposed socioeconomic inequalities in dental flossing among adults who participated in RaNCD cohort study, Ravansar, Iran. To the best of the authors' knowledge, no studies have so far been conducted on measuring socioeconomic inequality in the practice of dental floss as a recommended self-care dental practice. We found a prevalence of 11.74% for dental flossing, indicating not satisfactory flossing behavior in the sample. Previous studies [3, 26] also highlighted a poor dental hygiene behavior in Iran. A study on the general population in 2011 with 12,105 individuals reported a prevalence of 16.8% for dental flossing in Iran [3]. In addition to a low prevalence of dental flossing, we found an unequal distribution of the practice of dental floss favoring individuals with higher SES in Ravansar. Previous studies conducted on socioeconomic inequality in oral health in different countries generally suggest inequality in oral health status and behaviors [27-30]. For example, in line with our findings, a study conducted in Brazil indicated that preventive dental care was more concentrated among high-SES groups [16]. A study in the UK also found an unequal distribution in oral health behaviors favoring high-SES groups [30]. In addition, previous works have shown socioeconomic inequality in the practice of hygiene products such as mouthwashes and toothbrushes as well as receiving dental care [28, 29, 31 32].

The decomposition analysis showed that SES and level of education respectively made the most positive contributions to the socioeconomic inequality in flossing behavior. These results imply that the socioeconomic inequality in dental flossing would have been reduced if these determinants had no impact on oral health behaviors or were equally distributed across the SES groups. In accordance with our results, Asgari et al. found that daily tooth brushing and the practice of dental floss are significantly associated with socioeconomic status [33].

Previous studies also have indicated that SES and level of education are the main contributors to socioeconomic inequalities in oral health and the practice of dental care services [16, 30]. Other main contributors to the observed inequality were the place of residence and older age groups. Some studies have also indicated an association between the area of residence and oral health status [17, 34, 35]. In our sample, rural individuals flossed their teeth less frequently than urban individuals. This rural-urban gap may be due to the fact that rural areas tend to have a large proportion of individuals

Tab. III. Decomposition of concentration index for dental flossing.

	Marginal effects	Elasticity	Ck [1]	Cont. [2]	% Cont. [2]	Summed %
Sex						
Female	0.049	0.222	-0.075	-0.016	-5.1	-5.1
Age group						
35-44						
45-54	-0.032	-0.092	0.041	-0.003	-1.17	2.70
55-65	-0.093	-0.209	-0.070	0.012	3.87	
Marital status						
Married	-0.0007	-0.005	0.026	-0.0001	-0.04	-0.04
Education						
Illiterate						
Primary	0.058	0.131	0.004	0.0005	0.16	44.90
Intermediate	0.124	0.112	0.114	0.013	3.94	
Secondary	0.163	0.134	0.237	0.032	9.79	
Higher	0.251	0.163	0.620	0.101	31.00	
Socioeconomic status						
Poorest						
Second poorest	-0.002	-0.004	-0.453	0.002	0.68	50.58
Middle	0.010	0.018	0.0003	0.000	0.001	
Second richest	0.046	0.078	0.453	0.035	10.89	
Richest	0.082	0.140	0.906	0.127	39.00	
Place of residence						
Urban	0.050	0.252	0.136	0.034	10.55	10.55
Total explained				0.339	103.6	
Residual				-0.011	-3.6	
Total				0.327	100	

[1]: concentration index of each determinants; [2]: contribution of each determinant to the observed inequality.

with lower education levels and those with low SES. In general, having a higher level of education and living in a socioeconomically advantaged area result in further opportunities to adopt healthier habits and benefit from health-promoting behaviors [36, 37]. SES and level of education have remained important issues to consider in formulating policies to reduce inequalities in flossing behavior in developing countries including Iran. Our findings suggest that to address inequalities in dental flossing these factors should be considered in policy interventions. For example, providing special services to individuals of low-SES groups and those with lower educational levels may reduce socioeconomic inequality in flossing behavior. In addition, improving oral health literacy by providing educational programs especially in these groups may be effective in mitigating socioeconomic inequality in the practice of dental floss. The study had some limitations. First, although we used a relatively large sample, the participants were not necessarily representative of Iranian adults. Therefore, further studies on the inequality of flossing behavior at national and subnational levels in Iran are recommended. The cross- sectional nature of the study was another limitation, as it did not show causality. Longitudinal studies are recommended to be designed and conducted in the future to judge the causal relationship.

Conclusions

This study indicated a low prevalence and relatively a high degree of pro-rich inequality in the practice of dental floss among Iranian adults. Socioeconomic status, level of education and place of residence contributed the most to the measured inequality. These factors should be considered in formulating intervention programs.

Ethical statement

The ethics committee of Kermanshah University of Medical Sciences approved the study (Ethics Code: IR.KUMS.REC.1398.327).

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

MS and FN, contributed to conception and design of the study, analysis and interpretation of the data. MS and FN drafted and critically revised the manuscript. YP, BH and MMN contributed to data collection and critical revision of the manuscript. BKM and HA performed a search of the literature and contributed to critical revision of the manuscript. All authors read and approved the final manuscript.

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ORIGINAL ARTICLE

Risk factors for voice disorders in public school teachers in Cyprus

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Keywords

Voice disorders • Risk factors • Teachers, Cyprus

Summary

Aims. *The purpose of this study was to investigate risk factors for self-perceived voice disorders in teachers in Cyprus in order to determine the necessity for a preventative vocal hygiene education program which could improve their work performance.*

Methods. *An online questionnaire was completed by 449 teachers. The questionnaire extracted data regarding risk factors that may contribute to the development of voice disorders, occupational consequences of voice disorders and vocal hygiene education, as well as, a self-perceived severity of a participant's voice problem. Subjects were split into two groups, teachers with Voice Disorder Index (VDI) ≤ 7 and teachers with VDI > 7. The chi-squared test was used to explore the differences in responses for each voice risk factor, occupational consequence and vocal hygiene education between the two groups.*

Results. *Teachers in the VDI > 7 group were more likely to frequently experience nasal allergies and respiratory infections, coughing, throat clearing, stress and yelling, have shorter breaks between classes, use loud voice, use their voice to discipline students, teach above students talking, etc. than teachers in the VDI ≤ 7 group. Moreover, teachers in the VDI > 7 group were more likely to limit their ability to perform certain tasks at work and reduce their activities or interactions "3-5 or more days" annually due to voice problems.*

Conclusions. *Health, voice use, lifestyle, and environmental factors may play a part in the development of voice disorders in teachers and have an impact on their job. Therefore, a preventative vocal hygiene education program is suggested.*

Introduction and literature review

Teachers belong to one of the occupational groups that tend to overuse their voice (i.e., repeatedly use their voice or require heavy voice use) for their work and consequently have a tendency to have a higher prevalence of voice disorders in comparison to the general population worldwide [1-4]. Many different studies all over the world that investigated teachers' prevalence of voice disorders in different geographic areas and cultures indicated that teachers have a higher incidence of voice disorders. Roy et al. [1] explored the prevalence of voice disorders in elementary and secondary school teachers in comparison to the general population in the United States and revealed that teachers stated a significantly higher prevalence of having a present voice problem than nonteachers (11.0% for teachers vs. 6.2% for nonteachers). Behlau et al. [2] compared the frequency of occurrence of current voice disorders in Brazilian elementary and secondary school teachers and nonteachers that was found to be 11.6% for teachers and 7.5% for nonteachers. Trinite [5] investigated the prevalence of voice disorders in primary and secondary school teachers in Latvia and disclosed that 8% of the teachers self-reported that they currently had a voice disorder and 36.9% said they have experienced voice problems during the last 9 months. Seifpanahi et al. [3] compared the prevalence of voice disorders among teachers and nonteachers in Iran and found that 54.6% of teachers and 21.1% of nonteachers experienced vocal complaints. Devadas et al. [6] investigated the prevalence of voice problems among primary school teachers in India and discovered that 17.4% of the teachers self-reported voice problems. Lyberg-Ahlander [4] studied the prevalence of self-reported voice disorders in the general population in Sweden and revealed that the highest prevalence of voice problems was reported in teaching professions (19.3%).

Several recent studies identified risk factors that place teachers at risk for developing voice disorders in various countries. Rantala et al. [7] investigated associations between voice and postures used during teaching. Outcomes indicated that specific postures such as twisted head and torso and raised arms were associated with specific voice symptoms (e.g., voice breaks, aphonia etc.). Devadas et al. [6] investigated risk factors for voice problems among primary school teachers in India. Significant identified factors were: the number of years of teaching, high background noise levels while teaching, psychological stress while teaching, improper breath management (holding breath while speaking), upper respiratory tract infections, thyroid problems, and acid reflux. Bolbol et al. [8] studied risk factors for voice disorders among Egyptian school teachers. Significant risk factors pinpointed were the number of years of teaching (15 or more years of teaching) and the number of classes per week (15 or more classes per week). Abo-Hasseba et al. [9] assessed teachers' voice symptoms in

relation to noise in public and private schools in Upper Egypt and identified noise at work as being a risk factor for the development of voice disorders. Particularly, 82.2% of the teachers who reported moderate or severe dysphonia stated a feeling of sometimes or always being in noise during their working day and they needed to raise their voice. Alva et al. [10] explored various risk factors that influence the onset and progression of voice disorders in teachers in India and showed a statistically significant association between voice disorders and upper respiratory infections, Deviated Nasal Septum and gastroesophageal reflux disease. Trinite's [5] research looked into voice risk factors in teachers in Latvia and found that the chances of a teacher having a voice disorder increase if the following risk factors exist: extra vocal load (duties of a coach, conductor of choir, etc), shouting, throat clearing, neglecting personal health (e.g., teaching with a sore throat), background noise, chronic upper respiratory tract infections, allergies, job dissatisfaction, and stress at work. Seifpanahi et al. [3] studied voice risk factors among teachers and nonteachers in Iran and pinpointed a significantly higher vocal load risk factor (e.g., number of pupils in the classroom, number of teaching years, number of teaching hours per week, etc.) for teachers (70.77%) in comparison with nonteachers (27.44%).

Given the existence of such challenges in high risk populations such as teachers, voice disorders may impact teachers' life, as well as, their work such as affecting their work performance and attendance. Few investigations examined the specific occupational effects of voice disorders in teachers such as the effects on work attendance, work performance and future career choices. Van Houtte et al. [11] investigated voice related absenteeism in kindergarten, elementary and high school teachers and found that teachers experienced a significantly higher number of missed days of work because of their voice compared to the control group. More precisely, 34.6% of the teachers missed 1 day, 29.3% missed 1 week, 4.75% missed 2 weeks and 6.8% missed more than 2 weeks of work. Roy et al. [12] examined the effects of voice disorders on work performance and attendance in teachers and nonteachers and revealed that more than 43% of teachers had reduced activities or interactions for at least 1 day due to their voice problems. In addition, 18.3% of teachers versus 7.2% of non-teachers had missed at least 1 day of work and 3% of teachers versus 1.3% of nonteachers had missed more than 5 days of work due to their voice problems.

Taking into consideration the existing data on the high prevalence of voice disorders in teachers and the impact that voice disorders can have on their work, as well as, the abundance of data on examining risk factors for developing voice pathologies in teachers worldwide; the aim of this study is to investigate the prevalence and risk factors as well as the occupational impact of voice disorders in preschool-kindergarten and grade 1st-6th school teachers in Cyprus in order to determine the need for vocal hygiene education in this population.

Methods

Design of the questionnaire

The questionnaire was uploaded online via a Survey Monkey website and was set up to not allow more than one completion from the same participant (Appendix A). It included 58 questions which were constructed based on the researchers' clinical experience, feedback received from teachers who completed a preliminary pilot study and other questionnaires that exist in the voice disorder literature [13-15]. It consisted of five parts. One section was "Demographic Information" which consisted of questions 1-6 that inquired information about the participant's age, gender, region of origin, region of work, etc. Another section was "Risk Factors for Voice Disorders" that included questions 7-51 and was divided into four parts, which included: 1) risk factors related to general health such as nasal allergies, gastroesophageal reflux, and upper respiratory infections; 2) risk factors related to voice use such as years of teaching, teaching grade, teaching subject, teaching hours per week; 3) risk factors related to lifestyle such as smoking, alcohol consumption, caffeine use, water intake, stress; and 4) risk factors related to the environment such as the physical size of the classroom, level and source of noise at work and air quality at work. Another section was the "Occupational Consequences of Voice Disorders" that consisted of questions 52-54 which requested information on work absenteeism and reduction of duties due to voice problems. One more part was "Vocal Hygiene Education" which entailed questions 55-56 that requested information on vocal hygiene education during teachers' training and its usefulness. The other unit of the online questionnaire was the "Voice Disorder Index" (VDI) which was comprised of question 57. The VDI is a reliable instrument that portrays the subject's perceived severity of his/her voice problem as it relates to his/her quality of life [16]. It entails twelve statements that are used in the Voice Handicap Index-30, four of those statements are also included on the Voice Handicap Index-10 [16, 17]. Its range of scores is 0-48. A score of 0-7 shows normal voice whereas a score of 8-48 signifies a voice which is slightly (i.e., scores 8-14), moderately (i.e., scores 15-22) or profoundly disordered (i.e., scores 23-48) [16] (F. Ingolf, personal communication, June 26, 2017).

Participants

An email with a link to an online questionnaire was sent to primary public school teachers in Cyprus via their school inspector, principle or speech therapist. Also, a message with a link to an online questionnaire was posted on teachers' social media groups. Four hundred and forty-nine out of four thousand seven hundred questionnaires were completed, yielding about a 10% response rate. Participants were 25-60 years old and were preschool/kindergarten (n = 148) and grade 1st-6th (n = 301) public school teachers. They consisted of 422 females and 27 males who work in primary schools

in various geographic rural and urban regions of Cyprus (i.e., Nicosia (n = 158), Limassol (n = 186), Larnaca (n = 48), Famagusta (n = 20) and Paphos (n = 37)). Participants were divided into two groups (i.e., Group 1: VDI ≤ 7; n = 135 and Group 2: VDI > 7; n = 314) based on their VDI score. The participants' mean and range score on their VDI were 13.49 and 48 respectively.

Procedures

The subsequent procedures were followed. In stage one, either an email with a link to an online questionnaire was sent to primary public-school teachers or/and a message with a link to the electronic questionnaire was posted on teachers' social groups in Cyprus. In stage two, each subject was requested to complete questions 1 to 56 of the survey that inquired information on demographic information, voice disorder risk factors and occupational consequences, as well as, vocal hygiene education. In Step three, every participant was asked to complete question 57 which was the VDI. Subjects' responses on question 57 were scored and were given a self-perceived severity of their voice problem (i.e., normal, slightly, moderately or profoundly disordered) as it relates to their quality of life. Subjects whose VDI score was normal were placed into the VDI ≤ 7 group which is defined as the group of teachers who sense that they do not have voice difficulties that impact their quality of life. Subjects whose VDI score was slightly, moderately or profoundly disordered were assigned to the VDI > 7 group which is defined as the group of teachers who feel that they have voice difficulties that impact their quality of life.

Data analysis

The chi-squared test of goodness of fit was applied to investigate the differences in responses between the teachers with VDI ≤ 7 and those with VDI > 7 with regard to risk factors related to general health, voice use, lifestyle, and environment, as well as, occupational effects of voice disorders and vocal hygiene education. The significance level was appointed to 0.05 throughout. An adjusted residual analysis was further employed to identify groups for voice risk factors, occupational consequences and vocal hygiene education that were responsible for the significant chi-square statistic [18, 19]. A residual value greater than 1.96 or lower than -1.96 indicated that the group made a significant contribution to the chi-square statistic for a voice risk factor, occupational consequence, etc. The Statistical Package for the Social Sciences, Version 22 (SPSS Inc.) was used for all statistical analyses.

Results

The results of the present investigation indicate that the estimated prevalence of self-perceived voice problems in the sample of 449 preschool/kindergarten and grade 1st-6th public-school teachers investigated is 69.9%. Particularly, 314 out of 449 teachers examined received a VDI score 8-48 which indicates a voice that is slightly, moderately, or profoundly disordered.

The results of the current study additionally show that the risk for developing voice disorders in preschool/ kindergarten and grade 1st-6th school teachers in Cyprus involves risk factors related to general health, voice use, lifestyle, and the environment. Tables I-IVshow the significant risk factors detected and the adjusted residual values for each risk factor group.

Risk factors related to general health

The significant risk factors recognized and the adjusted residual values for the risk factors associated to general health are displayed in Table I.

The VDI > 7 class had significantly more individuals who had "frequently" (32.2% vs 23.0%, z = 2.0) experienced nasal allergies (e.g., nasal discharge, stuffy nose, sneezing) than the VDI ≤ 7 group, and significantly fewer participants who had "never" (7.3% vs 14.8%, z = -2.5) had nasal allergies [χ^2 (4, n = 449) = 10.81, $p < 0.05$]. A significantly higher number of participants in the VDI > 7 category reported to "frequently" (39.2% vs 21.5%, z = 3.6) and significantly fewer individuals declared to "never" (6.7% vs 12.6%, z = -2.1) and "infrequently" (19.4% vs 28.1%, z = -2.0) experience upper respiratory infections (e.g., pharyngitis and laryngitis) than the VDI ≤ 7 group [χ^2 (4, n = 449) = 19.78, $p < 0.05$].

Risk factors related to voice use

The significant risk factors identified and the adjusted residual values for the risk factors related to voice use are shown in Table II.

A significantly higher number of participants in the VDI > 7 group reported to teach kindergarten (36.6% vs 26.7%, z = 2.0) and significantly fewer subjects noted to teach 6th grade (5.4% vs 11.1%, z = -2.2) compared with the VDI ≤ 7 group (χ^2 (7, n = 449) = 17.32, $p < 0.05$).

The VDI ≤ 7 category had significantly more subjects who stated that their longest break between classes is more than 91 minutes (9.6% vs 2.2% vs, z = 3.5) than the VDI > 7 category (χ^2 (4, n = 449) = 15.40, $p < 0.05$). A significantly lower number of subjects in the VDI > 7 group stated to use "not loud" (0.6% vs 7.4%, z = -4.1) and "slightly loud" (11.8% vs 21.5%, z = -2.7) voice in class compared to the VDI ≤ 7 category. In contrast, a significantly higher number of participants in the VDI > 7 group reported to use "very loud" (33.8% vs 20.7% vs, z = 2.8) and "excessively loud" (4.8% vs 0.7% vs, z = 2.1) voice in class than the VDI > 7 group (χ^2 (4, n = 449) = 31.92, $p < 0.001$).

The number of participants in the VDI > 7 category who stated to "never" (0.6% vs 3.0%, z = -2.0) and "rarely" (4.1% vs 12.6%, z = -3.3) use their voice to discipline students was significantly lower than in the VDI ≤ 7 category and the number of participants in the VDI > 7 category who stated to "frequently" (49.4% vs 40.7%, z = 1.7) and "always" (21.0% vs 10.4%, z = 2.7) use their voice to discipline students was significantly

Tab. I. Risk factors related to general health in teachers in the VDI ≤ 7 and VDI > 7 groups showing the percent of those responding to the statements.

Risk factors	VDI ≤ 7 teachers (n = 135)		VDI > 7 teachers (n = 314)		Adjusted residual	P-value[1]
	N	%	N	%		
Nasal allergies						
Never	20	14.8	23	7.3	2.5	
Infrequently	35	25.9	64	20.4	1.3	
Sometimes	40	29.6	110	35.0	-1.1	**0.029**
Frequently	31	23.0	101	32.2	-2.0	
Always	9	6.7	16	5.1	0.7	
Gastroesophageal reflux						
Never	61	45.2	121	38.5	1.3	
Infrequently	35	25.9	82	26.1	0.0	
Sometimes	24	17.8	62	19.7	-0.5	0.595
Frequently	10	7.4	36	11.5	-1.3	
Always	5	3.7	13	4.1	-0.2	
Upper respiratory infections						
Never	17	12.6	21	6.7	2.1	
Infrequently	38	28.1	61	19.4	2.0	
Sometimes	49	36.3	94	29.9	1.3	**0.001**
Frequently	29	21.5	123	39.2	-3.6	
Always	2	1.5	15	4.8	-1.7	

[1]: Pearson's Chi-Square test. Significant differences between teachers in the VDI ≤ 7 and the VDI > 7 groups are indicated in bold in the last column.

Tab. II. Risk factors related to voice use in teachers in the VDI ≤ 7 and VDI > 7 groups showing the percent of those responding to the statements.

Risk factors	VDI ≤ 7 teachers (n = 135)		VDI > 7 teachers (n = 314)		Adjusted residual	P-value[1]
	N	%	N	%		
Age						
25-34	47	34.8	120	38.2	-0.7	
35-44	66	48.9	157	50.0	-0.2	
45-54	22	16.3	33	10.5	1.7	0.202
55-60	0	00.0	4	1.3	-1.3	
Teaching years						
≤ 5	16	11.9	47	15.0	-0.9	
6-10	34	25.2	74	23.6	0.4	
11-20	61	45.2	147	46.8	-0.3	0.705
≥ 21	24	17.8	46	14.6	0.8	
Nature of employment						
Teaching	112	83.0	268	85.4	-0.6	
Teaching + duties	23	17.0	46	14.6	0.6	0.520
Grade being taught						
Kindergarten	36	26.7	115	36.6	-2.0	
1	17	12.6	42	13.4	-0.2	
2	6	4.4	31	9.9	-1.9	
3	7	5.2	21	6.7	-0.6	
4	9	6.7	21	6.7	0.0	**0.015**
5	8	5.9	17	5.4	0.2	
6	15	11.1	17	5.4	2.2	
None	37	27.4	50	15.9	2.8	
Teaching a split-grade						
No	118	87.4	281	89.5	-0.6	
Yes	17	12.6	33	10.5	0.6	0.520

Continues

Follows

Tab. II. Risk factors related to voice use in teachers in the VDI ≤ 7 and VDI > 7 groups showing the percent of those responding to the statements.

Risk factors	VDI ≤ 7 teachers (n = 135)		VDI > 7 teachers (n = 314)		Adjusted residual	P-value[1]
	N	%	N	%		
Split-grade being taught						
N/A	118	87.4	286	91.1	-1.2	
1-2	3	2.2	11	3.5	-0.7	
2-3	5	3.7	5	1.6	1.4	
3-4	3	2.2	5	1.6	0.5	0.402
4-5	2	1.5	1	0.3	1.4	
5-6	4	3.0	6	1.9	0.7	
Subject being taught						
Greek	77	57.0	160	51.0	1.2	
Math	3	2.2	11	3.5	-0.7	
Physics	6	4.4	9	2.9	0.9	
English	5	3.7	14	4.5	-0.4	0.090
Music	7	5.2	9	2.9	1.2	
Physical education	0	0.0	6	1.9	-1.6	
Arts	7	5.2	6	1.9	1.9	
Other	30	22.2	99	31.5	-2.0	
Teaching hours per week						
≤ 23 x 40 min	27	20.0	58	18.5	0.4	
24-28 x 40 min	64	47.4	129	41.1	1.2	0.283
29 x 40 min	44	32.6	127	40.4	-1.6	
Teaching hours per week in the past						
≤ 23 x 40 min	24	17.8	60	19.1	-0.3	
24-28 x 40 min	27	20.0	51	16.2	1.0	0.624
29 x 40 min	84	62.2	203	64.6	-0.5	
Duration of most frequent classes						
< 40 min	6	4.4	24	7.6	-1.2	
40 min	7	5.2	26	8.3	-1.2	0.211
80 min	122	90.4	264	84.1	1.8	
Duration of most frequent classes in the past						
< 40 min	14	10.4	31	9.9	0.2	
40 min	6	4.4	29	9.2	-1.7	0.221
80 min	115	85.2	254	80.9	1.1	
Duration of breaks between classes						
10 min	12	8.9	45	14.3	-1.6	
20 min	51	37.8	139	44.3	-1.3	
21-60 min	40	29.6	87	27.7	0.4	**0.004**
61-90 min	19	14.1	36	11.5	0.8	
≥ 91 min	13	9.6	7	2.2	3.5	
Duration of shortest break between classes						
10 min	118	87.4	284	90.4	-1.0	
20 min	9	6.7	22	7.0	-0.1	
21-60 min	7	5.2	8	2.5	1.4	0.221
61-90 min	1	0.7	0	0.0	1.5	
Maximum number of students in classroom						
≤ 10	13	9.6	17	5.4	1.6	
11-15	12	8.9	21	6.7	0.8	
16-20	37	27.4	69	22.0	1.2	0.092
21-25	73	54.1	207	65.9	-2.4	

Continues

Follows

Tab. II. Risk factors related to voice use in teachers in the VDI ≤ 7 and VDI > 7 groups showing the percent of those responding to the statements.

Risk factors	VDI ≤ 7 teachers (n = 135)		VDI > 7 teachers (n = 314)		Adjusted residual	P-value[1]
	N	%	N	%		
Maximum number of students in classroom in the past						
≤ 10	10	7.4	13	4.1	1.4	
11-15	7	5.2	20	6.4	-0.5	
16-20	27	20.0	49	15.6	1.1	0.282
21-25	91	67.4	232	73.9	-1.4	
Voice loudness in class						
Not loud	10	7.4	2	0.6	4.1	
Slightly loud	29	21.5	37	11.8	2.7	
Moderately loud	67	49.6	154	49.0	0.1	**0.000**
Very loud	28	20.7	106	33.8	-2.8	
Excessively loud	1	0.7	15	4.8	-2.1	
Voice loudness in class in the past						
Not loud	6	4.4	8	2.5	1.1	
Slightly loud	19	14.1	28	8.9	1.6	
Moderately loud	64	47.4	139	44.3	0.6	0.168
Very loud	42	31.1	122	38.9	-1.6	
Excessively loud	4	3.0	17	5.4	-1.1	
Voice loudness outdoors (e.g., teaching physical education, supervising children during recess, etc.)						
N/A	1	0.7	2	0.6	0.1	
Not loud	3	2.2	8	2.5	-0.2	
Slightly loud	15	11.1	22	7.0	1.5	
Moderately loud	42	31.1	75	23.9	1.6	0.268
Very loud	63	46.7	167	53.2	-1.3	
Excessively loud	11	8.1	40	12.7	-1.4	
Voice loudness at home						
Not loud	39	28.9	84	26.8	0.5	
Slightly loud	53	39.3	112	35.7	0.7	
Moderately loud	38	28.1	98	31.2	-0.6	0.576
Very loud	5	3.7	16	5.1	-0.6	
Excessively loud	0	0.0	4	1.3	-1.3	
Singing in the classroom						
Never	20	14.8	25	8.0	2.2	
Infrequently	26	19.3	58	18.5	0.2	
Sometimes	35	25.9	72	22.9	0.7	0.098
Frequently	28	20.7	71	22.6	-0.4	
Always	26	19.3	88	28.0	-2.0	
Vocally discipline students						
Never	4	3.0	2	0.6	2.0	
Infrequently	17	12.6	13	4.1	3.3	
Sometimes	45	33.3	78	24.8	1.9	**0.000**
Frequently	55	40.7	155	49.4	-1.7	
Always	14	10.4	66	21.0	-2.7	
Using microphone when teaching						
Never	134	99.3	300	95.5	2.0	
Infrequently	1	0.7	7	2.2	-1.1	
Sometimes	0	0.0	3	1.0	-1.1	0.365
Frequently	0	0.0	2	0.6	-0.9	
Always	0	0.0	2	0.6	-0.9	

Continues

Follows

Tab. II. Risk factors related to voice use in teachers in the VDI ≤ 7 and VDI > 7 groups showing the percent of those responding to the statements.

Risk factors	VDI ≤ 7 teachers (n = 135)		VDI > 7 teachers (n = 314)		Adjusted residual	P-value[1]
	N	%	N	%		
Using microphone when teaching in the past						
Never	134	99.3	301	95.9	1.9	
Infrequently	1	0.7	8	2.5	-1.3	
Sometimes	0	0.0	4	1.3	-1.3	0.284
Always	0	0.0	1	0.3	-0.7	
Teaching above students talking						
Never	43	31.9	69	22.0	2.2	
Infrequently	45	33.3	92	29.3	0.9	
Sometimes	23	17.0	63	20.1	-0.7	**0.036**
Frequently	22	16.3	73	23.2	-1.7	
Always	2	1.5	17	5.4	-1.9	
Speaking over a natural breath cycle						
Never	26	19.3	16	5.1	4.7	
Infrequently	47	34.8	70	22.3	2.8	
Sometimes	34	25.2	114	36.3	-2.3	**< 0.001**
Frequently	25	18.5	96	30.6	-2.6	
Always	3	2.2	18	5.7	-1.6	
Coughing during the day						
Never	18	13.3	11	3.5	3.9	
Infrequently	47	34.8	81	25.8	1.9	
Sometimes	49	36.3	131	41.7	-1.1	**< 0.001**
Frequently	19	14.1	80	25.5	-2.7	
Always	2	1.5	11	3.5	-1.2	
Clearing throat during the day						
Never	32	23.7	52	16.6	1.8	
Infrequently	36	26.7	84	26.8	0.0	
Sometimes	41	30.4	69	22.0	1.9	**0.012**
Frequently	22	16.3	93	29.6	-3.0	
Always	4	3.0	16	5.1	-1.0	
Yelling						
Never	7	5.2	3	1.0	2.8	
Infrequently	36	26.7	37	11.8	3.9	
Sometimes	61	45.2	125	39.8	1.1	**< 0.001**
Frequently	29	21.5	132	42.0	-4.2	
Always	2	1.5	17	5.4	-1.9	

[1]: Pearson's Chi-Square test. Significant differences between teachers in the VDI ≤ 7 and the VDI > 7 groups are indicated in bold in the last column.

higher than in the VDI ≤ 7 group (χ^2 (4, n = 449) = 23.91, p < 0.001).

A significantly higher number of teachers in the VDI ≤ 7 category reported to "never" (31.9% vs 22.0%, z = 2.2) teach above students talking than the teachers in the VDI ≤ 7 group [χ^2 (4, n = 449) = 10.25, p < 0.05].

The VDI > 7 category had significantly less participants who declared to "never" (5.1% vs 19.3%, z = -4.7) and "rarely" (22.3% vs 34.8%, z = -2.8) and significantly more subjects who stated to "sometimes" (36.3% vs 25.2%, z = 2.3) and "frequently" (30.6% vs 18.5%, z = 2.6) speak over a natural breath cycle (i.e., they say the last words of a sentence when they do not have sufficient air) compared with the VDI ≤ 7 category [χ^2 (4, n = 449) = 37.05, p < 0.001].

The number of subjects in the VDI > 7 group who noted to "never" (3.5% vs 13.3%, z = -3.9) cough during the day was significantly less and the number of participants who stated to "frequently" (25.5% vs 14.1%, z = 2.7) cough was significantly greater than in the VDI ≤ 7 group [χ^2 (4, n = 449) = 24.41, p < 0.001].

A significantly greater number of subjects in the VDI > 7 party testified to "frequently" (29.6% vs 16.3%, z = 3.0) clear their throat throughout the day than in the VDI ≤ 7 party [χ^2 (4, n = 449) = 12.80, p < 0.05].

The number of participants who testified to "never" (1.0% vs 5.2%, z = -2.8) yell was significantly less in the VDI > 7 group and the number of subjects who reported to "frequently" (42.0% vs 21.5%, z = 4.2) yell was significantly greater than in the VDI ≤ 7 group [χ^2 (4, n = 449) = 35.68, p < 0.001].

Tab. III. Risk factors related to lifestyle in teachers in the VDI ≤ 7 and VDI > 7 groups showing the percent of those responding to the statements.

Risk factors	VDI ≤ 7 teachers (n = 135)		VDI > 7 teachers (n = 314)		Adjusted residual	P-value[1]
	N	%	N	%		
Smoking						
Never	99	73.3	245	78.0	-1.1	
Infrequently	9	6.7	11	3.5	1.5	
Sometimes	1	0.7	19	6.1	-2.5	**0.020**
Frequently	16	11.9	22	7.0	1.7	
Always	10	7.4	17	5.4	0.8	
Smoking in the past						
Current smoker	18	13.3	14	4.5	3.4	
Never	82	60.7	191	60.8	0.0	
Infrequently	7	5.2	29	9.2	-1.4	
Sometimes	11	8.1	40	12.7	-1.4	**0.006**
Frequently	12	8.9	20	6.4	1.0	
Always	5	3.7	20	6.4	-1.1	
When did former smoker stopped smoking						
N/A	115	85.2	267	85.0	0.0	
<1	2	1.5	5	1.6	-0.1	
1-3	3	2.2	8	2.5	-0.2	0.720
3-5	6	4.4	7	2.2	1.3	
> 5	9	6.7	27	8.6	-0.7	
Drinking alcohol						
Never	21	15.6	71	22.6	-1.7	
Infrequently	70	51.9	135	43.0	1.7	
Sometimes	35	25.9	88	28.0	-0.5	0.349
Frequently	8	5.9	19	6.1	-0.1	
Always	1	0.7	1	0.3	0.6	
Drinking caffeine						
Never	4	3.0	9	2.9	0.1	
Infrequently	11	8.1	25	8.0	0.1	
Sometimes	21	15.6	34	10.8	1.4	0.472
Frequently	58	43.0	126	40.1	0.6	
Always	41	30.4	120	38.2	-1.6	
Taking medications						
Never	21	15.6	43	13.7	0.5	
Infrequently	68	50.4	125	39.8	2.1	
Sometimes	22	16.3	80	25.5	-2.1	0.106
Frequently	18	13.3	42	13.4	0.0	
Always	6	4.4	24	7.6	-1.2	
Drinking water						
≤ 2 glasses per day	19	14.1	44	14.0	0.0	
3-5	54	40.0	109	34.7	1.1	
6-8	34	25.2	100	31.8	-1.4	0.529
> 8	28	20.7	61	19.4	0.3	
Having stress and anxiety						
Never	4	3.0	2	0.6	2.0	
Infrequently	11	8.1	13	4.1	1.7	
Sometimes	44	32.6	78	24.8	1.7	**0.021**
Frequently	53	39.3	153	48.7	-1.8	
Always	23	17.0	68	21.7	-1.1	
Daily hours of sleep						
≤ 6 hours	52	38.5	122	38.9	-0.1	
7	63	46.7	153	48.7	-0.4	
8	16	11.9	34	10.8	0.3	0.787
> 8	4	3.0	5	1.6	1.0	

[1]: Pearson's Chi-Square test. Significant differences between teachers in the VDI ≤ 7 and the VDI > 7 groups are indicated in bold in the last column.

Risk factors related to lifestyle

The significant risk factors distinguished and the adjusted residual values for the risk factors related to lifestyle use are revealed in Table III.

The VDI > 7 category had significantly more participants who noted to "sometimes" (6.1% vs 0.7%, z = 2.5) smoke than the VDI ≤ 7 category [χ^2 (4, n = 449) = 11.61, p < 0.05].

The number of participants in the VDI > 7 group who stated to "never" (0.6% vs 3.0%, z = -2.0) have had stress and anxiety was significantly less than in the VDI ≤ 7 group [χ^2 (4, n = 449) = 11.59, p < 0.05].

Risk factors related to environment

The significant detected risk factors and the adjusted residual values for the risk factors related to the environment are displayed in Table IV.

Tab. IV. Risk factors related to the environment in teachers in the VDI ≤ 7 and VDI > 7 groups showing the percent of those responding to the statements.

Risk factors	VDI ≤ 7 teachers (n = 135)		VDI > 7 teachers (n = 314)		Adjusted residual	P-value[1]
	N	%	N	%		
Physical size of the most frequent classroom in workday						
Small	34	25.2	85	27.1	-0.4	
Medium	84	62.2	202	64.3	-0.4	0.421
Large	17	12.6	27	8.6	1.3	
Physical size of the most frequent classroom in workday in the past						
Small	33	24.4	85	27.1	-0.6	
Medium	82	60.7	200	63.7	-0.6	0.215
Large	20	14.8	29	9.2	1.7	
Air moisture in classroom						
Not at all moist	85	63.0	160	51.0	2.3	
Moderately moist	48	35.6	145	46.2	-2.1	0.057
Very moist	2	1.5	9	2.9	-0.9	
Air dryness in classroom						
Not at all dry	30	22.2	55	17.5	1.2	
Moderately dry	88	65.2	208	66.2	-0.2	0.377
Very dry	17	12.6	51	16.2	-1.0	
Dust exposure in classroom						
Not at all	7	5.2	7	2.2	1.7	
Small amount	24	17.8	48	15.3	0.7	
Moderate amount	47	34.8	118	37.6	-0.6	0.194
Large amount	49	36.3	106	33.8	0.5	
Excessive amount	8	5.9	35	11.1	-1.7	
Noise from passing airplanes and/or street						
Not at all noisy	42	31.1	65	20.7	2.4	
Slightly noisy	46	34.1	123	39.2	-1.0	
Moderately noisy	38	28.1	74	23.6	1.0	**0.011**
Very noisy	7	5.2	46	14.6	-2.9	
Extremely noisy	2	1.5	6	1.9	-0.3	
Outside noise (e.g., construction, lawnmowers, industrial activity)						
Not at all noisy	51	37.8	81	25.8	2.6	
Slightly noisy	49	36.3	119	37.9	-0.3	
Moderately noisy	17	12.6	77	24.5	-2.8	**0.009**
Very noisy	14	10.4	34	10.8	-0.1	
Extremely noisy	4	3.0	3	1.0	1.6	

Continues

Follows

Tab. IV. Risk factors related to the environment in teachers in the VDI ≤ 7 and VDI > 7 groups showing the percent of those responding to the statements.

Risk factors	VDI ≤ 7 teachers (n = 135)		VDI > 7 teachers (n = 314)		Adjusted residual	P-value[1]
	N	%	N	%		
Noise from children playing outside						
Not at all noisy	22	16.3	33	10.5	1.7	
Slightly noisy	51	37.8	75	23.9	3.0	
Moderately noisy	30	22.2	99	31.5	-2.0	**0.004**
Very noisy	27	20.0	86	27.4	-1.7	
Extremely noisy	5	3.7	21	6.7	-1.2	
Noise from children having physical education outside						
Not at all noisy	28	20.7	46	14.6	1.6	
Slightly noisy	52	38.5	101	32.2	1.3	
Moderately noisy	31	23.0	93	29.6	-1.4	0.122
Very noisy	21	15.6	57	18.2	-0.7	
Extremely noisy	3	2.2	17	5.4	-1.5	
Noise from inside the building (e.g., classrooms, hallways)						
Not at all noisy	23	17.0	38	12.1	1.4	
Slightly noisy	68	50.4	127	40.4	1.9	
Moderately noisy	34	25.2	101	32.2	-1.5	**0.042**
Very noisy	8	5.9	37	11.8	-1.9	
Extremely noisy	2	1.5	11	3.5	-1.2	
Noise from inside the classroom (e.g., children talking, chairs scraping on the floor)						
Not at all noisy	7	5.2	3	1.0	2.8	
Slightly noisy	60	44.4	77	24.5	4.2	
Moderately noisy	42	31.1	94	29.9	0.2	**0.000**
Very noisy	21	15.6	104	33.1	-3.8	
Extremely noisy	5	3.7	36	11.5	-2.6	
Noise from heating or air conditioning						
Not at all noisy	83	61.5	156	49.7	2.3	
Slightly noisy	35	25.9	100	31.8	-1.3	
Moderately noisy	14	10.4	41	13.1	-0.8	0.173
Very noisy	2	1.5	13	4.1	-1.4	
Extremely noisy	1	0.7	4	1.3	-0.5	
Electronic noise (e.g., computers, lights)						
Not at all noisy	67	49.6	117	37.3	2.4	
Slightly noisy	57	42.2	131	41.7	0.1	
Moderately noisy	8	5.9	43	13.7	-2.4	**0.012**
Very noisy	2	1.5	15	4.8	-1.7	
Extremely noisy	1	0.7	8	2.5	-1.3	
Echo in the classroom when speaking						
Not at all noisy	111	82.2	208	66.2	3.4	
Slightly noisy	19	14.1	68	21.7	-1.9	
Moderately noisy	4	3.0	25	8.0	-2.0	**0.007**
Very noisy	0	0.0	9	2.9	-2.0	
Extremely noisy	1	0.7	4	1.3	-0.5	
Noise from public address system (e.g., microphones, speakers)						
Not at all noisy	83	61.5	157	50.0	2.2	
Slightly noisy	42	31.1	104	33.1	-0.4	
Moderately noisy	8	5.9	36	11.5	-1.8	0.062
Very noisy	2	1.5	15	4.8	-1.7	
Extremely noisy	0	0.0	2	0.6	-0.9	

[1]: Pearson's Chi-Square test. Significant differences between teachers in the VDI ≤ 7 and the VDI > 7 groups are indicated in bold in the last column.

A significantly higher number of subjects in the VDI > 7 group proclaimed to hear a large amount of noise (14.6% vs 5.2%, z = 2.9) and a significantly fewer number of participants stated to hear no noise at all (20.7% vs 31.1%, z = -2.4) generated from the passage of airplanes and/or from the road at their workplace than the VDI ≤ 7 group [χ^2 (4, n = 449) = 13.00, p < 0.05].
The VDI > 7 category had significantly more subjects who reported to hear "moderate" (24.5% vs 12.6%, z = 2.8) and significantly fewer subjects who stated to hear "no" (25.8% vs 37.8%, z = -2.6) external noise derived from construction sites, lawnmowers, industrial activity, etc. at their workplace in comparison to the VDI ≤ 7 category [χ^2 (4, n = 449) = 13.55, p < 0.05].
The number of participants in the VDI > 7 category who stated to hear "moderate" noise that originated (31.5% vs 22.2%, z = 2.0) from children playing outside in their workplace was significantly greater than the VDI ≤ 7 group. The number of participants who noted to hear a "small" (23.9% vs 37.8%, z = -3.0) amount of noise from this source was significantly lower in the VDI > 7 category group than the VDI ≤ 7 group [χ^2 (4, n = 449) = 15.42, p < 0.05].
A significantly higher number of subjects in the VDI > 7 group reported to hear an "excessive" (11.5% vs 3.7%, z = 2.6) and "great" (33.1% vs 15.6%, z = 3.8) amount of noise within the classroom (e.g., children who talk, chairs that scrape on the floor) and a significantly fewer number of subjects stated to hear "small" (24.5% vs 44.4%, z = -4.2) and "no" (1.0% vs 5.2%, z = -2.8) noise within the classroom than the VDI ≤ 7 group [χ^2 (4, n = 449) = 36.60, p < 0.001].
A significantly higher number of teachers in the VDI > 7 group, reported hearing a "moderate" (13.7% vs 5.9%, z = 2.4) amount of noise and significantly lower percentage stated hearing "no" (37.3% vs 49.6%, z = -2.4) noise from electronic devices (e.g., computers and lights) than the VDI ≤ 7 group [χ^2 (4, n = 449) = 12.79, p < 0.05].
The VDI > 7 group had significantly more subjects who stated to hear a "great" (2.9% vs 0.0%, z = 2.0) and "moderate" (8.0% vs 3.0%, z = 2.0) amount of echo in class when they teach and significantly fewer subjects who declared to hear "no" (66.2% vs 82.2%, z = -3.4) echo in the classroom compared with the VDI ≤ 7 group [χ^2 (4, n = 449) = 13.96, p < 0.05].

VOICE DISORDERS OCCUPATIONAL CONSEQUENCES AND USEFULNESS OF VOCAL HYGIENE PROGRAM

The outcomes of the survey show the consequences of voice disorders on teachers' occupation and the helpfulness of vocal education seminars. The significant consequences of voice disorders and vocal hygiene valuableness are pinpointed in Tables V and VI along with their residual values.
A significantly higher number of subjects in the VDI > 7 group declared to "frequently" (29.3% vs 7.4%, z = 5.1) and significantly fewer number of subjects noted to "rarely" (22.0% vs 36.3%, z = -3.2) and "never" (7.0% vs 15.6%, z = -2.8) allow their voice problems to limit their ability to perform certain tasks in the workplace (e.g., teaching, etc.) than in the VDI ≤ 7 group [χ^2 (4, n = 449) = 43.54, p < 0.001].
The number of participants in the VDI > 7 category who reported to have reduced their activities (e.g., teaching) or interactions annually due to voice problems "3 to 4 days" (25.5% vs 11.1%, z = 3.4) and "5 or more days" (19.1% vs 5.9%, z = 3.6) was significantly greater than in the VDI ≤ 7 category. The number of participants in the VDI > 7 category who stated to have reduced their activities or interactions annually because of voice issues "0 days" (24.2% vs 40.0%, z = -3.4) was significantly lower in the VDI > 7 category than in the VDI ≤ 7 category [χ^2 (4, n = 449) = 44.06, p < 0.001].
A significantly higher number of participants in the VDI > 7 group declared that voice hygiene seminars during their training would have been useful to them (98.4% vs 92.6%, z = 3.1) and significantly fewer subjects stated that voice hygiene seminars would not have been useful (1.6% vs 7.4%, z = -3.1) than in the VDI ≤ 7 category [χ^2 (1, n = 449) = 9.89, p < 0.05].

Discussion

The present investigation, which represents the first survey that investigated prevalence, risk factors and occupational consequences of self-perceived voice problems in Cypriot public school teachers, revealed that the estimated prevalence of self-reported voice problems in the sample of 449 preschool-kindergarten and grade 1st-6th public school teachers investigated is 69.9%. This outcome may be partly attributable to the fact that the survey may have attracted teachers who have voice problems. Nevertheless, this finding corroborates with previously reported research which indicated that the prevalence of self-reported voice disorders in one hundred and four elementary, secondary and high school teachers in Iran was 54.6% [3]. On the other hand, it contradicts other earlier reported studies which revealed that the prevalence of voice disorders was 11.0% for elementary and secondary school teachers in the State of Iowa and Utah [1], 11.6% for Brazilian elementary and secondary school teachers [2], 8% for primary and secondary school teachers in Latvia [5] and 17.4% for primary teachers in India [6].
The current research study also revealed that teachers with a VDI > 7 were more likely to frequently experience upper respiratory infections (e.g., pharyngitis, laryngitis, etc.) and less likely to have never or infrequently experienced this health condition than the teachers with a VDI ≤ 7. These results are consistent with previously reported findings which indicated that teachers with VD (Voice Disorders) were more likely to experience upper respiratory tract infections than teachers with NVD (No Voice Disorders) [5, 6, 10, 20].

Tab. V. Occupational consequences of voice problems in teachers in the VDI ≤ 7 and VDI > 7 groups showing the percent of those responding to the statements.

Risk factors	VDI ≤ 7 teachers (n = 135)		VDI > 7 teachers (n = 314)		Adjusted residual	P-value[1]
	N	%	N	%		
Missed days of work annually due to voice problems (e.g., sore throat)						
N/A	13	9.6	8	2.5	3.3	
0 days	70	51.9	143	45.5	1.2	
At least 1 day	20	14.8	47	15.0	0.0	**0.005**
At least 2 days	15	11.1	43	13.7	-0.7	
At least 3 days	7	5.2	34	10.8	-1.9	
At least 4 days	10	7.4	39	12.4	-1.6	
Voice problems limited ability to do certain tasks (e.g., teaching)						
N/A	10	7.4	6	1.9	2.9	
Never	21	15.6	22	7.0	2.8	
Infrequently	49	36.3	69	22.0	3.2	**0.000**
Sometimes	45	33.3	125	39.8	-1.3	
Frequently	10	7.4	92	29.3	-5.1	
Days that activities (e.g., teaching) were reduced annually due to voice problems						
N/A	12	8.9	4	1.3	4.0	
0 days	54	40.0	76	24.2	3.4	
1-2	46	34.1	94	29.9	0.9	**0.000**
3-4	15	11.1	80	25.5	-3.4	
≥ 5	8	5.9	60	19.1	-3.6	

[1]: Pearson's Chi-Square test. Significant differences between teachers in the VDI ≤ 7 and the VDI > 7 groups are indicated in bold in the last column.

Tab. VI. Vocal hygiene education for teachers in the VDI ≤ 7 and VDI > 7 groups showing the percent of those responding to the statements.

Risk factors	VDI ≤ 7 teachers (n = 135)		VDI > 7 teachers (n = 314)		Adjusted residual	P-value[1]
	N	%	N	%		
Received vocal hygiene education during training						
No	115	85.2	270	86.0	-0.2	
Yes	20	14.8	44	14.0	0.2	0.824
Seminars on vocal hygiene education during training would have been beneficial						
No	10	7.4	5	1.6	3.1	
Yes	125	92.6	309	98.4	-3.1	**0.002**

[1]: Pearson's Chi-Square test. Significant differences between teachers in the VDI ≤ 7 and the VDI > 7 groups are indicated in bold in the last column.

Moreover, the results of our study showed that the VDI > 7 class had significantly more individuals who had "frequently" experienced nasal allergies (e.g., nasal discharge, stuffy nose and sneezing) and significantly fewer participants who have "never" had allergies compared to the VDI ≤ 7 group. The current finding is in sync with Trinite's [5] research that reported that the primary and secondary teachers in Latvia who suffer from respiratory allergies are 5.5 times more likely to have voice problems than the ones without allergies. Furthermore, Roy et al. [12] also indicated that the prevalence of VD was significantly higher for participants with respiratory allergies, and the outcomes of Simberg's et al. [21] investigation also suggested that participants with allergies had more voice disorders symptoms than those without allergies. In contrast, Devadas et al. [6] revealed that nasal allergies are not a significant risk factor in Indian teachers with self-reported voice problems in comparison with teachers with no voice problems.

Another significant finding of the survey disclosed that a significantly higher number of participants in the VDI > 7 group reported to teach kindergarten and fewer subjects reported to teach 6th grade than in the VDI ≤ 7 group. This result agrees with Munier's & Kinsella's [22] investigation, which reported that teachers of the junior classes were more vulnerable to develop a voice problem as vocal fatigue and dry throat were reported more frequently by teachers of the junior classes than those of the senior classes.

In contrast, this result disagrees with Da Rocha et al's [23] investigation, which reported that teachers in Brazil who lectured in the fourth grade and below presented with a lower risk (20% less) of having a perceived voice disorder than the teachers who lectured in the fifth grade and up. Also, this outcome is inconsistent with Houtte's, Claeys', Wuyts' & van Lierde's [11] findings which found that there was no significant difference in teaching different grade levels between the Belgian teachers with voice problems when comparing them to teachers without voice problems.

Another key finding of this study revealed that there were more teachers in the VDI > 7 group who reported using "very loud" and "excessively loud" voice in class and fewer subjects who stated to use "not at all loud" and "slightly loud" voice compared to the VDI ≤ 7 group. Similarly, Bolbol, Zalat, Hammam, and Elnakeb [8] identified that high voice loudness is a significant voice disorder risk factor that affects elementary, middle, and high school teachers' voice in Egypt. Sathyanarayan, Boominathan and Nallamuthu [24] found that speaking in an uncomfortable loud voice was identified as one of the vocal abuse or misuse behaviors frequently used by teachers in India. Moreover, Ferreira et al. [25] found that speaking loudly was significantly associated with hoarseness and vocal fatigue in Brazilian teachers. On the other hand, Devadas et al. [6] found no significant difference between teachers with voice disorders and the ones with no voice disorders who used soft, loud or too loud vocal loudness while teaching.

One more outcome that the research indicated is that there were fewer participants in the VDI > 7 category who stated to "never" and "rarely" and more participants who stated to "always" use their voice to discipline students than in the VDI ≤ 7 group. This result supports the findings of De Alvear, Javier Barón & Ginés Martínez-Arquero [26] that revealed that children's indiscipline significantly increased the chances of kindergarten and elementary school teachers in Spain having vocal problems.

The results additionally showed that teachers with VDI > 7 were less likely to "never" and "rarely" and more likely to "sometimes" and "frequently" speak over a natural breath cycle (i.e., they say the last words of a sentence when they do not have sufficient air) than the teachers with VDI ≤ 7. Our investigation is the first study that investigated the factor speaking over a natural breath cycle in teachers and identified it as a significant risk factor for voice disorders among preschool-kindergarten and grade 1st-6th school teachers in Cyprus.

Furthermore, more teachers in the VDI > 7 group stated "frequently" coughing, clearing their throat and yelling throughout the day than those in the VDI ≤ 7 party. Likewise, Trinite [5] identified that throat clearing had a statistical significant impact on teachers' voice as 18.3% of the teachers in the voice disorder group had the habit of clearing their throats compared to 8% in control group. Also, Seifpanahi et al. [3] reported that Iranian teachers with voice complaints were more likely to experience coughing and throat clearing than teachers without voice complaints. Similarly, Devadas et al. [6] revealed that teachers with voice problems were more likely to yell in the classroom than teachers with no voice problems.

An additional significant finding of the survey disclosed that there were more teachers in the VDI > 7 category who reported to "sometimes" currently smoke than teachers in the VDI ≤ 7 category. This finding is in accordance with the findings of Preciado-Lopez et al. [27] which reported that significantly more dysphonic teachers smoke compared with non-dysphonic ones. Conversely, Trinite [5] did not confirm any statistically significant correlation between smoking and the occurrence of voice disorders in Latvian teachers. Also, Devadas et al. [6] found no significant relationship between teachers reporting voice problems and smoking. Likewise, de Medeiros et al. [20] revealed that smoking was not statistically associated with probable dysphonia in Brazilian female public school teachers.

Another important result of this study showed that teachers in the VDI > 7 group were less likely to report "never" having stress and anxiety than those in the VDI ≤ 7 group. A similar tendency is observed in Trinite's [5] research who stated that the likelihood of voice problems increased in teachers who felt regular stress in their working place for various reasons. Specifically, 62.1% of teachers with voice disorders considered that children generated stress, and 51.5% of them mentioned that overloading caused stress. Likewise, Devadas et al. [6] indicated that a higher percentage of teachers in the voice disorder (VD) group reported that they were stressed while teaching than the teachers in the no voice disorder (NVD) group. In contrast, Pereira [28] examined stress symptoms and its impact on voice in teachers with dysphonia compared with teachers with no voice changes and found no significant association between dysphonia and stress.

Other key findings of this investigation demonstrated that there were more teachers in the VDI > 7 category who reported to hear "moderate" or "great" and fewer subjects who stated to hear "no" or "small" noise generated from construction sites, lawnmowers and industrial activity, as well as, children playing outside in their place of work and echo in the classroom when speaking than the teachers in the VDI ≤ 7 category. Conversely, Preciado-Lo´pez et al. [27] indicated that there were no statistically significant differences between the normal and the dysphonic teachers' responses with regards to the amount of noise that originates from construction work and children playing in the school yard.

One other crucial outcome of this investigation is that teachers in the VDI > 7 group were more likely to hear a large amount of noise and less likely to hear no

noise at all generated from the passage of airplanes and/or from the road at their workplace than the teachers in VDI ≤ 7 group. This result agrees with Phadke's [29] research which revealed a significant correlation between classroom location being close to main traffic roads and the frequency of laryngeal and neck pain in teachers. In contrast, Preciado-Lopez et al. [27] indicated that there were no statistically significant differences between the normal and the dysphonic teachers' responses with regards to the amount of noise that comes from the road in their classrooms.

Another significant finding of our investigation disclosed that there were more teachers in the VDI > 7 group who reported to hear an "excessive" and "great" amount of noise within the classroom (e.g., children who talk and moving chairs) and fewer who stated to hear "small" and "no" noise within the classroom than in the VDI ≤ 7 group. Similar to the current study, Preciado-Lopez et al. [27] indicated that there were statistically significant differences between the normal and the dysphonic teachers' responses with respect to the amount of noise that comes from inside the classroom (i.e., the murmur of the students and the students moving chairs and tables). Also, Devadas et al. [6] disclosed that a significantly higher percentage of teachers in the voice problem group reported a higher level of student noise in the classroom than the teachers in the no voice problem group.

In general research studies indicate that teachers who experience noise at their workplace generated from different sources such as airplanes, roads, construction sites, children playing outside and children's murmur in the classroom may be more perceptible to voice disorders. Devadas [6] revealed that teachers who experienced high background noise in the classroom (generated from student noise, external noise and fan or air conditioning noise) were found to be at a 4.4 times higher risk of developing voice problems than teachers who did not experience high background noise. A possible rationale is that speaking in high background noise increases the vocal loading because the speaker automatically increases the loudness level of a voice signal so that he/she can be heard. An increase in loudness may increase the medial compression of the vocal folds that may increase the risk of vocal fatigue [6] and lead to voice pathologies. Furthermore, our investigation did not find any significant correlation between noises generated from inside the building such as other classrooms, hallways, etc. and noise resulting from computers and projectors. This result may be attributable to the facts that the primary schools in Cyprus usually are not designed to have inside hallways and the projectors and computers may not always be turned on. In contrast, Phadke [29] showed a significant association between frequent laryngeal or neck pain symptoms and noise from other classrooms. Out of 44.8% of teachers who declared to hear noise from neighboring classrooms, 13.5% stated experiencing a daily recurrence and 9.4% experienced a monthly recurrence of laryngeal pain. Additionally, Trinite [5] identified a statistically significant association between noise generated from computers and projectors and the occurrence of voice problems in teachers.

Other substantial findings that this survey disclosed is that there were more teachers in the VDI > 7 group who declared that "often" their voice problems limited their ability to perform certain tasks in their workplace (e.g., teaching etc.) and reduced their activities (e.g., teaching etc.) or interactions "3 to 5 or more days" annually than teachers in the VDI ≤ 7 group. The results from this study are in general agreement with the outcomes from an earlier report by Roy et al. [12] which revealed that teachers were significantly more likely to report that their voice limited their ability to do certain tasks at their job and experienced a significantly higher number of days in which they intentionally reduced their activities or interactions because of their voice problems than nonteachers. Particularly, 43% of teachers versus 16.0% of nonteachers stated that they reduced activities or interactions for at least 1 day because of their voice problems.

An additional significant result of the survey disclosed that more teachers (98.4% vs 92.6%) in the VDI > 7 group declared that voice hygiene seminars during their training would have been useful and fewer subjects (1.06% vs 7.4%) stated that voice hygiene seminars would not have been useful compared with teachers in the VDI ≤ 7 category.

Similarly, Yiu (2002) stated that more than 50% of practicing and prospective teachers believed that information on breathing exercises and vocal hygiene strategies would help them prevent voice problems.

Conclusions/implications of conclusions

The present survey is the first study to investigate risk factors that may lead to self-perceived voice disorders in public-school teachers in Cyprus. The results of the study concluded that health (i.e., nasal allergies and upper respiratory infections), voice use (e.g., teaching lower grades, having shorter breaks between classes, using loud voice, etc.), lifestyle (i.e., smoking and stress), and environmental factors (e.g., teaching in a noisy environment where noise is generated from the passage of airplanes and/or roads, children playing outside, children talking within the classroom etc.) are job related risk factors that may contribute to the development of voice disorders in public school teachers in Cyprus. The results of the current investigation also determined the occupational impact of voice disorders on teachers which is that voice problems often limit teachers' ability to perform certain tasks in their job (e.g., teaching) and obligate them to reduce their activities (e.g., teaching) or interactions 3-5 or more days annually. The outcomes of the present research also showed that the estimated prevalence of self-reported voice problems in four

hundred and forty-nine preschool-kindergarten and grade 1st-6th public school teachers surveyed is 69.9%. Additionally, the results revealed that more participants in the VD group felt that vocal hygiene seminars during their training would have been useful. These conclusions infer that the development and implementation of a preventative voice hygiene program is recommended. The voice hygiene program can provide guidelines to current and future teachers to inhibit them from developing voice disorders and consequently improve their occupational performance. The results of the investigation disclosed that the strategies of the voice hygiene program should aim to promote optimal voice production and to eliminate abusive voice behaviors and may include:

1. consulting a doctor for experiencing gastroesophageal reflux and nasal allergies;
2. consulting teachers to have at least an hour and a half of a break between classes;
3. modeling techniques such as the silent cough and or the sip of water to reduce throat clearing;
4. receiving voice therapy training that focuses on eliminating talking over a natural breath cycle (e.g., instruct the teacher to say as many numbers as possible in one breath and stop before he/she feels any strain);
5. counseling teachers to use a microphone when teaching;
6. encouraging teachers to eliminate smoking and yelling [30, 31];
7. advising them to close classroom windows and doors to eliminate outside noise;
8. advising them to wait until the noise within the classroom (e.g., students murmur, moving chairs) stops before they start or continue talking [30, 32].

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

The individual contributions of authors to the manuscript should be specified in this section.

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Appendix A: risk factors for voice disorders questionnaire

Please note the answer that is most appropriate for you. Answer all questions. Please note that there is no right or wrong answer.

1.DEMOGRAPHIC DATA

1. How old are you?	25-34 years old ☐	35-44 ☐	45-54 ☐	55-60 ☐
2. What is your gender?	Male ☐	Female ☐		
3. What position do you hold?	Preschool/Kindergarten Teacher ☐	Teacher ☐	Assistant Director ☐	Director ☐	Substitute Kindergarten Teacher ☐	Substitute Teacher ☐
4. From which geographical region of Cyprus do you come from?	Nicosia ☐	Limassol ☐	Larnaca ☐	Famagusta ☐	Paphos ☐
5. Where is the school you work for?	City ☐	Village ☐			
6. In which geographical region of Cyprus do you work?	Nicosia ☐	Limassol ☐	Larnaca ☐	Famagusta ☐	Paphos ☐

2. RISK FACTORS FOR VOICE DISORDERS

RISK FACTORS RELATED TO GENERAL HEALTH

	Never	Infrequently	Sometimes	Frequently	Always
7. Do you have nasal allergies (e.g., runny nose, stuffy nose, sneezing, etc.)?	☐	☐	☐	☐	☐
8. Do you have gastroesophageal reflux (i.e., backflow of stomach fluid into your esophagus and mouth)?	☐	☐	☐	☐	☐
9. Do you have upper respiratory tract infections (e.g., pharyngitis and laryngitis)?	☐	☐	☐	☐	☐

RISK FACTORS RELATED TO VOICE USE

10. How many years have you been teaching?	≤ 5 ☐	6-10 ☐	11-20 ☐	≥ 21 ☐
11. What is the nature of your work?	Teaching ☐	Teaching and administrative duties ☐	No teaching and administrative duties ☐	

12. Which class do you teach most of your teaching time?	Preschool/Kindergarten ☐	1st ☐	2nd ☐	3rd ☐	4th ☐	5th ☐	6th ☐	I'm not responsible for a class ☐

13. Does your school have combined-grade classrooms?	No ☐	Yes ☐

14. Which combined-grade class do you teach (e.g., 1st and 2nd grade)?	N/A ☐	1st-2nd ☐	2nd-3rd ☐	3rd-4th ☐	4th-5th ☐	5th-6th ☐

15. What subject do you teach most of the time?	Greek ☐	Mathematics ☐	Natural Sciences ☐	English ☐	Music ☐	PE ☐	Art ☐	Other ☐

16. How many teaching hours per week do you have?	≤ 23 x 40 minutes per week ☐	24-28 x 40 minutes per week ☐	29 x 40 minutes per week ☐		
17. How many teaching hours per week did you have 5 years ago?	≤ 23 x 40 minutes per week ☐	24-28 x 40 minutes per week ☐	29 x 40 minutes per week ☐		
18. What is the longest duration of continuous teaching time without a break in your daily workday?	< 40 minutes ☐	40 minutes ☐	80 minutes ☐		
19. What was the longest duration of continuous teaching time without a break in your daily workday 5 years ago?	< 40 minutes ☐	40 minutes ☐	80 minutes ☐		
20. What is the duration of your longest break between classes?	10 minutes ☐	20 ☐	21-60 ☐	61-90 ☐	> 90 ☐
21. What is the duration of your shortest break between classes?	10 minutes ☐	20 ☐	21-60 ☐	61-90 ☐	> 90 ☐
22. What is the maximum number of students in your class?	≤ 10 ☐	11-15 ☐	16-20 ☐	21-25 ☐	
23. What is the maximum number of students in your class for the last 5 years?	≤ 10 ☐	11-15 ☐	16-20 ☐	21-25 ☐	
24. How loud are you using your voice in the classroom the current school year?	Not at all loud ☐	Slightly loud ☐	Moderately loud ☐	Very loud ☐	Excessively loud ☐
25. How loud were you using your voice in the classroom 3 years ago?	Not at all loud ☐	Slightly loud ☐	Moderately loud ☐	Very loud ☐	Excessively loud ☐
26. How loud do you use your voice outdoors (e.g., physical education and children supervision during recess, etc.)?	N/A ☐	Not at all loud ☐	Slightly loud ☐	Moderately loud ☐	Very loud ☐	Excessively loud ☐
27. How loud do you use your voice at home?	Not at all loud ☐	Slightly loud ☐	Moderately loud ☐	Very loud ☐	Excessively loud ☐
28. Do you sing in the classroom?	Never ☐	Infrequently ☐	Sometimes ☐	Frequently ☐	Always ☐
29. Do you use your voice to discipline students?	Never ☐	Infrequently ☐	Sometimes ☐	Frequently ☐	Always ☐
30. Do you use a microphone when teaching?	Never ☐	Infrequently ☐	Sometimes ☐	Frequently ☐	Always ☐
31. Did you use a microphone when teaching for the last 5 years?	Never ☐	Infrequently ☐	Sometimes ☐	Frequently ☐	Always ☐
32. Do you teach above students talking?	Never ☐	Infrequently ☐	Sometimes ☐	Frequently ☐	Always ☐
33. Do you speak over a natural breath cycle (e.g., Do you squeeze out the last words when you do not have enough air)?	Never ☐	Infrequently ☐	Sometimes ☐	Frequently ☐	Always ☐
34. Do you cough throughout the day?	Never ☐	Infrequently ☐	Sometimes ☐	Frequently ☐	Always ☐

	Never	Infrequently	Sometimes	Frequently	Always
35. Do you clear your throat throughout the day?	☐	☐	☐	☐	☐
36. Do you scream?	☐	☐	☐	☐	☐

RISK FACTORS RELATED TO LIFESTYLE

	Never	Infrequently	Sometimes	Frequently	Always
37. Do you currently smoke?	☐	☐	☐	☐	☐

	Current smoker	Never smoked	Infrequently	Sometimes	Frequently	Always
38. Have you smoked in the past?	☐	☐	☐	☐	☐	☐

	N/A	< 1 year ago	Before 1-3 years	Before 3-5 years	> 5 years
39. If you are a former smoker, when did you stop smoking?	☐	☐	☐	☐	☐

	Never	Infrequently	Sometimes	Frequently	Always
40. Do you drink alcohol?	☐	☐	☐	☐	☐
41. Do you drink caffeine (e.g., coffee, tea, and coke)?	☐	☐	☐	☐	☐
42. Are you taking medications?	☐	☐	☐	☐	☐

	≤ 2 glasses per day	3-5 glasses	6-8 glasses	> 8 glasses
43. Do you drink water?	☐	☐	☐	☐

	Never	Infrequently	Sometimes	Frequently	Always
44. Do you have stress and anxiety?	☐	☐	☐	☐	☐

	≤ 6 hours	7 hours	8 hours	> 8 hours
45. How many hours do you sleep daily?	☐	☐	☐	☐

RISK FACTORS RELATED TO THE ENVIRONMENT

	Small (< 40 m^2)	Medium (40-50 m^2)	Large (> 50 m^2)
46. What is the size of the classroom that you use frequently?	☐	☐	☐
47. What was the size of the classroom that you used most frequently the last 5 years?	☐	☐	☐

	Not humid at all	Moderately humid	Very humid
48. Do you consider the air to be humid in the classroom where you usually teach?	☐	☐	☐

	Not dry at all	Moderately dry	Very dry
49. Do you consider the air to be dry in the classroom where you usually teach?	☐	☐	☐

	Not at all	Small amount	Medium amount	Large amount	Excessive amount
50. To what extent are you exposed to dust in your workplace?	☐	☐	☐	☐	☐

51. To what extent do you experience noise from the following source?

	Not at all	Small amount	Medium amount	Large amount	Excessive amount
a. Passing airplanes and/or road noise	☐	☐	☐	☐	☐
b. Outside noises such as construction, lawnmowers, industrial activity, etc.	☐	☐	☐	☐	☐
c. Children playing outside.	☐	☐	☐	☐	☐
d. Children having physical education outside or inside.	☐	☐	☐	☐	☐
e. Noises from inside the building (e.g., classrooms, hallways, etc.)	☐	☐	☐	☐	☐

f. Noises from inside the classroom (e.g., children talking, chairs sliding on flooring, etc.)	☐	☐	☐	☐	☐
g. Heating or air conditioning noises.	☐	☐	☐	☐	☐
h. Electronic noises (e.g., computers, lights, etc.)	☐	☐	☐	☐	☐
i. Echoing in the classroom when you speak.	☐	☐	☐	☐	☐
j. Public address system (e.g., microphones, speakers, etc.)	☐	☐	☐	☐	☐

3. OCCUPATIONAL CONSEQUENCES OF VOICE DISORDERS

	N/A	0 days	At least 1 day	At least 2 days	At least 3 days	At least 4 or more days
52. How many missed days of work did you have yearly due to voice problems (e.g., sore throat)?	☐	☐	☐	☐	☐	☐

	N/A	Never	Infrequently	Sometimes	Frequently
53. Do you voice problems limit your ability to perform certain tasks in your workplace (e.g., teaching, etc.)?	☐	☐	☐	☐	☐

	N/A	0 days	1-2 days	3-4 days	5 or more days
54. How many days have you reduced your activities (e.g., teaching, etc.) or your interactions yearly because of your voice problems?	☐	☐	☐	☐	☐

4. VOCAL HYGIENE EDUCATION

	No	Yes
55. Have you received any vocal hygiene education during your training?	☐	☐

	No	Yes
56. Do you think seminars on vocal hygiene education during your training would have been beneficial to you?	☐	☐

5. VOICE DISORDER INDEX

57. These are statements that many people have used to describe their voices and the effects of their voices on their lives. Circle the response that indicates how frequently you have the same experience.
0=never, 1=almost never, 2=sometimes, 3=almost always, 4=always

The clarity of my voice is unpredictable.	0	1	2	3	4
My voice is worse in the evening.	0	1	2	3	4
I feel as though I have to strain to produce voice.	0	1	2	3	4
I am less outgoing because of my voice problem.	0	1	2	3	4
I tend to avoid groups of people because of my voice.	0	1	2	3	4
I feel left out of conversations because of my voice.	0	1	2	3	4
People have difficulty understanding me in a noisy room.	0	1	2	3	4
My family has difficulty hearing me, when I call them through the house.	0	1	2	3	4
My voice makes it difficult for people to hear me.	0	1	2	3	4
I feel embarrassed when people ask me to repeat.	0	1	2	3	4
I feel annoyed when people ask me to repeat.	0	1	2	3	4
I'm ashamed of my voice problem.	0	1	2	3	4

ORIGINAL ARTICLE

Social capital and related factors in Western Iran students

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Keywords

Social capital • Trust • Relationships in social networks • Community participation • Group participation

Summary

Background and aim. *Social capital involves a set of norms available in social systems which improves the interaction between people and reduces the costs of interactions and communications. The purpose of this research was to study the social capital of the students of Kurdistan University of Medical Sciences and its related factors, 2017.*
Material and methods. *The method of this study was the descriptive survey. The statistical sample of this study included all students of Kurdistan University of Medical Sciences among whom 378 students were selected randomly as the study sample. Delaviz questionnaire of social capital was employed for data collection and data analysis was performed using SPSS software, through descriptive statistics (mean, standard deviation) and Inferential statistics (U-Mann Whitney, Kruskal-Wallis).*
Results. *The mean of social capital was 70.56 ± 10/88. The minimum and maximum mean was measured for "participation in local community" and "group participation", respectively. In this study, there were significant associations between social capital and gender, field of study as well as marital status (p < 0/01).*
Conclusions. *Social capital is known as the most important factor for people dealing with stressful situations, and can facilitate toleration of problems for them. It can also support the health and life satisfaction of students.*

Introduction

Social capital is a relatively new concept, whose application began to expand in the 1990s in scholarly and academic circles, with the works of scholars such as James Coleman, Robert Putnam, Francis Fukuyama, and Pierre Bourdieu [1]. There are many definitions for this concept. Nahapit and Ghasal (1998) considered social capital as the sum of resources and values that exist within the network of personal and organizational relationships [2]. According to Fukuyama, social capital is a set of norms in social systems that promotes the level of cooperation of members of that society and reduces the costs of exchanges and communications [3]. Vilanova and Josa (2003) considered social capital as a management phenomenon with characteristics such as trust (norms), shared values and behaviors, relationships, cooperation, understanding, mutual commitment, and reciprocal networks [4].
The concept of social capital, which has a sociological root, is a lever of success and a suitable platform for the productivity of humans as well as physical capital and a way to achieve success and improve the performance of the organization [5]. The importance of social capital is that it brings individuals together (groups and organizations) and supports the successful accomplishment of tasks [6] by creating norms and mutual trust. In this way, it can fulfill the goals of the members [1] and enables individuals to engage in collective actions which improve interaction with each other [7]. This concept, as one of the social determinants of health, has been effective in mortality, mental disorders, and stress and has attracted a great deal of attention. In societies with a high social capital, the crime rate is lower, and as it improves, the quality of life of increases [8].
Social capital has an important role in various ways such as facilitating and accelerating the circulation of information and knowledge (whether tacit knowledge and codified knowledge) within the university, facilitating the formation of human capital, reducing costs such as control and monitoring costs, and facilitating access to individuals inside and outside the organization. In this way, the organizational goals can be achieved faster and more smoothly. Meanwhile, educational centers and universities, through education, play an important role in building up social capital and in enhancing social cohesion, participation, and confidence-building. In other words, the university can transfer the capital to cover the ideas, values, norms, and social trust of academics [9]. In relation to social capital and its positive effects on research students, the results of Razavizadeh et al.'s research revealed that the mean of social trust dimensions was 91.56, the average social support dimension was 54.22, and the average dimension of interpersonal relationships in students was 34.95. According to them, these three dimensions of

social capital in interaction of each other were associated with reduction of anxiety and depression, showing a positive and significant effect [10]. Also, the results of the research by Khosravi Shahi et al. indicated that the average social capital of the students was 54.56 and the mean of psychological well-being was 50.24. Further, there was a positive and significant correlation between social capital and psychological well-being of the students [11].

Indeed, social capital governs all the moments of everyday life and can affect the attitude of human beings [12]. It also plays a more important role than physical and human capital in societies, which is the coherence of division between human beings and organizations. Since students are the most important human capital and future resources of the country, when social capital and its dimensions are formed and spread among students, it helps students make extensive efforts for the country's comprehensive development. Identifying the effective factors in strengthening or weakening social capital is therefore important. In this regard, knowledge about their social capital and their relationship with each other is necessary for their social and cultural planning. Considering the importance of social capital in students and its positive effects, the purpose of this research was to study the social capital status of students of Kurdistan University of Medical Sciences and its related factors.

Method

This research is descriptive-analytic (cross-sectional). The statistical population of this study consisted of all students of Kurdistan University of Medical Sciences. The samples were selected using simple random sampling. The optimal sample size was obtained as 364 people using the Cochran formula and with a 5% error. Considering 10% of loss in the sample, a total of 400 individuals were considered as the sample. Further, 378 questionnaires were completed and analyzed. The data were collected using a social capital questionnaire. The questionnaire consisted of two parts of demographic questions (age, sex, grade, college, marital status) and the main questions of the research, ranked through the Likert scale of 5 degrees (score 4) to the opposite (score 0). This questionnaire has four components of trust (Questions 1 to 5), relationships in social networks (questions 6 to 13), community participation (questions 14-21), and group participation (questions 22-27). The content validity of the questionnaire was approved and Delaviz reported the reliability of this questionnaire with Cronbach's alpha 0.85 [13]. SPSS software version 22 was used for data analysis. Specifically, descriptive statistics (mean, standard deviation, frequency) and inferential statistics (Mann-Whitney and Kruskal-Wallis) were applied.

Results

The results of the data analysis revealed that 157 (41.5%) of the subjects were male and 221 (58.5%) were female. The age group of 20-22 years old claimed the largest frequency (40.7%). Also, 345 (91.3%) subjects were single and 25 (8.7%) were married, and 315 people were undergraduate students. The highest frequency of the college was related to Faculty of Paramedical Sciences (37.8%) while the minimum frequency belonged to dental school (4.5%). Further, the highest frequency was in the field of laboratory sciences (10.3%) and the lowest frequency was found in the field of master's courses (3.2%).

Table I presents the possible range, the observed range, as well as mean and the standard deviation of the social capital and its subgroups. The average total score of social capital was 70.56 ± 10.88 out of a total of 108. The highest scores belonged to the subgroup of group participation with a mean score of 16.85 ± 3.52 while the lowest score occurred in the subgroup of participation in local community with a mean score of 18.96 ± 3.90.

The results of the study indicated that there is a significant relationship between the gender of the students and the total score of social capital ($p < 0.016$), where the average total score of social capital of female students was higher than that of male students (Tab. II). Also, the mean scores of trust components, relationships in social networks, and group participation in girls were higher than in boys, but this difference was statistically significant only in the dimension of relationships in social networks ($p < 0.001$). The participation component in the local community was higher in boys than in girls, but this difference was not statistically significant ($p < 0.05$). The results also showed that the total score of social capital and its components was higher in married individuals than in single individuals, and these differences were statistically significant ($p < 0.05$) (Tab. II).

According to the results, the total social capital score of the 25-year-old and older group was the highest among all, but there was no significant difference between the age groups ($p < 0.05$). On the other hand, there was a significant difference only in the component of participation in the local community, among the components of social capital, in the subgroups of the age groups and the score of the age group was 25 and older, above all the total score of social capital and its components in PhD students was higher than other levels of education but there was no significant difference between them (Tab. III).

Based on the results, there was a significant relationship between the college of students' education and the total score of social capital ($p < 0.034$) where the highest social capital score of students was found at the faculty

Tab. I. Ranges, mean and standard deviation of social capital and its components.

Component	Possible range	View range	M ± SD
Trust	0-100	0-100	66.79 ± 15.28
Relationships in social networks	0-100	12.50-100	66.84 ± 13.16
Community participation	0-100	12.50-93.75	59.25 ± 12.19
Group participation	0-100	29.12-99.84	70.12 ± 14.68
Social capital (total score)	0-100	23-89.24	64.92 ± 10.01

of medicine with a mean and standard deviation of 75.26 ± 12.32 while the lowest mean score of social capital belonged to dental school with mean and standard deviation of 68.29 ± 7.58 (Tab. III).

The results of the data analysis showed that there was a significant relationship between the students' academic curriculum and the total score of social capital and its components ($p < 0.05$). Medical students with the mean and standard deviation of 75.96 ± 12.37 had the maximum, while the radiotherapy students with the mean and standard deviation of 65.25 ± 15.44 had the lowest overall score of social capital compared to other students (Tab. IV).

Tab. II. Difference of social capital and its components by gender and marriage.

Mean and standard deviation of social capital and its components																
Variable	**Group**	**Trust**	**p-value**	**95% CI**	**Relationships in social networks**	**p-value**	**95% CI**	**Community participation**	**p-value**	**95% CI**	**Group participation**	**p-value**	**95% CI**	**Social capital (total score)**	**p-value**	**95% CI**
Gender	**Male**	65.82 ± 18.49	0.86	(0.85-0.87)	64.23 ± 14/65	0.001	(0.00-0.001)	59.78 ± 11.30	0.77	(0.77-0.78)	70.72 ± 15.34	0.25	(0.24-0.26)	63.50 ± 11.78	0.01	(0.01-0.01)
	Female	67.48 ± 12.51			68.70 ± 11.67			58.49 ± 13.35			70.92 ± 14.17			65.93 ± 8.41		
Marital status	**Single**	66.69 ± 14.75	0.33	(0.32-0.34)	66.78 ± 12.80	0.99	(0.99-0.99)	59.12 ± 12.30	0.8	(0.79-0.80)	69.83 ± 14.53	0.24	(0.24-0.25)	64.78 ± 9.98	0.05	(0.79-0.81)
	Married	67.87 ± 20.23			67.51 ± 16.64			60.61 ± 11.12			73.11 ± 16.04			66.37 ± 10.34		

Tab. III. Difference of social capital and its components by age groups, educational level and college.

Mean and standard deviation of social capital and its components																
Variable	**Group**	**Trust**	**p-value**	**95% C**	**Relationships in social networks**	**p-value**	**95% CI**	**Community participation**	**p-value**	**95% CI**	**Group participation**	**p-value**	**95% CI**	**Social capital (total score)**	**p-value**	**95% CI**
Age groups	**Under 20**	66.05 ± 13.65	0.44	(0.43-0.45)	68.39 ± 11.34	0.35	(0.34-0.36)	58.36 ± 12.32	0.05	(0.04-0.05)	69.07 ± 15.21	0.81	(0.80-0.82)	64.74 ± 9.03	0.61	(0.60-0.62)
	22-20	66.52 ± 16.69			65.38 ± 14.88			59.37 ± 11.19			70.53 ± 13.77			64.56 ± 10.64		
	25-23	66.96 ± 12.78			67.01 ± 10.80			58.03 ± 11.94			69.68 ± 15.16			64.54 ± 9.41		
	25 and up	68.88 ± 19.38			69.53 ± 15.22			64.40 ± 15.62			71.87 ± 16.32			68.03 ± 10.83		
Educational level	**B.S. student**	66.27 ± 15.59	0.1	(0.102-0.11)	66.50 ± 13.49	0.70	(0.69-0.71)	59.17 ± 11.75	0.85	(0.85-0.86)	69.36 ± 14.84	0.1	(0.09-0.10)	64.53 ± 10.04	0.29	(0.28-0.30)
	M.Sc. student	65.71 ± 1.81			67.41 ± 8.64			59.37 ± 4.58			73.09 ± 11.95			65.58 ± 4.52		
	MD student	70.63 ± 15.02			69.01 ± 11.90			59.70 ± 16.24			47.34 ± 13.67			67.33 ± 10.76		
Faculty	**Medicine**	72.64 ± 14.20	0.11	(0.11-0.12)	70.40 ± 11.36	0.19	(0.18-0.20)	64.15 ± 14.88	0.005	(0.003-0.006)	73.53 ± 14.90	0.27	(0.26-0.28)	69.24 ± 11.34	0.03	(0.032-0.039)
	Dentistry	65.88 ± 14.27			65.80 ± 12.52			51.83 ± 14.28			72.67 ± 11.21			62.83 ± 6.97		
	Nursing & midwifery	68.00 ± 12.69			68.61 ± 9.35			60.44 ± 9.35			66.73 ± 14.96			65.26 ± 7.33		
	Paramedical	65.34 ± 16.86			64.96 ± 14.96			58.26 ± 11.31			70.05 ± 15.26			63.79 ± 10.59		
	Public health	66.27 ± 14.87			67.21 ± 13.14			59.40 ± 13.07			70.90 ± 13.96			65.15 ± 10.40		

Tab. IV. Difference between social capital and its components in terms of academic disciplines.

Mean and standard deviation of social capital and its components																
Academic discipline	**Trust**	**p-value**	**95% CI**	**Relationships in social networks**	**p-value**	**95% CI**	**Community participation**	**p-value**	**95% CI**	**Group participation**	**p-value**	**95% CI**	**Social capital (total score)**	**p-value**	**95% CI**
Nursing	71.40 ± 12.78	0.02	(0.02-0.02)	68.00 ± 9.47	0.02	(0.02-0.02)	57.12 ± 10.95	0.002	(0.001-0.003)	69.72 ± 9.85	0.04	(0.03-0.04)	65.39 ± 6.47	0.01	(0.008-0.01)
Medicine	73.12 ± 14.52			71.28 ± 11.12			64.45 ± 15.30			74.49 ± 14.84			69.89 ± 11.38		
Dentistry	65.88 ± 14.27			65.80 ± 12.52			51.83 ± 14.28			72.67 ± 11.21			62.83 ± 6.97		
Medical emergency	66.04 ± 21.86			72.39 ± 14.47			66.92 ± 14.18			69.85 ± 17.08			68.61 ± 11.98		
Laboratory sciences	68.97 ± 11.81			65.38 ± 12.42			56.08 ± 10.94			69.44 ± 15.12			63.81 ± 8.79		
Public health	65.39 ± 10.74			64.63 ± 12.75			59.45 ± 11.83			67.76 ± 13.46			63.55 ± 7.78		
Occupational health	64.58 ± 18.83			66.05 ± 14.13			56.85 ± 15.04			70.37 ± 16.35			63.63 ± 12.84		
Environmental health	69.26 ± 15.42			70.68 ± 12.78			62.22 ± 13.08			74.75 ± 11.92			68.40 ± 10.35		
Midwifery	65.60 ± 12.60			69.25 ± 12.68			64.12 ± 10.32			70.88 ± 17.29			67.01 ± 8.72		
Anesthesia	60.22 ± 15.31			63.21 ± 9.97			57.24 ± 8.14			70.72 ± 14.35			62.18 ± 7.73		
Surgical technology	67.14 ± 12.20			69.04 ± 2.18			59.37 ± 2.61			58.43 ± 13.88			63.08 ± 5.91		
Radiology	70.02 ± 4.20			68.22 ± 8.18			59.37 ± 8.90			70.02 ± 12.45			65.93 ± 4.46		
Radiotherapy	61.42 ± 22.18			58.75 ± 20.82			55.35 ± 10.54			68.46 ± 16.61			60.03 ± 14.21		
M.Sc. field	65.00 ± 3.21			65.62 ± 7.99			57.81 ± 2.49			74.88 ± 12.03			64.86 ± 4.49		

Discussion

The results of the study indicated that the average total score of social capital was 70.56 ± 10.88. The average of students' social capital was higher than moderate. This result was in line with the findings of the other studies [11, 14, 15]. Further, the highest score was found in the subgroup of group participation with a mean score of 16.85 ± 3.52 while the lowest score occurred in the subgroup of participation in the local community with an average score of 18.96 ± 3.90. In explaining the high level of social capital of students, some reasons can be mentioned such as ethnic and religious commonalities, speaking in mother tongue, and intergroup communication [16]. As evidence, most of the students of this university were Kurdish and had ethnic and religious commonalities. Indeed, students of Kurdistan University of Medical Sciences have a greater willingness to participate in social and group activities and have a great deal of trust in other people because of the characteristics mentioned.

The results also indicated a significant relationship between the gender of the students and the total score of social capital ($p < 0.016$). The average total score of social capital of female students was higher than that of male students, which is consistent with the results of studies by Sam Aram et al., Bagheri Yazdi, Gharibi et al., Muradyan Sarykhlyla, and Onyx and Boolen [17-21].

Further, the mean score of trust components, social networking relationships and group participation in girls was higher than that of boys, but this difference was statistically significant only in the dimension of relationships in social networks ($p < 0.001$). This finding was in line with the findings of Sa'idi, Hasanzadeh and Gharibi et al. [19, 22]. On the other hand, the participation component in the local community was significantly higher in boys than in girls, but this difference was not statistically significant ($p < 0.05$). This was consistent with the study of Gharibi and colleagues [19]. In explaining this finding, it can be stated that this situation is in part attributed to the socio-educational background of women and men in our society.

In addition, sociocultural factors may affect this finding. In explaining the high level of confidence in girls, women can be more confident as they have a personality trait making them more likely trust institutional trust compared to men.

The results also showed that the total score of social capital and its components was higher in married individuals than in single subjects ($p < 0.05$). This was in line with the study of Steel, Gribi et al. as well as Onyx and Bullen [14, 19, 22]. In explaining this finding, it can be said that marriage increases the range of interactions and participation in relationships and interpersonal, group, family, and social relationships, thereby increasing the ability of individuals in terms of social capital. Also, the association between married people and family as well as spouse's families and expansion of the scope of family-group interactions has increased the awareness of their emotions and their abilities. Further, due to the marital needs and community expectations of new roles, their trust and their formal participation also improve.

The results of data analysis indicated that there was a significant relationship between the students' academic curriculum and the total score of social capital and its components ($p < 0.05$).

In general, medical and nursing students had a higher degree of trust in social capital than in other fields. In explaining this finding, it can be said that since most medical and nursing students are in the educational-cultural environment and more than other students involved in human relationships with patients, they also feel that their interpersonal and social skills and abilities may be affected by these professional conditions. Finally, the results of this study showed no significant relationship between age or educational variables and social capital ($p < 0.05$).

Conclusions

The results of this study suggested that the average social capital of students was above average and the demographic factors of gender, marriage, and field of study were associated with social capital. Since social capital is the most powerful coping force for successful and easy confrontation at times of conflict with well-known challenging situations, it facilitates the management of problems. Further, given the importance of social health for students, social capital as a an important factor can support life satisfaction.

Studies have shown that the higher the social capital is, the lower the risk of alcohol, cigarettes, drugs, and sexual risk-taking will be [18]. So, it is important to recognize the factors that affect it. Therefore, it is recommended that this study be conducted in different cities and geographic areas. It can also be conducted in other ways such as interview or direct observation. Also, since social-communicative capabilities in the present age, including the need for strong social interaction and trust and security in human relationships, are essential, it is suggested that social abilities and adaptations be taught at different levels of family- social and educational background. This can be an important step in promoting the level of human relations and increasing social capital.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

Study design: ZR, GHK and AL. Data collection: MA. Data analysis: MM and AL. Study supervision: AV and AL. Manuscript writing and revisions: ZR, GHK and AV.

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ORIGINAL ARTICLE

Sun-safe behaviours, personal risk, level of concern, and knowledge about cutaneous melanoma in italy: time for social marketing?

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Keywords

Cutaneous melanoma • Prevention • Risk • Concern • Protective Behaviour • Knowledge • Social marketing

Summary

Introduction. *The incidence of cutaneous melanoma is increasing, although 80-95% of all deaths caused by melanoma can be avoided through protective behaviours. There is evidence that social marketing as an approach in public health can improve health-related behaviours and encourage sun-safe behaviours.*

Methods. *A multicentre survey was conducted to collect and compare data about cutaneous melanoma risk, knowledge, concern, and protective behaviours across Northern, Central, and Southern Italy, and explore how these data could potentially inform a social marketing intervention to improve sun-safe behaviours. Data were analysed using descriptive and inferential statistics.*

Results. *A total of 1,028 questionnaires were collected. Apart from 'Personal Risk' no statistically significant differences were found between the three regions. About 30% (n = 344) of the total sample had high levels of personal risk, and low levels of concern and protective behaviour, and over 70% (n = 711) gave priority to sun tanning. The worst scores were related to knowledge about melanoma (30% wrong answers, and over 40% 'don't know'). Protective behaviour was moderately correlated with age (p = 0.03). Personal risk was significantly higher in women (10.84 vs 10.05), and lower in individuals with a degree (9.46 vs 11.38; p < 0.001).*

Conclusions. *Over 70% of our sample gave priority to sun tanning, which combined with low levels of concern and knowledge about melanoma, and high levels of personal risk, confirm that much still needs to be done in terms of melanoma prevention, but all these are aspects that could be effectively addressed through social marketing interventions.*

Introduction

In the world, approximately 60,700 people die each year due to cutaneous melanoma, with a global incidence of 3.1% for a total of 287,723 cases [1]. In Europe, over 27,000 people die each year due to cutaneous melanoma, with an incidence of 3.4% for a total of 144,209 new cases in 2018 [1]. In Italy, in the last 20 years, the incidence of melanoma has increased by over 4% a year [2]. Currently, the incidence of melanoma in Italy is 3.0% for a total of 12,299 new cases in 2018, and a 5-year prevalence rate of 42,220 cases [1]. According to Globocan 2018, around 2,300 (1.3%) Italians die each year, and this rate is still increasing [1, 2].

Over 70% of the adults prefer to tan when on holiday, but Italians' average summer holidays have significantly reduced since 2000 [3]. According to the Italian National Statistics Institute the average length of stay in holiday resorts has gone down from 4.2 nights in 2000, to 3.4 nights in 2015 [4]. Therefore, given that there is evidence that Italian young people value a tanned look this could result in them trying to tan in a shorter time increasing the risk of sunburn [5, 6] and subsequently increase the risk of cutaneous melanoma [7, 8].

Cutaneous melanoma is the most aggressive of all skin tumours [5, 7] but also one of the most preventable cancers [9]. Studies in both Europe and the United States have shown that the use of sunscreen reduces the incidence of Melanoma by up to 34-38% [10, 11]. Given this evidence, it is important to implement appropriate preventive measures on a continued basis, and an effective solution could be offered by social marketing [12-15]. In addition, to be truly effective, interventions need to be adapted to the knowledge, beliefs and attitudes of the population and explore how these influence the motivation to adopt preventive behaviours [16, 17]. Furthermore, given Italy's geography that presents a long north to south peninsular it may be that this geographical status (and subsequent variations in climate) has an effect on sun exposure behaviour and knowledge. This geographical element has not been studied before in any nationally based surveys, thus we decided to build this aspect into our study.

The theoretical framework

The Health Belief Model (HBM) is a psychological model that attempts to explain and predict health behaviours [18-20] and is used to study problems related

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to compliance and preventive behaviours. 'Belief' plays an important role in moulding healthcare and lifestyle behaviours [19]. Knowing individuals' opinion about health problems, how they perceive facilitators and barriers to action, and their level of self-efficacy, enables to understand why health promoting behaviours are adopted.

The HBM defines the key factors that influence health behaviours, as an individual's perceived threat to disease (perceived susceptibility), belief of consequence (perceived severity), potential positive effects of action (perceived benefits), perceived barriers to action, exposure to factors that prompt action (cues to action), and confidence in the ability to succeed (self-efficacy) [20]. These perceptions are influenced by "Modifying Variables", such as age, gender, psychosocial factors, knowledge and experience about the disease [21]. Modifying variables also influence the perception of self-efficacy, which is the belief in one's ability to implement a certain type of behaviour [16, 17]. Finally, the HBM requires 'Cues to Action' to trigger the adoption of preventive behaviours. Cues to Action can either be internal (i.e. symptoms, concerns, wishes, etc.) or external (i.e. advertisement, influence by significant people etc.).

On the basis of the key factors of the Health Belief Model, in the present study we selected the following tool "A Questionnaire to measure melanoma risk, knowledge and protective behaviour" developed and validated by Gillespie et al. 2011 [22] between 2008 and 2010. Thanks to the compatibility of the questionnaire with the HBM, it was possible to incorporate the key results into a conceptual framework.

Social marketing

Social marketing has been defined as "the systematic application of marketing, alongside other concepts and techniques, to achieve specific behavioural goals, for a social good" [23]. Governments and health organisations regularly utilise social marketing strategies to convey health messages. Social marketing interventions generally aim to ensure that the target audience adopts the behaviour being promoted [24]. Social marketing techniques have been used successfully in public health interventions [25]. In particular social marketing has been used effectively in tackling sun safe health related behaviour change in Australia where a number of studies have highlighted the effectiveness of the use of social marketing in promoting sun-safe behaviours [26, 27].

For social marketing research and practice, HBM is a significant theoretical model when addressing issues for "at risk" populations who may not perceive themselves as such. HBM has been widely used in the application of social marketing in challenging a range of health-related behaviour change interventions. This paper provides a rationale for combining HBM with a social marketing framework to demonstrate the potential for social marketing intervention(s) to promote sun-safe behaviours.

The research hypothesis

Given the close link between melanoma and sunbathing behaviours and also considering that Italy has an extension of 1291 kilometres, we explored if there were any significant differences or features in the level of melanoma risk, concern, protective behaviour, and knowledge between Northern, Central and Southern Italy.

Aims

The objectives of this study were to:

1. validate the Italian version of the tool 'A Questionnaire to measure melanoma risk, knowledge and protective behaviour' by Gillespie et al. 2011 [22];
2. collect and compare data on melanoma risk, knowledge, concern, and protective behaviours between Northern, Central, and Southern Italy;
3. explore the potential for social marketing intervention to improve sun-safe behaviours in Italy.

Methods

The study design

This is a multicentre observational questionnaire-based survey study with the aim of surveying melanoma knowledge, behaviour and risk awareness using the Italian version of the "Questionnaire to measure melanoma risk, knowledge and protective behaviour" [22].

Translation and validation of the tool

Tool characteristics

"A Questionnaire to measure melanoma risk, knowledge and protective behaviour: Assessing content validity in a convenience sample of Scots and Australians" by Gillespie et al. [22] was selected for our study because it best reflected the theoretical framework of our study. The questionnaire consists of four items about personal data; three items on previous melanoma diagnosis; and 39 questions across four domains: Personal risk; Level of Concern; Protective Behaviour; and Knowledge about Melanoma. This latter domain, 'Knowledge about Melanoma', differed from the other domains because it contains questions regarding the factors that increase the risk of developing a melanoma, to which the responses were either correct or wrong. Respondents could also reply "I don't know", if they were not sure.

With regard to the calculation of the score, full details are provided in Gillespie et al. [22] who developed the original tool. The scores for each response were based on relative effect sizes from epidemiological meta-analyses [8, 28-33]. However, to provide an example, for each question respondents had to select an answer from a range of options. The number of options varied according to the type of question, and each option was associated with a score that reflected for instance the level of risk in the domain "Personal risk" [e.g. What happens to your skin in the sun? Never tans (score: 6); Tans with difficulty (score: 4); Tans easily (score: 2); Tans always (score: 0)]. Sometimes, the score a of response is below zero, like the following

question in the Domain "Protective Behaviour" [e.g. If you use a sun lamp, how often do you use it? Very infrequently (0); 1-3 times a year (-1); monthly (-2); weekly or more (-3)]. Then the overall scores for all the questions within each domain were summed up.
The four domains reflect the constructs of the Health Belief Model: the perception of risk, the perception of the seriousness of the disease, the perception of protective behaviours, and the perception of the factors that hinder protective behaviours. The above perceptions are influenced by personal characteristics (modifying variables) and by psychosocial variables, awareness and experience linked to melanomas.

Translation accuracy and face validity

To ensure consistency between the English original version and the Italian translation, we adopted the back-translation method. Two expert native Italian translators separately conducted the English-Italian forward translation. The two Italian versions were compared, and any differences were resolved following a discussion with the research team. The resulting Italian version was then translated back into English by a third translator. To check the face validity and clarity of the Italian version, in May 2013 it was piloted on 100 people in the waiting rooms of a dermatological hospital in Rome. We initially intended to pilot it on a sample of maximum 30 people, but while we were conducting the pilot study in the waiting rooms, more people than we needed asked us if they could also complete the questionnaire. The results of these 100 persons were not included in the results shown in the manuscript, because the purpose of the pilot was to ensure face validity.

Data collection

Sample and setting

Between June 2013 and January 2017, the questionnaire was administered to a general adult population in the waiting rooms of two dermatology outpatients' clinics, one in Genoa and one in Messina. In Rome, the questionnaire was administered to the general public, in the main streets of the city. Here respondents were asked to invite friends and relatives (snowball methodology). This enabled us to compare the sample of the dermatology clinics with that of the general public. In both cases, to ensure the highest possible level of representativeness of the characteristics of the general population, the only inclusion criterion was that respondents had to be adults aged ≥ 18 years. With regard to the sample size, we referred to the one chosen for the validation of the original questionnaire (n = 540) by Gillespie et al. [22]. According to the Health Belief Model, the independent variables of our study include age, gender, psychosocial factors (job, education, family member with melanoma or knowing someone with a melanoma), knowledge about melanoma, and direct experience of melanoma. Age was treated as a continuous variable. Gender, psychosocial factors and experience of melanoma were treated as nominal variables and knowledge of melanoma variables were used to create a total score for knowledge about melanoma and this was treated as a continuous variable.

Consent and confidentiality

Patients completed the questionnaires exclusively on a voluntary basis. To ensure anonymity, we did not collect the patients' names, addresses and dates of birth. All those who completed the questionnaire gave their consent.

Statistical analysis

The data from the paper questionnaires were manually coded and then entered into a Microsoft Excel database. Then all the data were exported into STATA SE13 software for statistical analysis. Data were analysed using a range of descriptive statistics (mean scores, standard deviations, minimum and maximum ranges, quartiles and 95% confidence intervals) and inferential statistics to examine relationships among variables and questionnaire domains (Cronbach's alpha, Spearman's correlation, t-test ANOVA and Chi Square tests).

Ethical approval and permissions

This study was approved by the Ethics Committee of the University of Genoa. Permission to collect data from patients in the waiting rooms was obtained from the two dermatology centres.

Results

Sample size and characteristics

We collected a total of 1028 questionnaires, of which 465 in Northern Italy (Genoa), 324 in Central Italy (Rome), and 239 in Southern Italy (Messina). Our total sample consisted of 415 males (40.3%) and 613 females (59.7%) for a total of 1028 individuals, and a mean age of almost 44 years. With regard to education, 167 (16.8%) had a secondary school certificate; 430 (43.4%) had a high school diploma; and 354 (35.7%) had a degree. With regard to occupation, 229 (25.8%) worked in an office, 118 (13.3%) had an intellectual/scientific profession, 71 (8%) were unskilled workers, 51 (5.7%) were unemployed, 19 (2.1%) were artisans or farmers, 84 (9.5%) were students, and 103 (11.6%) were retired. Of the total sample, 44 (4.3%) declared that they had a previous diagnosis of melanoma; 114 (11.2%) declared that they had a member in their family with a melanoma; and 373 (37.9%) declared that they knew someone apart from their family who had a melanoma (Tab. I).

Translation accuracy, face validity and reliability

The same questions were asked to everyone and at the end of this piloting phase only very few amendments were made to the questionnaire, such as the term "Caucasian", which was substituted with "having a white skin". This was necessary to ensure more clarity because many respondents misunderstood the meaning of this term. Consequently, to resolve this issue fully we changed also the respective question "What is your ethnic origin?" into: "What is the colour of your skin?" Considering the total sample of 1028 questionnaires, Cronbach's alpha was equal to 0.63 (range between < 0.5

Tab. I. Sample characteristics.

	Genoa	Rome	Messina	Total
Total sample distribution	465	324	239	1,028
Mean age				
Years (standard deviation)	45.1 (± 16.5)	42.0 (± 14.3)	44.6 (± 18.1)	43.9 (± 16.3)
	N (%)	**N (%)**	**N (%)**	**N (%)**
Gender				
Male	191 (41.1)	142 (43.8)	82 (34.3)	415 (40.3)
Female	274 (58.9)	182 (56.2)	157 (64.6)	613 (59.7)
Education				
Elementary	17 (3.7)	14 (4.5)	8 (3.5)	39 (3.9)
Secondary school	60 (13.2)	48 (15.4)	59 (26.1)	167 (16.8)
High school	224 (49.2)	105 (33.8)	101 (44.7)	430 (43.4)
Degree	153 (33.6)	144 (46.3)	57 (23.5)	354 (35.7)
None	1 (0.2)	-	1 (0.4)	2 (0.2)
Occupation				
Manager executives	15 (3.5)	9 (3.7)	13 (6.0)	37 (4.2)
Intellectual/scientific job	52 (12.1)	44 (18.2)	22 (10.1)	118 (13.3)
Technician	6 (1.4)	14 (5.8)	-	20 (2.3)
Office job	106 (24.8)	96 (39.7)	27 (12.4)	229 (25.8)
Commercial & service	26 (6.1)	26 (10.7)	6 (2.8)	58 (6.5)
Artisan & farmer	9 (2.1)	8 (3.3)	2 (0.9)	19 (2.1)
Driver	6 (1.4)	3 (1.2)	-	9 (1.0)
Unskilled worker	37 (8.6)	24 (9.9)	10 (4.6)	71 (8.0)
Army/police	10 (2.3)	10 (4.1)	1 (0.5)	21 (2.4)
Student	44 (10.3)	7 (2.9)	33 (15.1)	84 (9.5)
Unemployed	19 (4.4)	-	32 (14.7)	51 (5.7)
Housewife	31 (7.2)	1 (0.3)	36 (16.5)	68 (7.6)
Retired	67 (15.7)	-	36 (16.5)	103 (11.6)
Have you ever had a melanoma diagnosed in the past?				
No	411 (89.3)	311 (95.4)	221 (93.2)	943 (92.2)
Don't know	25 (5.4)	6 (1.8)	5 (2.1)	36 (3.5)
Yes	24 (5.2)	9 (2.8)	11 (4.6)	44 (4.3)
In your family, has anyone had a melanoma?				
No	341 (74.5)	258 (79.9)	191 (80.6)	790 (77.6)
Don't know	66 (14.4)	22 (6.8)	26 (11.0)	114 (11.2)
Yes	51 (11.1)	43 (13.3)	20 (8.4)	114 (11.2)
Apart from your family, do you know anyone who has had a melanoma?				
No	229 (49.9)	167 (51.5)	123 (52.3)	519 (52.7)
Don't know	62 (13.5)	28 (8.6)	36 (15.3)	92 (9.4)
Yes	168 (36.6)	129 (39.8)	76 (32.3)	373 (37.9)

and ≥ 0.9); therefore, the internal consistency of the questionnaire was acceptable [34].

Spearman's correlation between the four domains of the questionnaire in the total sample: "Personal Risk"; "Level of Concern"; "Protective Behaviour"; and "Knowledge about Melanoma" was low but positive, and significant correlations were found between: "Personal Risk" and "Knowledge about Melanoma" (Rho = 0.1328, $p < 0.001$); "Level of Concern" and "Protective Behaviour" (Rho = 0.2800, $p < 0.001$); "Level of Concern" and "Knowledge about Melanoma" (Rho = 0.1903, $p < 0.001$); and "Knowledge about Melanoma" and "Protective Behaviour" (Rho = 0.2180, $p < 0.001$).

Independent variables

The relationships between the independent variables and the domains of the questionnaire were as follows:

- *age*: only "Protective behaviour" showed a moderate correlation with age ($r = 0.259$ and $p = 0.03$);
- *gender*: only "Personal Risk" was found to be significantly higher in women (10.84 vs 10.05), whereas "Melanoma Knowledge" was higher in men (3.46 vs 2.97);
- *education*: there was a significant difference between those who have a degree and those with secondary education (9.46 vs 11.38; $p < 0.001$) only for "Personal Risk";
- *occupation*: no significant differences were found;
- *family member with melanoma* or *knowing someone with a melanom*a: no statistically significant differences were found for these variables.

Total mean differences between Northern, Central and Southern Italy

We did not find any statistically significant differences between Northern (Genoa), Central (Rome), and Southern Italy (Messina) on the total score of the questionnaire. However, there were some statistically significant differences between cities on specific domains.

For "Personal Risk" domain (score range from -2 to 22) the global mean score was 10.5. Genoa obtained the highest mean score (11.1), followed by Rome (10.3), and

Messina (9.5) and the score on this domain was statistically significantly lower for Messina than the other two cities. On the domain of 'Melanoma Knowledge' (score range from -6 to 20) the global mean score was 3.1. Rome obtained the highest mean score (3.6), followed by Messina (2.91), and Genoa (2.9) and the score for Rome was statistically significantly higher for Rome than Genoa.

Descriptive results

Domain 1: "Personal Risk"

Although there were no statistically significant differences between North, Central, and Southern Italy. However, some noteworthy facts emerged from our data.

In the domain of 'Personal Risk' (Tab. II) the main differences between the three regions involved two items: '*How many moles do you have?*' and '*Do you have large moles with an irregular edge and/or colour?*' In the first case, 8.1% of the respondents from Genoa replied 'none' compared to 26.9% from Messina. In the second case, 13.9% of the respondents from Rome replied 'don't know' compared to 40.6% from Messina. Interestingly, over 36% of the total sample never tanned or tanned with difficulty, approximately the same percentage (35.2%) had freckles, and almost 48% had more than 20 moles. Another interesting fact was that about one-third of the total population had experienced a bad sunburn for more than three times, and that 27% of the total sample did not know if they had large moles with an irregular

Tab. II. A comparison between Northern (Genoa), Central (Rome), and Southern (Messina) Italy with regard to the number of responses given to the items in the Domain of "Personal Risk".

Domain 1 "Personal Risk"	Response items	Genoa % (n)	Rome % (n)	Messina % (n)	Total % (n)
1. What happens to your skin in the sun?	Never tans, always burns	11.7% (54)	7.4% (24)	14.2% (34)	10.9% (112)
	Tans with difficulty	25.6% (119)	29.4% (96)	21.3% (51)	25.9% (266)
	Tans easily	56.8% (262)	52.5% (171)	52.5% (126)	54.4% (559)
	Tans and never burns	5.6% (26)	10.7% (35)	12.1% (29)	8.8% (29)
2. Does your skin have freckles?	Yes	40.6% (185)	33.1% (107)	27.9% (67)	35.2% (359)
	No	59.4% (271)	66.3% (214)	72.1% (173)	66.6% (658)
3. How many moles do you have?	None	8.1% (36)	10.3% (33)	26.9% (61)	13.1% (130)
	Less than 20	34.8% (162)	43.9% (140)	37.0% (84)	39.0% (386)
	More than 20	55.3% (245)	45.8% (146)	36.1% (82)	47.8% (473)
4. Do you have large moles with an irregular edge and/or colour?	Yes	29.0% (131)	13.6% (44)	25.0% (57)	23.1% (232)
	No	30.5% (138)	72.5% (235)	56.1% (128)	49.9% (501)
	Don't know	40.5% (183)	13.9% (45)	18.9% (43)	27.0% (271)
5. What is your natural hair colour?	Black/brown	85.5% (396)	84.0% (273)	89.0% (211)	85.9% (880)
	Blond	11.0% (51)	12.9% (42)	9.7% (23)	11.3% (116)
	Red	3.5% (16)	3.1% (10)	1.3% (3)	2.8% (29)
6. What is the colour of your skin?	White	66.3% (305)	64.0% (210)	70.1% (169)	66.7% (684)
	Brown/yellow	32.9% (151)	33.9% (110)	29.0% (70)	32.3% (331)
	Black	0.9% (4)	1.2% (4)	0.8% (2)	1.0% (10)
7. How many times in your life have you had a bad sunburn?	Never	19.9% (92)	16.9% (55)	30.5% (73)	21.4% (220)
	Once or twice	44.7% (207)	45.7% (149)	44.4% (106)	44.9% (462)
	3 or more	35.4% (164)	37.4% (122)	25.1% (60)	33.7% (346)

edge and/or colour, and therefore do not check their moles. This confirms that 27% of our total sample (n = 271) are at risk and do not check their moles.

Domain 2: "Level of Concern"

The responses given to the items in the Domain of "Level of Concern" did not vary much across the three regions, despite Rome included the general public and Genoa and Messina included people sitting in the waiting rooms of dermatology clinics. However, the samples from Genoa and Messina were approximately 15% more likely to check their skin for moles than the Rome sample. In addition, over 80% (n = 831) of the total sample had not consulted a physician in the past 6 months to have their moles checked, and over 34% (n = 351) declared that they would unlikely see a physician in the next 6 months (Tab. III).

Domain 3: "Protective Behaviour"

The level "Protective Behaviour" did not vary significantly between Rome and the other two regions. Over 17.1% (n = 79) of the sample in the North used sunlamps and over 27% (n = 62) in the South did not protect their skin from the sun. In all the regions, very few people used protective clothing (3.2%), stayed in the shade (2.7%), and avoided sun during the warmest hours of the day (0.6%). Finally, about one third of the total population (n = 335) would seek medical advice 'When possible' if they noticed a new mole (Tab. IV).

Domain 4: "Knowledge about Melanoma"

Unlike the previous three domains, this domain on "Knowledge about Melanoma" were asked to reply 'yes' or 'no' to each question, but only one answer was correct (Tab. V). Respondents also had the option to reply 'Don't know' if they were not sure. Obviously, respondents were not aware which one was correct.

Over 40% replied 'don't know' in 11 of the 18 items. Interestingly, the Rome general public sample scored better (3.6) than Messina (2.91), and Genoa (2.9). Therefore, being a dermatology patient does not necessarily entail higher levels of melanoma knowledge.

In addition, two-thirds of our sample did not know that 'Having blue eyes', 'fair hair', and 'red hair', were risk factors for the development of melanoma. With regard to 'Getting sunburned' and 'Prolonged exposure to the sun', respectively 15.1% (n = 154) and 16.9% (n = 170) gave the wrong answer or 'did not know' their risky nature.

Regarding misconceptions about melanoma, 36.4% (n = 359) replied that it can be completely prevented and 44.3% (n = 437) did not know; 29.8% (n = 289) did not know if it could heal without treatment; and, 32.8% (n = 324) did not know that it would lead to death if not treated. (Tab. V)

Discussion

No statistically significant differences were found between Northern, Central and Southern Italy. However, the mean scores showed that there was a moderate level of "Personal Risk" (means score = 10.5; range from -2 to 22), a moderate "Level of Concern" (mean score 4.8; range from 1 to 10), a sufficient level of "Protective Behaviour" (mean score = 6.8; range from 3 to 12), and a poor level of "Melanoma Knowledge" (mean score = 3.1; range

Tab. III. A comparison between Northern (Genoa), Central (Rome), and Southern (Messina) Italy with regard to the number of responses given to the items in the Domain of "Level of Concern".

Domain 2 "Level of concern"	Response items	Genoa % (n)	Rome % (n)	Messina % (n)	Total % (n)
Have you consulted your GP about any moles or skin blemishes in the past 6 months?	Yes	12.7% (59)	24.2% (79)	26.0% (63)	19.5% (201)
	No	87.3% (405)	75.8% (247)	74.0% (179)	80.5% (831)
How likely are you to see your GP about any moles or skin blemishes in the next 6 months?	Very likely	18.1% (83)	20.3% (66)	22.3% (53)	19.8% (202)
	Likely	38.9% (178)	23.7% (77)	29.8% (71)	31.9% (326)
	Not likely	32.5% (149)	38.2% (124)	32.8% (78)	34.4% (351)
	Very unlikely	10.5% (48)	17.8% (58)	15.1% (36)	13.9% (142)
Do you check your skin for moles?	Yes	73.9% (342)	60.3% (196)	76.3% (184)	70.2% (722)
	No	26.1% (121)	39.7% (129)	23.7% (57)	29.8% (307)
If yes, how often?	More than once a month	20.3% (71)	16.3% (33)	28.0% (51)	21.1% (155)
	Once a month	27.4% (96)	25.7% (52)	23.1% (42)	25.9% (190)
	Once or twice a year	52.3% (183)	57.9% (117)	48.9% (89)	53.9% (389)

Tab. IV. "Protective Behaviour": a comparison between Northern (Genoa), Central (Rome), and Southern (Messina) Italy with regard to the number of responses given to the items in the Domain of "Protective Behaviour".

Domain 3 "Protective Behaviour"	Response items	Genoa % (n)	Rome % (n)	Messina % (n)	TOTAL % (n)
Do you try to get a suntan when at home or on holiday?	Yes	74.3% (338)	66.5% (216)	67.4% (157)	70.2% (711)
	No	25.7% (117)	33.5% (109)	32.6% (76)	29.8% (302)
Do you use a sunlamp (tanning bed)?	Yes	17.1% (79)	9.9% (32)	9.4% (22)	13.1% (133)
	No	82.9% (382)	90.1% (291)	90.6% (213)	86.9% (886)
If yes, how frequently do you use the sunlamp (tanning bed)?	Rarely	56.4% (44)	52.4% (22)	96.0% (24)	62.1% (90)
	1-3 times a year	35.9% (28)	28.6% (12)	4.0% (1)	28.3% (41)
	Monthly	5.1% (4)	16.7% (7)	0% (0)	7.6% (11)
	Weekly or more often	2.6% (2)	2.4% (1)	0% (0)	2.1% (3)
Do you try to protect your skin when at home or on holiday?	Yes,	84.8% (392)	77.6% (249)	72.9% (167)	79.8% (808)
	No	15.2% (70)	22.4% (72)	27.1% (62)	20.2% (204)
If yes, how?	Sunscreen	70.8% (363)	67.7% (221)	56.3% (136)	70.5% (720)
	Protective clothing	2.9% (14)	4.3% (14)	1.6% (4)	3.2% (32)
	Stay in the shade	2.2% (11)	2.4% (8)	3.6% (8)	2.7% (27)
	Avoid sun at its peak	1.0% (5)	0% (0)	0.4% (1)	0.6% (6)
In the last 5 years, how many times have you taken a holiday in a sunny location?	Never	9.0% (41)	6.1% (20)	22.7% (51)	11.1% (112)
	1-2 times	21.6% (98)	14.4% (47)	18.7% (42)	18.6% (187)
	3-4 times	24.7% (112)	24.2% (79)	11.6% (26)	21.6% (217)
	5 or more times	44.7% (203)	55.2% (180)	47.1% (106)	48.7% (489)
If you noticed a new mole, what would you do?	Visit your GP	46.7% (210)	54.7% (175)	60.9% (134)	52.4% (519)
	Ask partner or a friend to look at it	22.9% (103)	17.5% (56)	15.0% (33)	19.4% (192)
	Ignore it	30.4% (137)	27.8% (89)	24.1% (53)	28.2% (279)
How soon would you seek medical advice if you noticed a new mole?	Within 1 month	39.2% (177)	42.2% (137)	52.9% (118)	43.2% (432)
	Within 2 months	4.7% (21)	8.6% (28)	6.7% (15)	6.4% (64)
	Within 3 months	16.9% (76)	16.3% (53)	9.9% (22)	15.1% (151)
	When possible	37.3% (168)	31.7% (103)	28.7% (64)	33.5% (335)
	Never	2.0% (9)	1.2% (4)	1.8% (4)	1.7% (17)

from -6 to 20) throughout Italy, where Rome obtained the highest mean score (3.60), followed by Messina (2.91), and Genoa (2.90) thus confirming the results of similar studies [35, 36]. Moreover, these results highlighted the need for a wide-scale intervention based on social marketing [9, 10]). Therefore, we decided to apply the key findings of the present study to the HBM. The resulting model of health beliefs of Italians about sun safety was then incorporated into a conceptual framework linking the perceptions and health opinions with social marketing

Tab. V. The comparison between Genoa, Rome and Messina in Domain 4: "Knowledge about Melanoma".

Domain 4 "Knowledge about Melanoma"	Response Items	Genoa % (n)	Rome % (n)	Messina % (n)	Total % (n)
Which of the following 12 factors increase the risk of developing a melanoma?					
a) Having a lot of moles	**Yes (correct)**	48.8% (225)	56.1% (183)	58.4% (128)	53.3% (536)
	No (wrong)	18.9% (87)	15.6% (51)	17.4% (38)	17.5% (176)
	Don't know	32.3% (149)	28.2% (92)	24.2% (53)	29.2% (294)
b) A particular diet	Yes (wrong)	4.6% (21)	8.3% (27)	11.5% (24)	7.2% (72)
	No (correct)	50.8% (223)	54.9% (179)	52.6% (110)	52.5% (522)
	Don't know	44.7% (205)	36.8% (120)	35.9% (75)	40.2% (400)
c) A fair complexion	**Yes (correct)**	68.1% (314)	74.2% (242)	71.2% (153)	70.8% (709)
	No (wrong)	8.0% (37)	6.4% (21)	9.8% (21)	7.9% (79)
	Don't know	23.9% (110)	19.3% (63)	19.1% (41)	21.4% (214)
d) Drinking alcohol regularly	Yes (wrong)	8.1% (37)	11.3% (37)	13.0% (27)	10.2% (101)
	No (correct)	36.8% (169)	45.4% (93)	44.7% (93)	41.3% (410)
	Don't know	55.1% (253)	43.3% (141)	42.3% (88)	48.5% (482)
e) Getting sunburned	**Yes (correct)**	82.1% (380)	88.0% (286)	85.8% (194)	84.8% (860)
	No (wrong)	3.2% (15)	2.8% (9)	6.2% (14)	3.7% (38)
	Don't know	14.7% (68)	9.2% (30)	8.0% (18)	11.4% (116)
f) Prolonged exposure to the sun	**Yes (correct)**	79.4% (365)	87.4% (284)	85.4% (187)	83.1% (836)
	No (wrong)	5.4% (25)	3.1% (10)	5.9% (13)	4.8% (48)
	Don't know	15.6% (72)	9.5% (31)	8.7% (19)	12.1% (122)
g) Smoking	Yes (wrong)	22.7% (105)	28.2% (92)	34.0% (73)	26.9% (270)
	No (correct)	22.3% (103)	28.8% (94)	28.8% (62)	25.8% (259)
	Don't know	55.0% (254)	42.9% (140)	37.2% (80)	47.3% (474)
h) Having blue eyes	**Yes (correct)**	16.7% (77)	17.8% (58)	10.0% (21)	15.7% (156)
	No (wrong)	36.1% (166)	40.9% (133)	50.7% (107)	40.8% (406)
	Don't know	47.2% (217)	41.2% (134)	39.3% (83)	43.6% (434)
i) Having green eyes	Yes (wrong)	11.7% (54)	14.8% (48)	6.3% (13)	11.6% (115)
	No (correct)	38.0% (175)	40.6% (132)	52.2% (108)	41.8% (415)
	Don't know	50.2% (231)	44.6% (145)	41.5% (86)	46.6% (462)

Continues

Follows

Tab. V. The comparison between Genoa, Rome and Messina in Domain 4: "Knowledge about Melanoma".

Domain 4 "Knowledge about Melanoma"	Response Items	Genoa % (n)	Rome % (n)	Messina % (n)	Total % (n)
Which of the following 12 factors increase the risk of developing a melanoma?					
j) Having red hair	**Yes (correct)**	26.9% (124)	40.6% (131)	22.0% (46)	30.3% (301)
	No (wrong)	26.0% (120)	21.4% (69)	38.3% (80)	27.1% (269)
	Don't know	47.1% (217)	38.1% (123)	39.7% (83)	42.6% (423)
k) Having fair hair	**Yes (correct)**	23.8% (110)	31.3% (102)	19.2% (40)	25.3% (252)
	No (wrong)	29.8% (138)	25.5% (83)	40.4% (84)	30.6% (305)
	Don't know	46.4% (215)	43.3% (141)	40.4% (84)	44.1% (440)
l) Having dark hair	Yes (wrong)	3.9% (18)	1.2% (4)	3.9% (8)	3.0% (30)
	No (correct)	51.0% (235)	55.5% (181)	57.8% (119)	53.9% (535)
	Don't know	45.1% (208)	43.3% (141)	38.3% (79)	43.1% (428)
How worried would you be if you noticed that a mole…					
a) became irregular in shape?	Very worried	42.3% (196)	44.2% (144)	48.4% (109)	44.3% (449)
	Worried	49.2% (228)	43.3% (141)	44.0% (99)	46.2% (468)
	Not very worried	6.5% (30)	11.3% (16)	7.1% (16)	8.2% (83)
	Not worried	1.9% (9)	1.2% (4)	0.4% (1)	1.4% (14)
b) became irregular in colour?	Very worried	44.3% (204)	43.7% (142)	47.3% (97)	44.7% (443)
	Worried	47.3% (218)	44.3% (144)	44.9% (92)	45.8% (454)
	Not very worried	6.7% (31)	10.5% (34)	7.3% (15)	8.1% (80)
	Not worried	1.5% (8)	1.5% (5)	0.5% (1)	1.4% (14)
c) grew in size?	Very worried	48.5% (224)	48.3% (157)	51.7% (106)	49.1% (487)
	Worried	40.3% (186)	38.5% (125)	39.5% (81)	39.5% (392)
	Not very worried	9.1% (42)	12.3% (40)	7.8% (16)	9.9% (98)
	Not worried	2.2% (10)	0.9% (3)	1.0% (2)	1.5% (15)
Can a melanoma…					
a) be completely prevented?	Yes (wrong)	34.3% (157)	36.3% (118)	41.2% (84)	36.4% (359)
	No (correct)	19.0% (87)	19.4% (63)	20.1% (41)	19.4% (191)
	Don't know	46.7% (214)	44.3% (144)	38.7% (79)	44.3% (437)
b) heal without therapy?	Yes (wrong)	5.1% (23)	5.6% (18)	0.5% (1)	4.3% (42)
	No (correct)	59.2% (267)	67.4% (217)	78.8% (156)	65.9% (640)
	Don't know	35.7% (161)	27.0% (87)	20.7% (41)	29.8% (289)

Continues

Follows

Tab. V. The comparison between Genoa, Rome and Messina in Domain 4: "Knowledge about Melanoma".

Domain 4 "Knowledge about Melanoma"	Response Items	Genoa % (n)	Rome % (n)	Messina % (n)	Total % (n)
Can a melanoma...					
c) be cured if treated early?	**Yes (correct)**	77.8% (357)	76.6% (249)	81.3% (174)	78.2% (780)
	No (wrong)	1.7% (8)	2.2% (7)	2.8% (6)	2.1% (21)
	Don't know	20.5% (94)	21.2% (69)	15.9% (34)	19.7% (197)
d) lead to death if not treated?	**Yes (correct)**	62.7% (288)	65.4% (212)	65.0% (134)	64.1% (643)
	No (wrong)	3.1% (14)	1.2% (4)	6.3% (13)	3.1% (31)
	Don't know	34.2% (157)	33.3% (108)	28.6% (59)	32.8% (324)
In men, the commonest part of the body to find a melanoma is:	The face (wrong)	3.9% (18)	3.7% (12)	10.7% (23)	5.3% (53)
	The back (correct)	30.9% (141)	30.8% (100)	23.7% (51)	29.3% (292)
	The leg (wrong)	2.9% (13)	4.0% (13)	2.8% (6)	3.2% (32)
	Other?	0.7% (3)	1.8% (6)	2.3% (5)	1.4% (14)
	Don't know	61.6% (281)	59.7% (194)	60.5% (130)	60.7% (605)
In women, the commonest part of the body to find a melanoma is:	The face (wrong)	8.3% (38)	5.6% (18)	13.7% (29)	8.5% (85)
	The back (wrong)	13.7% (63)	12.3% (40)	15.6% (33)	13.7% (136)
	The leg (correct)	9.8% (45)	12.7% (41)	5.7% (12)	9.8% (98)
	Other?	2.0% (9)	2.8% (9)	3.8% (8)	2.6% (26)
	Don't know	66.2% (304)	66.7% (216)	61.3% (130)	65.3% (650)

constructs. Table VI shows the application of the study's findings to the health belief model.

Increasing awareness through improving the factual knowledge people have about melanoma is insufficient to facilitate behaviour change alone. Interventions need to motivate and inform perceptions, as well as educate and provide realistic ways to help people adopt healthier behaviours. The use of social marketing techniques to promote the prevention of melanoma has been found to be effective in other countries [13] and has proven to be an effective theory to base skin health interventions upon. In young people, the technique of 'channel analysis' can assist in determining the best ways to deliver health messages – for example, the use of social media to inform and educate [15] and also using social media to link skin health activities with role models young people admire [12]. Social marketing theory also requires health promoters to be realistic and pragmatic about what type of messages they are championing, for instance, the social pressure to be tanned is so ingrained in Italy that a message focussed on avoiding the sun completely is unlikely to resonate. It may be more beneficial to promote gradual tanning and how skin awareness can help build a 'safer' tan. Also, recognising that social marketing and health research tells us that overly negative messages can be less effective than more positive ones – framing 'safer' tanning alongside the message that it provides a longer lasting tan may be helpful [14].

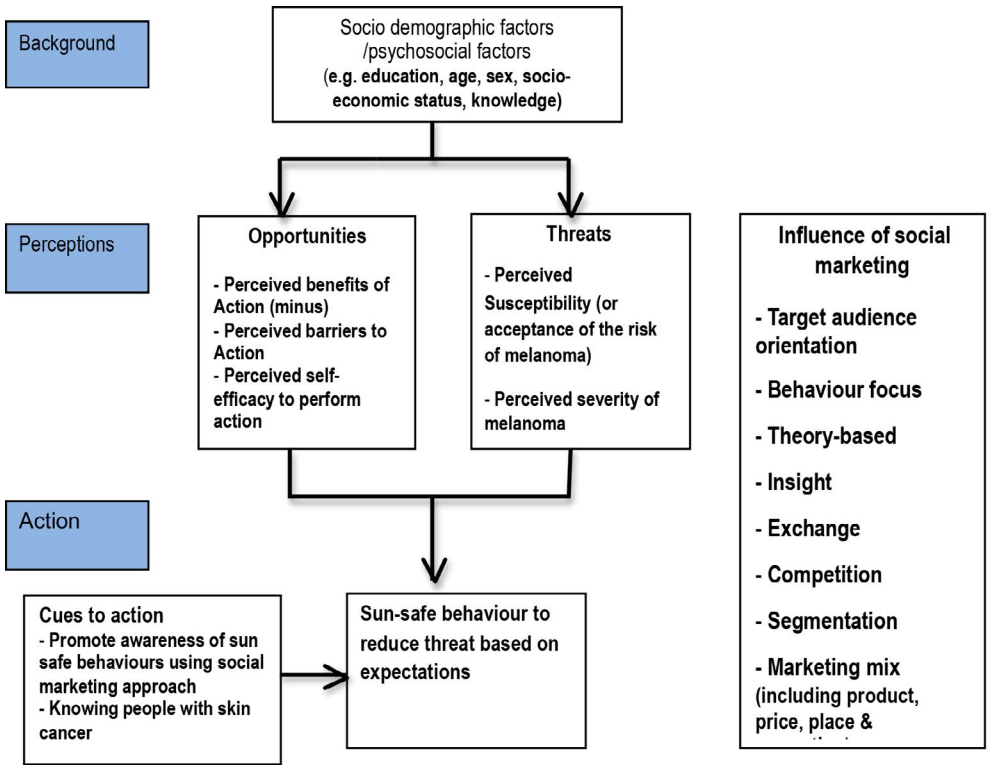
The development of a conceptual framework offers an attempt to understand and assess the key issues relating to the prevention of melanoma by adopting a social marketing approach. The framework represents and conveys factors that foster or hinder the prevention of cutaneous melanoma and that can be used to inform and shape a social marketing response to this issue (Fig. 1).

This conceptual framework may be used to understand the likelihood of Italians carrying out sun-safe protective actions. Community-level social marketing interventions can benefit from utilising the framework developed as it provides an understanding of the target audience's perceptions and beliefs, enabling a real behaviour change to occur. The framework enables us to address the desired behaviour intention as a product to be 'sold' to the target market, while

Tab. VI. Application of the study findings to the Health Belief Model (HBM).

HBM concepts	Definition	Application of study findings
1. Perceived susceptibility	One's belief of the chances of getting a condition	– Low levels of concern – High levels of personal risk particularly amongst women – and those less well educated – Low level of protective behaviour
2. Perceived severity	One's belief of how serious a condition and its consequences are	– Lack of knowledge about melanoma
3. Perceived benefits	One's belief in the efficacy of the advised action to reduce risk or seriousness of impact	– Reduce risk of developing a melanoma – Early detection of melanoma
4. Perceived barriers	One's belief in the tangible and psychological costs of the advised behaviour	– Positive perceptions and priority of a sun tan – Hassle of protection (e.g. sunscreen hats covering up) – Being outdoors
5. Cues to action	Strategies to activate "readiness"	– Promote awareness of sun safe behaviours using social marketing approach – Knowing people with skin cancer
6. Self-efficacy	Confidence in one's ability to take action	– Ability to carry out sun-safe behaviours – Use the correct sunscreen and ability to apply correctly – Be able to check moles/freckles effectively
Modifying variables	Influences on perceptions	– Age – Gender – Psychosocial factors (job, education) – Family member with melanoma or knowing someone – with a melanoma – Knowledge about melanoma – Direct experience of melanoma

Fig. 1. A conceptual framework illustrating the influence of social marketing on the constructs of the HBM in relation to skin cancer prevention in Italy.



encompassing necessary areas, such as promotional strategies and products development to bring about behaviour change. This strategy could be a direct intervention to either reduce the desire for a tan, increase the social acceptability of adopting specific sun protection practices, or even alter the social norm of complacence. A risk reduction strategy could also include the use of tangible products, such as a fake tan, to provide safer alternatives for hard-to-change behaviours.

Limitations

This study did not explore the reasons of the sample's behaviours. Moreover, no qualitative data about self-efficacy issues were collected to understand, for instance, if people felt they correctly used sunscreen and checked their moles. Finally, apart from comparing the general public with those in the dermatology waiting rooms, no other potential confounding variables were considered.

Conclusions

In the last 20 years, the incidence of melanoma has increased by over 4% a year [2] and the moderate mean scores for 'Personal Risk', 'Level of Concern', and 'Protective Behaviour' combined with the poor levels of 'Melanoma Knowledge' are by no means encouraging. In fact, many respondents showed a lack of skin awareness and a misconception of the deadly nature of melanoma. This confirms that more still needs to be done to implement and promote sun-safe behaviours. Therefore, there is an ethical imperative to promote the importance of adopting protective behaviors. A social marketing intervention based on the Health Belief Model could offer an effective solution for a wide-scale intervention to 'nudge' and equip people with the motivation to proactively undertake preventive behaviours.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

The individual contributions of authors to the manuscript are as follows:
GA, AB, LG, EC, SPC, AP and LS contributed to the conception and the design of this study; GA, RW, MH, AB, MZ, GC, and LS contributed to data collection, analysis, and interpretation; GA, RW, MH, LG, EC, SPC, AP, and LS have been involved in drafting, editing and revising critically this manuscript. All authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

International epidemiology of liver cancer: geographical distribution, secular trends and predicting the future

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Keywords

Incidence • Mortality • Trend • Liver Cancer • The world

Summary

Background. *Liver cancer (LC) is ranked seventh common cancer in terms of the incidence; and the fourth in terms of the mortality of cancer in the world. The aim of this study was to investigate the international distribution of the incidence and mortality of LC in 2018 based on various socio-economic and political divisions in the world.*

Material and methods. *This study was conducted through the use of the incidence and mortality cancer data from GLOBOCAN Project in 2018. The Age-Standardized Incidence Rate (ASIR) and Age Standardized Mortality Rate (ASMR) of LC were expressed per 100,000 people. In the current report, we used Pearson correlation method to assess the correlation between ASIR and ASMR. Statistical significance was considered to be $P < 0.05$.*

Results. *The highest ASIR and ASMR of LC occurred in Asia (ASIR = 11.4 and ASMR = 10.5), and Western Pacific Region of the World Health Organization (ASIR = 17.4 and ASMR = 15.8), and those regions with income level equal to upper middle income (ASIR = 13.4 and ASMR = 6.6). Furthermore, the lowest ASIR and ASMR of LC occurred in in Latin America and Caribbean (ASIR = 5) and Europe (ASMR = 4.4), the South-East Asia region (ASIR = 4.5 and ASMR = 4.3), and regions with Low middle income (ASIR = 5.7) and regions with high income (ASMR = 2.7).*

Conclusions. *LC is one of the most important cancer forms in the world in terms of incidence and mortality. It is important to prevent exposure to known risk factors for LC by increasing the level of knowledge and attitudes of the community and prevent of morbidity and mortality of the population with early diagnosis and treatment of patients.*

Introduction

Despite the advances in preventing and controlling non-infectious diseases in recent decades, the incidence and prevalence of these diseases have increased dramatically [1]. Cancer is the second cause of death in most countries after cardiovascular diseases [2-6]. There were 24.5 million new cancer cases and 9.6 million cancer deaths worldwide in 2017, and led to 233.5 million Disability-Adjusted Life Year (DALYs), of which 3% came from Years lived with disability (YLDs) and 97% came from Years of Life Lost (YLLs). Globally, the odds of developing cancer in lifetime were 33% for men and 25% for women. Between 2007 and 2017, the Age-Standardized Incidence Rate (ASIR) for all cancers has increasing trend, but Age-Standardized Mortality Rate(ASMR) has decreasing trend [7]. Liver is an important body organ that plays an key role in the detoxification, excretion of waste, and the metabolism of glucose and fats [8]. Liver cancer (LC) is ranked seventh among cancers in terms of the incidence; and since most cases of LC are diagnosed at advanced stages of disease, its fatality is high, so that this cancer is ranked fourth among other types of cancers in terms of the mortality [9]. Globally, there were 953000 new cases and 819 000 deaths of LC in 2017. LC led to 20,800,000 DALYs in 2017, which 1% coming from YLDs and 99% coming from YLLs. Generally, LC was more common in men, so lifetime odds of developing LC for men were 1 in 42 and for women 1 in 118. Population growth and population aging were the main causes of the increase of LC from 705000 cases in 2007 to 953000 cases in 2017 [7]. The most important risk factors associated with the incidence of LC are diagnosed, and most of them can be prevented and altered at the individual and social levels. Therefore, the incidence of LC and ultimately the rate of its mortality can be reduced in societies by taking appropriate measures [10].

LC can be categorized into three main forms with different risk factors associated with each of them. Hepatocellular carcinoma (HCC) is the most important LC form which is caused by the following cases: chronic infection with hepatitis B and C viruses; food contamination with aflatoxins; alcoholic cirrhosis; smoking, diabetes, overweight and obesity. Cholangiocarcinoma is the second most important LC form which is mainly caused by the following factors:

infestation with liver flukes, Opistorchis viverrini and Clonorchis sinensis. Angiosarcoma is a very rare type of LC occurring in exposure to Vinyl chloride [11].
In the world, the ASIR of LC is 16 per 100,000 men and 6 per 100,000 women. The ASIR of LC in less developed countries is higher than developed countries (12 versus 5.4 per 100,000) [12]. Since the LC is a very high prevalent cancer and has high mortality due to the late diagnosis, it is considered to be a major health problem which imposes a large burden in term DALYs (YLL and YLD) on countries. Due to the high importance of this cancer, various studies have been conducted on estimating its burden on developed countries [11, 13]. Nevertheless, there are a few studies on distribution of LC at the international level [14]. Since obtaining the appropriate information to properly understand distribution of any disease in terms of person, place, and time is the first and most important necessity for appropriate measures and interventions to reduce the incidence and mortality of any disease, the present study was conducted with the aim to investigate the international distribution of the incidence and mortality of LC in 2018 based on various socio-economic and political divisions in the world. In addition, present study predicts the trends of incidence and mortality of LC during 2018 to 2040 in worldwide.

Materials and methods

In the present study, we extracted data on the incidence and mortality rate of LC in 184 countries from the International Agency for Research on Cancer (IARC) (Project GLOBOCAN, 2018). GLOBOCAN is a database of various types of cancers created by World Health Organization (WHO) [15, 16]. It covers information on the number, raw rates, and age standardization of cancer incidence, and mortality for different regions and countries. Currently, the available data in GLOBOCAN is known as one of the newest international databases on the cancer. Based on the data of GLOBOCAN project, it is possible to investigate and compare the incidence and mortality of cancer based on the type of cancer, age and gender groups for different regions of the world.
The present study categorized and presented the information on the Age-Standardized Incidence Rate (ASIR) and Age Standardized Mortality Rate (ASMR) of LC based on the continents (Africa, Latin America and Caribbean, Northern America, Europe, Oceania, Asia), income levels(high income, upper middle income, low middle income, and low income),human development index(HDI) (very high, high, medium, low, China and India),WHO regions (Africa region (AFRO), Americas region (PAHO), East Mediterranean region (EMRO), Europe region (EURO), South-East Asia region (SEARO) and Western Pacific region (WPRO)), and World regions(Australia and New Zealand, Caribbean, central America, central and eastern Europe, eastern Africa, eastern Asia, Melanesia, Micronesia, middle Africa, north America, northern Africa, northern Europe, Polynesia, south America, south-central Asia, south-eastern Asia, southern Africa, southern Europe, western Africa, western Asia, and western Europe).

Human Development Index (HDI)

Human Development Index (HDI) is a summary measure of average achievement in key dimensions of human development: life expectancy, education, and per capita income. The HDI is the geometric mean of normalized indices for each of the three dimensions with rang from 0 to 1 [17].

Statistical analysis

We provided the information about the incidence and mortality of LC based on the number, raw rates and the Age-Standardized rates in 2018. We also expressed raw and standardized rates of incidence and mortality per 100,000 people. Geographical distribution map was prepared for the incidence and mortality of this disease based on the Age-Standardized rates. In GLOBOCAN project, predicting the number of incidence and mortality of LC in 2020, 2025, 2030, 2035 and 2040 is calculated by multiplying the age-specific incidence rates estimated for 2018, by the corresponding anticipated population for 2020, 2025, 2030, 2035 and 2040 [9]. Detailed descriptions of applied methods are presented in previous reports [11-14]. In the current report; we used Pearson correlation method in order to assess the correlation between ASIR and ASMR of LC. Statistical significance was considered as $P < 0.05$. All P-values reported in this study are two-sided. Also, statistical analyses were performed using SPSS (Version 16.0, SPSS Inc.).

Results

The ASIR and ASMR of LC in the world

In 2018, 841,080 new cases of LC were diagnosed worldwide. Of them 596,574 (70.92%) cases occurred in men and 244506 (29.08%) in women. In general, the ASIR of LC was equal to 9.3 (13.9 in men and 4.9 in women). The sex ratio (men to women ratio) of the newly diagnosed LC was equal to 2.43 (Fig. 1).
There were also 781,631 deaths from LC during this year. Of them, 548,375 (70.15%) cases occurred in men and 233,256 (29.85%) in women. In general, the ASMR of LC was equal to 8.5 (12.7 in men and 4.6 in women). The sex ratio of the mortality of LC was equal to 2.35 (Fig. 2).

The ASIR and ASMR of LC based on the continents

The ASIR of LC was equal to 6.6 (10.1 in men, and 3.4 in women) in North America, 5.1 (8 in men, and 2.7 in women) in Europe, 6.9 (10.1 in men and 3.7 in women) in Oceania, 11.4 (17.1 in men and 5.9 in

Fig. 1. Distribution of new LC cases worldwide in 2018.

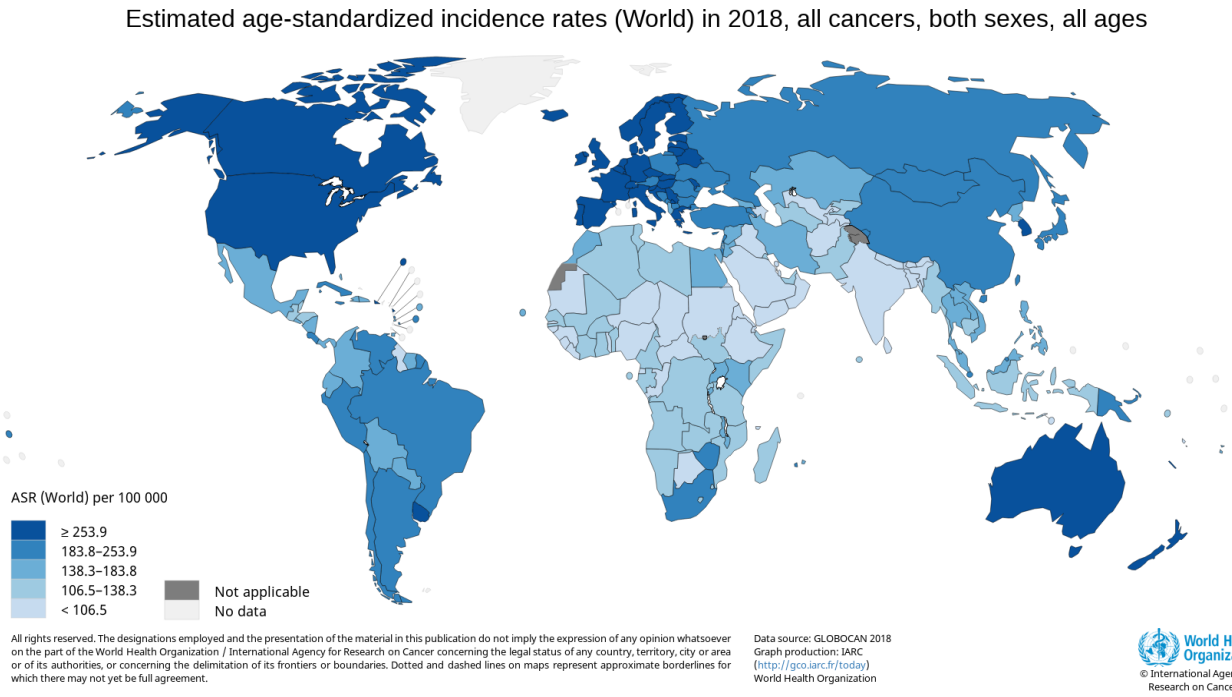
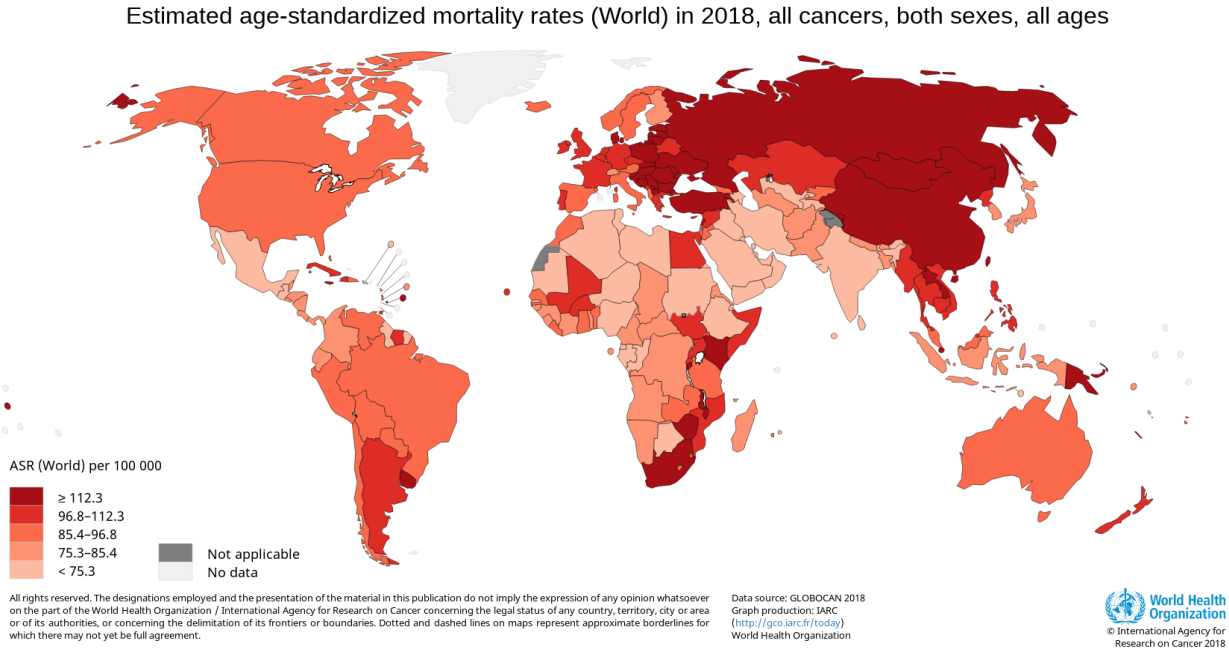


Fig. 2. Distribution of LC mortality worldwide in 2018.



women) in Asia, 5 (6.1 in men and 4.1 in women) in Latin America and Caribbean, and 8.4 (12 in men and 5.3 in women) in Africa. Of the total number of this disease in the world, the highest proportion occurred in Asia and the lowest proportion in Oceania, so that 72.47% of cases occurred in Asia, 9.8% in Europe, 4.97% in North America, 4.56% in Latin America and Caribbean, 7.73% in Africa and 0.47% in Oceania (Tab. I, Figs. 1-4). In addition, numbers, crude rate and ASIR of LC in worldwide countries are visible in the Supplementary data (Tab. SI).

The ASMR of LC was equal to 4.8 (7.1 in men, and 2.8 in women) in North America, 4.4 (6.8 in men, and 2.4 in women) in Europe, 10.5 (15.8 in men and 5.5 in women) in Asia, 5.8 (8.3 in men and 3.4 in women) in Oceania, 4.8 (7.1 in men and 2.8 in women) in Latin America and Caribbean, and 8.3 (11.9 in men and 5.2 in women) in Africa. Of the total number of deaths

Tab. I. The age-standardized incidence rate of liver cancer in different regions of the world in 2018.

Population		All			Men			Women		
		Numbers	Crude rate	ASR (W)	Numbers	Crude rate	ASR (W)	Numbers	Crude rate	ASR (W)
World		841,080	11	9.3	596,574	15.5	13.9	244,506	6.5	4.9
WHO regions	WHO Africa region (AFRO)	37,036	3.4	6	23,719	4.4	8.1	13,317	2.5	4.1
	WHO Americas region (PAHO)	80,251	7.9	5.6	50,684	10.1	7.8	29,567	5.8	3.7
	WHO East Mediterranean region (EMRO)	39,415	5.7	7.9	26,936	7.5	10.7	12,479	3.7	5
	WHO Europe region (EURO)	91,988	10	5.1	61,546	13.7	7.9	30,442	6.4	2.8
	WHO South-East Asia region (SEARO)	84,733	4.3	4.5	59,783	5.9	6.5	24,950	2.6	2.6
	WHO Western Pacific region (WPRO)	507,501	26.2	17.4	373,794	37.9	26.4	133,707	14.1	8.5
Continents	Africa	64,779	5	8.4	43,530	6.8	12	21,249	3.3	5.3
	Asia	609,596	13.4	11.4	443,744	19.1	17.1	165,852	7.5	5.9
	Europe	82,466	11.1	5.1	55,825	15.5	8	26,641	6.9	2.7
	Latin America and the Caribbean	38,400	5.9	5	20,784	6.5	6.1	17,616	5.3	4.1
	North America	41,851	11.5	6.6	29,900	16.6	10.1	11,951	6.5	3.4
	Oceania	3,988	9.7	6.9	2,791	13.5	10.1	1 197	5.8	3.7
Human Development Index (HDI)	China	392,868	27.6	18.3	292,898	40	27.6	99,970	14.5	9
	High HDI	76,109	19.1	13.8	46,301	27.2	20.8	29,808	10.7	7.2
	India	27,670	2	2.2	18,807	2.7	3.1	8,863	1.4	1.4
	Low HDI	33,447	3.3	6	21,138	4.1	7.9	12,309	2.4	4.3
	Medium HDI	115,604	5.2	5.9	82,796	7.2	8.6	32,808	3.1	3.3
	Very high HDI	195,092	14.1	6.9	134,426	19.6	10.6	60,666	8.6	3.5
Income levels	High income	167,606	13.8	6.6	116,876	19.3	10.2	50,730	8.3	3.3
	Low income	29,774	4	6.9	19,080	5.1	9.4	10,694	2.8	4.6
	Low middle income	148,420	4.9	5.7	104,493	6.8	8.2	43,927	3	3.2
	Upper middle income	480,356	18.3	13.4	345,927	26.1	20.2	134,429	10.3	7
World regions	Australia and New Zealand	2,921	9.9	5.7	2,115	14.4	8.8	806	5.4	2.7
	Caribbean	2,923	6.6	5	1,706	7.8	6.3	1,217	5.5	3.8
	Central America	11,229	6.3	6.3	5,513	6.2	6.7	5,716	6.3	6
	Central and Eastern Europe	22,784	7.8	4	13,737	10	6.2	9,047	5.9	2.5
	Eastern Africa	11,550	2.7	4.8	7,011	3.3	6.2	4,539	2.1	3.6
	Eastern Asia	467,327	28.3	17.7	343,523	40.6	26.8	123,804	15.3	8.7
	Melanesia	915	8.7	11.4	557	10.4	14.2	358	6.9	8.9
	Micronesia	85	16	15.2	69	25.7	25.6	16	6.1	5.4
	Middle Africa	6,010	3.6	6.5	4,137	4.9	9.4	1,873	2.2	3.9
	North America	41,851	11.5	6.6	29,900	16.6	10.1	11,951	6.5	3.4
	Northern Africa	27,935	11.7	14.1	19,912	16.7	20.8	8,023	6.8	7.8
	Northern Europe	10,997	10.5	4.7	7,086	13.7	6.6	3,911	7.4	2.9
	Polynesia	67	9.7	9.2	50	14.2	14.4	17	5	4.1
	South America	24,248	5.7	4.6	13,565	6.4	5.8	10,683	4.9	3.5
	South-Central Asia	44,010	2.2	2.5	29,027	2.9	3.4	14,983	1.6	1.7
	South-Eastern Asia	89,010	13.6	13.3	65,407	20	21	23,603	7.2	6.6
	Southern Africa	2,710	4.1	4.9	1,692	5.2	7.4	1,018	3	3.2
	Southern Europe	25,026	16.4	6.8	17,702	23.7	10.9	7,324	9.4	3.1
	Western Africa	16,574	4.3	8.3	10,778	5.6	11.1	5,796	3.1	5.7
	Western Asia	9,249	3.4	4	5,787	4.1	5.4	3,462	2.7	2.8
	Western Europe	23,659	12.2	5.3	17,300	18.1	8.4	6,359	6.5	2.5

Fig. 3. Age standardized incidence rates of LC by sex in the worldwide in 2018.

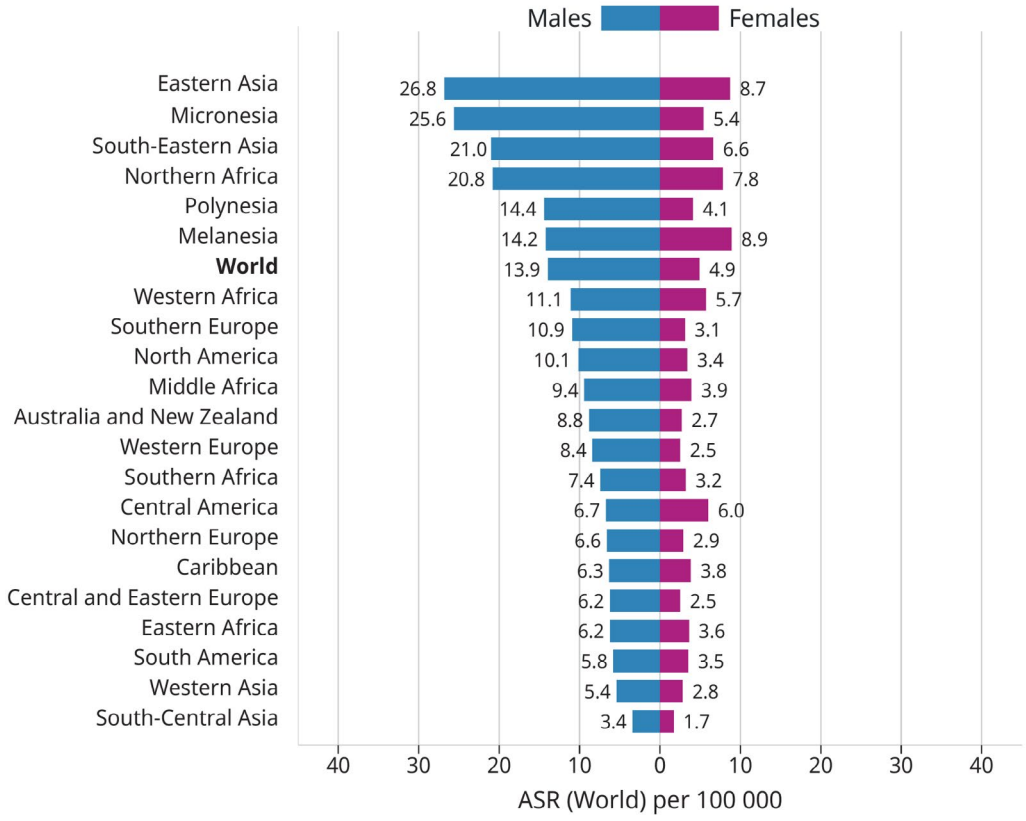
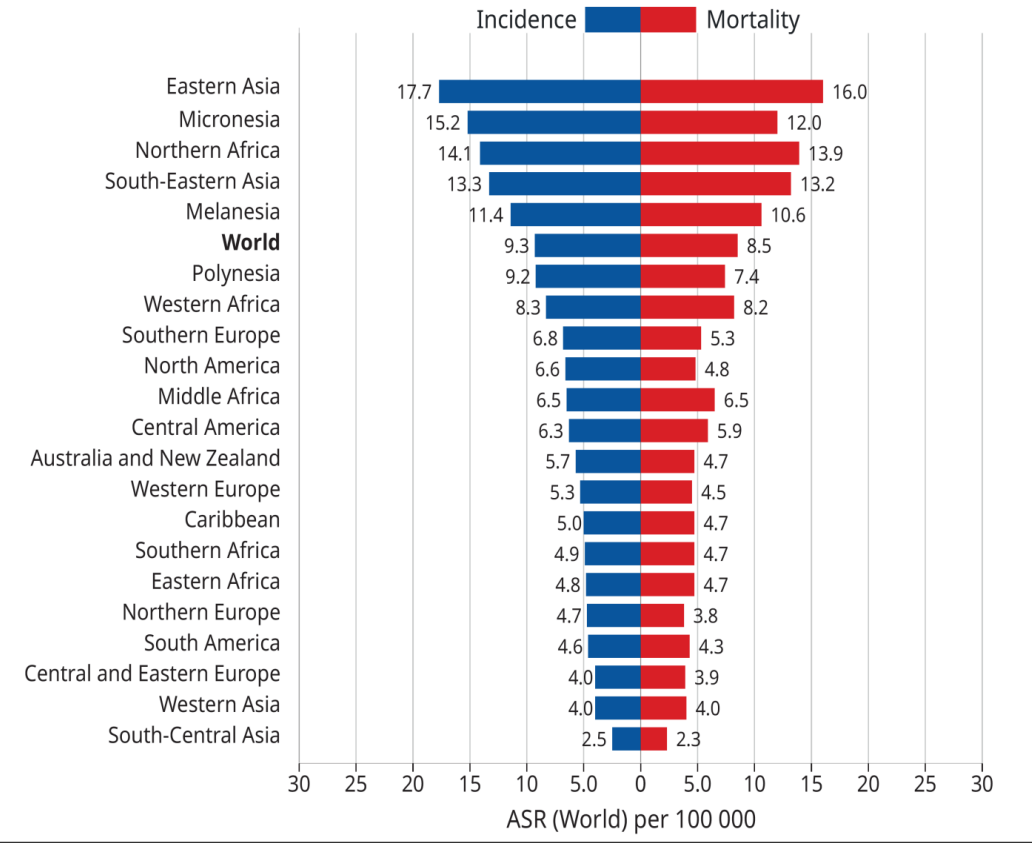


Fig. 4. Age standardized incidence and mortality rates of LC in the worldwide in 2018.



Tab. II. The age-standardized mortality rate of liver cancer in different regions of the world in 2018.

Population		All			Men			Women		
		Numbers	Crude Rate	ASR (W)	Numbers	Crude Rate	ASR (W)	Numbers	Crude Rate	ASR (W)
World		781,631	10.2	8.5	548,375	14.2	12.7	233,256	6.2	4.6
WHO regions	WHO Africa region (AFRO)	36,239	3.4	5.9	23,315	4.3	8	12,924	2.4	4
	WHO Americas region (PAHO)	70,775	7	4.8	42,539	8.5	6.3	28,236	5.5	3.4
	WHO East Mediterranean region (EMRO)	38,637	5.6	7.8	26,358	7.4	10.5	12,279	3.7	5
	WHO Europe region (EURO)	86,407	9.4	4.4	55,850	12.5	6.8	30,557	6.4	2.5
	WHO South-East Asia region (SEARO)	81,347	4.1	4.3	57,697	5.7	6.2	23,650	2.4	2.4
	WHO Western Pacific region (WPRO)	468,065	24.2	15.8	342,501	34.7	24.1	125,564	13.3	7.8
Continents	Africa	63,562	4.9	8.3	42,786	6.7	11.9	20,776	3.2	5.2
	Asia	566,269	12.5	10.5	410,223	17.6	15.8	156,046	7	5.5
	Europe	77,375	10.4	4.4	50,365	14	6.8	27,010	7	2.4
	Latin America and the Caribbean	36,436	5.6	4.7	19,650	6.1	5.7	16,786	5.1	3.9
	North America	34,339	9.4	4.8	22,889	12.7	7.1	11,450	6.2	2.8
	Oceania	3,650	8.8	5.8	2,462	11.9	8.3	1,188	5.8	3.4
Human Development Index (HDI)	China	368,960	25.9	17.1	273,014	37.3	25.6	95,946	13.9	8.6
	High HDI	73,651	18	13	45,107	25.5	19.4	28,544	10.3	6.8
	India	25,627	1.9	2	17,548	2.5	2.8	8,079	1.2	1.3
	Low HDI	32,674	3.2	5.9	20,754	4.1	7.9	11,920	2.3	4.2
	Medium HDI	113,443	5	5.7	81,390	7	8.3	32,053	3	3.2
	Very high HDI	167,010	12	5.3	110,379	16.1	8.1	56,631	8.1	2.9
Income levels	High income	47,477	7.8	2.7	47,477	7.8	2.7	47,477	7.8	2.7
	Low income	10,295	2.7	4.5	10,295	2.7	4.5	10,295	2.7	4.5
	Low middle income	42,245	2.9	3.1	42,245	2.9	3.1	42,245	2.9	3.1
	Upper middle income	129,546	10	6.6	129,546	10	6.6	129,546	10	6.6
World regions	Australia and New Zealand	2,709	9.2	4.7	1,881	12.8	7	828	5.6	2.5
	Caribbean	2,791	6.3	4.7	1,588	7.3	5.8	1,203	5.4	3.7
	Central America	10,672	5.9	5.9	5,324	6	6.4	5,348	5.9	5.5
	Central and Eastern Europe	22,745	7.8	3.9	13,581	9.9	6.1	9,164	5.9	2.4
	Eastern Africa	11,251	2.6	4.7	6,799	3.2	6.2	4,452	2	3.5
	Eastern Asia	427,932	25.9	16	312,228	36.9	24.2	115,704	14.3	8
	Melanesia	819	7.8	10.6	491	9.2	13.1	328	6.3	8.3
	Micronesia	68	12.8	12	54	20.1	19.8	14	5.3	4.9
	Middle Africa	5,853	3.5	6.5	4,056	4.8	9.5	1,797	2.1	3.9
	North America	34,339	9.4	4.8	22,889	12.7	7.1	11,450	6.2	2.8
	Northern Africa	27,505	11.6	13.9	19,570	16.4	20.4	7,935	6.7	7.7
	Northern Europe	9,997	9.5	3.8	6,088	11.8	5.2	3,909	7.4	2.5
	Polynesia	54	7.8	7.4	36	10.2	10.6	18	5.3	4.5
	South America	22,973	5.4	4.3	12,738	6	5.5	10,235	4.7	3.4
	South-Central Asia	40,812	2.1	2.3	27,060	2.7	3.2	13,752	1.4	1.5
	South-Eastern Asia	88,429	13.5	13.2	65,238	19.9	20.9	23,191	7.1	6.5
	Southern Africa	2,597	3.9	4.7	1,614	5	7.1	983	2.9	3.1
	Southern Europe	21,996	14.4	5.3	14,800	19.8	8.3	7,196	9.2	2.6
	Western Africa	16,356	4.3	8.2	10,747	5.6	11.1	5,609	3	5.6
	Western Asia	9,096	3.4	4	5,697	4	5.4	3,399	2.6	2.8
	Western Europe	22,637	11.7	4.5	15,896	16.6	7	6,741	6.9	2.2

of LC in the world, the highest proportion occurred in Asia and the lowest proportion in Oceania, so that 72.44% of cases occurred in Asia, 9.89% in Europe, 4.39% in North America, 4.66% in Latin America and Caribbean, 8.13% in Africa and 0.49% in Oceania (Tab. II, Figs. 1-4). In addition, numbers, crude rate and ASMR of LC in worldwide countries are visible in the Supplementary data (Tab. SII).

The ASIR and ASMR of LC according to the WHO classification

The ASIR of LC was equal to 17.4 (26.4 in men, and 8.5 in women) in WPRO, 5.1(7.9 in men, and 2.8 in women) in EURO, 5.6 (7.8 in men and 3.7 in women) in PAHO, 4.5 (6.5 in men and 2.6 in women) in SEARO, 7.9 (10.7 in men and 5 in women) in EMRO, and 6 (8.1 in men and 4.1 in women) in AFRO. Of the total incidence of this disease, 60.33% occurred in WPRO, 10.93% in EURO, 9.54% in PAHO, 10.07% in SEARO, 4.68% in EMRO, and 4.46% in AFRO (Tab. I).

The ASMR of LC was equal to 15.8(24.1 in men, and 7.8 in women) in WPRO, 4.4 (6.8 in men, and 2.5 in women) in EURO, 4.8 (6.3 in men and 3.4 in women) in PAHO, 4.3 (6.2 in men and 2.4 in women) in SEARO, 7.8 (10.5 in men and 5 in women) in EMRO, and 5.9 (8 in men and 4 in women) in AFRO. Of the total mortality of this disease, 59.88% occurred in WPRO, 11.05% in EURO, 9.05% in PAHO, 10.4% in SEARO, 4.94% in EMRO, and 4.68% in AFRO (Tab. II).

The ASIR and ASMR of LC according to the levels of Human Development Index (HDI)

The ASIR of LC was equal to 6.9 (10.6 in men, and 3.5 in women) in regions with very high HDI, 13.8 (20.8 in men, and 7.2 in women) in regions with high HDI, 5.9 (8.6 in men and 3.3 in women) in regions with medium HDI, 6 (7.9 in men and 4.3 in women) in regions with low HDI, 18.3 (27.6 in men and 9 in women) in China, and 2.2 (3.1 in men and 1.4 in women) in India. Of the total incidence of this disease, 23.19% occurred in regions with very high HDI, 9.04% in regions with high HDI, 13.74% in regions with medium HDI, 3.97% in regions with low HDI, 46.70% in China,and 3.28% in India (Tab. I)

The ASMR of LC was equal to 5.3 (8.1 in men, and 2.9 in women) in regions with very high HDI, 13 (19.4 in men, and 6.8 in women) in regions with high HDI, 5.7 (8.3 in men and 3.2 in women) in regions with medium HDI, and 5.9 (7.9 in men and 4.2 in women) in regions with low HDI. Of the total incidence of this disease, 21.36% occurred in regions with very high HDI, 9.42% in regions with high HDI, 14.51% in regions with medium HDI, and 4.18% in regions with low HDI, 47.20% in China,and 3.33% in India (Tab. II).

Predicting the incidence and mortality of LC from 2018 to 2040

The number of new cases of LC is predicted to increase from 841,080 case in 2018 to 883,925 (+5.1%), 997,895 (+18.6%), 1,118,358 (+33.0%), 1,241,726 (+47.6%) and 1361836 (+61.9%) case in 2020, 2025, 2030, 2035 and 2040, respectively.In addition, the number of mortality from LC increases from 781631 case in 2018 to 821,727 (+5.1), 930,121 (+19.0%), 1,046,114 (+33.8%), 1,166,317 (+49.2%) and 1,284,252 (+64.3%) case in 2020, 2025, 2030, 2035 and 2040, respectively (Tab. III).

Relationship between ASIR and ASMR of LC worldwide

There was a statistically significant correlation between ASIR and ASMR of LC worldwide at the level of 0.987 ($P \geq 0.001$). This correlation was equal to 0.994 ($P \geq 0.001$) in Asia, 0.848 ($P \geq 0.001$) in Europe, 0.996 ($P \geq 0.001$) in Africa, 0.964 ($P \geq 0.001$) in the Latin America and the Caribbean and 0.764 ($P = 0.010$) in Oceania (Fig. 5).

Discussion

The present study was based on data from GLOBOCAN PROJECT that was internationally conducted by WHO in 2018. The study aimed to examine the geographical distribution of incidence and mortality of LC based on geographical, political and economic divisions at the international level. It also predicts the number of incidence and mortality cases of LC from 2018 to 2040.

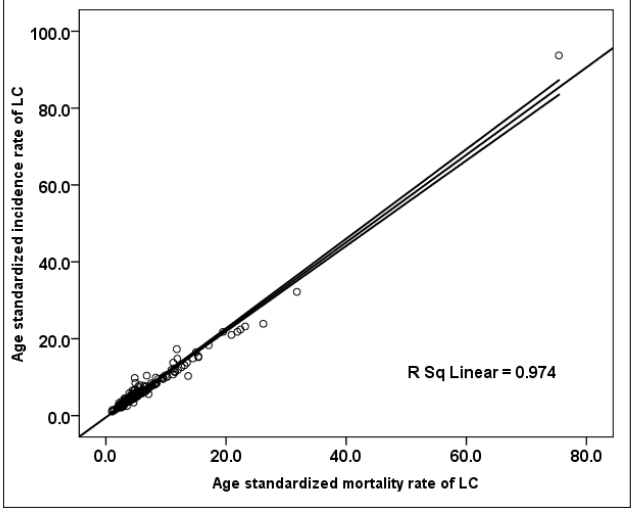
Cancer is considered as an important health problem in developing countries, especially Asian countries, so that it is one of the most important causes of death in some Asian countries such as South Korea and Japan. It seems that if current management plans and strategies are not changed, the number of deaths from cancer will increase by more than 7000000 per year in these areas until 2020 [18, 19]. According to this, current study found that most cases of incidence and mortality of LC occurred in less developed regions of the world in 2018. According to a research by Chang et al., hepatocellular carcinoma (HCC) caused by the chronic infection with hepatitis B was more common in areas with a low and moderate HDI mostly in Asia and Africa [20]. On the other hand, the increased incidence of hepatocellular carcinoma in developed countries was due to the higher prevalence of alcohol consumption and hepatitis C infection [21].

Distribution of cancer in different regions of the world varies according to the HDI. Different cancers are considered as the most common cancers in regions with low, medium, high and very high HDI. Lung, colorectal, prostate, and breast cancers are considered as the most common cancers in areas with high and very high HDI; and they account for more than 50% of all new cancer cases in these areas. Meanwhile, in areas with low and moderate HDI, the lung, breast, colorectal, stomach, liver and cervical cancers are also diagnosed as cancers with the highest incidence and severity. However, in areas with low HDI, cancers associated with infectious agents account for a high proportion of cancer incidence and mortality [21-23].

Tab. III. Predicting the incidence and mortality cases of LC from 2018 to 2040.

Year		2018	2020		2025		2030		2035		2040	
Event	Sex	Number	Number	Demographic change (APC 0%)	Number	Demographic change (APC 0%)	Number	Demographic change (APC 0%)	Number	Demographic change (APC 0%)	Number	Demographic change (APC 0%)
Incidence	Males	596,574	626,767	30,193 (+5.1%)	706,015	109,441 (+18.3%)	788,519	191,945 (+32.2%)	872,035	275,461 (+46.2%)	952,887	356,313 (+59.7%)
	Females	244,506	257,158	12,652 (+5.2%)	291,880	47,374 (+19.4%)	329,839	85,333 (+34.9%)	369,691	125,185 (+51.2%)	408,949	164,443 (+67.3%)
	Both sexes	841,080	883,925	42,845 (+5.1%)	997,895	156,815 (+18.6%)	1,118,358	277,278 (+33.0%)	1,241,726	400,646 (+47.6%)	1,361,836	520,756 (+61.9%)
Mortality	Males	548,375	576,354	27,979 (+5.1%)	650,956	102,581 (+18.7%)	729,536	181,161 (+33.0%)	809,877	261,502 (+47.7%)	888,195	339,820 (+62.0%)
	Females	233,256	245,373	12,171 (+5.2%)	279,165	45,909 (+19.7%)	316,578	83,322 (+35.7%)	356,440	123,184 (+52.8%)	396,057	162,801 (+69.8%)
	Both sexes	781,631	821,727	40,096(+5.1%)	930,121	148,490 (+19.0%)	1,046,114	264,483 (+33.8%)	1,166,317	384,686 (+49.2%)	1,284,252	502,621 (+64.3%)

Fig. 5. Correlation of ASIR and ASMR of LC.



In 2018, the incidence of LC was 5.1 and 6.6 per 100,000 people in Europe and North America, respectively. While the incidence of this disease was 11.4 and 8.4 in Asia and Africa, respectively, indicating the high incidence of disease in less developed regions of the world. Top ten countries with the highest incidence of LC in 2018 were as follows: Mongolia with ASIR = 117, Egypt with ASIR = 49, Viet Nam with ASIR = 39, The Gambia with ASIR = 36.5, Lao People's Democratic Republic with ASIR = 33.4, Thailand with ASIR = 32.2, Guinea with ASIR = 27.9, Republic of Korea with ASIR = 27.7, China with ASIR = 27.6,and Democratic Republic of Korea with ASIR = 25.4 [21]. Among 10 countries with the highest standardized LC incidence worldwide, 3 countries were located in Africa and 7 countries in Asia. Most of these countries with low or moderate HDI were located in less developed regions [6, 24-29].

In the present study, there was a significant statistical correlation between ASIR and ASMR of LC in the world, Europe, Asia, Africa, the Oceania, and the United States, in other words, an increase in the incidence of LC significantly enhanced its mortality rate. Therefore, appropriate and applied measures and programs should be adopted in areas with the highest incidence of LC, for primary and secondary prevention of disease with the aim to reduce the incidence and mortality of LC [30, 31]. Accordingly, it is suggested conducting case-control and cohort studies in countries and regions with the highest incidence of LC with the aim to diagnose the most important risk factors of this cancer and the risk attributable to each of these factors in order to perform appropriate regional planning to reduce the incidence of disease. Furthermore, patients need to be diagnosed and treated at early stages of disease by conducting appropriate screening programs in order to reduce the rate of disease mortality in these areas in the long term.

Limitations of the study

The quality of the collected cancer data in the GLOBOCAN project is not similar in all countries, especially those with medium or low HDI, so that the estimates of some countries are based on the recorded cases of cancer in limited areas or based on estimates from neighboring countries [24]. Please, see the Supplementary data (Tabs. SIII, SIV). for more information.

Conclusions

LC is one of the most important cancers in the world in terms of incidence and mortality. It is important to prevent exposure to known risk factors for LC by increasing the level of knowledge and attitudes of the community. In addition, it is necessary that health policy makers have appropriate planning for providing suitable diagnostic and medical service to prevent of morbidity and mortality of the population with early diagnosis and treatment of patients.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

AMH conceived the idea of the study and approved the final draft of the manuscript. MM and KAB wrote the first draft of the manuscript and carried out the data analysis. All authors contributed to the revising and editing of the article and the final version of the article was approved by them.

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Supplementary data

Tab. S1. The age-standardized incidence rate of LC in 185 countries of the world in 2018.

Countries	All				Male				Female			
	Numbers	Uncertainty interval	Crude Rate	ASR (W)	Numbers	Uncertainty interval	Crude Rate	ASR (W)	Numbers	Uncertainty interval	Crude Rate	ASR (W)
Afghanistan	642	[491.6-838.4]	1.8	3.9	391	[280.8-544.4]	2.1	4.9	251	[159.9-394.1]	1.4	3
Albania	435	[374.3-505.5]	14.8	7.8	265	[218.1-322.0]	17.9	10	170	[134.3-215.2]	11.7	5.7
Algeria	563	[455.6-695.7]	1.3	1.4	311	[231.8-417.3]	1.5	1.6	252	[185.8-341.8]	1.2	1.3
Angola	581	[368.5-915.9]	1.9	3.6	382	[225.1-648.2]	2.5	5.2	199	[81.3-486.8]	1.3	2.3
Argentina	2 343	[2028.2-2706.6]	5.2	3.6	1 364	[1134.2-1640.3]	6.2	5	979	[776.7-1234.0]	4.3	2.5
Armenia	474	[370.1-607.1]	16.2	9.7	263	[206.2-335.5]	19.1	13.5	211	[57.5-775.0]	13.6	6.9
Australia	2 438	[2235.6-2658.7]	9.8	5.7	1 729	[1572.3-1901.4]	14	8.6	709	[574.1-875.6]	5.7	2.9
Austria	1 121	[970.7-1294.6]	12.8	5.4	750	[629.9-893.0]	17.5	8.2	371	[287.6-478.7]	8.3	3
Azerbaijan	384	[338.4-435.7]	3.9	3.6	192	[161.9-227.8]	3.9	4.1	192	[159.1-231.7]	3.9	3.2
Bahamas	14	[7.2-27.2]	3.5	2.3	10	[4.1-24.4]	5.1	3.9	4	[1.5-10.8]	2	1.1
Bahrain	30	[19.1-47.2]	1.9	3.4	20	[11.1-36.0]	2	3.9	10	[4.9-20.4]	1.7	2.7
Bangladesh	3 128	[2395.3-4084.9]	1.9	2.2	2 352	[1689.1-3275.0]	2.8	3.3	776	[494.2-1218.5]	0.94	1.1
Barbados	14	[7.2-27.1]	4.9	2.4	7	[2.7-18.1]	5.1	3	7	[2.8-17.6]	4.7	1.9
Belarus	555	[471.5-653.3]	5.9	3.3	318	[262.1-385.8]	7.2	4.9	237	[174.9-321.2]	4.7	2.1
Belgium	1 006	[929.9-1088.3]	8.7	4.3	638	[585.3-695.4]	11.2	5.9	368	[292.9-462.3]	6.3	2.9
Belize	19	[11.0-32.7]	5	8.4	14	[6.8-28.7]	7.4	12.2	5	[2.2-11.5]	2.6	4.4
Benin	298	[196.8-451.3]	2.6	5.1	233	[129.9-417.8]	4.1	9.8	65	[36.0-117.3]	1.1	2.1
Bhutan	35	[30.8-39.7]	4.3	5.3	28	[23.9-32.8]	6.5	7.8	7	[5.7-8.6]	1.8	2.3
Bolivia, Plurinational State of	678	[585.7-784.8]	6	6.1	303	[243.2-377.5]	5.4	5.6	375	[308.3-456.2]	6.7	6.7
Bosnia and Herzegovina	552	[454.5-670.4]	15.8	7.4	295	[228.3-381.2]	17.1	9.1	257	[190.8-346.2]	14.4	5.9
Botswana	62	[44.4-86.6]	2.7	3.9	40	[26.3-60.9]	3.5	6.4	22	[12.7-38.1]	1.9	2.3
Brazil	12 463	[11341.2-13695.8]	5.9	4.7	7 317	[6491.1-8248.0]	7.1	6.3	5 146	[4415.6-5997.2]	4.8	3.4
Brunei	38	[23.0-62.8]	8.8	9.9	32	[17.7-57.9]	14.3	17	6	[2.4-15.3]	2.8	3.1
Bulgaria	559	[491.7-635.6]	7.9	3.6	377	[298.3-476.4]	11	5.7	182	[155.7-212.7]	5	1.8
Burkina Faso	1 296	[553.2-3036.0]	6.6	13.8	789	[319.9-1946.2]	8	19.2	507	[39.4-6517.7]	5.1	9.7
Burundi	400	[211.8-755.3]	3.6	6.3	270	[118.6-614.4]	4.9	9	130	[47.7-354.1]	2.3	3.9

Cabo Verde	44	[29.2-66.4]	8	10.7	24	[13.6-42.3]	8.7	11.3	20	[11.0-36.3]	7.2	9.3
Cambodia	2 546	[1376.1-4710.4]	15.7	21.8	1 691	[810.9-3526.2]	21.3	34.6	855	[275.1-2656.9]	10.3	12.7
Cameroon	955	[617.8-1476.4]	3.9	6.1	724	[436.5-1200.9]	5.9	9.3	231	[98.1-543.8]	1.9	3.1
Canada	3 889	[3592.5-4210.0]	10.5	5.3	2 608	[2364.3-2876.9]	14.2	7.6	1 281	[1119.5-1465.8]	6.9	3.2
Central African Republic	149	[94.5-234.9]	3.1	5.1	104	[61.3-176.5]	4.5	7.5	45	[18.4-110.1]	1.9	3.1
Chad	405	[256.9-638.5]	2.6	5.5	280	[165.0-475.1]	3.6	7.8	125	[51.1-305.8]	1.6	3.4
Chile	1 582	[1230.7-2033.6]	8.7	5.4	871	[618.9-1225.8]	9.7	6.9	711	[491.0-1029.7]	7.7	4.2
China	392 868	[386346.0-399500.0]	27.6	18.3	292 898	[287242.0-298665.0]	40	27.6	99 970	[96758.9-103288.0]	14.5	9
Colombia	2 279	[1874.9-2770.3]	4.6	3.9	1 195	[915.2-1560.3]	4.9	4.6	1 084	[814.0-1443.5]	4.3	3.3
Comoros	29	[15.4-54.8]	3.5	5.7	18	[7.9-41.0]	4.3	7.6	11	[4.0-30.0]	2.7	4.1
Congo, Democratic Republic of	3 613	[2291.8-5695.9]	4.3	8	2 431	[1432.6-4125.1]	5.8	11.5	1 182	[483.2-2891.5]	2.8	5
Congo, Republic of	207	[157.7-271.7]	3.8	5.9	146	[105.1-202.7]	5.4	8.6	61	[37.6-99.1]	2.3	3.4
Costa Rica	427	[297.4-613.1]	8.6	6.3	248	[142.8-430.6]	10	7.9	179	[110.9-289.0]	7.2	4.8
Croatia	639	[549.6-742.9]	15.3	6.3	410	[343.8-488.9]	20.4	9.9	229	[171.2-306.3]	10.6	3.4
Cuba	837	[730.9-958.4]	7.3	3.8	498	[419.4-591.3]	8.7	4.7	339	[271.9-422.6]	5.9	2.9
Cyprus	75	[55.3-101.8]	6.3	3.4	51	[35.1-74.1]	8.6	5	24	[14.1-40.9]	4	2
Czechia	1 063	[946.6-1193.7]	10	4.2	679	[592.7-777.8]	13	6.1	384	[307.4-479.7]	7.1	2.6
Côte d'Ivoire	1 121	[932.5-1347.6]	4.5	8.4	703	[562.0-879.4]	5.6	9.7	418	[302.5-577.6]	3.4	6.9
Denmark	611	[537.3-694.8]	10.6	4.9	426	[364.9-497.4]	14.9	7.3	185	[146.9-233.0]	6.4	2.6
Djibouti	19	[10.1-35.9]	2	2.6	11	[4.8-25.0]	2.3	3.1	8	[2.9-21.8]	1.7	2.2
Dominican Republic	718	[587.6-877.3]	6.6	6.5	400	[304.1-526.2]	7.4	7.6	318	[237.0-426.6]	5.8	5.5
Ecuador	979	[846.0-1132.9]	5.8	5.3	483	[389.7-598.6]	5.7	5.7	496	[406.4-605.3]	5.9	4.9
Egypt	25 399	[23831.9-27069.1]	25.6	32.2	18 471	[17185.0-19853.3]	36.8	49	6 928	[6050.8-7932.4]	14.1	16.7
El Salvador	514	[417.9-632.1]	8	6.7	208	[156.0-277.3]	6.9	6.4	306	[227.1-412.3]	9	6.9
Equatorial Guinea	44	[27.9-69.4]	3.3	4.7	34	[20.0-57.7]	4.7	6	10	[4.1-24.5]	1.7	3
Eritrea	92	[48.7-173.7]	1.8	3.3	50	[22.0-113.8]	1.9	3.7	42	[15.4-114.4]	1.6	2.9
Estonia	103	[82.3-128.9]	7.9	3.2	61	[45.4-82.0]	10	5.1	42	[29.8-59.2]	6.1	2
Eswatini	37	[25.3-54.0]	2.7	3.9	20	[12.0-33.4]	3	5	17	[9.7-29.8]	2.4	3.2
Ethiopia	1 608	[1052.3-2457.1]	1.5	2.7	749	[409.9-1368.7]	1.4	2.6	859	[473.1-1559.6]	1.6	2.7
Fiji	76	[65.3-88.4]	8.3	8.3	53	[44.2-63.5]	11.5	12.3	23	[17.4-30.4]	5.1	4.9
Finland	550	[475.8-635.7]	9.9	3.6	347	[283.3-425.0]	12.7	5.2	203	[165.1-249.7]	7.2	2.3
France	10 624	[10156.6-11112.9]	16.3	7.8	8 382	[7967.5-8818.1]	26.1	13.3	2 242	[2033.8-2471.5]	6.8	2.7

France, Guadeloupe	34	[21.8-53.1]	7.6	3.7	22	[12.7-38.1]	10.6	6.2	12	[5.6-25.7]	5	1.7
France, La Réunion	85	[65.0-111.2]	9.6	6	58	[41.8-80.4]	13.6	9.1	27	[16.8-43.3]	5.9	3.3
France, Martinique	39	[26.8-56.8]	10.1	4.1	25	[15.6-40.0]	14.3	5.9	14	[7.5-26.3]	6.7	2.7
France, New Caledonia	38	[24.5-58.9]	13.6	10.4	25	[14.8-42.3]	17.7	14.3	13	[5.9-28.5]	9.4	6.9
French Guiana	21	[11.0-40.1]	7.2	8.5	18	[8.0-40.6]	12.4	15.5	3	[1.0-8.7]	2.1	2.3
French Polynesia	34	[22.3-51.9]	11.9	9.5	23	[11.7-45.3]	15.8	13.4	11	[6.4-19.0]	7.8	5.6
Gabon	55	[36.9-81.9]	2.7	3.3	35	[21.5-56.9]	3.3	3.9	20	[10.0-40.1]	2	2.6
Gaza Strip and West Bank	47	[24.1-91.8]	0.93	1.8	31	[14.5-66.4]	1.2	2.4	16	[3.9-65.3]	0.64	1.3
Georgia	380	[322.7-447.5]	9.7	5.4	235	[198.7-278.0]	12.6	8.3	145	[81.0-259.4]	7.1	3.1
Germany	8 883	[8277.0-9533.3]	10.8	4.2	6 191	[5716.5-6704.9]	15.3	6.4	2 692	[2311.4-3135.2]	6.4	2.3
Ghana	2 753	[2402.2-3155.0]	9.3	15.4	2 016	[1717.8-2365.9]	13.7	24.4	737	[568.3-955.7]	5	7.6
Greece	1 642	[1486.9-1813.2]	14.7	5.7	1 121	[986.4-1274.0]	20.4	8.6	521	[445.3-609.6]	9.2	3.3
Guam	31	[25.3-37.9]	18.7	14.8	25	[20.0-31.2]	29.8	24.5	6	[3.7-9.8]	7.3	5.3
Guatemala	1 787	[1592.4-2005.4]	10.4	14.9	854	[723.0-1008.8]	10.1	15.8	933	[795.3-1094.6]	10.7	14.1
Guinea	1 582	[1242.4-2014.4]	12.1	21.8	969	[717.7-1308.3]	14.8	27.9	613	[408.0-921.0]	9.4	16.3
Guinea-Bissau	126	[53.8-295.2]	6.6	11.9	84	[34.1-207.2]	8.9	17.3	42	[3.3-539.9]	4.3	7.3
Guyana	20	[11.9-33.7]	2.6	2.7	10	[4.9-20.5]	2.5	2.7	10	[4.7-21.5]	2.6	2.7
Haiti	664	[543.7-810.9]	6	8.1	354	[288.2-434.8]	6.4	9.5	310	[132.7-724.1]	5.5	6.8
Honduras	403	[300.0-541.4]	4.3	5.7	302	[206.1-442.5]	6.4	9.2	101	[63.4-160.8]	2.1	2.7
Hungary	1 087	[959.0-1232.1]	11.2	5.4	770	[665.5-890.9]	16.7	9.2	317	[248.3-404.8]	6.2	2.4
Iceland	15	[9.0-25.0]	4.4	2.5	12	[6.2-23.4]	7.1	4.1	3	[1.4-6.6]	1.8	0.95
India	27 670	[26091.1-29344.5]	2	2.2	18 807	[17531.4-20175.5]	2.7	3.1	8 863	[7961.8-9866.2]	1.4	1.4
Indonesia	18 468	[16124.1-21152.6]	6.9	7.6	14 238	[12130.6-16711.6]	10.6	12.4	4 230	[3276.2-5461.5]	3.2	3.4
Iran, Islamic Republic of	3 492	[3303.2-3691.6]	4.3	4.7	1 999	[1860.1-2148.3]	4.8	5.3	1 493	[1368.0-1629.4]	3.7	4.1
Iraq	539	[478.6-607.0]	1.4	2.7	278	[236.4-326.9]	1.4	3.1	261	[219.2-310.8]	1.3	2.4
Ireland	363	[301.4-437.2]	7.6	4.3	275	[207.5-364.5]	11.5	6.8	88	[68.6-112.8]	3.6	2
Israel	336	[281.8-400.6]	4	2.6	200	[159.9-250.2]	4.8	3.5	136	[102.4-180.6]	3.2	1.7
Italy	12 325	[11947.7-12714.2]	20.8	7.9	8 742	[8418.2-9078.3]	30.2	12.8	3 583	[3391.8-3784.9]	11.8	3.5
Jamaica	106	[80.2-140.1]	3.7	2.9	55	[37.8-80.1]	3.8	3	51	[33.6-77.3]	3.5	2.8
Japan	35 535	[34730.5-36358.1]	27.9	7.6	23 448	[22796.6-24118.0]	37.8	12.3	12 087	[11621.1-12571.5]	18.6	3.5
Jordan	188	[148.6-237.8]	1.9	3.1	101	[74.4-137.2]	2	3.4	87	[60.3-125.6]	1.8	2.7
Kazakhstan	1 122	[1045.7-1203.9]	6.1	5.6	655	[597.0-718.6]	7.3	8.2	467	[419.0-520.5]	4.9	3.9

Kenya	1 346	[1050.6-1724.5]	2.6	5.3	761	[556.8-1040.0]	3	6.2	585	[389.4-878.9]	2.3	4.5
Korea, Democratic Republic of	5 718	[5354.5-6106.2]	22.3	16.5	3 831	[3524.8-4163.8]	30.6	25.4	1 887	[1695.9-2099.6]	14.4	9
Korea, Republic of	16 510	[15880.0-17165.0]	32.3	17.3	12 180	[11648.7-12735.6]	47.6	27.7	4 330	[3998.8-4688.6]	16.9	8.2
Kuwait	121	[94.5-155.0]	2.9	5.2	88	[65.4-118.3]	3.7	6.2	33	[21.0-51.8]	1.8	3.7
Kyrgyzstan	456	[371.5-559.7]	7.4	9.5	267	[200.2-356.1]	8.8	13	189	[141.2-252.9]	6.1	6.9
Lao People's Democratic Republic	1 035	[559.4-1914.9]	14.9	22.4	712	[341.4-1484.7]	20.5	33.4	323	[103.9-1003.7]	9.3	13.1
Latvia	152	[112.4-205.5]	7.9	3.1	63	[43.0-92.3]	7.1	3.8	89	[54.4-145.7]	8.5	2.6
Lebanon	227	[185.8-277.3]	3.7	3.2	133	[102.4-172.8]	4.4	3.6	94	[68.9-128.2]	3.1	2.6
Lesotho	68	[39.0-118.4]	3	4.4	41	[20.3-82.7]	3.7	6.6	27	[10.9-66.8]	2.3	3
Liberia	412	[175.9-965.1]	8.5	15.2	247	[100.1-609.3]	10.1	18.9	165	[12.8-2121.1]	6.9	11.7
Libya	191	[125.0-291.8]	3	4.1	98	[55.9-171.9]	3	4.4	93	[48.8-177.3]	2.9	3.8
Lithuania	246	[206.6-292.9]	8.6	3.8	160	[121.7-210.3]	12.1	6.5	86	[68.4-108.1]	5.5	1.9
Luxembourg	70	[48.8-100.5]	11.9	6.5	48	[30.8-74.8]	16.2	9.1	22	[11.8-41.0]	7.5	4.2
Madagascar	898	[475.6-1695.7]	3.4	5.8	584	[256.6-1329.0]	4.5	8.3	314	[115.3-855.3]	2.4	3.6
Malawi	291	[162.5-521.2]	1.5	2.1	167	[78.6-354.9]	1.8	2.4	124	[49.5-310.7]	1.3	1.8
Malaysia	1 944	[1785.5-2116.6]	6.1	6.3	1 460	[1322.7-1611.5]	8.8	9.5	484	[409.4-572.1]	3.1	3.1
Maldives	27	[20.7-35.3]	6.1	8.3	22	[15.8-30.6]	8.7	12.3	5	[3.2-7.9]	2.6	3.7
Mali	598	[473.6-755.0]	3.1	6.3	438	[335.3-572.2]	4.6	10.2	160	[99.3-257.8]	1.7	2.9
Malta	22	[13.9-34.8]	5.1	2.2	15	[8.4-26.9]	6.9	3.5	7	[3.3-14.6]	3.3	0.94
Mauritania	320	[136.6-749.6]	7	11.3	221	[89.6-545.1]	9.7	16.8	99	[7.7-1272.7]	4.4	6.6
Mauritius	63	[46.6-85.1]	5	3.2	36	[24.3-53.3]	5.7	4	27	[16.9-43.2]	4.2	2.6
Mexico	7 265	[6896.2-7653.6]	5.6	5.4	3 450	[3220.8-3695.5]	5.3	5.5	3 815	[3522.2-4132.1]	5.8	5.4
Mongolia	2 241	[2129.2-2358.6]	71.8	93.7	1 299	[1214.3-1389.6]	84.2	117	942	[870.8-1019.0]	59.7	74.1
Montenegro	52	[34.8-77.6]	8.3	3.9	33	[19.8-55.0]	10.6	5.7	19	[10.0-36.2]	6	2.5
Morocco	428	[294.4-622.3]	1.2	1.1	243	[147.9-399.3]	1.4	1.4	185	[104.7-326.9]	1	0.95
Mozambique	1 200	[953.3-1510.5]	3.9	6.6	675	[499.9-911.4]	4.5	8.8	525	[366.9-751.1]	3.4	5
Myanmar	5 304	[2866.9-9812.9]	9.8	10.1	3 532	[1693.8-7365.1]	13.4	14.6	1 772	[570.2-5506.5]	6.4	6.2
Namibia	48	[30.2-76.2]	1.9	2.8	31	[17.3-55.7]	2.5	4.2	17	[8.0-36.2]	1.3	1.8
Nepal	282	[195.5-406.8]	0.95	1.1	175	[110.2-277.8]	1.2	1.5	107	[58.7-195.1]	0.7	0.82
New Zealand	483	[398.0-586.2]	10.2	5.8	386	[267.1-557.8]	16.5	10	97	[76.9-122.4]	4	2
Nicaragua	565	[470.3-678.7]	9	10.5	322	[256.8-403.7]	10.4	13.6	243	[177.6-332.4]	7.6	8
Niger	775	[505.4-1188.4]	3.5	7.3	587	[355.8-968.3]	5.2	11.5	188	[82.7-427.6]	1.7	3.3

Nigeria	5 129	[3969.6-6626.9]	2.6	5.1	3 087	[2271.3-4195.7]	3.1	5.9	2 042	[1281.7-3253.2]	2.1	4.3
Norway	334	[280.6-397.5]	6.2	3.4	248	[191.3-321.4]	9.2	5.3	86	[68.0-108.7]	3.2	1.5
Oman	117	[80.4-170.3]	2.4	4.4	90	[56.8-142.7]	2.8	5.8	27	[14.1-51.6]	1.7	2.7
Pakistan	4 381	[3740.5-5131.2]	2.2	3.1	2 729	[2244.4-3318.3]	2.6	3.8	1 652	[1262.9-2160.9]	1.7	2.3
Panama	249	[195.8-316.7]	6	4.8	115	[82.3-160.7]	5.5	4.9	134	[94.8-189.4]	6.5	4.7
Papua New Guinea	732	[634.1-845.0]	8.7	11.9	425	[360.6-500.9]	9.9	14	307	[228.7-412.1]	7.4	10
Paraguay	181	[129.6-252.8]	2.6	2.8	115	[73.9-179.0]	3.3	3.7	66	[39.6-109.9]	1.9	2
Peru	2 317	[2021.7-2655.4]	7.1	6.6	1 104	[914.3-1333.1]	6.8	6.8	1 213	[995.8-1477.6]	7.4	6.4
Philippines	9 628	[9132.7-10150.2]	9	11.5	6 848	[6430.4-7292.7]	12.8	17.8	2 780	[2522.5-3063.7]	5.3	6.2
Poland	2 569	[2346.3-2812.9]	6.7	3.2	1 541	[1364.3-1740.6]	8.4	4.7	1 028	[897.4-1177.6]	5.2	2.1
Portugal	1 386	[1234.7-1555.8]	13.5	5.4	983	[859.6-1124.1]	20.2	9.2	403	[321.0-506.0]	7.4	2.2
Puerto Rico	351	[310.6-396.7]	9.6	5.2	251	[219.6-286.9]	14.3	8.9	100	[68.7-145.5]	5.3	2.3
Qatar	42	[31.5-56.1]	1.6	4.1	37	[26.5-51.7]	1.8	5.7	5	[2.8-8.9]	0.74	1.8
Republic of Moldova	852	[708.4-1024.7]	21.1	13.8	539	[430.5-674.8]	27.8	20.9	313	[226.4-432.7]	14.9	8.4
Romania	3 451	[3253.3-3660.7]	17.6	8.4	2 229	[2065.1-2405.9]	23.5	12.7	1 222	[1113.6-1340.9]	12.1	4.9
Russian Federation	10 349	[10051.8-10655.0]	7.2	3.9	5 946	[5700.9-6201.6]	8.9	6	4 403	[4228.8-4584.4]	5.7	2.5
Rwanda	737	[498.4-1089.8]	5.9	10.1	483	[296.1-788.0]	7.9	14.7	254	[132.5-486.9]	4	6.6
Saint Lucia	4	[2.4-6.6]	2.2	1.5	3	[1.7-5.4]	3.4	2.2	1	[0.40-2.7]	1.1	0.83
Samoa	16	[10.0-25.7]	8.1	9.8	14	[6.6-29.9]	13.7	17.3	2	[1.1-3.7]	2.1	2.5
Sao Tome and Principe	8	[3.4-18.7]	3.8	8.3	7	[2.8-17.3]	6.7	14.8	1	[0.10-12.9]	0.95	2.6
Saudi Arabia	905	[764.2-1071.7]	2.7	4.5	676	[554.5-824.2]	3.5	6.2	229	[165.6-316.6]	1.6	2.5
Senegal	1 075	[458.9-2518.3]	6.6	12.6	673	[272.8-1660.1]	8.4	18	402	[31.3-5167.9]	4.9	8.4
Serbia	772	[671.3-887.8]	8.8	4.4	460	[383.8-551.3]	10.7	5.9	312	[250.4-388.8]	7	3.2
Sierra Leone	406	[370.8-444.6]	5.3	10	248	[222.7-276.2]	6.5	12.6	158	[133.5-187.0]	4.1	7.5
Singapore	1 378	[1234.4-1538.3]	23.8	12.3	1 000	[882.0-1133.7]	34.9	19.5	378	[277.0-515.8]	12.9	5.9
Slovakia	512	[461.2-568.4]	9.4	5	335	[294.2-381.5]	12.6	7.7	177	[148.5-210.9]	6.3	2.9
Slovenia	292	[243.0-350.8]	14	5.8	216	[166.6-280.1]	20.9	9.7	76	[58.7-98.4]	7.3	2.3
Solomon Islands	41	[34.5-48.7]	6.6	10.3	32	[26.1-39.3]	10.1	15.5	9	[6.6-12.4]	2.9	5.1
Somalia	253	[134.0-477.7]	1.7	3.4	132	[58.0-300.4]	1.7	3.6	121	[44.4-329.6]	1.6	3.2
South Africa	2 495	[2258.3-2756.5]	4.3	5	1 560	[1372.5-1773.2]	5.5	7.6	935	[797.8-1095.8]	3.2	3.3
South Sudan	397	[210.2-749.6]	3.1	5.1	249	[109.4-566.7]	3.8	6.5	148	[54.3-403.1]	2.3	3.8
Spain	6 630	[6218.4-7068.8]	14.3	6.5	4 976	[4616.0-5364.1]	21.9	10.9	1 654	[1462.6-1870.4]	7	2.4

Sri Lanka	767	[644.7-912.5]	3.7	2.7	472	[387.5-574.9]	4.7	3.6	295	[204.3-426.0]	2.7	1.9
Sudan	942	[640.2-1386.1]	2.3	3.8	581	[360.6-936.1]	2.8	4.8	361	[186.9-697.3]	1.7	2.8
Suriname	34	[22.7-51.0]	6	5.6	25	[14.9-42.0]	8.8	9	9	[4.7-17.2]	3.2	2.6
Sweden	974	[880.1-1077.9]	9.8	4.5	641	[567.0-724.7]	12.8	6.5	333	[278.2-398.6]	6.7	2.6
Switzerland	946	[875.7-1021.9]	11.1	4.8	664	[607.6-725.7]	15.7	7.3	282	[241.3-329.6]	6.5	2.7
Syrian Arab Republic	380	[194.6-742.2]	2.1	3	200	[93.4-428.1]	2.2	3.4	180	[44.1-734.9]	2	2.6
Tajikistan	272	[219.9-336.5]	3	4.7	163	[124.4-213.6]	3.6	6	109	[77.2-153.9]	2.4	3.7
Tanzania, United Republic of	1 537	[1081.3-2184.8]	2.6	4.9	1 162	[757.1-1783.4]	4	8.1	375	[202.6-694.2]	1.3	2.2
Thailand	23 296	[22644.5-23966.2]	33.7	21	16 299	[15759.3-16857.2]	48.3	32.2	6 997	[6638.4-7375.0]	19.7	11.4
The former Yugoslav Republic of Macedonia	185	[122.7-278.9]	8.9	5	121	[71.5-204.9]	11.6	7.1	64	[33.2-123.2]	6.1	3.1
The Netherlands	1 001	[891.7-1123.7]	5.9	2.5	620	[527.1-729.2]	7.3	3.4	381	[323.1-449.3]	4.4	1.8
The Republic of the Gambia	319	[273.7-371.9]	14.7	23.9	245	[205.5-292.1]	22.9	36.5	74	[54.1-101.3]	6.8	12
Timor-Leste	38	[20.5-70.3]	2.9	5.3	27	[12.9-56.3]	4	7.3	11	[3.5-34.2]	1.7	3.2
Togo	312	[280.2-347.5]	3.9	6.9	207	[182.0-235.4]	5.2	9.7	105	[86.2-127.9]	2.6	4.4
Trinidad and Tobago	66	[45.7-95.4]	4.8	3.3	36	[21.7-59.7]	5.3	3.9	30	[17.5-51.3]	4.3	2.8
Tunisia	355	[254.1-496.0]	3	2.6	163	[105.7-251.5]	2.8	2.5	192	[113.5-324.7]	3.3	2.7
Turkey	4 362	[3969.3-4793.5]	5.3	4.5	2 779	[2484.7-3108.1]	6.9	6.6	1 583	[1328.5-1886.2]	3.8	2.8
Turkmenistan	281	[237.9-331.8]	4.8	6	175	[141.4-216.5]	6.1	8.4	106	[81.2-138.3]	3.6	4.1
Uganda	1 811	[1416.2-2315.9]	4.1	7.6	1 169	[847.3-1612.8]	5.3	10.1	642	[438.5-939.9]	2.9	5.4
Ukraine	1 787	[1660.4-1923.2]	4.1	2.2	1 003	[910.7-1104.6]	4.9	3.2	784	[700.0-878.1]	3.3	1.6
United Arab Emirates	97	[76.6-122.9]	1	4.2	62	[46.2-83.2]	0.9	4.3	35	[23.5-52.0]	1.3	4.3
United Kingdom	7 618	[7346.6-7899.4]	11.4	5.1	4 832	[4625.2-5048.1]	14.7	7	2 786	[2611.0-2972.7]	8.3	3.3
United States of America	37 948	[37032.2-38886.5]	11.6	6.8	27 282	[26426.9-28164.8]	16.9	10.4	10 666	[10267.4-11080.1]	6.5	3.4
Uruguay	158	[123.5-202.2]	4.6	2.6	114	[78.7-165.1]	6.8	4.4	44	[31.5-61.4]	2.5	1.3
Uzbekistan	1 455	[1332.6-1588.7]	4.5	5.6	792	[705.3-889.4]	4.9	6.8	663	[579.4-758.7]	4.1	4.6
Vanuatu	28	[17.1-45.8]	9.9	13.1	22	[12.8-37.9]	15.4	20.2	6	[1.9-18.8]	4.3	6.2
Venezuela, Bolivarian Republic of	1 193	[1044.6-1362.5]	3.7	3.6	646	[523.7-796.8]	4	4.3	547	[460.8-649.4]	3.4	3
Viet Nam	25 335	[23627.6-27165.8]	26.3	23.2	19 568	[18064.2-21197.0]	41	39	5 767	[4999.5-6652.4]	11.8	9.5
Yemen	620	[511.0-752.3]	2.1	4.4	402	[315.1-512.9]	2.8	6.3	218	[158.6-299.7]	1.5	2.7
Zambia	194	[114.5-328.7]	1.1	2.2	108	[54.7-213.1]	1.2	2.8	86	[37.3-198.4]	0.97	1.8

Zimbabwe	577	[468.9-710.0]	3.4	6.9	321	[246.0-418.9]	3.9	8.7	256	[183.9-356.4]	3	5.6
World	841 080	[817635.0-865198.0]	11	9.3	596 574	[576976.0-616838.0]	15.5	13.9	244 506	[231861.0-257840.0]	6.5	4.9

Tab. SII. The age-standardized mortality rate of LC in 185 countries of the world in 2018.

Countries	**All**				**Male**				**Female**			
	Numbers	**Uncertainty interval**	**Crude Rate**	**ASR (W)**	**Numbers**	**Uncertainty interval**	**Crude Rate**	**ASR (W)**	**Numbers**	**Uncertainty interval**	**Crude Rate**	**ASR (W)**
Afghanistan	621	[487.6-790.9]	1.7	3.8	374	[277.1-504.9]	2	4.7	247	[164.1-371.8]	1.4	2.9
Albania	430	[370.0-499.7]	14.7	7.6	259	[213.1-314.8]	17.5	9.6	171	[135.1-216.5]	11.8	5.7
Algeria	544	[424.3-697.5]	1.3	1.4	302	[213.8-426.6]	1.4	1.6	242	[169.2-346.1]	1.2	1.2
Angola	547	[355.7-841.3]	1.8	3.5	350	[212.3-577.1]	2.3	4.8	197	[84.5-459.0]	1.3	2.3
Argentina	2 113	[1963.0-2274.4]	4.7	3.2	1 206	[1095.1-1328.2]	5.5	4.4	907	[809.3-1016.4]	4	2.3
Armenia	455	[370.9-558.2]	15.5	9.4	262	[214.2-320.4]	19	13.5	193	[65.9-565.6]	12.4	6.3
Australia	2 356	[2200.3-2522.8]	9.5	4.8	1 617	[1485.9-1759.6]	13.1	7.2	739	[657.8-830.2]	5.9	2.6
Austria	947	[852.6-1051.8]	10.8	4.3	696	[618.1-783.7]	16.2	7.2	251	[200.5-314.2]	5.6	1.8
Azerbaijan	374	[320.8-436.0]	3.8	3.5	184	[149.5-226.4]	3.7	3.9	190	[151.2-238.7]	3.8	3.2
Bahamas	14	[7.9-24.8]	3.5	2.3	10	[4.6-21.5]	5.1	3.9	4	[1.7-9.4]	2	1.1
Bahrain	28	[16.2-48.3]	1.8	3.3	18	[9.0-36.1]	1.8	3.7	10	[4.2-23.9]	1.7	2.7
Bangladesh	2 841	[2230.6-3618.4]	1.7	2	2 117	[1568.3-2857.7]	2.5	3.1	724	[481.0-1089.7]	0.88	0.99
Barbados	14	[7.8-25.0]	4.9	2.4	7	[3.0-16.1]	5.1	3	7	[3.1-15.7]	4.7	1.9
Belarus	374	[311.0-449.8]	4	2.2	249	[195.9-316.5]	5.7	3.8	125	[93.7-166.8]	2.5	1.1

Belgium	1 004	[926.6-1087.9]	8.7	3.6	630	[576.2-688.9]	11.1	5.1	374	[305.7-457.6]	6.4	2.1
Belize	19	[11.9-30.4]	5	8.4	14	[7.5-26.0]	7.4	12.2	5	[2.4-10.2]	2.6	4.4
Benin	309	[193.6-493.1]	2.7	5.3	237	[122.8-457.4]	4.1	9.9	72	[37.0-139.9]	1.3	2.3
Bhutan	33	[28.8-37.8]	4	5.1	27	[22.8-32.0]	6.2	7.6	6	[4.8-7.5]	1.6	2
Bolivia, Plurinational State of	667	[580.7-766.1]	5.9	6	299	[242.8-368.2]	5.3	5.5	368	[305.7-443.1]	6.6	6.6
Bosnia and Herzegovina	524	[473.3-580.2]	15	6.4	276	[240.0-317.4]	16	7.9	248	[213.8-287.7]	13.9	5.2
Botswana	60	[40.7-88.4]	2.6	3.8	39	[23.9-63.6]	3.4	6.3	21	[11.1-39.7]	1.8	2.2
Brazil	11 797	[11462.0-12141.8]	5.6	4.4	6 906	[6660.3-7160.7]	6.7	5.9	4 891	[4664.0-5129.1]	4.6	3.2
Brunei	31	[20.2-47.6]	7.1	8.3	26	[14.1-48.0]	11.6	14	5	[2.7-9.1]	2.4	2.8
Bulgaria	585	[515.5-663.9]	8.3	3.6	378	[328.0-435.6]	11.1	5.4	207	[156.5-273.8]	5.7	2
Burkina Faso	1 269	[682.7-2358.8]	6.4	13.5	771	[399.5-1488.1]	7.8	18.7	498	[77.5-3198.4]	5	9.5
Burundi	409	[213.6-783.0]	3.6	6.6	288	[124.3-667.2]	5.2	9.7	121	[43.5-336.8]	2.1	3.8
Cabo Verde	47	[32.7-67.5]	8.5	11.2	26	[15.8-42.8]	9.4	11.8	21	[12.4-35.5]	7.6	9.7
Cambodia	2 546	[1408.7-4601.4]	15.7	21.9	1 695	[839.2-3423.4]	21.4	34.7	851	[284.2-2548.5]	10.2	12.7
Cameroon	895	[581.9-1376.5]	3.6	6	683	[414.2-1126.1]	5.5	9.2	212	[91.0-494.0]	1.7	2.9
Canada	3 845	[3578.4-4131.4]	10.4	4.5	2 318	[2129.3-2523.5]	12.6	6	1 527	[1334.5-1747.3]	8.2	3.2
Central African Republic	133	[86.5-204.5]	2.8	4.8	91	[55.2-150.0]	3.9	6.9	42	[18.0-97.9]	1.7	2.9
Chad	372	[241.9-572.1]	2.4	5.3	254	[154.1-418.8]	3.3	7.5	118	[50.6-275.0]	1.5	3.3
Chile	1 448	[1336.6-1568.7]	8	4.9	781	[701.3-869.8]	8.7	6.1	667	[591.7-751.9]	7.3	3.9
China	368 960	[363309.0-374699.0]	25.9	17.1	273 014	[268132.0-277985.0]	37.3	25.6	95 946	[93128.5-98848.7]	13.9	8.6

Colombia	2 216	[2048.6-2397.1]	4.5	3.8	1 156	[995.2-1342.7]	4.8	4.5	1 060	[966.6-1162.5]	4.2	3.2
Comoros	28	[14.6-53.6]	3.4	5.8	18	[7.8-41.7]	4.3	7.8	10	[3.6-27.8]	2.4	3.9
Congo, Democratic Republic of	3 624	[2356.4-5573.6]	4.3	8.1	2 479	[1503.5-4087.3]	5.9	11.9	1 145	[491.4-2668.1]	2.7	4.9
Congo, Republic of	186	[136.9-252.6]	3.4	5.4	131	[90.5-189.6]	4.8	8	55	[31.9-95.0]	2	3.2
Costa Rica	395	[331.3-470.9]	8	5.6	238	[188.7-300.2]	9.6	7.2	157	[120.0-205.4]	6.3	4.1
Croatia	547	[483.6-618.7]	13.1	5.2	364	[314.8-420.8]	18.1	8.4	183	[145.0-231.0]	8.5	2.6
Cuba	773	[691.1-864.6]	6.7	3.3	448	[388.7-516.3]	7.8	4.1	325	[270.9-390.0]	5.7	2.6
Cyprus	101	[77.6-131.5]	8.5	4.6	64	[46.1-88.9]	10.8	6.3	37	[23.8-57.5]	6.2	3
Czechia	874	[784.7-973.4]	8.2	3.2	565	[491.2-649.9]	10.8	4.8	309	[261.0-365.8]	5.7	2
Côte d'Ivoire	1 130	[914.3-1396.5]	4.5	8.4	712	[550.3-921.2]	5.6	9.8	418	[288.2-606.3]	3.4	6.9
Denmark	580	[501.2-671.2]	10.1	4.2	370	[304.9-449.1]	12.9	5.9	210	[168.1-262.3]	7.3	2.6
Djibouti	17	[8.9-32.5]	1.8	2.4	10	[4.3-23.2]	2.1	2.9	7	[2.5-19.5]	1.4	2
Dominican Republic	650	[548.9-769.8]	6	5.8	353	[280.1-444.9]	6.5	6.7	297	[231.8-380.6]	5.4	5
Ecuador	953	[860.4-1055.6]	5.7	5.1	471	[405.2-547.5]	5.6	5.5	482	[419.3-554.1]	5.7	4.7
Egypt	25 084	[23515.3-26757.3]	25.2	31.8	18 209	[16924.1-19591.5]	36.2	48.4	6 875	[5993.1-7886.7]	14	16.6
El Salvador	500	[416.7-599.9]	7.8	6.5	202	[156.8-260.2]	6.7	6.2	298	[229.2-387.4]	8.8	6.8
Equatorial Guinea	42	[27.3-64.6]	3.2	4.9	33	[20.0-54.4]	4.5	6.5	9	[3.9-21.0]	1.5	2.9
Eritrea	90	[47.0-172.3]	1.7	3.2	49	[21.2-113.5]	1.9	3.7	41	[14.7-114.1]	1.6	2.8
Estonia	95	[76.6-117.9]	7.3	2.9	57	[43.0-75.6]	9.3	4.8	38	[27.2-53.1]	5.5	1.6
Eswatini	35	[22.4-54.6]	2.5	3.9	19	[10.4-34.7]	2.8	5	16	[8.3-30.9]	2.2	3.2
Ethiopia	1 656	[1032.5-2655.9]	1.5	2.7	759	[387.7-1485.8]	1.4	2.7	897	[461.5-1743.3]	1.7	2.8

Fiji	75	[56.2-100.2]	8.2	8.2	53	[37.6-74.7]	11.5	12.2	22	[12.8-37.7]	4.9	4.6
Finland	579	[507.0-661.2]	10.4	3.6	377	[312.9-454.2]	13.8	5.5	202	[167.2-244.1]	7.2	2.1
France	10 063	[9742.7-10393.8]	15.4	6.3	7 376	[7117.9-7643.5]	23	10.4	2 687	[2487.4-2902.6]	8.1	2.6
France, Guadeloupe	30	[19.9-45.2]	6.7	2.6	20	[12.0-33.4]	9.6	4.2	10	[5.0-19.9]	4.1	1.3
France, La Réunion	89	[69.1-114.6]	10.1	6.1	60	[44.0-81.9]	14	9.3	29	[18.8-44.7]	6.4	3.3
France, Martinique	38	[26.1-55.4]	9.9	3.8	22	[13.4-36.2]	12.6	5.1	16	[9.0-28.4]	7.6	2.7
France, New Caledonia	26	[16.8-40.3]	9.3	6.8	19	[11.3-32.0]	13.5	10.6	7	[3.1-15.6]	5	3.4
French Guiana	12	[7.5-19.2]	4.1	4.9	11	[5.2-23.3]	7.6	9.5	1	[0.50-1.8]	0.69	0.7
French Polynesia	34	[22.3-51.8]	11.9	9.5	23	[12.2-43.3]	15.8	13.4	11	[6.2-19.4]	7.8	5.6
Gabon	52	[35.4-76.4]	2.5	3.3	33	[20.6-52.8]	3.1	3.9	19	[9.7-37.2]	1.9	2.6
Gaza Strip and West Bank	45	[24.8-81.7]	0.89	1.8	30	[15.3-58.9]	1.2	2.4	15	[4.3-52.9]	0.6	1.2
Georgia	370	[319.4-428.6]	9.5	5.2	227	[195.2-264.0]	12.2	8	143	[84.8-241.3]	7	3
Germany	8 643	[8358.0-8937.7]	10.5	3.8	5 936	[5685.9-6197.1]	14.6	5.7	2 707	[2566.0-2855.7]	6.5	2.1
Ghana	2 737	[2351.4-3185.8]	9.3	15.4	2 000	[1673.3-2390.5]	13.6	24.3	737	[551.7-984.5]	5	7.6
Greece	1 478	[1355.7-1611.4]	13.3	4.5	984	[880.2-1100.0]	17.9	6.7	494	[430.8-566.4]	8.7	2.7
Guam	25	[19.8-31.5]	15.1	11.9	20	[15.4-26.0]	23.8	19.2	5	[3.1-8.1]	6.1	4.9
Guatemala	1 741	[1578.0-1920.8]	10.1	14.5	832	[721.8-959.0]	9.8	15.4	909	[793.3-1041.6]	10.4	13.8
Guinea	1 413	[1098.3-1817.8]	10.8	19.5	866	[633.2-1184.3]	13.2	25	547	[357.8-836.2]	8.4	14.5
Guinea-Bissau	127	[68.3-236.1]	6.7	12	85	[44.0-164.1]	9.1	17.5	42	[6.5-269.7]	4.3	7.4
Guyana	20	[12.2-32.7]	2.6	2.8	10	[5.0-20.0]	2.5	2.8	10	[5.0-20.0]	2.6	2.7
Haiti	653	[539.3-790.6]	5.9	7.8	347	[285.0-422.5]	6.3	9.1	306	[135.9-689.2]	5.4	6.6
Honduras	378	[320.9-445.2]	4	5.4	275	[218.2-346.6]	5.9	8.2	103	[81.7-129.8]	2.2	2.9
Hungary	920	[829.5-1020.4]	9.5	4.4	628	[556.7-708.5]	13.6	7.3	292	[238.6-357.4]	5.8	2.1

Iceland	24	[16.9-34.1]	7.1	3.5	17	[9.9-29.3]	10	5.1	7	[4.4-11.1]	4.2	2
India	25 627	[24053.8-27303.2]	1.9	2	17 548	[16268.1-18928.7]	2.5	2.8	8 079	[7196.8-9069.3]	1.2	1.3
Indonesia	18 148	[15797.0-20848.8]	6.8	7.5	14 047	[11925.3-16546.2]	10.5	12.3	4 101	[3158.3-5325.1]	3.1	3.3
Iran, Islamic Republic of	3 439	[3311.2-3571.7]	4.2	4.7	1 977	[1881.3-2077.6]	4.8	5.2	1 462	[1378.8-1550.2]	3.6	4.1
Iraq	538	[472.1-613.1]	1.4	2.7	279	[233.5-333.4]	1.4	3.1	259	[213.7-313.9]	1.3	2.3
Ireland	380	[326.5-442.3]	7.9	4	245	[190.8-314.6]	10.3	5.7	135	[111.3-163.8]	5.6	2.5
Israel	397	[342.9-459.6]	4.7	3	234	[201.5-271.7]	5.6	4.1	163	[96.1-276.6]	3.8	2
Italy	10 535	[10214.5-10865.6]	17.8	5.7	7 127	[6846.9-7418.6]	24.6	9.2	3 408	[3246.8-3577.2]	11.2	2.7
Jamaica	103	[81.0-130.9]	3.6	2.7	54	[39.1-74.6]	3.7	2.9	49	[34.3-70.1]	3.4	2.6
Japan	28 986	[28306.8-29681.5]	22.8	5.4	18 539	[17987.1-19107.9]	29.9	8.6	10 447	[10055.0-10854.2]	16	2.7
Jordan	178	[135.6-233.6]	1.8	2.9	95	[66.8-135.1]	1.9	3.3	83	[54.2-127.2]	1.7	2.6
Kazakhstan	989	[920.0-1063.2]	5.4	5	605	[551.7-663.4]	6.8	7.6	384	[341.7-431.6]	4	3.3
Kenya	1 331	[1004.0-1764.6]	2.6	5.3	752	[527.0-1073.0]	3	6.2	579	[364.4-920.1]	2.3	4.4
Korea, Democratic Republic of	5 246	[4891.0-5626.7]	20.5	15	3 498	[3194.0-3830.9]	27.9	23.5	1 748	[1566.0-1951.2]	13.4	8
Korea, Republic of	12 122	[11758.6-12496.6]	23.7	11.8	8 819	[8516.9-9131.8]	34.5	19.5	3 303	[3102.9-3516.0]	12.9	5.2
Kuwait	114	[84.2-154.3]	2.7	5	82	[57.5-116.9]	3.4	6	32	[18.2-56.2]	1.8	3.6
Kyrgyzstan	415	[351.0-490.7]	6.8	8.7	252	[199.1-319.0]	8.3	12.2	163	[128.4-206.9]	5.3	6
Lao People's Democratic Republic	1 032	[571.0-1865.1]	14.8	22.4	713	[353.0-1440.0]	20.5	33.4	319	[106.5-955.3]	9.1	13
Latvia	138	[113.6-167.6]	7.2	3.1	87	[69.5-108.9]	9.8	5.3	51	[34.1-76.2]	4.9	1.6
Lebanon	216	[172.5-270.5]	3.5	3	127	[94.6-170.5]	4.2	3.5	89	[62.8-126.1]	2.9	2.5
Lesotho	67	[39.2-114.6]	3	4.4	41	[20.8-80.9]	3.7	6.6	26	[10.8-62.5]	2.2	3

Liberia	422	[227.0-784.4]	8.7	15.4	254	[131.6-490.2]	10.4	19.2	168	[26.2-1079.0]	7	11.9
Libya	147	[93.6-230.8]	2.3	3.3	71	[39.0-129.1]	2.2	3.4	76	[38.2-151.0]	2.4	3.1
Lithuania	222	[181.4-271.7]	7.7	3.3	136	[104.8-176.5]	10.3	5.5	86	[62.5-118.4]	5.5	1.8
Luxembourg	53	[39.1-71.9]	9	4.4	36	[24.8-52.3]	12.1	6.5	17	[10.0-28.8]	5.8	2.5
Madagascar	908	[474.3-1738.4]	3.5	6	586	[252.9-1357.6]	4.5	8.5	322	[115.7-896.4]	2.4	3.8
Malawi	312	[163.0-597.3]	1.6	2.5	185	[79.9-428.6]	1.9	2.9	127	[45.6-353.5]	1.3	2
Malaysia	1 933	[1760.2-2122.7]	6	6.3	1 467	[1315.9-1635.5]	8.9	9.6	466	[387.6-560.3]	3	3
Maldives	26	[25.8-26.2]	5.9	8.2	21	[20.8-21.2]	8.3	12.1	5	[4.9-5.1]	2.6	3.7
Mali	545	[416.8-712.6]	2.9	5.9	402	[295.6-546.7]	4.2	9.7	143	[82.6-247.5]	1.5	2.7
Malta	24	[15.5-37.2]	5.6	2.4	16	[9.2-27.9]	7.4	3.6	8	[3.9-16.4]	3.7	1.1
Mauritania	326	[175.4-606.0]	7.2	11.5	224	[116.1-432.3]	9.8	16.9	102	[15.9-655.1]	4.5	6.7
Mauritius	53	[38.9-72.1]	4.2	2.7	27	[17.6-41.4]	4.3	2.9	26	[16.7-40.6]	4.1	2.4
Mexico	6 868	[6578.5-7170.2]	5.3	5.1	3 361	[3175.3-3557.5]	5.2	5.3	3 507	[3283.0-3746.3]	5.3	4.9
Mongolia	1 773	[1671.3-1880.9]	56.8	75.4	1 067	[988.2-1152.0]	69.1	98.4	706	[643.5-774.6]	44.7	56.8
Montenegro	52	[36.6-74.0]	8.3	3.9	33	[21.1-51.7]	10.6	5.7	19	[10.8-33.5]	6	2.5
Morocco	411	[270.9-623.6]	1.1	1.1	236	[135.7-410.4]	1.3	1.3	175	[92.8-330.0]	0.96	0.9
Mozambique	1 173	[905.2-1520.0]	3.8	6.7	700	[499.2-981.6]	4.7	9.4	473	[316.0-708.1]	3	4.7
Myanmar	5 360	[2965.8-9687.1]	10	10.1	3 571	[1768.1-7212.3]	13.6	14.7	1 789	[597.4-5357.6]	6.5	6.3
Namibia	47	[27.5-80.4]	1.8	2.9	31	[15.7-61.1]	2.5	4.2	16	[6.7-38.4]	1.2	1.8
Nepal	260	[181.6-372.2]	0.88	1	154	[97.9-242.2]	1.1	1.3	106	[58.8-191.0]	0.7	0.8
New Zealand	353	[292.6-425.9]	7.4	3.9	264	[192.7-361.7]	11.3	6.4	89	[70.2-112.9]	3.7	1.7
Nicaragua	533	[457.3-621.2]	8.5	9.9	290	[240.1-350.3]	9.4	12.3	243	[187.1-315.7]	7.6	8

Niger	759	[481.0-1197.7]	3.4	7.2	590	[345.9-1006.5]	5.3	11.5	169	[70.3-406.1]	1.5	3
Nigeria	5 154	[3920.8-6775.0]	2.6	5.1	3 192	[2300.6-4428.9]	3.2	6.1	1 962	[1193.5-3225.3]	2	4.2
Norway	328	[276.8-388.6]	6.1	2.9	220	[179.6-269.5]	8.1	4.2	108	[79.3-147.1]	4.1	1.7
Oman	111	[72.5-170.0]	2.3	4.3	86	[50.9-145.2]	2.7	5.6	25	[12.0-52.2]	1.5	2.6
Pakistan	4 222	[3585.2-4971.9]	2.1	3	2 608	[2130.5-3192.6]	2.5	3.6	1 614	[1222.5-2130.8]	1.7	2.2
Panama	238	[194.3-291.5]	5.7	4.6	112	[84.5-148.5]	5.4	4.7	126	[94.1-168.7]	6.1	4.5
Papua New Guinea	635	[373.9-1078.4]	7.5	10.9	354	[188.2-665.8]	8.3	12.5	281	[106.4-742.2]	6.8	9.4
Paraguay	182	[136.9-242.0]	2.6	2.9	114	[78.2-166.2]	3.3	3.7	68	[44.0-105.0]	2	2.1
Peru	2 239	[2074.3-2416.8]	6.9	6.3	1 057	[948.1-1178.4]	6.5	6.5	1 182	[1061.6-1316.1]	7.3	6.2
Philippines	9 485	[8937.5-10066.0]	8.9	11.4	6 776	[6312.7-7273.3]	12.6	17.7	2 709	[2428.3-3022.2]	5.1	6
Poland	2 230	[2092.9-2376.1]	5.9	2.7	1 305	[1194.3-1426.0]	7.1	3.9	925	[844.7-1013.0]	4.7	1.7
Portugal	1 372	[1217.2-1546.5]	13.3	5.2	980	[840.0-1143.3]	20.1	8.9	392	[324.1-474.1]	7.2	2.1
Puerto Rico	375	[327.9-428.9]	10.2	5.3	249	[207.0-299.5]	14.2	8.5	126	[103.7-153.2]	6.6	2.8
Qatar	40	[29.0-55.2]	1.5	4	35	[24.3-50.4]	1.7	5.6	5	[2.6-9.6]	0.74	1.8
Republic of Moldova	700	[601.9-814.1]	17.3	11.2	448	[372.8-538.4]	23.1	17.3	252	[193.4-328.4]	12	6.7
Romania	3 141	[2976.7-3314.4]	16	7.5	2 003	[1869.4-2146.1]	21.1	11.3	1 138	[1044.6-1239.8]	11.3	4.4
Russian Federation	11 192	[10886.5-11506.1]	7.8	4.1	6 432	[6187.1-6686.6]	9.6	6.4	4 760	[4575.8-4951.6]	6.2	2.6
Rwanda	704	[463.7-1068.9]	5.6	10.2	457	[271.0-770.7]	7.5	14.9	247	[123.3-494.8]	3.9	6.5
Saint Lucia	4	[2.6-6.2]	2.2	1.1	3	[1.8-5.0]	3.4	2	1	[0.40-2.4]	1.1	0.34
Samoa	7	[3.0-16.3]	3.5	4.8	5	[1.8-13.6]	4.9	7.1	2	[0.40-9.7]	2.1	2.6
Sao Tome and Principe	8	[3.8-16.8]	3.8	8.3	7	[3.2-15.4]	6.7	14.8	1	[0.10-9.2]	0.95	2.6

Saudi Arabia	852	[693.0-1047.5]	2.5	4.2	636	[499.2-810.3]	3.3	5.8	216	[145.4-320.9]	1.5	2.4
Senegal	1 083	[582.6-2013.1]	6.6	12.6	679	[351.8-1310.5]	8.5	18	404	[62.9-2594.7]	4.9	8.5
Serbia	892	[806.1-987.0]	10.2	4.7	515	[449.0-590.7]	12	6.3	377	[324.4-438.1]	8.4	3.5
Sierra Leone	374	[337.3-414.7]	4.8	9.5	225	[199.0-254.3]	5.9	11.9	149	[123.0-180.5]	3.8	7.2
Singapore	1 298	[1199.2-1405.0]	22.4	11.4	924	[840.8-1015.5]	32.3	17.7	374	[323.3-432.6]	12.8	5.7
Slovakia	473	[421.0-531.4]	8.7	4.3	302	[265.6-343.4]	11.4	6.7	171	[125.8-232.4]	6.1	2.5
Slovenia	268	[234.6-306.2]	12.9	5	175	[148.3-206.6]	16.9	7.6	93	[74.4-116.3]	8.9	2.6
Solomon Islands	55	[32.3-93.6]	8.8	13.7	43	[22.8-81.1]	13.6	20.7	12	[4.5-31.8]	3.9	6.7
Somalia	241	[125.9-461.4]	1.6	3.3	123	[53.1-285.0]	1.6	3.5	118	[42.4-328.5]	1.5	3.2
South Africa	2 388	[2231.2-2555.8]	4.2	4.8	1 484	[1362.9-1615.9]	5.3	7.2	904	[807.8-1011.6]	3.1	3.1
South Sudan	406	[212.1-777.3]	3.1	5.2	259	[111.8-600.0]	4	6.8	147	[52.8-409.2]	2.3	3.7
Spain	5 569	[5349.6-5797.4]	12	4.7	3 872	[3693.9-4058.7]	17	7.6	1 697	[1571.0-1833.0]	7.2	2
Sri Lanka	614	[497.3-758.2]	2.9	2.2	403	[317.2-512.0]	4	3.1	211	[135.1-329.6]	1.9	1.4
Sudan	906	[610.2-1345.2]	2.2	3.7	560	[343.7-912.4]	2.7	4.7	346	[176.4-678.6]	1.7	2.7
Suriname	43	[30.1-61.4]	7.6	7.1	26	[16.5-41.1]	9.1	9.7	17	[9.6-30.1]	6	4.9
Sweden	785	[709.2-868.9]	7.9	3.1	519	[456.4-590.2]	10.4	4.5	266	[225.5-313.8]	5.3	1.8
Switzerland	875	[764.9-1001.0]	10.2	4.1	567	[486.7-660.6]	13.4	5.8	308	[232.0-408.8]	7.1	2.6
Syrian Arab Republic	380	[208.6-692.2]	2.1	3	198	[100.1-391.5]	2.1	3.4	182	[51.6-641.8]	2	2.6
Tajikistan	253	[210.7-303.8]	2.8	4.4	153	[121.2-193.1]	3.3	5.5	100	[74.3-134.6]	2.2	3.4

Tanzania, United Republic of	1 516	[1028.7-2234.2]	2.6	5	1 146	[714.5-1838.0]	3.9	8.2	370	[187.6-729.7]	1.2	2.2
Thailand	23 154	[22448.8-23881.3]	33.5	20.9	16 284	[15696.9-16893.1]	48.3	32.3	6 870	[6486.9-7275.7]	19.4	11.1
The former Yugoslav Republic of Macedonia	187	[132.3-264.4]	9	5	122	[78.2-190.3]	11.7	7.1	65	[37.4-113.0]	6.2	3.1
The Netherlands	1 044	[966.3-1127.9]	6.1	2.5	648	[593.2-707.8]	7.6	3.3	396	[334.6-468.7]	4.6	1.7
The Republic of the Gambia	343	[288.1-408.4]	15.9	26.2	267	[218.6-326.1]	24.9	41.1	76	[53.2-108.6]	7	12.4
Timor-Leste	38	[21.0-68.7]	2.9	5.3	27	[13.4-54.5]	4	7.4	11	[3.7-32.9]	1.7	3.2
Togo	310	[279.7-343.6]	3.9	6.9	210	[185.7-237.5]	5.3	9.8	100	[82.8-120.7]	2.5	4.2
Trinidad and Tobago	63	[46.0-86.2]	4.6	3.2	34	[22.1-52.3]	5	3.7	29	[18.4-45.8]	4.2	2.7
Tunisia	356	[246.3-514.5]	3.1	2.6	147	[91.2-237.0]	2.6	2.3	209	[117.2-372.7]	3.5	2.8
Turkey	4 307	[4119.8-4502.7]	5.3	4.4	2 747	[2626.6-2872.9]	6.8	6.5	1 560	[1110.5-2191.5]	3.8	2.7
Turkmenistan	262	[226.7-302.8]	4.5	5.6	161	[133.8-193.8]	5.6	7.6	101	[80.1-127.3]	3.4	3.9
Uganda	1 552	[1169.7-2059.3]	3.5	6.7	947	[654.0-1371.2]	4.3	8.8	605	[390.3-937.8]	2.7	5.1
Ukraine	2 256	[2102.7-2420.5]	5.1	2.7	1 271	[1159.5-1393.2]	6.2	3.9	985	[882.8-1099.1]	4.2	1.8
United Arab Emirates	96	[73.6-125.2]	1	4.2	61	[43.8-84.9]	0.89	4.2	35	[22.4-54.6]	1.3	4.2
United Kingdom	6 836	[6586.4-7095.1]	10.3	4	4 042	[3845.3-4248.8]	12.3	5.3	2 794	[2642.3-2954.4]	8.3	2.8
United States of America	30 485	[29839.9-31144.1]	9.3	4.9	20 564	[19973.4-21172.1]	12.7	7.2	9 921	[9613.4-10238.4]	6	2.8
Uruguay	131	[103.7-165.5]	3.8	2.1	80	[55.1-116.1]	4.8	3.1	51	[37.7-69.0]	2.8	1.3
Uzbekistan	1 210	[1066.3-1373.1]	3.7	4.7	660	[554.6-785.5]	4.1	5.5	550	[457.5-661.1]	3.4	4
Vanuatu	28	[16.5-47.5]	9.9	13.1	22	[11.7-41.4]	15.4	20.2	6	[2.3-15.8]	4.3	6.2
Venezuela, Bolivarian Republic of	1 152	[1031.0-1287.1]	3.6	3.5	621	[521.2-739.9]	3.9	4.2	531	[460.1-612.8]	3.3	2.9

Viet Nam	25 404	[23442.7-27529.3]	26.3	23.2	19 708	[17974.3-21608.9]	41.3	39.1	5 696	[4832.2-6714.2]	11.7	9.4
Yemen	595	[486.6-727.6]	2.1	4.3	396	[307.4-510.2]	2.7	6.2	199	[142.9-277.1]	1.4	2.6
Zambia	173	[95.5-313.4]	0.98	2.1	101	[47.0-217.2]	1.2	2.7	72	[28.1-184.6]	0.81	1.5
Zimbabwe	580	[455.7-738.1]	3.4	7	324	[237.8-441.5]	3.9	8.8	256	[174.3-376.1]	3	5.6
World	781 631	[737605.0-828285.0]	10.2	8.5	548 375	[511583.0-587813.0]	14.2	12.7	233 256	[209922.0-259184.0]	6.2	4.6

Tab. SIII. Cancer incidence and mortality data: sources and methods by country.

Incidence	**Method**
1	National (or local with coverage greater than 50%) rates projected to 2018
2a	Most recent rates from a single registry applied to 2018 population
2b	Weighted/simple average of the most recent local rates applied to 2018 population
3a	Estimated from national mortality estimates by modelling, using mortality:incidence ratios derived from country-specific cancer registry data
3b	Estimated from national mortality estimates by modelling, using mortality:incidence ratios derived from cancer registry data in neighbouring countries
4	"All sites" estimates from neighbouring countries partitioned using frequency data
9	No data: the rates are those of neighbouring countries or registries in the same area
Mortality	
1	National rates projected to 2018
2a	Most recent rates from one source applied to 2018 population
2b	Weighted/simple average of the most recent local rates applied to 2018 population
3	Estimated from national incidence estimates by modelling, using incidence: mortality ratios derived from cancer registry data in neighbouring countries
9	No data: the rates are those of neighbouring countries in the same area

Tab. SIV. The method used in each country to calculate the incidence and attenuation of cancer in Global Cancer Observatory in 2018.

Country	Incidence		Mortality	
	Source	**Method**	**Source**	**Method**
Eastern Africa				
Burundi	No data	9	No data	3
Comoros	No data	9	No data	3
Djibouti	No data	9	No data	3
Eritrea	No data	9	No data	3
Ethiopia	Local	2a	No data	3
France, Reunion	*National*	2a	*National* (WHO)	1
Kenya	Local	2b	No data	3
Madagascar	No data	9	No data	3
Malawi	Local	2a	No data	3
Mauritius	National	1	National (WHO)	1
Mozambique	Local	2b	No data	3
Rwanda	Local	4	No data	3
Somalia	No data	9	No data	3
South Sudan	No data	9	No data	3
Tanzania	Local	2b	No data	3
Uganda	Local	2b	No data	3
Zambia	Local	2a	No data	3
Zimbabwe	Local	2b	No data	3
Middle Africa				
Angola	No data	9	No data	3
Cameroon	Local	2a	No data	3
Central African Republic	No data	9	No data	3
Chad	No data	9	No data	3
Congo	Local	2a	No data	3
Congo, Democratic Republic of	No data	9	No data	3
Equatorial Guinea	No data	9	No data	3
Gabon	No data	4	No data	3
Northern Africa				
Algeria	Local	2b	No data	3
Egypt	Local	2b	National (WHO)	3
Libya	Local	2a	No data	3
Morocco	Local	2b	National (WHO)	3
Sudan	Local	2b	No data	3
Tunisia	Local	2b	National (WHO)	3
Southern Africa				
Botswana	National	1	No data	3
Lesotho	No data	9	No data	3
Namibia	National	2a	No data	3
South African Republic	No data	3b	National (WHO)	1
Swaziland	National	2a	No data	3
Western Africa				

Cape Verde	No data	3b	National (WHO)	2a
Benin	Local	2a	No data	3
Burkina Faso	Local	9	No data	3
Cote d'Ivoire	Local	2a	No data	3
Ghana	Local	4	No data	3
Guinea	Local	2a	No data	3
Guinea-Bissau	No data	9	No data	3
Liberia	No data	9	No data	3
Mali	Local	2a	No data	3
Mauritania	No data	9	No data	3
Niger	Local	2a	No data	3
Nigeria	Local	2b	No data	3
Sao Tome and Principe	No data	3b	National (WHO)	2a
Senegal	No data	9	No data	3
Sierra Leone	No data	4	No data	3
The Gambia	National	1	No data	3
Togo	Local	4	No data	3
Caribbean				
Bahamas	No data	3b	National (WHO)	1
Barbados	No data	3b	National (WHO)	1
Cuba	Local	3b	National (WHO)	1
Dominican Republic	No data	3b	National (WHO)	1
France, Guadeloupe	*National*	1	*National*(WHO)	1
France, Martinique	*National*	1	*National*(WHO)	1
Haiti	No data	3b	National (WHO)	2a
Jamaica	Local	3b	National (WHO)	1
Puerto Rico	National	1	National (WHO)	1
Saint Lucia	No data	3b	National (WHO)	1
Trinidad and Tobago	No data	3b	National (WHO)	1
Central America				
Belize	No data	3b	National (WHO)	2a
Costa Rica	National	1	National (WHO)	1
El Salvador	No data	3b	National (WHO)	1
Guatemala	No data	3b	National (WHO)	1
Honduras	Local	2a	National (WHO)	2a
Mexico	No data	3b	National (WHO)	1
Nicaragua	No data	3b	National (WHO)	1
Panama	No data	3b	National (WHO)	1
South America				
Argentina	Local	3a	National (WHO)	1
Bolivia	Local	3b	National (WHO)	2a
Brazil	Local	3a	National (WHO)	1
Chile	Local	3a	National (WHO)	1
Colombia	Local	3a	National (WHO)	1
Ecuador	Local	3a	National (WHO)	1
French Guiana	*National*	1	*National*(WHO)	1
Guyana	No data	3b	National (WHO)	1
Paraguay	No data	3b	National (WHO)	1

Peru	Local	3a	National (WHO)	1
Suriname	No data	3b	National (WHO)	1
Uruguay	National	1	National (WHO)	1
Venezuela	No data	3b	National (WHO)	1
Northern America				
Canada	Local	1	National (WHO)	1
United States of America	National	1	National (WHO)	1
Eastern Asia				
China	Local	2b	Local	2b
Japan	Local	3a	National (WHO)	1
Korea, Democratic Republic of	No data	9	No data	9
Korea, Republic of	National	1	National (WHO)	1
Mongolia	National	2a	National	2a
South-Eastern Asia				
Brunei Darussalam	National	2a	National (WHO)	2a
Cambodia	No data	9	No data	3
Indonesia	National	4	No data	3
Lao People's Democratic Republic	No data	9	No data	3
Malaysia	Local	2b	National (WHO)	3
Myanmar	No data	9	No data	3
Philippines	Local	2b	National (WHO)	3
Singapore	National	1	National (WHO)	2a
Thailand	Local	2b	National (WHO)	3
Timor Leste	No data	9	No data	3
Viet Nam	Local	2b	National (Survey)	3
South Central Asia				
Afghanistan	No data	9	No data	3
Bangladesh	No data	9	No data	3
Bhutan	National (pathology-based register)	2a	No data	3
India	Local	2b	Regional	3
Iran, Islamic Republic of	Local	2b	National (WHO)	2a
Kazakhstan	National	2a	National (WHO)	2a
Kyrgyzstan	Local	3b	National (WHO)	1
Maldives	No data	9	No data	9
Nepal	Local	4	No data	3
Pakistan	Local	2b	No data	3
Sri Lanka	National	1	National (WHO)	3
Tajikistan	No data	3b	National (WHO) (ICD-9 limited sites).	2a
Turkmenistan	No data	3b	National (WHO) (ICD-10 limited sites).	1
Uzbekistan	National	2a	National (WHO)	1

Western Asia				
Azerbaijan	National	2a	National (WHO)	3
Armenia	No data	3b	National (WHO)	1
Bahrain	National	1	National (WHO)	3
Georgia	No data	3b	National (WHO)	1
Iraq	National	2a	No data	3
Israel	National	1	National (WHO)	1
Jordan	National	1	National (WHO)	3
Kuwait	National	1	National (WHO)	3
Lebanon	National	2a	No data	3
Oman	National	1	National (WHO)	3
Palestine	No data	9	National (WHO)	3
Qatar	National	2a	National (WHO)	3
Saudi Arabia	National	1	National (WHO)	3
Syrian Arab Republic	No data	9	No data	3
Turkey	Local	2b	National (WHO)	2a
United Arab Emirates	National	2a	No data	3
Yemen	Local	2b	No data	3
Eastern Europe				
Belarus	National	1	National (WHO)	1
Bulgaria	National	1	National (WHO, ICD-10 limited sites).	2a
Czech Republic	National	1	National (WHO)	1
Hungary	No data	3b	National (WHO)	1
Moldova	No data	3b	National (WHO)	1
Poland	Local	3a	National (WHO)	1
Romania	Local	3b	National (WHO)	1
Russian Federation	National	1	National (WHO, ICD-10 limited sites)	1
Slovakia	National	2a	National (WHO)	1
Ukraine	National	1	National (WHO, ICD-10 limited sites)	1
Northern Europe				
Denmark	National	1	National (WHO)	1
Estonia	National	1	National (WHO)	1
Finland	National	1	National (WHO)	1
Iceland	National	1	National (WHO)	1
Ireland	National	1	National (WHO)	1
Latvia	National	1	National (WHO)	1

Lithuania	National	1	National (WHO)	1
Norway	National	1	National (WHO)	1
Sweden	National	1	National (WHO)	1
United Kingdom	National	1	National (WHO)	1
Southern Europe				
Albania	No data	3b	National (WHO)	1
Bosnia Herzegovina	Local	3a	National (WHO)	2a
Croatia	National	1	National (WHO)	1
Cyprus	National	1	National (WHO)	1
FYR Macedonia	No data	3b	National (WHO)	1
Greece	No data	3b	National (WHO)	1
Italy	Local	3a	National (WHO)	1
Malta	National	1	National (WHO)	1
Montenegro	No data	3b	National (WHO)	1
Portugal	Local	3a	National (WHO)	1
Serbia	Local	3b	National (WHO)	1
Slovenia	National	1	National (WHO)	1
Spain	Local	3a	National (WHO)	1
Western Europe				
Austria	National	1	National (WHO)	1
Belgium	National	1	National (WHO)	1
France	Local	3a	National (WHO)	1
Germany	Local	1	National (WHO)	1
Luxembourg	National (pathology-based register)	3b	National (WHO)	1
The Netherlands	National	1	National (WHO)	1
Switzerland	Local	3a	National (WHO)	1
Australia/New Zealand				
Australia	National	1	National (WHO)	1
New Zealand	National	1	National (WHO)	1
Melanesia				
Fiji	No data	3b	No data	3
France, New Caledonia	*National*	2a	National (WHO)	2a
Papua New Guinea	Local	9	National	2a
Solomon Islands	No data	9	No data	3
Vanuatu	National	2a	No data	3
Micronesia				
Guam	No data	9	National	2a
Polynesia				
French Polynesia	*National*	2a	*National*	2a
Samoa	No data	9	No data	9

ORIGINAL ARTICLE

Occupational categories and cardiovascular diseases incidences: a cohort study in Iranian population

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Keywords

Occupation • ISCO category • Ischemic heart disease • Stroke

Summary

Introduction. *In spite of traditional cardiovascular risk factor, the different occupations can play an important role in cardiovascular disease (CVDs) incidence. We aimed to assess the correlation between the occupational classes, based on the International Standard Classification of Occupation (ISCO), and CVDs in Iran as a developing country.*

Methods. *We followed the 2440 men, aged 35-65 years and without history of CVDs over fourteen years; 2001 to 2015 during the Isfahan Cohort Study. ISCO was used to classify occupations into 10 categories. Incidence rates of ischemic heart diseases and stroke were recorded. Socioeconomic demographic data including marital state, income and place of living and metabolic risk factors were also recorded.*

Results. *The mean age was 46.97 ± 8.31 years old. 272 cardiovascular events (CVEs) were recorded that unstable angina was the highest recorded with 49% prevalence and the fatal stroke had the lowest outbreak (1%). The unemployed/jobless group and elementary occupations (9th ISCO category) had higher and lower relative frequency in CVEs respectively. There was non-significant decrease in CVEs in all of categories except of 4th (clerical support workers) and 10th (armed forces) groups in comparison to unemployed/jobless subjects (P > 0.05). After considering of the group 7 as a reference group (most absolute CVEs frequency), in fully adjustment analysis group 4 had significant risk for CVEs (P = 0.04).*

Conclusions. *This study indicates that working as clerical support workers (4th ISCO category) is associated with higher significant risk for IHD and stroke incidence in comparison to craft and related trades workers (7th group of ISCO).*

Introduction

Cardiovascular diseases (CVDs) including ischemic heart disease (IHD) and stroke are considered as a public health problem and were the most common underlying cause of death in the world [1]. The known risk factors for CVDs are genetics and family history, dyslipidemia, diabetes mellitus, hypertension, smoking and physical inactivity.

Nearly 80 percent of cardiovascular mortalities take place in countries with the low- and middle-income level which highlights socioeconomic status as a contributing and predictive factor on the CVDs. Given the significant role of occupation and career in the prediction of socio-economic status, it is only fair to discuss the occupational status as one of the main risk factors for cardiovascular disease and stroke. Numerous studies across the world have directly and indirectly, linked occupational factors and cardiovascular health condition. These studies identify factors such as shift work, overtime work, exposure to toxic chemicals and fumes, noise level, job stress, and sedentary behavior to be work-related environmental and psychosocial factors that associate with CVDs risk factors [2-6]. However, investigation of different occupational classes (based on professional skills or socioeconomic groups) instead of individual work space-related factors, gives us a broader view of the correlation between the risk of CVDs and occupational status [7, 8].

Therefore, the current study uses a cohort approach to describe the correlation between the occupational classes, based on the International Standard Classification of Occupation 2008 (ISCO-08), and CVDs in Iran as a developing country in the Middle East.

Patients and methods

The population and data collection

The Isfahan Cohort Study (ICS) is a population-based, longitudinal ongoing study that started with 6504 adults aged 35 and greater at baseline, living in urban and rural areas of three districts in central Iran who had participated in the baseline survey of a community trial for CVDs prevention and control, entitled Isfahan Healthy Heart Program (IHHP) [9, 10].

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Ethical approval was obtained from the ethics committee of Isfahan Cardiovascular Research Center (ICRC), as World Health Organization (WHO) collaborating center. After obtaining informed written consent and the baseline survey in 2001, follow-up of the participants has been carried out every two years by telephone, or home interviews, physical and biochemical measurements and hospital events record until 2015.

Given that most subjects were housekeeping female, this study was conducted on men aged 35 to 65 years between inclusion age of study population and Iranian Ministry of Labour and Social Affairs retirement age law. In total, 2440 men subjects (employed and unemployed/jobless) who did not have IHD and stroke were followed up for 14 years (2001 to 2015).

Questionnaires were completed for each person including age, occupations, marital state, income, place of living, smoking status and metabolic risk factors such as diabetes mellitus (DM), hypertension (HTN), dyslipidemia, metabolic syndrome and body mass index (BMI). Income was categorized based on the poverty boundary in Iran that was 5,000,000 Iranian Rials in 2001. A monthly income less than 5,000,000 was categorized as very low, 5,000,000 to 9,000,000 as low, 9,000,000 to 15,000,000 as middle, 15,000,000 to 20,000,000 was considered high and more than this level as very high income.

Occupational categories

The International Standard Classification of Occupation (ISCO) was used to classify occupations into ten occupational categories. The ISCO is a standard and validated category based on skill specialization and skill level [11]. If a person had worked in more than one occupational category, the main job (more work time) was the basis for classification. The major groups of ISCO consist of: 1) legislators, senior officials and managers; 2) professionals; 3) technicians and associate professionals; 4) clerical support workers; 5) service workers and shop and market sales workers; 6) skilled agricultural, forestry and fishery workers; 7) craft and related trades workers; 8) plant and machine operators, and assemblers; 9) elementary occupations; and 10) armed forces [11]. A control group including unemployed/jobless people was also selected for analysis and comparison.

Follow-up

Follow-up survey for cardiovascular events (CVE) including IHD and stroke was done along 14 years. The reported events were checked with the myocardial infarction (MI) and stroke registry database of the surveillance department, ICRC monthly in the three counties above. Two separate panels of specialists consisting of cardiologists and a neurologist reviewed and confirmed all relevant patient documents. The criteria for IHD were definite or probable acute MI, unstable angina (UA), and sudden cardiac death (SCD). The diagnosis of acute MI was based on the presence of at least two of the following criteria: 1) typical chest pain lasting more than 30 min; 2) ST-segment elevation > 0.1 mV in at least 2 adjacent electrocardiograph leads; and 3) an increase in serum levels of cardiac biomarkers including cardiac troponins, and creatine kinase (CK) and CK-MB [12]. The definition of UA required typical chest discomfort lasting more than 20 minute within the 24 h preceding hospitalization and representing a change in the usual pattern of angina or pain: occurring with a crescendo pattern, being severe and described as a frank pain [13]. The diagnosis of UA might be new or based on dynamic ST-interval, or T-wave changes in at least two contiguous ECG leads. Sudden cardiac death was defined as death within one hour of onset, a witnessed cardiac arrest, or abrupt collapse not preceded by > 1 hour of symptoms. Stroke was defined as a rapid-onset focal neurological disorder persisting at least 24 h and had a probable vascular origin by WHO stroke definition [14].

Statistical analysis

Continuous and categorical variables are reported as arithmetical mean value ± SD and absolute number (percent) respectively. Chi-square and independent T-test were used to compare risk factors between job categories (ISCO). The hazard ratio (HR) model with its 95% confidence interval (CI) for each ISCO category relative to the reference category was assessed when the control group (unemployed/jobless subjects) and 7th ISCO category (including most subjects and CVE) were selected as a reference category respectively. To adjust the potential confounding effects of the selected risk factors, adjusted cox regression models included age, socioeconomic and metabolic variables adjustment were performed. Statistical analysis was done by the Statistical Program for Social Sciences software 22 (SPSS 22). All differences were considered as statistically significant at a P value less than 0.050.

Results

A total of 2440 males with mean age 46.97 ± 8.31 years were classified and analyzed. 159 of them were unemployed or jobless who were considered as the control group. Table I presents the socioeconomic and metabolic characteristic of a participant in ISCO occupational categories. Except marital status and dyslipidemia, other basic characteristics had a significant difference between the groups ($P < 0.005$) (Tab. I). Income information was incomplete due to lack of representation of all individuals (especially those with high income). Most of the studied subjects were lived in the urban area, except for the 6th group who lived in the village according to their jobs (Tab. I).

In total, 272 CVE were recorded, as showed separately in Tab. II. The unstable angina was the highest recorded CVE with 49% prevalence, and the fatal stroke had the lowest outbreak (1%). The absolute frequency occurred in 7th group (craft and related trades workers) with 63 events; however, the unemployed/jobless group and

Tab. I. Socioeconomic and metabolic characteristic of participant in ISCO occupational categories.

Variables	ISCO Categories (n)											
	1st (86)	2nd (160)	3rd (13)	4th (257)	5th (458)	6th (332)	7th (710)	8th (218)	9th (8)	10th (39)	Control (159)	P-value
Age (year)	45.62 ± 8.00	44.52 ± 5.48	47.23 ± 6.68	43.96 ± 6.58	47.81 ± 8.56	50.14 ± 9.08	44.86 ± 7.28	46.30 ± 7.77	47.87 ± 8.98	43.25 ± 6.02	57.23 ± 6.06	0.000
Marital status n (%):												
• married	84 (98)	160 (100)	13 (100)	253 (98)	449 (98)	327 (98)	707 (99.5)	214 (98)	8 (100)	39 (100)	157 (99)	
• single	2 (2)	0	0	4 (2)	9 (2)	3 (1)	3 (0.5)	3 (1.5)	0	0	0	0.067
• divorced	0	0	0	0	0	0	0	1 (0.5)	0	0	0	
• dead spouse	0	0	0	0	0	2 (1)	0	0	0	0	2 (1)	
Income n (%):												
• very low	32 (37)	55 (34)	7 (54)	107 (42)	329 (72)	278 (84)	507 (71)	124 (57)	7 (87.5)	16 (41)	133 (84)	
• low	26 (30)	57 (35)	4 (31)	91 (35)	50 (11)	24 (7)	95 (13)	43 (20)	0	15 (38)	17 (11)	
• moderate	6 (7)	2 (1)	0	3 (1)	3 (1)	0	0	2 (1)	0	0	0	0.000
• high	2 (2)	1 (1)	0	2 (1)	1 (0.5)	0	0	1 (1)	0	0	0	
• very high	0	0	0	0	0	0	0	0	0	0	0	
Place of living n (%):												
• urban	76 (88)	138 (86)	10 (77)	215 (84)	375 (82)	68 (20)	529 (75)	166 (76)	7 (87.5)	34 (87)	144 (91)	0.000
• rural	10 (12)	22 (14)	3 (23)	42 (16)	83 (18)	264 (80)	181 (25)	52 (24)	1 (12.5)	5 (13)	15 (9)	
Diabetes mellitus n (%)	5 (6)	10 (6)	3 (23)	12 (5)	46 (10)	21 (6)	35 (5)	17 (8)	1 (12.5)	3 (8)	33 (21)	0.000
Dyslipidemia n (%)	79 (92)	136 (85)	13 (100)	223 (87)	363 (79)	275 (83)	589 (83)	187 (86)	7 (87.5)	34 (87)	131 (82)	0.078
Hypertension n (%)	16 (19)	28 (17.5)	2 (15)	42 (16)	93 (20)	108 (33)	108 (15)	34 (16)	0	7 (18)	63 (40)	0.000
Smoker n (%):												
• current	34 (40)	42 (26)	3 (23)	75 (29)	143 (31)	123 (37)	253 (36)	93 (43)	3 (37.5)	15 (38.5)	42 (26)	
• former	7 (8)	13 (8)	0	20 (8)	39 (9)	24 (7)	70 (10)	18 (8)	0	5 (13)	20 (13)	0.028
• never	45 (52)	105 (66)	10 (77)	162 (63)	275 (60)	184 (56)	387 (54)	106 (49)	5 (62.5)	19 (48.5)	96 (61)	
BMI n (%):												
• normal	39 (45)	77 (48)	4 (31)	112 (44)	192 (42)	189 (57)	353 (50)	76 (35)	3 (37.5)	9 (23)	60 (38)	
• overweight	28 (33)	68 (43)	6 (46)	111 (43)	203 (44)	112 (34)	285 (40)	100 (46)	3 (37.5)	20 (51)	71 (45)	0.000
• obese	19 (22)	15 (9)	3 (23)	34 (13)	63 (14)	31 (9)	72 (10)	42 (19)	2 (25)	10 (26)	28 (17)	
Metabolic syndrome n (%)	12 (14)	26 (16)	3 (23)	34 (13)	89 (20)	43 (13)	78 (11)	44 (20)	0	10 (26)	53 (33)	0.000

elementary occupations had higher and lower relative frequency in CVE respectively (Tab. II).

Table III presents crude, age-adjusted and fully adjusted (socioeconomic and metabolic variables) HR estimates among ISCO categories compared to unemployed/ jobless participants (control group). This analysis showed a non-significant decrease in CVE in all of categories except 4th (clerical support workers) and 10th (armed forces) groups ($P > 0.050$). After considering of the group 7 as a reference group, in fully adjustment analysis group 4 had significant risk for CVE ($P = 0.044$) as well as nonsignificant increases in 2nd, 3rd, 6th, 8th and 10th groups ($P > 0.05$) (Tab. IV).

Discussion

This prospective cohort study showed that working as clerical support workers (4th group of ISCO) is associated with higher significant risk for IHD and stroke incidence in comparison to craft and related trades workers (7th group of ISCO). This outcome also obtained for professional (2nd group), technicians and associate professionals (3rd group), skilled agricultural, forestry and fishery workers (6th group), plant and machine operators, and assemblers (8th group) and armed forces (10th group) with non-significant correlation. In comparison to unemployed/ jobless subjects, all of the ISCO groups (except 4th and

Tab. II. Numerical data of cardiovascular events between the ISCO categories and control group.

Cardiovascular events	ISCO Categories (n)											
	1st (86)	2nd (160)	3rd (13)	4th (257)	5th (458)	6th (332)	7th (710)	8th (218)	9th (8)	10th (39)	Control (159)	Total
Unstable Angina n (%)	3 (3)	11 (7)	1 (8)	18 (7)	22 (5)	13 (4)	31 (4)	13 (6)	0	4 (10)	18 (11)	134
Non-fatal myocardial infarction n (%)	6 (7)	5 (3)	0	8 (3)	11 (2)	6 (2)	11 (2)	4 (2)	0	2 (5)	8 (5)	61
Fatal myocardial infarction n (%)	0	0	0	1 (0.5)	0	3 (1)	2 (0.5)	1 (0.5)	0	0	0	7
Sudden cardiac death n (%)	0	0	1 (8)	1 (0.5)	6 (1)	8 (2)	7 (1)	4 (2)	0	0	4 (3)	31
Non-fatal stroke n (%)	0	1 (1)	0	5 (2)	9 (2)	2 (1)	11 (1)	3 (1)	0	0	5 (3)	36
Fatal stroke n (%)	1 (1)	0	0	0	0	0	1 (0.5)	0	0	0	1 (0.5)	3

Tab. III. Relation between ISCO occupational categories and cardiovascular events (ischemic heart dieses and stroke), unadjusted and adjusted hazard ratio (group control as reference).

Analysis	ISCO categories (n)									
	1st (86)	2nd (160)	3rd (13)	4th (257)	5th (458)	6th (332)	7th (710)	8th (218)	9th (8)	10th (39)
Model 1 HR (95% CI)	0.43 (0.21-0.87)*	0.35 (0.2-0.63)*	0.66 (0.16-2.76)	0.5 (0.31-0.80)*	0.39 (0.25-0.60)*	0.40 (0.24-0.64)*	0.32 (0.21-0.49)*	0.45 (0.27-0.75)*	–	0.61 (0.25-1.44)
Model 2 HR (95% CI)	0.69 (0.34-1.41)	0.70 (0.38-1.29)	0.99 (0.23-4.14)	0.97 (0.59-1.62)	0.59 (0.38-0.92)*	0.53 (0.33-0.87)*	0.60 (0.39-0.94)*	0.79 (0.46-1.34)	–	1.38 (0.56-3.37)
Model 3 HR (95% CI)	0.78 (0.36-1.67)	0.88 (0.46-1.65)	0.93 (0.22-3.94)	1.21 (0.72-2.04)	0.69 (0.44-1.08)	0.79 (0.46-1.34)	0.78 (0.49-1.22)	0.95 (0.55-1.62)	–	1.51 (0.61-3.69)
Model 1: unadjusted analysis (Crude Model); model 2: age adjusted analysis; model 3: multivariate (socioeconomic and metabolic variables) adjusted analysis; *: p-values less than 0.05.										

Tab. IV. Relation between ISCO occupational categories and cardiovascular events (ischemic heart dieses and stroke), unadjusted and adjusted hazard ratio (group 7 as reference).

Analysis	ISCO categories (n)									
	1st (86)	2nd (160)	3rd (13)	4th (257)	5th (458)	6th (332)	7th (710)	8th (218)	9th (8)	10th (39)
Model 1 HR (95% CI)	1.31 (0.67-2.57)	1.08 (0.63-1.85)	2.02 (0.49-8.29)	1.52 (1.00-2.32)*	1.18 (0.81-1.72)	1.22 (0.79-1.88)	1.00	1.38 (0.87-2.19)	–	1.86 (0.80-4.30)
Model 2 HR (95% CI)	1.14 (0.58-2.23)	1.16 (0.68-1.99)	1.63 (0.40-6.70)	1.61 (1.05-2.46)*	0.97 (0.66-1.43)	0.89 (0.57-1.38)	1.00	1.30 (0.82-2.08)	–	2.28 (0.98-5.28)
Model 3 HR (95% CI)	0.99 (0.48-2.04)	1.12 (0.64-1.96)	1.20 (0.29-4.96)	1.55 (1.01-2.40)*	0.88 (0.60-1.31)	1.01 (0.64-1.31)	1.00	1.21 (0.76-1.95)	–	1.93 (0.83-4.49)
Model 1: unadjusted analysis (Crude Model); model 2: age adjusted analysis; model 3: multivariate (socioeconomic and metabolic variables) adjusted analysis; *: p-values less than 0.05.										

10th groups) had a non-significant protective correlation with IHD and stroke incidence.

Based on our researches, studies on the relationship between classified occupations (especially based on skill) like ISCO category and CVDs, were few [15]. Most studies have examined the risk factors of occupational and environmental conditions and the occurrence of CVE and mortality [16, 17].

A case-control study was carried out by Malinauskiene et al. in Lithuania a country in a transition market economy to investigate the risk of a first time MI among different occupational categories in 25-64 year-old men. The occupational category used by them was ISCO. They showed that legislators, senior officials, and managers (1st ISCO category), professionals (2nd ISCO category), and plant and machine operators and assemblers (8th ISCO category) had a significantly higher risk of non-fatal first time MI compared to craft and related trades workers (7th ISCO category). The 4th ISCO category also had a non-significant increase risk for MI incidence. Their main explanation was the existence of occupational-psychological stressors, especially in the first category [15].

Our analysis did not show any significant predominance of metabolic and socioeconomic risk factors in group 4 and 7 (as baseline group). Therefore, it is not possible to associate this relationship with risk factors of the groups. These findings could be explained by the inactive and stressful nature of such occupations in Iran society.

In a prospective study by Li et al. in Japan, male workers with 40-59 years old were classified into manual and non-manual classes. The CVE including stroke, MI and SCD were assessed and did not reveal significant inequalities in the rate of cardiovascular events [18]. However, the incidence rate of MI in manual workers was non-significantly lower compared to non-manual workers. Their results were in contrast to another industrial county in Europe and United States of America (USA) that manual worker have a higher risk for cardiovascular risk factors and events [19-23]

Zhang et al. in a large prospective study USA showed that male white-collar occupations were associated with increased risk of SCD, when compared to blue-collar occupations. Since differences in conventional risk factors did not explain this elevated risk, they hypothesized that other factors such as behavioral and psychosocial stressors in the workplace warrants further investigation [24]. We also rely on the same reasoning to explain the meaningful association between group four and cardiovascular events.

To the best of our knowledge this study is among the first studies in Iran, the Middle East, and other developing countries that assess the relationship between occupations and cardiovascular disease. Given the occupational structure and cultural context of the area, we applied the ISCO classification which is a standard occupation classification and took into consideration the socioeconomic status of the individuals [11, 25]. As we mentioned earlier, Malinauskiene et al. has utilized this classification in Lithuania while most of the studies use more simplified models which could be one of the contributions of this study.

This study suffers from several limitations, first of all, there might be a misclassification of occupations because people might not have reported their jobs correctly. Secondly, some of the participants changed their job in the middle of the study and we decided to consider their former job if they spent longer time in that position. Thirdly, analyzing the sub-categories of ISCO was not in the scope of this study and we suggest future studies to focus on that.

Conclusions

This study indicates that working as clerical support workers (4th group of ISCO) is associated with higher significant risk for IHD and stroke incidence in comparison to craft and related trades workers (7th group of ISCO). In comparison to unemployed/jobless subjects, there was not a significant correlation between the nature of occupational categories and CVE incidence.

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Ethical approval: all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this study, ethical approval was obtained from the Ethics Committee of Isfahan Cardiovascular Research Center (ICRC), as WHO collaborating center.

Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

RG, MA, MKA and MS contributed to the conception and design of the study. NS, MS, MT and HR designed and contributed the Isfahan Cohort Study. MKA and RG conducted the data analysis and drafted the manuscript, and all authors revised it.

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ORIGINAL ARTICLE

Efficacy of water filters for dental chair units: assessment of the filtration action versus Coxsackievirus B5

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Keywords

Dental chair • Hydraulic system • Biological safety • Microbiological tests • Coxsackie virus

Summary

Introduction. *The microbiological safety and control of the water used in dental practice has a critical importance for avoiding cross-linked infections in the dental office. The aim of this study was to establish coxsackie virus filtration of the water applied to a dental unit.*
Methods. *A specific water filter-system was used, to verify the viral load in the outgoing water. The statistical analysis was performedusing the Shapiro-Wilk and t-Student test.*
Results. *The outcome of the evaluation of the virologic tests shows an excellent capability of virus filtration that attested 99.9999% in the volume analyzed. A statistical difference was found in the bacterial water contamination parameter before and after filtration. (P = 0.000000).*
Conclusions. *According to the tests, medical devices applied to a dental unit are able to filter viruses and therefore reduce risk of contamination in the dental office.*

Introduction

A dental unit is a system that delivers water to different points by a hydraulic system (HS): glasses for patients, water bottle tanks, ultrasonic scalers, handpieces for high-speed drills, and air and water syringes. To prevent the HS from being contaminated, the handpieces are manufactured with anti-retraction valves to prevent suck-back of contaminants from the oral cavity [1]. Water systems of domestic and old buildings, can be contaminated with legionellae and therefore represent a potential risk for the patients. Many microorganisms are detected in the hydraulic system of dental chairs such as *Ralstonia pickettii*, and *Sphingomonas paucimobilis*, *Pseudomonadaceae species*, including *Burkholderia cepacia*, *Chryseomonas luteola*, *Pseudomonas fluorescens* [2].
Natural and artificial water contains many microorganisms, fungi, bacteria and viruses [3, 4].
Coxsackieviruses are nonenveloped, positive-sense, single-stranded RNA viruses of the *Picornaviridae* family, genus *Enterovirus*. Enteric viruses are resistant in the environment, especially in water, and transmitted via the fecal-oral route, and by inhalation of water aerosolved particles [5].
These microorganisms can reach water systems, causing a potential risk of contamination to human health [6, 7]. In particular, they could contaminate dental units, increasing risk of cross- infection during surgery. Dental chair units contain systems providing water to cool soft and hard tissues during surgery and to cool down instruments and burs used in dental procedures. The Italian Ministry of Health in 2015 issued guidelines for the prevention of *Legionella*, according to which the dentist is responsible for both the sterility of the surgical environment and of the microbiological safety of the water circulating in the dental unit.
Then there is the possibility of cross contamination by inhalation of aerosol containing pathogenic originating from spray or rotating or ultrasonic instruments if *Legionella* or other bacteria or viruses are present in the circulating water systems [8]. In addition, there is an increased risk of contamination, during surgery, caused by the direct contact of spray or water with the patient's blood [9].
In order to reduce microbial contamination and the biofilm formation in the hydraulic system in a dental unit, it is recommended to disinfect the water, and to install filters able to reduce the microbial load [10, 11].
The aim of the present study was to investigate the capacity of a medical device of ultrafiltration for dental units to filtrate Coxsackieviruses.

Materials and methods

A total 18 filters of ultrafiltration were used in this study. The water filter used has a nano-reticular structure 0.05 µ with activated vegetable carbon added as a purifying and anti-odour agent for incoming water upstream of the dental unit, called Koala® filter (ODONTOKOALA

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Rome, Italy). This dental unit water filter system contains the finest coconut shell based granular activated carbon.
At the Department of Medical, Oral and Biotechnological Sciences of the University of Chieti-Pescara the tests were performed on the microbial colonies. The sterilizing efficacy of the filter under test was analysed towards microbial loads of Coxsackievirus B5, cultivated in monkey kidney cultures (RC37).
Two liters of sterile distilled water were contaminated with the viral culture at known titer.
Two liters of sterile distilled water were filtered to check for any initial contamination of the filtering system, then the contaminated sample was filtered (continuous physiological solution), with the same device.
The determination of the microbial load at 37°C on *Plate Count Agar* (PCA) was performed: the contaminated physiological sample was inoculated in cell cultures to verify initial viral titer. The filtered physiological sample was inoculated in cell cultures to determine residual viral load. Viral titer was established according to the Reed-Muench method, and was expressed in TCID50/25 µl [12].
Two trials were performed with Coxsackievirus B5 at initial titer of 10^6 $TCID_{50}$/25µl and 10^5 $TCID_{50}$/25 µl, by using a new filter. The water for dental use is considered contaminated when waterlines count are between 10,000 and 10,000,000 cfu/ml.

Statistical evaluation

A power analysis was performed using clinical software, freely available on the site http://clincalc.com/stats/samplesize.aspx, for determining the number of filters needed to achieve statistical significance for quantitative analyses of quantization of virus. A calculation model was adopted for dichotomous variables (yes/no effect) by putting the effect incidence designed to caution the reasons 15% for controls and 75% for treated. Alpha was set at 0.05, Beta at 0.3 and power at 0.7. The optimal number of filters for analysis is 16 implants.
The Shapiro-Wilk test was adopted to evaluate the normality of the study data and the viral quantitative differences between before and after water filtration were analyzed by the t Student Test.
A p-value ≤ 0.05 was considered statistically significant. Statistical analysis was performed using the Statview software from SAS Institute.

Results

The filters showed an effective retention capacity of the viral loads under examination, always recording a residual zero load, even in the presence of high initial contaminant loads (10^6 ufc/ml) with Coxsackievirus B5 used and in every case, demonstrating a reduction of 99.9999% in the volume analysed.
A statistical difference was found in the viral water contamination before and after filtration. (P = 0.000000).
In the tables below are the diagrams of the results obtained (Tab. I).

Discussion

In the present study Coxsackievirus B5 was used for its small size 30nm and if the filter works against this virus it will certainly work for *Legionella* which has a much larger size. Legionellae appear to have a coconut-bacillary shape with dimensions ranging from 0.3 to 0.9 µm wide and 1.5 to 5 µm of length.
Safety of patients and dental personnel requires the appropriate microbiological water quality in dental units [11]. During treatment, patients and dental workers are exposed both to direct contact with microbial-contaminated water in the form of splatter and contaminated aerosol emitted during work with unit handpieces, including rotating and ultrasonic instruments [3]. This is very important as it concerns medical and legal aspects.
Therefore, the use of a hygiene protocol, that guarantees a disinfection of the hydraulic system of the dental unit, is crucial in preventing cross-contamination, and to ensuring work safety, according to the current laws.
In accordance with the experiment, we can affirm that filters applied to a dental unit are able to guarantee disinfection of the water, acting as actual barriers, impermeable to the passage of microorganism.
A 0.05 µ ultrafiltration system was used, provided with a nanopore physical barrier, impermeable to viruses and bacteria, acting effectively and in safety, over a period of time equal to a year of work (8,000 liters) [11].
Therefore, the ultrafiltration system device was tested towards Coxsackievirus B5, a microorganism with equal or inferior dimensions to *Legionella*, in order to assess the absence of contamination in the water transiting in the filtering system.
The filter system was prior tested with sterile saline water to certify its sterilization in order to not null the results.
Activated vegetable carbon was placed inside the filtering system. This is, generally used to eliminate odours and chlorine from water, as well as to prevent the formation of algae in water circuits, but at the same time collects the bacterial charge beyond the membranes, for which the efficiency test performed on the filters used represents a significant data on the biological safety of the filter.

Conclusions

The results achieved showed that the filter system was able to completely eliminate viral charges present in the pre-contaminated water, both at medium and high concentrations, proving the effectiveness in sterilizing against bacterial and viral colonies, including *Legionella*.
It shows how the use of an ultrafiltration system guarantees a safe work environment, reducing the possibility of cross-contamination both for patients and for healthcare professionals.

Tab. I. Summary of the viral titer evaluated before and after water filtration [mean, SD].

Virus strain	Viral titer ($TCID_{50}$/25 µl)	Initial titer ($TCID_{50}$/25 µl)	White ($TCID_{50}$/25 µl)	Filtered ($TCID_{50}$/25 µl)	P-value
Cox B5	10^6	$3.16 \times 10^1 \pm 1.8$	0	0	P < 0.01 [**]
Cox B5	10^5	$1.58 \times 10^1 \pm 1.1$	0	0	P < 0.01 [**]

*: p < 0.05; **: p < 0.01.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

Conceptualization: AS; methodology: AS, GM, SO, LF, DCT; supervision: AS, GM; draft writing: AS; draft review: AS, SO, LF; validation: AS; resource: AS; software: AS, LF.

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Original article

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