

vol. n.
64/3

Cited in Index Medicus / Medline
NLM ID 921440 (Pub-Med)

September
2023

JOURNAL OF PREVENTIVE Medicine AND Hygiene

the original document of HIPPOCRATES' OATH



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Managing Editor: Patrizia Alma Pacini

Publisher: Pacini Editore Srl, Via Gherardesca 1, 56121 Pisa, Italy

Tel. +39 050 313011 - Fax +39 050 3130300

info@pacinieditore.it - www.pacinimedicina.it

Published online November 2023

Authorization Tribunale di Genoa, Italy n. 507 - 10/6/1960

Journal registered at "Registro pubblico degli Operatori della Comunicazione" (Pacini Editore srl registration n. 6269 - 29/8/2001).

Volume 64 - Issue 3 September 2023

www.jpmmh.org

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EDITORIAL

Optimal timing of measles vaccination in high-risk areas: Insights from MR-1 administration and subsequent dosing efficacy

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Keywords

Measles outbreak • Measles vaccination • MR vaccines • Measles infection • Young infant • Case study

Dear Editor,

Infectious diseases have historically represented a persistent threat, serving as a constant reminder of the delicate balance between human well-being and the latent hazards that persist throughout our societies. Measles, a highly contagious viral illness known for its severe impact on young children, represents a persistent adversary in the field of public health [1, 2]. Following exposure to the measles virus, approximately 90% of individuals without prior protection are susceptible to contracting the disease. In the year 1980, prior to the widespread implementation of measles vaccinations, the global count of measles-linked deaths reached a staggering 2.6 million [2, 3].

Despite these grim numbers, substantial progress has been made, with childhood immunization preventing over 56 million measles-related fatalities between the years 2000 and 2021. In India, measles emerges as a significant childhood health threat, with a median case fatality ratio (CFR) of 2.5% [2]. From October 2022 to March 2023, a total of 68,473 measles cases were reported in India [4]. Regrettably, India reports a majority of the world's measles-related deaths.

Inadequate measles coverage and a high case fatality rate are caused by a number of factors, according to a critical analysis of current strategies and how they are being applied in the field. These barriers include socio-demographic factors such as high birth order, low family income, low education for the parents, and a lack of knowledge about measles and the measles vaccine, and low public confidence in vaccines. Inadequate infrastructure, manpower, and communication resources, difficulties with vaccine storage and transportation, as well as issues with maintaining the cold chain, are additional difficulties in reaching remote areas. Defects exist in surveillance programs for reporting adverse events following immunization and dealing with outbreaks. In addition, there are problems with the biomedical waste disposal [5, 6].

While states with better coverage only needed to improve routine immunization programs, some states and union territories with low measles coverage required catch-up immunization campaigns. Furthermore, the majority of the country's regions frequently have incomplete

virologic surveillance data. India has so far identified the genotypes D4, D7, D8, and B3 of the measles virus [5, 7, 8].

This article focuses on a particular instance of measles affected infant in Chandigarh's periurban region. On March 19, 2023, the case was reported to the district hospital. The medical staff at the urban health centre immediately started an aggressive response in the families around the afflicted infant after confirming the diagnosis in order to find any symptoms or exposure to the measles infection.

A male infant, seven months and four days old, who lived in a Chandigarh urban slum area was brought to the nearest Community Health Centre with complaints of a cold, cough, fever that persisted for five days, and maculopapular rashes (red, raised skin eruptions) over the face and trunk for three days, accompanied by 1-2 episodes of loose stools. After an assessment, the infant was referred to the district hospital for specialized care. Basic laboratory tests were performed following admission to establish the presence of measles by detecting Immunoglobulin M antibodies against the measles antigen. A single dosage of 1 lakh IU of Vitamin A syrup and intravenous fluids were administered for symptomatic management. The child's medical history did not include any notable incidents, surgeries, or allergies. His birth history was unremarkable, and he had received all the recommended vaccinations for his age, including those for Bacillus Calmette-Guerin, Hepatitis B, Pentavalent, Rotavirus, Oral polio (three doses), Pneumococcal conjugate, and two doses of Fractionate-Inactivated Poliovirus. The boy lives in a nuclear household with his mother and father in a rented two-room house; the father is a laborer. The boy was discharged from the hospital on the fourth day after his condition had improved and achieved hemodynamic stability. He was instructed to follow up in two days and given a prescription for Syrup Amoxyclav 128.5mg twice daily for five days.

An intensified case investigation was launched immediately as the Ig M ELISA test confirmed the diagnosis of measles. The child's parents were interviewed in order to identify potential sources of infection, but they denied having any prior known exposure to measles

cases or conditions. To measure illness dissemination and find susceptible children around the index case, a cross-sectional survey was carried out. The majority of the families in the study comprised up of migrant workers from nearby states like Bihar and Uttar Pradesh. A pre-designed and validated questionnaire containing information on family structure, size, socioeconomic status, immunization status of children under five years old, and measles cases was used for the survey, which was conducted by trained public health nurses. The case definition used for identifying measles cases included generalized maculopapular rashes accompanied by a history of fever, cough, coryza, red eye, or diarrhea. To find out whether kids under five had received their Measles and Rubella (MR) vaccinations, 100 houses close to the index case were polled. Children who had never received the Measles and Rubella vaccine were encouraged to do so and given the necessary support, resulting in 100% coverage in accordance with India's National Immunization Schedule. There were no confirmed measles cases, according to the survey.

To improve citizens' knowledge of the clinical characteristics, complications, prevention techniques, and control measures associated with measles, Mass health education campaigns were conducted. To reduce mortality among children under the age of five, Oral Rehydration Solution (ORS) packets were supplied along with instructions on how to prepare and use them. At the urban health training centre, initiatives to support Measles and Rubella vaccination were stepped up, with strict attention to administration and storage procedures. Integrated Child Development Services (ICDS) personnel worked with Anganwadi staff to conduct passive measles surveillance. Such monitoring is still essential for identifying changes in epidemiological patterns and assessing the success of regional immunization programmes.

The report deftly examines a case investigation and outbreak response in a high-risk urban slum in Northern India, illuminating the obstacles that the measles still poses despite persistent vaccination campaigns. Even with a vaccination rate of over 80%, measles continues to be a major cause of illness and mortality in children in India. A coverage rate of above 90% is necessary to further reduce the effects of the measles; hence strong reinforcement of routine vaccination practices is required [4, 10, 11]. The discussion emphasizes that through identifying underserved communities, raising community knowledge about immunization, and extending accessible healthcare facilities, this goal can be accomplished.

The effectiveness of measles vaccinations is demonstrated by the reported 92% vaccine efficacy after a single dosage and the skyrocketing to 100% after two doses [11]. The substantially reduced attack rate among children who received two doses of the vaccine during the outbreak supports this conclusion further [12]. These findings validate the effectiveness of the immunization strategy and highlight the pivotal role in lowering disease incidence.

It thoroughly examines the crucial argument around the administration of early MR doses and the best time to provide the measles immunization. When given to infants younger than nine months old, the MR-1 vaccine exhibits extraordinary seropositivity and strong immunization effectiveness [12]. Importantly, the age at which MR-1 is administered has no impact on the T-cell responses to subsequent doses, adding to the efficacy of the strategy. This discussion supports the rationale for initiating the MR-1 vaccine at six months of age, particularly in contexts of high disease prevalence, such as those seen during epidemics [1].

The discussion's findings are in line with the scientific title, emphasizing the critical nature of ideal vaccine storage, fortified routine immunization coverage, vitamin A supplementation, and improved healthcare systems for underserved populations. The debate offers a thorough foundation for comprehending the crucial importance of early measles immunization, especially in areas with high rates of transmission. The results confirm the central concept of the title by highlighting the critical role that timing of vaccination, particularly MR-1 injection, plays in generating substantial measles immunity.

To effectively combat the measles outbreak, it is essential to gain a deeper understanding of its underlying causes. This includes addressing the availability and accessibility of measles vaccines in remote or underserved areas, as well as overcoming logistical and supply chain challenges that may impede vaccine distribution. Moreover, it is crucial to enhance the capacity for proper vaccine handling and delivery, while also addressing community factors that influence vaccine hesitancy [13].

Implement targeted catch-up vaccination campaigns aimed at reaching older children who may have missed their initial vaccine doses, encourage community involvement by collaborating with local leaders and organizations to promote vaccination actively. Invest in strengthening routine immunization programs ensuring that children receive the recommended second dose of the measles vaccine. Additionally, establishing a robust surveillance system for prompt recognition of measles outbreaks and continuously analyze data for trend detection, enabling adaptive vaccination strategy adjustments. This comprehensive approach is vital for effectively addressing the ongoing measles outbreak.

In essence, the topic effectively endorses the title by providing an in-depth analysis of the optimal timing of measles shot and its efficacy, especially in high-risk areas. The findings distinctly highlight the significance of implementing this vaccination method into practice in order to enhance overall immunization coverage and hence significantly reduce the morbidity and mortality caused by measles.

Acknowledgements

None.

Conflict of interest statement

None.

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Received on August 26, 2023. Accepted on October 5, 2023.

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How to cite this article: Jose S. Optimal timing of measles vaccination in high-risk areas: Insights from MR-1 administration and subsequent dosing efficacy. *J Prev Med Hyg* 2023;64:E271-E273. <https://doi.org/10.15167/2421-4248/jpmh2023.64.3.3075>

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COVID-19

Impact of the COVID-19 pandemic on the infectious disease epidemiology

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Keywords

COVID-19 pandemic • Infectious diseases epidemiology • Mandatory notifications

Summary

Introduction. COVID-19 pandemic has exerted a huge impact on different aspects of public health. Mandatory notifications are a fundamental tool to have a general picture of infection disease spread in a population. The aim of this study was to evaluate the impact the COVID-19 pandemic had on infectious disease epidemiology.

Methods. We collected and analyzed all the infectious disease notifications made in the pre-pandemic (2017-2019) and the pandemic (2020-2022) three-years periods in the provincial territory of Messina, Italy.

Results. The total number of notifications significantly decreased by 41% in the pandemic period compared to the pre-pandemic one, with very high reduction of certain disease notifications such as measles and varicella. Similarly, other airborne infections, such as meningococcal meningitis and tuberculosis, underwent an

important decrease. Conversely, an increase was found for some infections such as syphilis and, especially, scabies that reported a percentage value of +159.9%.

Conclusions. The COVID-19 pandemic, reducing the possibility of microbial spread following to the lockdown and, in addition, to the constant use of face masks and other personal protective equipment, the frequent hand-washing, more ventilation of the living locals, and less gathering, surely reduced the occasions and the possibility to get many infections. On the other hands, the pandemic had a negative impact on scabies diffusion probably due to different causes among which the worsening of some poor realities, the restrictions that forced people to live in strict contact and, especially, the worsening of the conditions of the elderly living in care homes.

Introduction

Infectious diseases represent still a huge challenge for global public health and economic stability due to their high rate of mortality, disability and morbidity on a global level [1]. The recent COVID-19 pandemic that has been literally upset the world, as well as some health problems among which the resurgence of some old diseases such as syphilis or tuberculosis [2-4], and the dramatic spread of antibiotic-resistant bacteria in healthcare settings [5, 6], have aroused many concerns worldwide. For this reasons, the control of infectious diseases appears crucial for public health in order to reduce their incidence, prevalence or eliminating long-term impairments [7].

Currently, we have different effective weapons that allow to minimize the transmission of pathogens, among which a continuous monitoring of the notified cases thanks to mandatory notifications and specifically dedicated surveillance systems. In Italy, notification of infectious diseases is mandatory according to the Ministerial Decree 15 December 1990 [8]. Since 2019, the notification system has been changed and the new infectious disease reporting system (called PREMAL) has been activated. Reporting of probable or confirmed cases of an infectious disease is made by local General

Practitioners (GPs), Primary Care Pediatricians (PCPs) or hospital physicians. This completely online system uses the ICD9-CM coding for the classification of infectious diseases, and allows to face any emerging or emergency syndromes. In addition to this general system, there are other specific surveillance systems at national level, such as those for legionellosis, influenza and viral hepatitis [9]. This mandatory notification system allows for a continuous analysis at a central and local level.

To date, the COVID-19 pandemic has been caused in the world about 770,000,000 cases and 7,000,000 deaths (WHO, 2023) [10, 11]. This pandemic, also due to the transmission containment measures, such as general lockdowns, has caused a huge impact not only to the global economy, world industry, and the world food system but also to public health [12, 13].

Considering this premises, the aim of this study was to evaluate the impact that the COVID-19 pandemic has had on the epidemiology of infectious diseases through the analysis of the mandatory notifications made during the pre-pandemic and the pandemic period, evaluating the role that the pandemic had not only on general notifications but also understanding what diseases were most involved in this critical and unexpected situation.

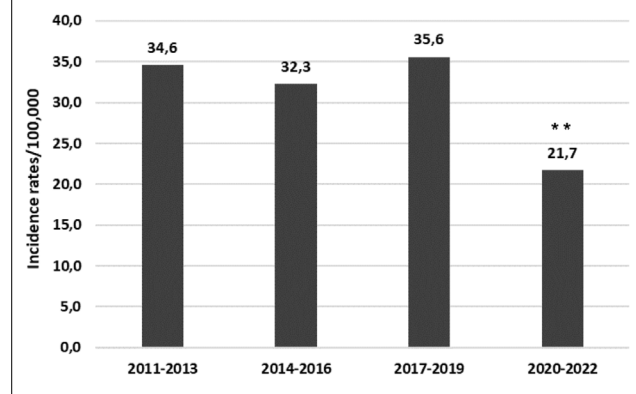
Methods

We carried out a cross-sectional study examining all the infectious disease notifications made in the three-year periods 2017-2019 and 2020-2022 in the Italian province of Messina, Italy. The provincial territory had, in the studied periods, an average population of 618,713 inhabitants, healthy administered by the Provincial Health Agency 5 (ASP 5), divided into eight districts, of which the largest one is represented by the Metropolitan city of Messina (comprising the 37% of the whole population). All the notifications made by the local physicians are managed by the Public Health, Epidemiology and Preventive Medicine Unit of the Messina ASP 5 Prevention Department, which has the task of insert the information into the IT platforms of the general (PREMAL) and specifically dedicated national websites. Specifically, in Italy some informative systems are completely dedicated to some diseases, among which the most important ones are the SEIEVA (Sistema Epidemiologico Integrato delle Epatiti Virali Acute, Integrated epidemiological system of acute viral hepatitis), the INFLUNET (Sistema Nazionale di Sorveglianza Epidemiologica e Virologica dell'Influenza, National System of Epidemiological and Virological Surveillance of Influenza), the Integrated Measles-Rubella Surveillance System, the Surveillance System of Legionellosis, and the Surveillance System of Invasive Bacterial Diseases caused by meningococcus, pneumococcus and *Haemophilus influenzae* b. The notification data collected by these systems were used to obtain disease incidence values, considering the resident population per each year in order to make a difference between the pre-pandemic (2017-2019) and the pandemic (2020-2022) period. Resident population data were collected using the specific website of the National Institute of Statistics (in Italian ISTAT). Statistical processing was performed using the Prism 4.0 software. Descriptive statistics were used to find the percentages and the 95% confidence interval (CI). Exact "F-tests" was performed in order to compare the mean values between the studied periods while a Spearman's correlation test was performed to evaluate the general trend of notifications made for all the notifiable diseases starting from 2011 to 2022. Significance was assessed at the $p < 0.05$ level.

Results

In the pandemic period (2020-2022), 393 infectious disease cases were notified, compared to 672 cases of the pre-pandemic one (2017-2019), with a percentage decrease of -41.5% ($p < 0.0001$). Specifically, in the pandemic period, absolute numbers of 135, 130 and 128 cases were notified in 2020, 2021 and 2022 respectively. To verify that this decrease was real and occurred properly in the pandemic period, we also have evaluated the number of notifications made in the previous three-year periods starting from 2011. In addition, to

Fig. 1. Incidence rates/100,000 resident population of the infectious disease notifications made from 2011 in the Messina provincial geographical area (" = $p < 0.01$).



evaluate that this decrease was not linked to changes in population, we have calculated the incidence rates based on resident population. Specifically, in the pre-pandemic period (2017-2019), the average incidence rate was 35.6/100,000 \pm 7.4 (95% CI: 27.2-44.0) while, in the pandemic period, the average incidence rate was 21.7/100,000 \pm 0.5 (95% CI: 21.1-22.3). Therefore, a significant percentage decrease of -39% between the average values of the two periods incidences was detected ($p = 0.0089$). Figure 1 shows the incidence rates of notified infectious diseases in the previous three-year periods starting from 2011.

Then, we evaluated the absolute numbers of the infectious disease notifications made in the pre-pandemic and the pandemic periods in order to calculate the corresponding percentage changes for the single notifiable infectious diseases. The results are shown in Table I.

Table I shows that a remarkable percentage decrease of notifications for certain infectious diseases occurred in the pandemic period compared to the pre-pandemic one. It is important to highlight that only three diseases had a percentage increase, *i.e.* syphilis, *non-tuberculous mycobacteriosis* and especially scabies that reported a very remarkable increase of +159.5% ($p < 0.0001$). Actually, also all the remaining diseases not individually considered and classified with the name "other" reported a remarkable increase. Under this denomination we considered some diseases such as leishmaniasis, listeriosis, leptospirosis, malaria, skin mycosis, tularemia, gonorrhea *etc.*, inconstantly present in our territory and rarely notified.

In the pandemic period, in Italy there was a complete lockdown starting from March 11th and until May 1st, 2020. It has been very interesting to evaluate the trend of the notifications made in that period of time compared to the rest of the year (Fig. 2).

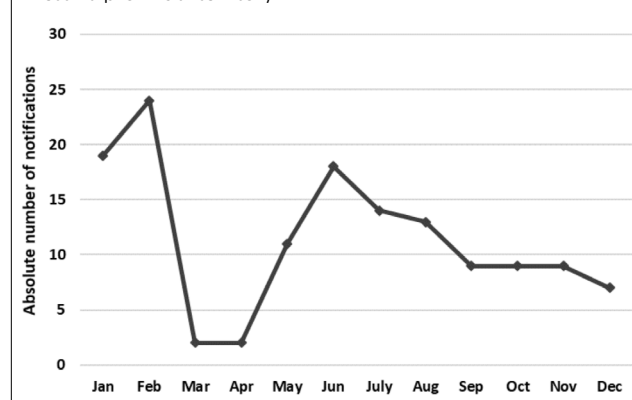
We can observe a remarkable and sudden decrease of notifications during the complete lockdown, with the notification of only 3 cases of scabies and 1 of varicella, with a rise in the next two months, followed by a decrease with a constant but lower presence in the rest of the year.

Tab. I. Comparison between the absolute numbers of the infectious disease notifications made in the pre-pandemic (2017-2019) and pandemic (2020-2022) periods, with corresponding percentage changes ($\Delta\%$) and statistical significance.

	2017-2019 absolute number of notifications	2020-2022 absolute number of notifications	$\Delta\%$	Fisher test
Acute hepatitis B	6	2	-66.7%	ns
Brucellosis	24	11	-54.2%	$p = 0.0352$; OR = 0.4727
Hepatitis A	27	1	-96.3%	$p < 0.0001$; OR = 0.0382
Legionellosis	13	10	-23.1%	ns
Measles	97	0	-100%	$p < 0.0001$; OR = 0.0053
Meningoencephalitis	25	7	-72.0%	$p = 0.002$; OR = 0.2888
Mumps	9	3	-66.7%	ns
Non-tuberculous mycobacteriosis	9	13	+44.4%	ns
Non-typhoid salmonellosis	26	25	-3.8%	ns
Pediculosis	5	3	-40%	ns
Pertussis	9	0	-100%	$p = 0.0031$; OR = 0.0543
Rickettsiosis	10	4	-60.0%	ns
Rubella	1	0	0%	ns
Scabies	79	205	+159.5%	$p < 0.0001$; OR = 2.677
Scarlet fever	24	2	-91.7%	$p < 0.0001$; OR = 0.0859
Syphilis	17	22	+29.4%	ns
Tetanus	3	0	-100%	ns
Tuberculosis	75	42	-44.0%	$p = 0.0039$; OR = 0.5775
Varicella	201	16	-92.0%	$p < 0.0001$; OR = 0.0821
Others	12	26	+116.7%	ns
Total	672	393	-41.5%	$p < 0.0001$; OR = 0.6093

ns: not significant.

Fig. 2. Absolute numbers of notifications made in 2020 in the Messina provincial territory.



However, in order to evaluate the real role played by the pandemic in the observed decreases and to exclude that the latter were due to a decrease already existing in the previous years, we consider the notifications for each notifiable disease made in the previous pre-pandemic nine-year period starting from 2011. The results are shown in Table II.

Airborne infectious diseases

MEASLES, MUMPS, RUBELLA, VARICELLA, PERTUSSIS AND SCARLET FEVER

For these diseases, very high values of percentage

decreases occurred between the three-year pandemic period and the three-year pre-pandemic one (Tab. I). Specifically, measles ($p < 0.0001$) and pertussis ($p = 0.0031$) had a complete decrease (no cases) while mumps notifications fell by two third (-66.7%). Rubella was present with only 1 case in the pre-pandemic period and no case was notified in the pandemic one. However, considering all the pre-pandemic nine-years only pertussis ($p = 0.0032$), varicella ($p = 0.0047$) and scarlet fever ($p = 0.0320$) had a significant correlation (Tab. II). A particular mention has to be made for varicella that was by far the most notified disease in the last twenty years in our geographical area [14]. Specifically, for this disease we observed a highly significant difference between the two different considered periods of time ($p < 0.0001$), confirmed by a highly significant correlation considering the pre-pandemic nine-year period and the pandemic one ($p = 0.0047$). Figure 3 shows the three-year trend of varicella notification in our area starting from 2011.

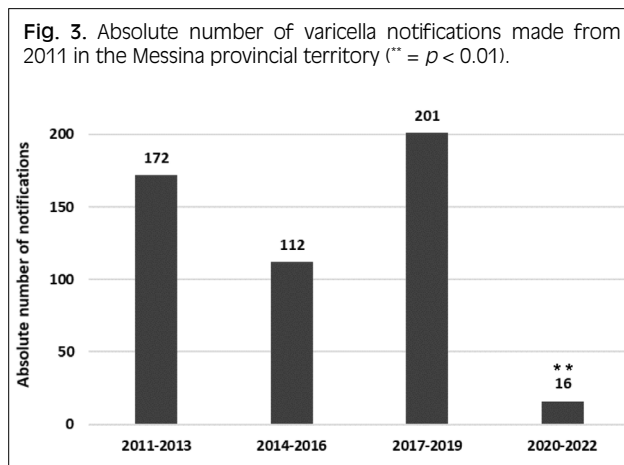
TUBERCULOSIS

Tuberculosis reported a highly significant difference of -44.0% between the pre-pandemic period and the pandemic one ($p = 0.0039$) (Tab. I). A highly significant correlation was found also considering the entire period under study ($p = 0.0446$) (Tab. II). In the pandemic period, the disease affected men for 70%, of which 45.0% Italians and 55.0% foreigners. The mean age of affected people was 41 ± 23.9 (min. 16; max. 86). These features are very similar to those found in the pre-pandemic period when the mean age was 38.4 ± 25.1 (min. 1; max.

Tab. II. General trend of notifications made in the period 2011-2022 and statistical evaluation between the pandemic period (2020-2022) and the pre-pandemic one (2011-2019).

	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	Spearman's test
Acute hepatitis B	3	1	2	2	0	2	2	4	0	0	1	1	ns
Brucellosis	16	11	32	17	13	137	11	6	7	5	4	2	$p = 0.0046$
Hepatitis A	6	3	2	0	1	0	22	3	2	1	0	0	ns
Legionellosis	0	1	0	2	0	0	1	5	7	3	2	4	ns
Measles	31	1	0	0	1	0	63	33	1	0	0	0	ns
Meningoencephalitis	7	8	14	12	20	15	12	9	4	3	2	2	$p = 0.0045$
Mumps	3	6	0	0	1	3	2	5	2	0	2	1	ns
Non-tuberculous mycobacteriosis	3	2	2	1	1	0	0	5	4	5	6	1	ns
Non-typhoid salmonellosis	7	12	8	3	3	8	4	15	7	13	8	4	ns
Pediculosis	0	25	30	63	0	0	0	5	0	0	2	1	ns
Pertussis	7	2	3	2	6	2	3	2	4	0	0	0	$p = 0.0032$
Rickettsiosis	8	14	8	3	8	5	6	2	2	1	0	2	$p = 0.0102$
Rubella	1	11	0	0	0	0	1	0	0	0	0	0	ns
Scabies	0	15	21	8	17	0	0	46	33	52	68	85	$p = 0.0043$
Scarlet fever	30	7	11	0	2	36	15	5	4	2	0	0	$p = 0.0320$
Syphilis	9	4	6	2	7	10	4	9	4	10	3	9	ns
Tetanus	0	0	1	0	1	0	1	1	1	0	0	0	ns
Tuberculosis	38	27	23	16	24	29	29	27	19	17	20	6	$p = 0.0446$
Varicella	29	33	110	51	23	38	129	32	40	11	4	1	$p = 0.0047$
Other	27	26	13	38	2	32	26	11	20	12	8	9	ns
TOTAL	225	209	286	220	130	317	331	225	161	135	130	128	$p = 0.0282$

ns: not significant.



83) and the most affected people were men (72.3%) of which 47.4% Italians and 52.6% foreigners. However, despite the reduction observed during the pandemic, this disease was constantly present in our territory in the last decade, with 88 and 70 cases notified in 2011-2013 and 2014-2016 respectively.

MENINGOENCEPHALITIS

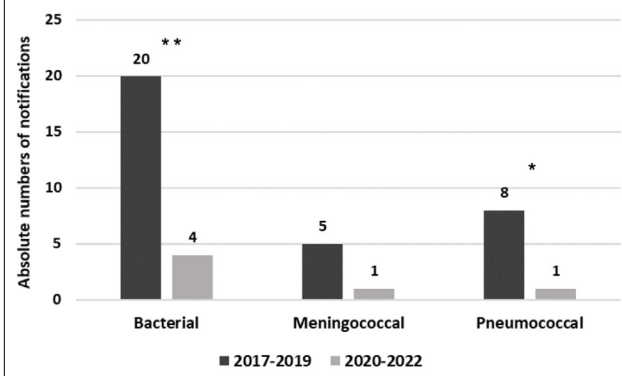
Meningoencephalitis reported a significant percentage decrease of -72.0% compared to the pre-pandemic period ($p = 0.002$) (Tab. I). A highly significant correlation was found also considering the entire period under study ($p = 0.0045$) (Tab. II). However, this general value includes infections of both bacterial and viral etiology.

Specifically, bacterial forms decreased of -80.0% ($p = 0.0028$; OR = 0.2063) in the pandemic period compared to the pre-pandemic one, with meningococcal and pneumococcal forms that decreased of -80.0% (ns) and -87.5% ($p = 0.0304$; OR = 0.1146) respectively. In fact, only 4 cases of bacterial meningitis, of which one of meningococcal and one of pneumococcal origin, occurred in 2020-2022, compared to 20 cases, of which 5 of meningococcal and 8 of pneumococcal origin, occurred in the pre-pandemic period. The significance was also confirmed for bacterial meningitis considering the nine-year period ($p = 0.0350$) but not for meningococcal and pneumococcal forms (Fig. 4).

FOODBORNE INFECTIOUS DISEASES

Hepatitis A was the foodborne disease reporting the highest decrease compared to the pre-pandemic period (-96.3%) ($p < 0.0001$) (Tab. I). However, we did not find a significant correlation considering the whole period under study (Tab. II). This situation was probably due to the quite constant low reporting of this disease with only an isolate occurrence, in the pre-pandemic period, of an outbreak of 22 cases occurred in 2017 in a population composed especially of men (89.3%) for the most part (76.7%) aged 25-64 and reporting, in most cases, homosexual habits. An important decrease (-54.2%) occurred also for brucellosis ($p = 0.0352$) (Tab. I), a disease constantly present in our territory characterized by occasional occurrence of outbreaks, of which the last one occurred in 2016 [15]. For this disease, a significant correlation was also found considering the whole

Fig. 4. Differences between pre-pandemic and pandemic period concerning bacterial meningitis, meningococcal and pneumococcal forms (* = $p < 0.05$; ** = $p < 0.01$).



period under study ($p = 0.0046$) (Tab. II). In this group of diseases, the only one that did not report a decrease was non-typhoid salmonellosis whose notification rate was quite constant (only -3.8%) between the two considered periods of time. No correlation was also found considering the whole period under study.

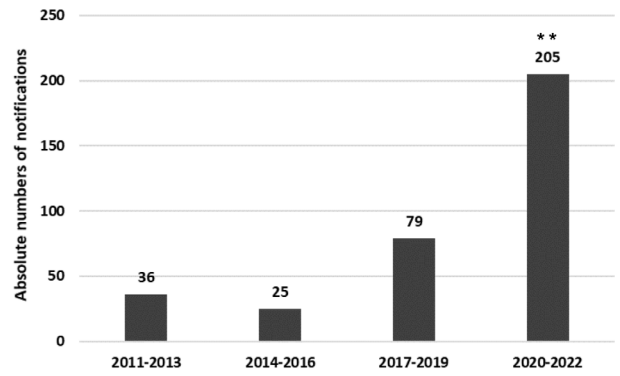
SEXUALLY-TRANSMITTED INFECTIONS

Among STIs, some cases of acute hepatitis B and syphilis were notified in the pandemic period. For the first one, only few cases were reported in both the two period under study, with a not significant percentage decrease of -66.7% (Tab. I). No significant correlation was found considering also the whole period. The same was for syphilis for which, however, was reported a quite high increase (+29.4%) in the pandemic period compared to the pre-pandemic one (Tab. I). Anyway, considering the whole period, no significant correlation was found. In fact, the disease was always present with a quite constant low number of cases. In the pandemic period, syphilis affected especially men (95.4%) with a mean age of 34.8 ± 17.1 (min. 1; max. 79) for the most part of Italian nationality (90.5%). The same personal details were found in the cases notified in the pre-pandemic period.

VECTOR-BORNE AND PARASITIC DISEASES

Rickettsiosis is an endemic disease in our geographical area and, in the pandemic period, it reported a not significant percentage decrease of -70% compared to the pre-pandemic one (Tab. I). However, considering the whole period under study, a significant correlation was found ($p = 0.0102$) between the pandemic period and the nine previous pre-pandemic years ($p = 0.0102$) (Tab. II). A separate mention has to be made for scabies because while almost all the notifiable diseases decreased or remained quite stable during the considered periods of time, scabies reported a high significant percentage increase of +159.9% in the pandemic period compared to the pre-pandemic one ($p < 0.0001$) (Tab. I). This increase was reported also considering the whole period under study with a significant correlation ($p = 0.0043$) (Tab. II). Specifically, the increase was present in all

Fig. 5. Absolute number of scabies notifications made from 2011 in the Messina provincial territory (data of 2022 referred to the period 1st January-31st October) (** = $p < 0.01$).



the pandemic period with 52, 68 and 85 notifications in 2020, 2021 and 2022, respectively. In the pandemic period, the disease affected men with a little higher percentage (57.9%) than women. The mean age of affected people was 42.8 ± 25.9 (min. 1; max. 93) but the disease was evenly distributed in all the different age groups. The majority of the sample (92.6%) was of Italian nationality. However, there was a big difference between the two groups because Italians cases had a median age of 48 (IQR: 20-63; min. 1, max 93) while foreign ones had a median age of 17 (IQR: 17-23; min. 4; max. 58). Indeed, affected foreigners were minors (< 18) in 66.7% of cases while Italians were over-60s in almost one-third of cases. Figure 5 shows the trend of scabies notification in our territory starting from 2011.

Discussion

The COVID-19 pandemic has upset each field of human life with a huge impact on different aspects of society. Healthcare has been one of the most affected field both in terms of provided care and also as preventive tools [16-18]. Italy is a high-income country with a typical epidemiological situation characterized by a constant and remarkable reduction of infectious diseases overtime thanks to high hygienic-sanitary standards and also to significant vaccination policies [19]. Anyway, and without any doubts, COVID-19 pandemic has exerted an impact on infectious disease epidemiology and for many different reasons.

Our study aimed to compare the epidemiological situation of infectious diseases before and during the pandemic in a provincial geographical area of a typical high-income country, which is Italy, through the analysis of mandatory notifications. Furthermore, in order to better understand the real role played by the pandemic, we also evaluated the significance between the reduction observed during the pandemic and the trend of notifiable infectious diseases in the previous nine-year pre-pandemic period. In a previous study [14], we showed a marked and constant decrease of infectious

diseases during the last two decades except for some foodborne diseases (*i.e.* hepatitis A, brucellosis and non-typhoid salmonellosis) and syphilis. The remarkable and significant decrease of notifications that we observed in our geographical area in the pandemic period was in line with what reported by previous evidences [20-22]. This decrease involved almost all airborne diseases but only for some of them, such as varicella, pertussis and tuberculosis, which were always present in our territory despite the availability of effective vaccines against some of them, we observed a real role played by the pandemic. COVID-19 pandemic was probably able to cause this reduction in different ways: 1) decreasing the possibility of viral circulation following both to a lower people movement and gathering possibility that occurred in general and specifically during the lockdown and the constant wearing of face masks and other PPEs; 2) the frequent hand-washing, that is, without any doubt, one of the most important preventive action against the spread of infectious diseases; 3) the habit to increase ventilation of living environments. However, despite strong and valid evidences highlight the key role played by the pandemic in the reduction of infectious disease notifications, we cannot exclude a possible role of the widespread phenomenon of underreporting that is a well-known malpractice present in ordinary situations [23], and that it could be stressed in the extraordinary situation given by the pandemic, due to the huge load exerted on healthcare professionals, especially involved for the most part in managing the pandemic.

Actually, regarding varicella, we have to highlight that vaccination against MMRV is currently mandatory in Italy and starting from 2017, after a recent measles outbreak occurred in Italy in the same year with a high number of cases reported, also, in our geographical area [24, 25]. However, we can exclude that such a reduction can be due to an improvement of vaccination coverage, because only children of 3-4 years have been involved by this change considering that the first dose of MMRV vaccine is administered in Italy at 13th-15th month of life. Moreover, an average increase of only 5% and 10% was reported from 2017 to 2019 for MMR and varicella vaccines respectively.

A similar conclusion can be made also for bacterial meningitis that reported, in the pandemic period, a remarkable decrease in line with other literature data [26]. This is especially valid for meningococcal forms for which the closure of schools and other aggregation places for young people and the constant use of face masks played without any doubts a positive role in the case reduction. For pneumococcal forms, besides the same conditions, we can also assume an important role played by the drastic decrease of influenza cases occurred in Italy especially during the 2020-2021 season [27], given that pneumococcal disease, including meningitis, can occur as complication of influenza, especially in the elderly [28].

About foodborne infectious diseases, hepatitis A showed the highest reduction but linked especially to the lack of outbreaks during the pandemic period. Actually, the

most cases notified during the pre-pandemic period were due to an outbreak occurred in 2017 in men having sex with men (MSM), similarly to other important outbreaks occurred in the same period in other parts of Italy and in different countries worldwide [29-32]. Moreover, in contrast to a reduction of non-typhoid salmonellosis reported by the ECDC in 2020 [33], we have found the constant presence of this disease during the pre- and the pandemic period. In addition, we have found a complete opposed situation because the most part of notifications made during the pandemic period occurred exactly in 2020, therefore in the full pandemic phase. However, no cases were notified in the first semester, when Italy was in the complete lockdown, but after June, with the reopening of food commercial activities. This epidemiological situation was probably due to the more and more common habit to eat raw and low cooked food, condition recognized as one of the main sources of salmonellosis [34], bought from the large distribution and/or delivered directly to your own home. For instance, food delivery has been recently associated with some non-typhoid salmonellosis outbreak [35].

Syphilis registered a percentage increase of almost 30% compared to the pre-pandemic period. Actually, this disease has been constantly present in our territory during the last twenty years with a remarkable increase compared to other infections. This is in line with data from different countries where syphilis has been a resurgent disease especially in some particularly at-risk group of population [3, 14, 36, 37]. Probably, the detected increase was potentially a natural consequence of the already reported increase during the pre-pandemic period and, considering that most of the diagnosis occur in an advanced clinical phase, we can hypothesize this detected trend. Like non-typhoid salmonellosis, also for syphilis no cases were notified in the lockdown period.

A separate mention has to be made for scabies, which reported a remarkable increase in the pandemic period compared to the previous one. Actually, this disease showed already a certain increase in the pre-pandemic period compared to the previous years. We can hypothesize that the pandemic could have exacerbated an already existing situation characterized by a general increasing trend linked to various variable. This situation is in line with what reported by other countries where an analogous increase was detected in last years [38-40]. Many reasons can be hypothesized to explain this increase. An important role might have been played by the remarkable economic crisis induced by the pandemic in Italy [41], especially in those families that already lived into very poor conditions, which are well-known factors favoring scabies onset. Moreover, we can assume that, in 2020, during the lockdown, people were forced to spend more time at home and therefore with relatives, increasing the risk of transmitting the parasite through direct contact or by fomites in those family groups with poorest living conditions. In addition, the pandemic with its huge impact on health services that determined an engulf of the waiting lists, especially for those health specialties not linked to acute diseases such as dermatology,

along with population's fear of leaving home unless it was strictly necessary, not seeking medical attention, caused a late in diagnosis with consequences in the next years and a remarkable increase of diagnosis and notifications. A further explanation can be deduced by the very remarkable age difference between Italians and foreigners. Probably, affected foreigners were young irregular migrants living in reception centers distributed in our territory that was, in last years, interested by a massive irregular migration flow [42], while, regarding Italians, given the presence of the disease in many elderly people, we can assume a role of some care homes, where important outbreaks can occur, as showed by previous studies [43, 44]. Probably, the pandemic induced a higher isolation of the elderly living in care homes due to the very severe restrictions adopted by the structures that did not allow relatives to visit their loved ones. Moreover, many health personnel of these structures were affected by COVID-19 with the worsening of the assistance time quality and quantity.

Conclusions

Our analysis highlighted how the COVID-19 pandemic have impacted the epidemiology of infections in a geographical area belonging to a high-income country that have assisted to a progressive decline of infectious diseases overtime. This decrease was particularly marked during the pandemic period with a general percentage decrease of many infectious diseases. Many factors emphasized by the pandemic, such as social restrictions, the constant use of face masks and other personal protective equipment, the frequent hand-washing, living in more ventilated locations, and less gathering possibilities, reduced the occasions to get especially airborne infections that, among all communicable diseases, have the highest incidence in developed countries. However, to this epidemiological picture we can also assume a potential role played by the always present phenomenon of underreporting, which might have been strengthened by such extraordinary situation given by the pandemic, due to the huge load of healthcare professionals involved, for the most part, in managing the pandemic.

Acknowledgments

Not applicable.

Informed consent statement

Not applicable.

Funding

This research did not receive any specific grant from

funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare no conflicts of interest.

Authors' contributions

AF, ADP: Conceptualization. AF, AL, GV, GG and BR: Methodology. AF, GV: Formal analysis, data curation and writing - original draft. GDA, CR, SS: Resources. All Authors revised the manuscript and gave their contribution to improve the paper. All authors read and approved the final manuscript.

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Received on March 29, 2023. Accepted on July 26, 2023.

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How to cite this article: Facciola A, Laganà A, Genovese G, Romeo B, Sidoti S, D'Andrea G, Raco C, Visalli G, Di Pietro A. Impact of the COVID-19 pandemic on the infectious disease epidemiology. *J Prev Med Hyg* 2023;64:E274-E282. <https://doi.org/10.15167/2421-4248/jpmh2023.64.3.2904>

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COVID-19

Burnout prevention in healthcare professionals during COVID-19

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Keywords

Burnout • COVID-19 • MBI • Mindfulness

Summary

Introduction. Burnout syndrome represents the pathological outcome of a stressful process that mainly affects the “helping professions”. During the COVID-19 pandemic, pressure on healthcare systems has led to an increase in psychological distress among healthcare workers. The aim of this study is to verify whether the practice of relaxation techniques in healthcare workers can improve emotional balance and stem burnout.

Methods. A small sample of 40 female rehabilitation therapists were divided into two groups (20 experimental group subjects and 20 control group subjects). The Maslach Burnout Inventory was administered to both groups, after informed consent, to highlight

the correlation between working hours exceeding 30 hours per week and burnout, by subjecting the experimental group to mindfulness sessions between T0 and T1.

Results. The data analysis highlighted a decrease in burnout in the experimental group after the mindfulness sessions.

Conclusions. The findings suggest that these relaxation techniques can be effective in stemming burnout and promoting psychological well-being. It is therefore possible to hypothesize that such increased and prolonged activities could show a more evident and statistically significant improvement.

Introduction

The burnout syndrome, introduced by Herbert Freudenberger in 1974, indicates a situation of exhaustion characterized by frequent absences due to illness, resistance to go working sense of failure, tendency to isolation, loss of interest and loss of ability to concentrate [1]. Subsequently, it indicates a form of reaction to work stress typical of the helping professions (nurses, doctors, teachers, lawyers, policemen, *etc.*), in which the relationship with the patient/user assumes a negative relevance. The burnout syndrome therefore represents the pathological outcome of a stressful process that affects people who practice the “helping professions”. When they fail to respond adequately to excessive loads of occupational stress and if not properly treated, they can develop a slow process of “attrition” and psychophysical decay due to the lack of energy to support and control stress. In such conditions the subjects can no longer discern their own life from that of the patients / users, due to the excessive burden of the problems of the assisted persons and this mechanism of excessive identification with the users determines the attrition of the worker [2].

During the COVID-19 pandemic, the pressure on health systems has led to an increase in psychological distress among health workers. Burnout has consistently shown in healthcare professionals the dose-response relationship with poor patient safety outcomes associated with anxiety, depression, stress, early retirement, substance abuse, and suicide [3]. This phenomenon

has led to the implementation of interventions by the World Health Organization, in consideration of the negative impact on the costs borne by Health Services. The criticalities of the health emergency continue over time, even if with minor outcomes and the consequences for health workers involve psychic distress and a mix of personal fears and occupational stress that become chronic and determine burnout with three dimensions: emotional exhaustion, depersonalization and feelings of reduced personal fulfillment [4]. During the SARS-CoV-2 pandemic, burnout among healthcare workers has not been fully understood, especially with regard to the different facets between work environment and concomitant psychological responses, such as anxiety and depression. The pandemic has required healthcare workers to endure a period of high workload under stressful conditions with rapidly changing guidelines and redistribution in unknown high-risk settings, while evoking the fear of transmitting the infection to loved ones. A recent review by Petros Galanis and colleagues, examining burnout and associated risk factors in nurses during the COVID-19 pandemic, highlighted that emotional distress, depression and anxiety are more frequent and significant in healthcare workers employed in front line in high risk departments compared to exposed to low risk [5]. In a 2020 study Benjamin Y.Q. Tan et al. through the answers to 3 validated questionnaires, they investigated how doctors, nurses, healthcare assistants and administrative staff of 4 public hospitals in Singapore involved in the treatment of COVID-19 cases, highlighted susceptibility to burnout,

suggesting adequate training as the best interpandemic clinical practice and work shifts of less than 8 hours to implement coping strategies and stem the effects of burnout [6]. Soto-Rubio A et al., in a cross-sectional study, state that an essential protective factor against psychosocial risks is emotional intelligence, correlated to psychophysical health, job satisfaction, greater work commitment with consequent reduction in burnout. This study analyzing a sample of 125 Spanish nurses, during the rise and peak of the COVID-19 pandemic, calculates hierarchical linear regression models considering levels of emotional intelligence and social support as moderating and protective effects of psychosocial risks, burnout and psychosomatic disorders [7].

OBJECTIVES

Our study has two objectives: to analyze, in a small sample of female rehabilitation therapists, the correlation between working hours exceeding 30 hours per week and burnout, also considering the levels of the subscales of the Maslach Burnout Inventory, highlighting how during health emergencies, it may prove useful to carry out relaxation techniques to improve emotional balance and stem burnout in healthcare personnel.

Methods

The observational study recruited a small number of subjects as a result the spread of the SARS-CoV pandemic, limited only to the staff of a Rehabilitation Center which never interrupted its activity during the health emergency and none of the participants had contracted COVID-19.

All subjects voluntarily participated in the study after information and informed consent. The limitation of the study is the small number of subjects, all female. The study sample, made up of 40 professionals from a Sicilian Rehabilitation Center for adult and children patients, all female, is divided into two groups, comparable in socio-demographic characteristics (Tab. I):

1. An experimental group of n. 20 subjects;
2. A control group of n. 20 subjects.

After the data sheet with age, seniority, education and lifestyle habits to both groups in January 2022, (at time T0) during the morning work shift, the Maslach Burnout

Tab. II. Scoring Maslach Burnout Inventory (MBI).

Maslach Burnout Inventory (MBI)	Emotional exhaust	Depersonalization	Professional achievement
High	24 ≥	9 ≥	0-29
Medium	15-23	4-8	30-36
Low	0-14	0-3	37 ≥

Inventory (MBI) is administered in a maximum time of 15 minutes. Subsequently, in June 2022, (at time T1) under the same space-time conditions, both groups were again administered the Maslach Burnout Inventory (MBI) [8]. The MBI it investigates the frequency of sensations that the subject experiences relative to each of the three subscales: Emotional Exhaustion (EE), Depersonalization (DP), Professional Achievement (PA), evaluated using a six-degree response mode on a Likert scale with range from 0 to 6, where 0 means that this situation has never occurred and 6 means that it has occurred every day. If the scores in the EE and DP subscales are high, while the PA subscale scores are low, a high degree of burnout will be obtained. If the scores are average in the three subscales, you will get an average degree of burnout. If the scores of the EE and DP subscales are low, while the PA subscale scores are high, there will be a low degree of burnout. The scoring mode is that proposed by Christina Maslach, whose threshold values are shown in the Table II. The control group was administered only the MBI at both T0 and T1, while the experimental group underwent mindfulness sessions lasting 30 minutes between T0 and T1, with 2 weekly meetings. The practice of mindfulness can, therefore, be considered as a sort of process which, through the implementation of particular meditation techniques, leads the individual to be aware of himself, of his own thoughts, of his own sensations and of reality, understood as here and now. The mindfulness sessions included, within a multisensory room, meditation exercises in a supine position, based on breathing and deep relaxation, to increase one's body perception with the aim of creating greater awareness in the individual [9].

STATISTICAL ANALYSIS

Data analysis was carried out, conducted using the SPSS-25 software, in order to analyze the correlations between the different variables under examination with two objectives.

Objective 1: at time T0 to analyze, in the experimental group and in the control group, the correlation between working hours (greater than 30 hours per week) and the three subscales of the MBI: Emotional Exhaustion (EE), Depersonalization (DP), Professional Achievement (PA). Objective 2: in the time span between T0 and T1 compare, in the experimental group the averages of the three subscales of the MBI: Emotional Exhaustion (EE), Depersonalization (DP), Professional Achievement (PA).

Tab. I. Socio-demographic characteristics of the sample.

Population under study: n.40 women	
Age (years ± SD)	44.19 ± 11.62
Sex	Female
Educational level (years)	16
Marital status	Yes
Children	Yes
Working Seniority (years)	14
Smoking	No
Alcohol	No
Drugs	No

Fig. 1. Burnout level of the experimental group at time T0.

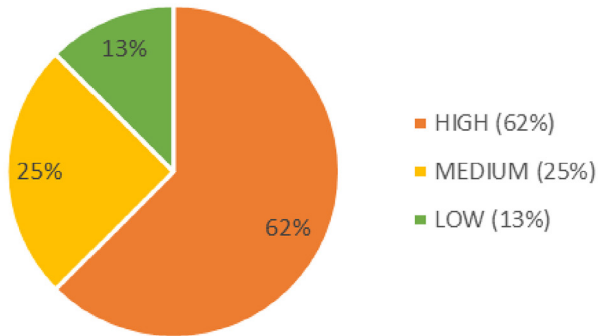


Fig. 2. Burnout level of the control group at time T0.

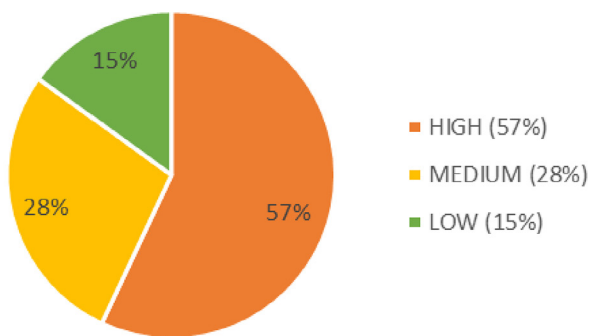
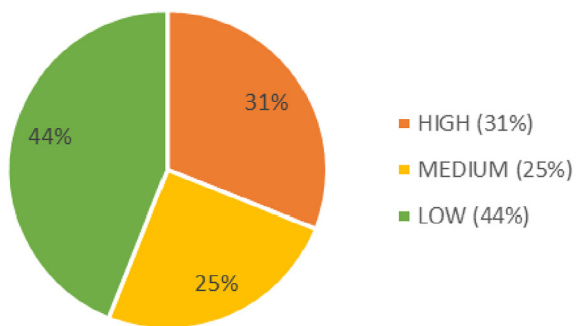


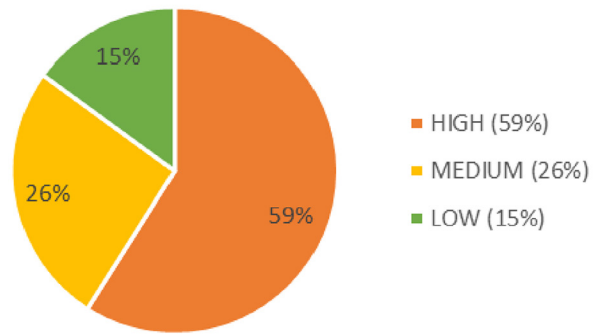
Fig. 3. Burnout level of the experimental group at time T1.



Results

For both groups, the scores for the 3 subscales of the MBI were calculated: Emotional Exhaustion, Depersonalization and Professional Achievement. In the experimental group at time T0, the calculation of the scores of the 3 subscales showed burnout levels distributed as follows: 62% of the subjects reported a high burnout level, 25% medium level and only 13% low (Fig. 1). Again at time T0 in the control group, the calculation of scores at the 3 subscales of the MBI showed in 57% of the subjects a high burnout level, in 28% of them a medium level and in 15% a low level (Fig. 2). At time T1, the MBI was administered again to both the experimental and control groups, in the same

Fig. 4. Burnout level of the control group at time T1.



spatiotemporal conditions with the difference that the experimental group performed mindfulness sessions in the time frame between T0 and T1. The administration of MBI in the experimental group at T1 shows that the scores reported in the 3 subscales determine: in 31% a high level of burnout, in 25% a medium level of burnout and in 44% a low level of burnout (Fig. 3). In the control group at T1 no statistically significant differences emerged: 59% reported a high level of burnout, 26% a medium level and 15% a low level (Fig. 4).

Objective 1: as can be seen from Table III, working hours above 30 h correlates positively with the MBI subscale Emotional Exhaustion (made with Pearson correlation: $r = 0.538$; $p < 0.05$). This denotes for both groups that the more time the subject spends at work, the more he experiences emotional exhaustion. Depersonalization positively correlates with Emotional Exhaustion, while it correlates negatively with Professional Achievement. Therefore, the analysis showed a statistical significance between working hours and the scores of the three subscales at time T0 for all 40 subjects in the sample under study.

Objective 2: in the experimental group the comparison of the averages of the three subscales of Emotional Exhaustion, Depersonalization and Professional Achievement at time T0 and T1, statistically indicates the presence of a slight improvement in the level of burnout. It is evident from Table IV, that the average of the scores of the 20 subjects of the experimental group regarding emotional exhaustion and depersonalization at time T0 is greater, while at time T1 it is reduced, conversely, the average of professional achievement has increased.

Discussion and conclusions

Various studies suggest that different factors are associated with burnout and underline the multidimensionality of burnout [10, 11]. Comparing groups with high and low levels of burnout, a study showed that long working hours correlate significantly with burnout and working time is more associated with burnout among individuals under the age of 50, women and physically inactive or sedentary employees [12]. A research by Koinis and collaborators has analyzed and highlighted how the

Tab. III. Experimental group: Pearson T0 correlation between working time and MBI

		Working hours > 30h	Emotional Exhaustion	Depersonalization	Professional Achievement
Working hours > 30h	Pearson correlation	1			
Emotional Exhaustion	Pearson correlation	.538*	1		
Depersonalization	Pearson correlation	.290	.665**	1	
Professional achievement	Pearson correlation	-.215	-.609*	-.602*	1

* The correlation is significant at level 0.05 (two-tailed). ** The correlation is significant at level 0.01 (two-tailed).

Tab. IV. Experimental group: average comparison of the 3 MBI subscales at T0 and T1

	Times	Subjects	Average	Standard Deviation
Working hours > 30h	T0	n. 20	0.94	0.250
	T1	n. 20	0.94	0.250
Emotional Exhaustion	T0	n. 20	30.56	13.165
	T1	n. 20	22.31	11.080
Depersonalization	T0	n. 20	7.13	6.541
	T1	n. 20	2.75	4.626
Professional Achievement	T0	n. 20	38.75	5.273
	T1	n. 20	42.13	3.810

lack of emotional regulation and coping strategies can determine harmful effects on the psychophysical health and job satisfaction of health workers, particularly in nurses, resulting in stress and burnout [13]. According Stella Dorz et al. [14], sex seems to have an influence on burnout, in the sense that men experience high levels of “depersonalization”, while women tend to be more easily “emotionally exhausted”. During the COVID-19, working in crowded hospitals, night shifts and/or for long hours, lack of sufficient access to personal protective equipment have favored burnout syndrome [15]. A review aims to explain the potential impact of coronavirus disease (COVID-19) on the mental well-being of healthcare professionals by describing the associated psychological disorders and experiences that may arise in relation to COVID-19, in particular acute stress disorder (ADS), post-traumatic stress disorder (PTSD) and mass trauma. The review suggests also measures as possible interventions for the treatment and prevention of trauma, stress and burnout with the aim of understanding the emotional state of health workers during the pandemic and stemming mental illnesses and psychotraumas underlying COVID-19 [16]. It is important that hospitals provide for the basic physiological needs of health workers, supplying adequate nutrition, ensuring rotations are adhered to for sufficient rest, limiting overwork that is a known driver for burnout, providing psychological support and a comfortable environment, and offering cognitive-behavioral therapy that has proven useful in previous outbreaks [17]. Social support has also been identified as an important protective factor against trauma [18,19] together with support of psychoeducational workshops that provide information about the potential psychological effects that can occur during a pandemic [20-22]. It is necessary in times of pandemic to think about treating stress by developing

psychological strategies for all health workers and not just for those working on the front line. It is a challenge to design programs to alleviate burnout by focusing on reprocessing traumatic memories. Some research suggests the use of psychological micro-practices, which are activities that focus on better management of the emotional aspects of stress [23, 24], with mindfulness practices to manage the emotional symptoms of exhaustion and depersonalization [25-28]. The call to create programs to prevent PTSD and burnout during the SARS-CoV-2 pandemic inspired our study that highlighted in our sample the negative correlation between burnout and working hours. It was not possible to highlight a correlation between the degree of burnout and gender since the entire sample was female and this represents a limitation of the study. The mindfulness activity improved the empowerment of each operator, albeit in the short period of time of the investigation limited for contingent reasons. The survey was born with the aim of assessing whether these mindfulness activities carried out during work can promote a condition of global well-being, enhancing the ability to control and the awareness in order to improve health, lifestyle and above all organizational well-being. The results suggest that these relaxation techniques may be effective for occupational stress and burnout as they improve psychological well-being [16]. It is possible that such prolonged mindfulness activities could show a more noticeable and statistically significant improvement. An important sign noted is that all subjects in our sample expressed a desire to increase and continue mindfulness. Caregivers felt more considerate of patients and reported improved interpersonal relationships with problem-solving and fewer conflicts at work. Our study has methodological limitations: the small number of the sample, the administration of a single questionnaire, the

short time frame of the study, but it would be desirable to introduce periodic mindfulness sessions for all health personnel within the work shifts constantly and continuously to allow operators to obtain a space and a “dedicated and special” time in which it becomes possible to dedicate themselves to sharing and expressing their own anxieties and personal experiences, integrating and experiencing states of well-being, providing new strategies. In this way the operator no longer perceives himself as an individual but as part of a group to which he feels he belongs, which he influences and by which he is mutually and positively influenced and this improves both the relationship with colleagues and feeds a better relational competence with the humanization of the patient who in this way will be considered as a human being in his totality.

Acknowledgements

This research received no external funding.

Funding

This research received no external funding.

Informed Consent Statement

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

Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

EM: Conceived and designed. EGC: Analysis of data. All authors have read and agreed to the published version of the manuscript.

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Received on March 30, 2023. Accepted on October 10, 2023.

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How to cite this article: Micali E, Chiarella EG. Burnout prevention in healthcare professionals during COVID-19. *J Prev Med Hyg* 2023;64:E283-E288. <https://doi.org/10.15167/2421-4248/jpmh2023.64.3.2906>

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COVID-19

Effectiveness of a vaccine recovery plan after the COVID-19 pandemic in the Siracusa Local Health Authority, Italy. Results of one year follow-up

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Keywords

COVID-19 pandemic • Childhood immunization • Vaccine coverage • Missed vaccinations • Recovery plan • Vaccine-preventable diseases • Catch-up programmes

Summary

Introduction. The COVID-19 pandemic has strongly impacted on the immunization services around the world, threatening the gains made in the control of vaccine-preventable diseases.

Methods. A vaccination recovery plan of missed vaccinations has been put in place in the LHA of Siracusa after the pandemic. We compared 2021 and 2020 vaccination coverage by age group and vaccine type after one year of follow-up of the recovery plan. The Chi-square test was executed on proportions for the years 2021 vs 2020. Results were considered statistically significant at a two-tailed p -value ≤ 0.05 .

Results. 36-month coverage rates were 92.5% for polio and 93.7% for measles-containing-vaccine, representing -0.3% and -1.8% decreases, respectively, as compared to 2020. By 8 years of age (booster doses), immunisation coverage was 80.7% for polio and 80.1% for measles, representing a -5.7% and -3.7%, respectively, compared to 2020. 36-month coverage was 56.6% for Men B

(-5.0% as compared to 2020), 73.2% for Men ACW135Y/C (+1.1% as compared to 2020) and 86.9% for PNC vaccine (-1.7%, as compared to 2020). Regarding HPV vaccination, in 2021, vaccine coverage was 44.2% (-4.4% compared to 2020). Compared to the previous report, the VC difference among the cohorts narrowed for all almost vaccinations, except for the anti-men B and the anti-HPV vaccination, for which we recorded an increase in VC difference, and for men ACW135Y/C, for which a significant increase has been recorded.

Conclusions. Despite the efforts to organize and realize an extensive and well-designed vaccination recovery, our data show that even after the 1-year follow-up, globally deficits in coverage for these routine vaccinations persist, although there has been a substantial and significant recovery of missed vaccinations, especially among younger children and for primary cycles.

Introduction

A significant and deleterious effect of the COVID-19 pandemic was the decline in vaccination coverage (VC), especially in the first wave, when many vaccinations have been often delayed and/or cancelled, evidenced by epidemiological studies conducted in many countries all over the world and by WHO global immunisation surveillance and monitoring, threatening the gains made in the control of vaccine-preventable diseases (VPDs) for the past decades [1-8]. The causes of the drop of vaccinations are different: social distancing measures, reallocation of health care workers, de-prioritization of routine health care services, and concerns that patients and caregivers seeking routine preventive services, like vaccinations, may be exposed to COVID-19 [5, 9].

Previous research show that the most affected vaccinations by the pandemic have been the non-mandatory ones, particularly those addressing the adolescent and adult population, such as immunization against papillomavirus and that the reductions in vaccination rates were highest among older children (10-17 years) vs new-borns (0-2 years) and young children (3-9 years) [7, 10-12].

Left unaddressed, declines in VC will cause a resurgence in disease outbreaks leaving communities across the world at risk of disease and death from VPDs [13-16]. Interim guidelines warning about the risk of VPDs outbreaks have been published, which could cause further pressure on health services [17-19].

The drop of VC rate may represent a particular threat for low- and middle-income countries (LMIC's) for battling the pandemic alongside pre-existing challenges, including the threat of other VPDs [20-22]. Reduction in VC was also observed in industrialized countries [10, 22-27].

For vaccination coverage to recover to pre-pandemic levels, immediate and sustained catch-up efforts are necessary [28]. Efforts are needed to administer missed doses to adolescents nearing the end of the recommended vaccine age windows [29-31].

Improving routine immunization program capacity is essential for countries to adeptly prevent, manage, and recover from outbreak-prone VPDs, as well as VPD-attributable longer-term cancers and diseases [11].

In this study, we assessed the effects of a recovery vaccination program on routine childhood VC in the

Siracusa Local Health Authority (LHA), just over 380,000 inhabitants, in south Italy after the impact of the COVID-19 pandemic of some different cohorts. In more details, we evaluated the vaccination coverage of the same subjects reported in a previous publication, after one year of follow-up [32].

The goals of this analysis are to estimate the level of routine vaccination coverage and above all to evaluate the results of catch-up vaccination strategy have had on curtailing vaccination deficits in this area.

Material and methods

An extensive and well-designed vaccination recovery plan has been put in place in the LHA of Siracusa after the pandemic. The plan included several phases: active calls for children who had missed vaccinations during the pandemic; extraordinary openings of vaccination centres; prioritizing vulnerable people, children and adult, according to their health status and their priorities; and finally, prioritizing the younger children and the completion of primary courses, regardless of the vaccinations, with a special attention for those of the first two years of life.

The birth cohorts, population, target age group, number of doses and year of administration are showed in Table I. Vaccine coverage was calculated using the number of vaccinated in the numerator (extracted from the official records of Epidemiology Unit of the local Health Department) and the eligible population in the denominator (according to Istat data, Italian National Statistical Institute).

We used polio and measles-containing-vaccine as the usual proxy for the hexavalent vaccine (polio, diphtheria, tetanus, hepatitis B, pertussis, *Haemophilus influenzae* type b) and quadrivalent vaccine (measles, rubella, mumps and chicken pox) or trivalent vaccine (measles, rubella, mumps) respectively, since these vaccines are administered in six-in-one and four-in-one (or three-in-one) vaccine formulations in Italy. As for polio, measles-containing-vaccine, men B, men ACW135Y/C and PNC vaccination, we used the

available data at 36 months of age, even though these vaccines are usually administered in the first two years of life according to Italian and regional immunization schedule [33, 34], comparing VC rates for the years 2020 (administered till December 2020 to the 2017 cohort) and 2021 (administered till December 2021 to the 2018 cohort).

Polio with diphtheria, tetanus, pertussis and measles with rubella, mumps and chicken pox (the latter being mandatory only for children born after the 2017) vaccinations are boosted at 6 years of age, mandatorily. We used data on polio and measles vaccinations in 2021 (VC 2021) to the 2013 cohort (8 years old), as well as data on vaccinations administered through the year 2020 (VC 2020) to the 2012 cohorts (8 years old).

Regarding anti-HPV vaccination, we used the full-cycle coverage for 15-year-old (2005 cohort in 2020, 2006 cohort in 2021) since it is offered during the 12th year of life, according to national and regional immunization schedule [33, 34].

The vaccination against rotavirus were not impacted by the recovery plan, being this vaccine administered in the first weeks of life, so the related data are the same reported in the previous report [32].

For all vaccinations, data are reported for birth cohort and a complete vaccination cycle, regardless of the schedule adopted and the vaccine type administered.

We performed a statistical analysis at 36 months (polio, measles, men B, men ACW135Y/men C vaccinations; cohort 2017 and 2018), 8 years (polio and measles booster doses; cohort 2012 and 2013) and 15 years (HPV; cohort 2005 and 2006) for mandatory and recommended vaccinations.

The Chi-square test was executed on proportions for the years 2021 vs 2020. Analysis findings were considered statistically significant at a two-tailed p -value ≤ 0.05 .

Results

The 2020 and 2021 VC rates for all vaccinations are reported in Table II.

With reference to the mandatory childhood immunisations,

Tab. I. VDP, birth cohort, population, target group, number of doses and year of administration of vaccinations to assess the vaccine coverage.

VDP	Mandatory/ Recommended	Birth cohort	Eligible population [§]	Target age group	Number of doses	Year of vaccine administration (1 st January-31 st December)
Polio, Measles, Men B, Men ACW135Y/Men C	Mandatory	2017	3,155	36 months	3 for polio and 3 (or 4) for Men B; 1 for measles and Men ACW135Y/C	2020
	Recommended	2018	3,090			2021
Polio, Measles	Mandatory	2012	3,605	8 years	4 for polio; 2 for measles	2020
		2013	3,408			2021
HPV	Recommended	2005	3,909	15 years	2 or 3	2020
		2006	3,890			2021

[§] Data from www.demoistat.it.

VDP: vaccine-preventable disease; Men B, ACW135Y and C: *Neisseria meningitidis* serogroups B; ACW135Y and C; PNC: *Streptococcus pneumoniae*; HPV: human papillomavirus.

Tab. II. Vaccine coverage rates (%) registered for mandatory and recommended vaccinations at 36 months, 8 years and 15 years of age, stratified by vaccine type and year of administration, along with the percentage differences between the 2020 and 2021 rates in Siracusa Local Health Authority.

Target age group	VDP	VC Rates (%) by Year of Vaccine Administration		% Difference (2021 vs 2020)	p-value*
		2020	2021		
		Cohort 2017	Cohort 2018		
36 months	Polio	92.8	92.5	-0.2	0.7
	Measles	95.5	93.7	-1.8	< 0.01
	PNC	88.6	86.9	-1.7	< 0.05
	Men B	61.6	56.6	-5.0	< 0.001
	Men ACW135Y	72.7	73.2	+1.1	0.3
		cohort 2012	cohort 2013		
8 years	Polio	86.4	80.7	-5.7	< 0.001
	Measles	83.9	80.1	-3.7	< 0.001
		cohort 2005	cohort 2006		
15 years	HPV	48.6	44.2	-4.4	< 0.001
	HPV females	57.8	52.9	-4.9	< 0.01
	HPV males	39.9	36.3	-3.6	< 0.05

* Chi-square test (2021 vs. 2020); VC: vaccination coverage; VDP: vaccine-preventable disease.

Men B, ACW135Y and C: *Neisseria meningitidis* serogroups B, ACW135Y and C; PNC: *Streptococcus pneumoniae*; HPV: human papillomavirus

in 2021, 36-month coverage rates were 92.5% for polio (hexavalent vaccine) and 93.7% for measles-containing-vaccine, representing -0.3% (not statistically significant) and -1.8% decreases, respectively, as compared to 2020. By 8 years of age (booster doses), immunisation coverage was 80.7% for polio and 80.1% for measles, representing a -5.7% and -3.7%, respectively, compared to 2020. With reference to the recommended childhood immunisations, in 2021, 36-month coverage was 56.6% for Men B (-5.0% as compared to 2020), 73.2% for Men ACW135Y/C (+1.1% as compared to 2020; not statistically significant) and 86.9% for PNC vaccine (-1.7%, as compared to 2020). Regarding HPV vaccination, in 2021, vaccine coverage was 44.2% (-4.4% compared to 2020; -4.9% in females and -3.6% in males). Compared to the previous report (Tab. III), the VC difference among the cohorts was -0.2% for polio (hexavalent vaccine); -1.8% for measles-containing-vaccine (primary vaccination course doses) and -5.7%

and -3.7% for booster doses (8 years of age) (Tab. III, column B).

Discussion

Similar to what has been noted nationally and in other countries, the vaccine coverage of routine childhood immunisations was negatively affected during the COVID-19 pandemic also in the LHA of Siracusa.

We showed reductions in VC for all vaccines and age groups investigated in 2021 compared with the previous year (range from -0.3% to -5.7%), except for the men ACW135Y vaccination (+1.1%).

The observed reduction of VC was greater for children aged > 36 months compared to the younger (-4.6% vs -1.5%) and for booster doses compared to the primary vaccinations (-4.7% vs -1.0%).

VC rates for mandatory vaccinations decreased in 2021 compared with 2020 (-2.9%; range from -0.3% to

Tab. III. % Differences among the cohorts in each survey (column A and B) and among the two different surveys (see the text).

Target age group	VDP	% Difference 2020 vs 2019 (%)	% Difference 2021 vs 2020 (%)	% VC recovery from survey (A) to survey (B) (%) (*)
36 months	Polio	-1.4	-0.2	+82
	Measles	-3.8	-1.8	+52
	PNC	-2.4	-1.7	+30
	Men B	-4.6	-5.0	-9
	Men ACW135Y/Men C	-5.6	+1.1	+120
8 years	Polio	-7.8	-5.7	+26
	Measles	-5.0	-3.7	+27
15 years	HPV	-4.3	-4.4	-2
	HPV females	-4.8	-4.9	-1
	HPV males	-3.4	-3.6	-4

Men B, ACW135Y and C: *Neisseria meningitidis* serogroups B, ACW135Y and C; PNC: *Streptococcus pneumoniae*; HPV: human papillomavirus

(*) Comparison of the two surveys: positive values indicate a narrowing of the vaccination coverage gap between the two surveys, negative values an increase in the gap.

-5.7%), while recommended vaccinations ranged from +1.1% to -5.0% (-2.5%).

Compared to the previous report [32], we observed a positive and significant percentage reduction of the difference in VC between the two surveys for all compulsory vaccinations, with a greater recovery for primary vaccination courses: 82% for polio and 52% for measles-containing-vaccine (primary cycle), 27% and 26% for polio and measles-containing-vaccine of booster doses, respectively. A positive and significant reduction was also observed for PNC vaccination (-30%) (Tab. III, column C).

As mentioned above, a little increased difference between the two surveys was observed for Men B (-9%) and for HPV vaccination, (-2% overall, -1% and -4% for females and males, respectively).

Finally, a significant increase in VC for men ACW135Y/C vaccination in 2021 vs 2020 has been recorded (+120%) (Tab. III, column C).

Our findings show that the infants were less likely to miss their vaccination than older toddlers during the COVID-19 pandemic in the LHA of Siracusa, as a result of a correct attempt to give priority to the infants and to primary cycles, but also it may suggest that parents put the vaccination of their infants at priority. This is consistent with other findings [35, 36].

During the pandemic, a significant drop in vaccinations coverage was observed in Italy [37, 38]. According to a survey of the Italian Ministry of Health, vaccination activity has slowed down, even if with regional differences [39, 40]. The most affected vaccinations by the pandemic have been the non-mandatory ones, particularly those addressing the adolescent and adult population, such as immunization against papillomavirus [40]. Even prior to the COVID-19 pandemic, vaccine coverage for the adolescent vaccine was suboptimal particularly for HPV [41, 42]. For example, lower HPV vaccination coverage may have long term health implications, resulting in excess cases

of genital warts, CIN1/2/3 and cervical cancer as well as other HPV-related diseases and cancers, with potential to slow progress made in recent years toward the goal of eliminating cervical cancer [43]. Catch-up programs are essential to try to reach the optimal level of coverage targeted by the Italian National Immunization Plan, that is 95% for both males and females of 11-year-old [44]. Our findings are consistent with national data (Tab. IV), except for men B vaccination (Siracusa -5.5; Italy +7.7) and men ACW135Y vaccination (Siracusa +1.1; Italy -6.3) [45, 46]. Regarding the HPV vaccination, the observed difference largely depends on the different HPV vaccination strategies in the Italian regions for the 2005 and 2006 cohorts. Indeed, the HPV-vaccination campaign started irregularly in Italy in 2007, with pre-adolescent girls as the primary target; later, other cohorts were introduced such as 12-year-old boys. Moreover, the start of the vaccination campaign was not uniform in Italy [47].

A decline in immunizations could endanger the vaccination coverage target that is necessary for herd immunity against diseases [21, 48, 49]. In such circumstances, an increased risk of resurgence of VPDs that were controlled or eliminated in children who missed vaccinations during the pandemic is expected, thereby posing a twofold challenge to public health systems [50, 51], especially in the low-income countries [52, 53].

Despite the reductions in vaccination coverage, we did not register an increase in VPD outbreaks in the LHA of Siracusa in the last years (Tab. V). At least in the short-term, the impact of the pandemic on possible VPD outbreaks has been balanced by public health measures (personal protective equipment, hand hygiene, quarantine/isolation, physical distancing), which likely prevented the spread of other respiratory diseases as well. Similar data have registered in the rest of Italy, where no increase in outbreaks due to VPDs has been recorded [38, 54, 55]. Other countries reported different data in VPDs rates [56-58].

Tab. IV. Vaccine coverage rates (%) registered for mandatory and recommended vaccinations at 36 months, 8 years and 15 years of age, stratified by vaccine type and year of administration, along with the percentage differences between the 2020 and 2021 rates in Italy.

Target age group	VDP	VC Rates (%) by Year of Vaccine Administration		% Difference (2021 vs 2020)
		2020	2021	
		Cohort 2017	Cohort 2018	
36 months	Polio	95.6	95.0	-0.6
	Measles	93.8	94.9	+1.1
	PNC	91.7	91.1	-0.6
	Men B	71.0	78.7	+7.7
	Men ACW135Y	50.3	44.0	-6.3
		Cohort 2012	Cohort 2013	
8 years	Polio	88.9	86.9	-2.0
	Measles	89.0	87.0	-2.0
		Cohort 2005	Cohort 2006	
15 years	HPV	41.3	60.7	+19.5
	HPV females	63.3	69.5	+6.2
	HPV males	20.3	54.2	+33.6

Men B, ACW135Y and C: *Neisseria meningitidis* serogroups B, ACW135Y and C; PNC: *Streptococcus pneumoniae*; HPV: human papillomavirus.

Tab. V. Number of Vaccine-Preventable-Diseases (VPDs) in Siracusa Local Health Authority, 2019-2022.

VDP	2019	2020	2021	2022
Measles	3	1	0	0
Chicken pox	17	6	8	6
Invasive bacterial diseases (IBDs)	2	0	2	2

IBDs: *Neisseriae meningitides*, *Streptococcus pneumoniae*, *Haemophilus influenzae*

To avert the reported vaccination disruptions, World Health Organization released guiding principles suggesting compensation strategies for the disrupted immunization plan [17-19]. Any interrupted immunization services should be resumed, and catch-up vaccinations offered as quickly as possible [59, 60].

The urgency for efficient catch-up immunisation approaches needs emphasis again. For VC to recover to pre-pandemic levels, immediate and sustained catch-up efforts are necessary. These strategies may need to be tailored to specific age groups and other priorities. For example, identifying vulnerable people, children and adult, who have been missed during these disruptions and providing targeted catch-up services for these people, will be crucial for full recovery [61, 62].

Vaccinations services will still need innovative and impactful strategies to ensure that people who missed vaccines catch up and to return vaccination coverage to levels attained before the COVID-19 pandemic, and even higher levels [58, 61]. Specific strategies for recovery and expansion of routine immunisation services will vary by context.

There are potential barriers to achieving the necessary catch-up rates required to reverse the deficit resulting from the pandemic. For instance, it may not be feasible for providers to sustain catch-up efforts of this magnitude for the remainder of the catch-up period, as health care personnel and resources are already constrained. The staff of the vaccination services were not rarely understaffed, even before the pandemic, and lacking in some skills, such a strong ability of an effective communication to a wider public [63]. In addition, parents and providers may have vaccine hesitancy and adolescents may surpass the recommended age to receive these vaccines [64].

In addition to the last challenge, vaccine fatigue is becoming a growing concern for Public Health, after nearly three years of non-stop discussion about viruses and vaccines - some of it extremely contentious [65-67]. Vaccine fatigue is understood as people's inertia or inaction towards vaccine information or instruction due to perceived burden and burnout [66]. It is of crucial importance to avoid vaccine fatigue from progressing into worse forms on vaccine non-adoption, e.g., vaccine hostility and vaccine hesitancy.

To the best of our knowledge, it is the first study that assess the effects of an extensive and well-defined recovery program of missed vaccinations due to the pandemic in a specific area in Italy.

We think that local level analysis is very useful to plan tailored and efficient catch-up strategies, and to verify the effectiveness of the recovery plan of missing vaccinations. In addition, is important for efficient catch-up strategies

and future vaccinations campaigns also considering the characteristics of the local context or the different target groups based on their vaccination status and others group-specific characteristics (tailored approach), rather than one-size fits-all approach (uniform approach) [65]. Moreover, any recovery strategy must be measured with the effective availability of properly trained personnel, to cope with new challenges for vaccines, including vaccine hesitancy and vaccine fatigue, misinformation regarding safety and effectiveness of vaccinations in the mainstream media and social media. Nowadays, vaccine hesitancy and the 'infodemic' it fuels are key drivers of under-vaccination across the globe [64, 67-72].

Regarding limitations, we did not consider the possible temporal delay in the administration of vaccines, such as hexavalent, quadrivalent, men B and men ACW135Y vaccinations, which should be administered within the first year of life or at the beginning of the second year of life, according to the immunization calendar. Second, social determinants such level of the education, family income, social isolation, geographic location, or ethnic minorities, are important drivers of vaccination uptake behaviours and it is known that the COVID-19 pandemic has exacerbated the effects of those determinants [73-74]. Despite this, social determinants were not evaluated due to insufficient data availability. For the same reason, vaccine hesitancy has not been investigated, even though it is one of the top threats to public health and the nature of its challenge continues to shift with the social landscape [75].

Conclusions

Despite the efforts to organize and realize an extensive and well-designed vaccination recovery, our data show that even after the 1-year follow-up, globally deficits in coverage for these routine vaccinations persist, although there has been a substantial and significant recovery of missed vaccinations, especially among younger children and for primary cycles. For the 0-3 age group, VC uptake rebounded to near pre-pandemic levels for hexavalent vaccine, measles-rubella-mumps-chicken pox vaccine and PNC vaccine, exceeding the pre-pandemic level for Men ACW135Y/C vaccine.

The COVID-19 pandemic has reversed years of progress to expand vaccination programs around the world, reach target vaccination coverage rates, and achieve vaccine equity [30, 31].

Catch-up strategies in the next years are required for vaccination coverage to reach pre-pandemic levels, especially among adolescents.

It is therefore essential to try to implement even more

expanded catch-up interventions and to continue with vaccination programs involving more and more professionals close to children, adolescents and to their families such as general practitioners, paediatricians, gynecologists, midwives, and teachers.

Understanding the magnitude of these vaccination deficits is critical to reducing the risk of future outbreaks and potential increases in diseases prevalence.

Acknowledgements

The authors would like to thank all the health professionals involved in the routine immunisation activities in the LHA of Siracusa.

Funding

This research received no external funding.

Informed consent statement

Ethical review and approval were waived for this study due to the use of anonymised and aggregated data on vaccination status.

Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

FC: Conceptualization; FC: methodology; FC, EDP, FB, CR: acquisition of data; FC, FB, EDP, MLC: formal analysis and interpretation of data; FC: writing - original draft preparation; FC, FB: writing - review and editing; FC statistical analysis; FC, EDP, MLC: supervision and project administration.

All authors have read and agreed to the submitted version of the manuscript.

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Received on June 19, 2023. Accepted on September 15, 2023.

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How to cite this article: Contarino F, Di Pietro E, Randazzo C, Bella F, Contrino ML. Effectiveness of a vaccine recovery plan after the COVID-19 pandemic in the Siracusa Local Health Authority, Italy. Results of one year follow-up. *J Prev Med Hyg* 2023;64:E289-E297. <https://doi.org/10.15167/2421-4248/jpmh2023.64.3.3001>

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COVID-19

Is single point HbA1c a reliable predictor for death in severe COVID-19?

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Keywords

HbA1c • Death • COVID-19 • Predictor

Summary

Introduction. The severity of COVID-19 infection is affected by several risk factors such as Diabetes Mellitus (DM). The current study aimed to determine the effect of single-point HbA1c on the severity and mortality of hospitalized COVID-19 patients.

Methods. This cross-sectional study was conducted among hospitalized moderate and severe COVID-19 patients in Baharloo Hospital in Iran between December 23rd and February 23rd, 2021. The patients have been diagnosed by Polymerase Chain Reaction (PCR) and Chest Computed Tomography (CT) imaging as COVID-19. Demographic data, clinical presentation, laboratory results, and treatments along with the HbA1c data were included.

Results. 165 COVID-19 cases were included in this study; 126 (76.4%) of which were severe cases. 89 (53.9%) patients were male, with a mean age of 59.89 ± 16.59 years. Severe COVID-19 patients were more prone to a longer hospital stay, and a higher level of inflammatory mediators, compared to the moderate COVID-19 patients ($p < 0.05$). No significant association was found between single point HbA1c, FBS, and severity and mortality of COVID-19 cases ($p > 0.05$).

Conclusions. Single point HbA1c was not a reliable mediator for the prediction of severity or death in hospitalized COVID-19 patients.

Introduction

Since the appearance of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) also named the COVID-19 pandemic, the world faces more than 6 million deaths and more than 600 million infections [1-3]. For COVID-19 severity, some risk factors were found. There are metabolic disorders, immunodeficiency, cancer, hypertension, and obesity. 25 to 45 percent of COVID-19 patients suffer from more than one comorbidity [4, 5]. The global prevalence of DM is 9.3 %, and this metabolic disease bears significant implication on the severity and outcome of both infectious and non-infectious illnesses (e.g., cancer, cerebrovascular diseases, ischemic heart diseases) [6-8]. Previous studies revealed that chronic hyperglycemia was related to the death rate in severe acute respiratory syndrome (SARS) and Middle East Respiratory Syndrome (MERS) [7, 9]. In chronic hyperglycemia, immune system functions such as Cell-Mediated Immunity (CMI), Humoral Mediated Immunity (HMI), and antioxidant and neutrophil function are disturbed [10]. Also, poor control of DM ends up in different complications such as obesity, ischemic cardiac diseases, and renal disorders) [11] that would increase the patient's death rate. Monitoring of chronic hyperglycemia might be of some value, to prevent these complications. One important and easy access tool is HbA1c (glycosylated hemoglobin) test, which shows

the average 3 months blood glucose level. We conducted this study between December 23rd and February 23rd, 2021 to determine the role of HbA1c for prediction of COVID-19 severity of admitted COVID-19 cases. The current study also tried to reveal the role of DM on the mortality of hospitalized COVID-19 patients

Material and Methods

STUDY DESIGN

In the current cross-section study, that conducted between December 23rd and February 23rd, 2021, 165 hospitalized COVID-19 positive patients were included. The HbA1c test, demographic data, medical history, signs and symptoms of COVID-19 patients, lab test results, and outcomes of the treatment were collected and analyzed. The association between HbA1c, DM, and COVID-19 severity were investigated in the COVID- 19 patients.

SUBJECTS

Inclusion and Exclusion criteria

Hospitalized COVID-19 patients with age more than 18 years old (diagnosed by PCR test/CT scan) whose checking HbA1c levels were included. Patients younger than 18 years old, without HbA1c levels, and with poorly controlled diabetes were excluded.

Sampling and Data collection

- The sample selection method was simple Random Sampling. Medical records were used to obtain information on the patients admitted to Baharloo hospital. The cases were selected using the simple random sampling. The demographic data, medical history, signs and symptoms of COVID-19, lab test results, and outcomes of the treatment were collected. The recruited patients COVID-19 vaccination status has not been investigated in this research.

Study Procedures

Diabetes was determined using patients' past diagnosed medical history or was newly defined if the HbA1c level at admission was $\geq 6.5\%$. Patient medical files were used to obtain information on the admitted patients. No intervention was made.

STATISTICAL CONSIDERATIONS

Data analysis

Continuous variables were represented by mean and SD, while categorical variables were represented in the form of the number and percentage. Paired T-test were used for the comparison of continuous variables, and Chi-square and Fisher's exact tests were used for making comparisons between categorical variables. Data were analyzed using IBM SPSS statistic 25 (IBM corporation, Armonk, NY, USA).

Results

Out of 165 COVID-19 patients, 126 (76.4%) were severe and 39 (23.6%) were moderate COVID-19 cases (Tab. I). Totally, the mean age of the patient population was 59.89 ± 16.59 years. The patients with severe form (Mean age 57.98 ± 16.55) were significantly younger than moderate cases (Mean age 66.03 ± 15.35) (p -value: 0.008). COVID-19 cases with cardiovascular diseases were more likely to present as severe COVID-19 form compared to the patients without cardiovascular diseases, 9.1% and 6.1% respectively ($p = 0.037$) (Tab. II). In terms of vital signs and imaging, oxygen saturation (O2S) in severe form (85.31 ± 8.11) was significantly lower than moderate COVID-19 (90 ± 5.08) (p -value: 0.001). Also, the percentage of chest CT involvement in severe form

(46.07 ± 25.46), was significantly more than in moderate cases (20.26 ± 17.39) (p -value: 0.000).

The hospital lengths of stays in severe COVID-19 patients were longer than moderate cases (9.94 ± 6.87 vs 6.92 ± 4.24 days) ($p = 0.002$). Regarding the laboratory results, there were statistically significant differences between moderate and severe groups in C-Reactive Protein (CRP), Lactate dehydrogenase (LDH), Aspartate Aminotransferase (AST), Ferritin, Calcium, ($p < 0.05$). There was an association between HbA1c and DM and family history of DM (Tab. III). Among the laboratory findings, FBS was significantly related with HbA1c levels (Tab. IV). There was no significant association between COVID-19 severity and mortality with HbA1c levels (Tab. V). Also, there was no significant relationship between DM, anti-hyperglycemic drugs usage, and mortality (Tab. VI).

Discussion

The SARS-CoV-2 coronavirus pandemic is taking a heavy burden worldwide. The mortality rates of COVID-19 pneumonia have been reported as 4.3% to 14.6% [12]. Comorbidities, such as cerebrovascular disease, cardiovascular disease, and diabetes mellitus increase the severity and mortality COVID-19. To minimize the impact of this pandemic, boosting health care system preparedness as well as controlling or decreasing the comorbidities seems essential [13, 14]. DM as a chronic disease causes a high burden on the health system, about 422 million people in the world have DM [15]. Chronic hyperglycemia links with negative consequences of both noninfectious and infectious illnesses and its connection with mortality of influenza, SARS (Severe Acute Respiratory Syndrome) and MERS (Middle East Respiratory Syndrome) was studied [16]. The present study was conducted to find out whether single-point HbA1c and FBS were related to the COVID-19 severity and death rate in admitted COVID-19 patients. According to the recent study, there was a significant difference between moderate and severe COVID-19 patients in terms of acute phase reactants (*i.e.*, CRP, LDH, Ferritin). In severe COVID-19 infection, cytokine storm and hypoxemia result in diffuse tissue damage [17] and increase the level of inflammatory mediators [12]. HbA1c is an easy-access laboratory test, that represents the average recent 3 months glucose serum level and relates with the risks of long-term DM complications [18] (*i.e.*, renal, cardiovascular, central nervous system, ophthalmic) [11]. In the present study, no significant difference was found between moderate and severe COVID-19 patients in terms of HbA1c by both univariate and multivariate analysis. Some studies emphasized the association of HbA1c with COVID-19 severity [19, 20]. DM was also linked with increase in the rate of other infectious diseases such as MERS, SARS, and Influenza [21]. According to the present study, the prevalence of DM in admitted COVID patients was 41.8%, which is more than former studies (7.4-

Tab. I. Frequency of severity variables in hospitalized COVID-19 patients.

Variables (criteria for severe disease)	Total (N = 165)
Involvement in lung CT scan $\geq 50\%$ (n, %)	76 (46.1)
SPO2 room air $< 94\%$ (n, %)	57 (34.5)
CRP ≥ 100 mg/L (n, %)	77 (46.7)
LDH ≥ 1000 IU/L (n, %)	32 (19.4)
People who had at least one of the criteria for severe disease (n, %)	126 (76.4)

Tab. II. Characteristics of COVID-19 patients by disease severity.

Variables	Total (N = 165)	Moderate (n = 39)	Severe (n = 126)	p
Age (Mean \pm SD) years	59.89 \pm 16.59	66.03 \pm 15.35	57.98 \pm 16.55	0.008
Sex (n, %)				
Male	89 (53.9)	17 (10.3)	72 (43.6)	0.138
Female	76 (46.1)	22 (13.3)	54 (32.7)	
BMI (Mean \pm SD)	28.75 \pm 5.07	28.51 \pm 4.9	28.82 \pm 5.1	0.746
Comorbidities type (n, %)				
Hypertension (HTN)				0.967
Yes	63 (38.2)	15 (9.1)	48 (29.1)	
No	102 (61.8)	24 (14.5)	78 (47.3)	
Cardiovascular disease (n, %)				0.037
Yes	25 (15.2)	10 (6.1)	15 (9.1)	
No	140 (84.8)	29 (17.6)	111 (76.3)	
Kidney disease (n, %)				0.429
Yes	2 (1.2)	0	2 (1.2)	
No	163 (98.8)	39 (23.6)	124 (75.2)	
Thyroid disease (n, %)				0.331
Yes	3 (1.8)	0	3 (1.8)	
No	162 (98.2)	39 (23.6)	123 (74.5)	
Pulmonary disease (n, %)				0.690
Yes	3 (1.8)	1 (0.6)	2 (1.2)	
No	162 (98.2)	38 (23)	124 (75.2)	
Cerebrovascular disease (n, %)				0.769
Yes	11 (6.7)	3 (1.8)	8 (4.8)	
No	154 (93.3)	36 (21.8)	118 (71.5)	
Diabetes mellitus (DM) (n, %)				0.317
Yes	69 (41.8)	19 (11.5)	50 (30.3)	
No	96 (58.2)	20 (12.1)	76 (46.1)	
History of family diabetes (n, %)				0.664
Yes	67 (40.6)	17 (10.3)	50 (30.3)	
No	98 (59.4)	22 (13.3)	76 (46.1)	
Pre diabetic history (n, %)				0.942
Yes	26 (15.8)	6 (3.6)	20 (12.1)	
No	139 (84.2)	33 (20)	106 (64.2)	
Vital signs and imaging				
Clinical characteristics (Mean \pm SD)				
SpO2 on admission (%)	86.46 \pm 7.78	90 \pm 5.08	85.31 \pm 8.11	0.001
SpO2 room air (%)	94.88 \pm 4.31	96.96 \pm 1.23	94.36 \pm 4.64	0.000
Heart rate (beats/minute)	87.61 \pm 17.54	87.58 \pm 16.40	87.62 \pm 17.9	0.991
Respiratory rate (breaths/minute)	20.24 \pm 11.22	18.76 \pm 2.82	20.69 \pm 12.68	0.355
Systole blood pressure (mm hg)	124.03 \pm 16.13	127.72 \pm 12.31	122.95 \pm 16.98	0.119
Diastole blood pressure (mm hg)	74.31 \pm 14.86	75.25 \pm 16.09	74.04 \pm 14.53	0.669
Temperature (degree Celsius)	36.84 \pm 0.61	36.78 \pm 0.91	36.86 \pm 0.49	0.525
Lung involvement in CT scan (%)	39.97 (26.17)	20.26 \pm 17.39	46.07 \pm 25.46	0.000
Laboratory characteristics (Mean \pm SD)				
HbA1c%	6.74 \pm 1.81	6.58 \pm 1.43	6.79 \pm 1.91	0.548
FBS mg/dL	186.94 \pm 86.36	189.24 \pm 92.24	186.23 \pm 84.90	0.862
CRP mg/L	99.81 \pm 71.33	39.90 \pm 27.09	118.16 \pm 70.65	0.000
Ferritin ng/mL	565.01 \pm 390.77	421.92 \pm 361.82	604.36 \pm 390.65	0.017
BUN mg/dL	54.89 \pm 44.04	51.69 \pm 32.90	55.88 \pm 47.02	0.605
Cr mg/dL	1.14 \pm 0.84	0.97 \pm 0.42	1.19 \pm 0.92	0.147
CPK mcg/L	379.18 \pm 805.84	336.14 \pm 790.17	391.68 \pm 813.06	0.717
LDH IU/L	786.37 \pm 367.54	562.08 \pm 160.87	851.48 \pm 385.05	0.000
D. Dimer μ/mL	1.77 \pm 3.00	1.66 \pm 1.23	1.81 \pm 5.34	0.804
Vit D ng/mL	27.34 \pm 14.73	28.28 \pm 13.43	27.10 \pm 15.09	0.716
Ca mg/dL	8.54 \pm 0.63	8.71 \pm 0.55	8.48 \pm 0.64	0.051
Alb g/dL	4.13 \pm 0.59	4.22 \pm 0.61	4.10 \pm 0.59	0.345
AST U/L	58.88 \pm 55.62	40.16 \pm 22.77	64.50 \pm 61.17	0.000
ALT U/L	52.11 \pm 63.70	37.86 \pm 30.54	56.39 \pm 70.24	0.121
Troponin ng/mL	0.70 \pm 4.27	0.13 \pm 0.340	0.97 \pm 4.80	0.403
WBC $\times 10^9$/L	8.94 \pm 6.78	9.34 \pm 10.73	8.81 \pm 5.01	0.672
Eosinophil %	2.19 \pm 0.85	2.39 \pm 0.82	2.13 \pm 0.86	0.093
Neutrophils %	80.52 \pm 9.24	79.15 \pm 6.09	80.95 \pm 10	0.290
Monocytes %	2.94 \pm 0.85	3.21 \pm 0.96	2.86 \pm 0.81	0.025
Lymphocyte %	13.80 \pm 6.89	15.46 \pm 5.66	13.29 \pm 7.17	0.085
Hb g/dL	12.87 \pm 3.63	12.49 \pm 1.70	12.99 \pm 4.05	0.459
Plt $\times 10^9$/L	227.09 \pm 113.73	210.74 \pm 89.64	232.19 \pm 120.12	0.305
Antihyperglycemic treatment (n, %)*				
Metformin	55 (42.6)	12 (9.3)	43 (33.3)	0.665
NPH	43 (33.3)	14 (10.9)	29 (22.5)	
NPH. regular	14 (10.9)	5 (3.9)	9 (7)	
LANTUS.NOVO RAPID	8 (6.2)	1 (0.8)	7 (5.4)	
Glibenclamide	3 (2.3)	1 (0.8)	2 (1.6)	
Novomix	6 (4.7)	1 (0.8)	5 (3.9)	
Days of hospitalization (Mean \pm SD)	9.21 \pm 6.46	6.92 \pm 4.24	9.94 \pm 6.87	0.002
Death (n, %)	28 (17)	3 (1.8)	25 (15.2)	0.077

* N:129

Tab. III. Association of HbA1c with Metabolic disorder.

Variables (N = 165)	HbA1c (Mean± SD)	p
Sex		
Male	6.61 ± 1.57	0.342
Female	6.88 ± 2.06	
Hypertension (HTN)		
Yes	6.90 ± 1.62	0.372
No	6.64 ± 1.92	
Cardiovascular disease		
Yes	6.92 ± 1.93	0.591
No	6.71 ± 1.79	
Kidney disease		
Yes	6.50 ± 0.56	0.850
No	6.74 ± 1.82	
Thyroid disease		
Yes	6.46 ± 1.28	0.791
No	6.74 ± 1.82	
Pulmonary disease		
Yes	6.70 ± 1.50	0.967
No	6.74 ± 1.82	
Cerebrovascular disease		
Yes	6.81 ± 1.77	0.899
No	6.73 ± 1.82	
Diabetes mellitus (DM)		
Yes	7.34 ± 1.99	0.000
No	6.30 ± 1.53	
Family history of diabetes		
Yes	7.48 ± 2.11	0.000
No	6.23 ± 1.36	
Pre diabetic history		
Yes	7.19 ± 2.40	0.288
No	6.65 ± 1.67	

20%) [6]. The prevalence of DM in Iran is 10.4% [22], our cases were moderate and severe COVID-19, so their comorbidities and DM might be more than in earlier studies.

On the other hand, the hyperglycemic condition was occurred in COVID-19 patients, even without any previous history of DM through direct damage of pancreatic cells by viruses, stress induced hyperglycemia, severe sepsis or 4- treatments (*e.g.*, corticosteroids in severe cases) [23].

Chronic hyperglycemia decreases the host immune system function against pathogens in the followings ways; decrease in T cell function, increases the cytokines production and Angiotensin Converting Enzyme (ACE) receptor expression. With accumulation of ACE 2, pulmonary muscle strength and its elasticity decreases, ends in pulmonary dysfunction. In the other words, viral clearance decreases, and inflammatory response increases [11, 24-28]. In the recent study, there was no correlation between DM, HbA1c, and COVID-19 severity, similar the multivariable modality by French researchers, that found no association between HbA1c and COVID-19 severity in the first week of COVID 19 patients' admission [29]. Also, another study on HbA1c, found no links between infection severity and HbA1c in both outpatient and inpatient COVID-19 cases,

Tab. IV. Correlation of HbA1c with Laboratory Characteristics.

Variables	HbA1c	
	R*	p
Age	0.022	0.783
FBS	0.496	0.000
CRP	0.017	0.830
Ferritin	-0.002	0.983
BUN	0.131	0.094
Cr	0.057	0.470
CPK	-0.123	0.121
LDH	-0.015	0.852
D. Dimer	0.005	0.953
Vit D	0.004	0.963
Ca	0.123	0.117
Alb	-.031	0.702
AST	-0.110	0.167
ALT	-0.060	0.454
Troponin	-0.030	0.757
WBC	0.135	0.085
Eosinophil	0.049	0.538
Neutrophils	-0.035	0.659
Monocytes	0.061	0.438
Lymphocyte	0.032	0.688
Hb	0.019	0.808
Plt	0.066	0.399
SPO2 on admission	-0.127	0.116
SPO2 room air	0.051	0.552
Lung involvement in CT scan	0.027	0.726

* R: Pearson correlation coefficient.

however [28]. Although, some researchers indicated that single-point HbA1c can predict the infection severity in admitted COVID-19 patients [25], another insisted that longitudinal HbA1c (during 2 to 3 years) was significantly linked with COVID-19 severity [11]. Longitudinal HbA1c reflects the long-term glucose control in the patients. However, some researchers did not find any association between COVID severity and HbA1c, either single point or longitudinal HbA1c [7, 13, 28, 30] even in admitted cases [2, 6]. 40 days follow-up of diabetic COVID-19 patients found that DM was not a factor for death in COVID-19 cases, however, it predisposed COVID-19 patients to Acute Respiratory Distress Syndrome (ARDS) [5, 31]. In the recent study, no association was found between DM, HbA1c, and the severity of COVID-19, it might

Tab. V. Association of HbA1c levels with disease severity & mortality.

Variables (N = 165)	Normal ≤ 5.69 (n = 28)	Pre-diabetic (5.70-6.49) (n = 137)	Diabetic ≥ 6.50 (n = 137)	p
Severity (n, %)				
Yes	39 (23.6)	38 (23)	49 (29.7)	0.634
No	12 (7.3)	9 (5.5)	18 (10.9)	
Death (n, %)				
Yes	7 (4.2)	7 (4.2)	14 (8.5)	0.533
No	44 (26.7)	40 (24.2)	53 (32.1)	

Tab. VI. Association of mortality with DM & anti-hyperglycemic drugs use.

Variables (N = 165)	Death (n, %) (n = 28)	Alive (n, %) (n = 137)	p
DM			
Yes	13 (7.9)	56 (33.9)	0.587
No	15 (9.1)	81 (49.1)	
Use anti-hyperglycemic drugs			
Yes	23 (13.9)	106 (64.11)	0.743
No	5 (3.1)	31 (18.89)	

be due to: 1) Some newly diagnosed DM cases, so the duration of hyperglycemia might be less than 3 months; 2) There was no categorization of DM type (type 1, type 2); HbA1c is related to Type 2 DM [11]; 3) In the present study, COVID-19 virus subtypes, age, and comorbidities might be different with other studies [6, 27, 28].

This study is one of the few studies on the association of HbA1c and DM in moderate and severe admitted COVID-19 in the Middle East region. This study had the following limitations; it was conducted in a single center and there was no data regarding the type of DM and its duration.

Conclusions

Single point HbA1c cannot be a reliable tool for prediction of hospitalized COVID-19 cases severities and outcomes. Future multi-center studies with a large sample size that measure both single and longitudinal HbA1c are recommended.

Acknowledgments

The authors would like to thank Baharloo Hospital personnel for contribution. This research received no external funding.

Ethical considerations

this study had been done after Tehran University Medical Student ethic committee approval (IR.TUMS.MEDICINE.REC.1400.1015).

Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

HH, MA: Conceptualization, investigation, data curation, formal analysis, writing-original draft preparation and editing. YA: Methodology, formal analysis. MZ, NF: data curation, writing-original draft preparation. All authors have read and agreed to the published version of the manuscript.

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Received on July 14, 2023. Accepted on October 5, 2023.

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How to cite this article: Hosamirudari H, Alimohamadi Y, Akrami M, Zahra M, Faraji N. Is single point HbA1c a reliable predictor for death in severe COVID-19? *J Prev Med Hyg* 2023;64:E298-E303. <https://doi.org/10.15167/2421-4248/jpmh2023.64.3.3032>

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COVID-19

Analysis of death risk factors among COVID-19 patients in Yazd, Iran: A case-cohort study

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Keywords

COVID-19 • Iran • Epidemiologic Studies • Risk factors • Mortality • SARS-CoV-2

Summary

Background. The COVID-19 epidemic control has become a global challenge and many contributing variables are still unknown to policymakers. This case-cohort study was conducted to investigate the risk factors of mortality in COVID-19 patients.

Methods. This case-cohort study was conducted on 956 samples in Ardakan and Meybod counties, Yazd Province, between February 20 and May 20, 2020. The data collection tool was a researcher-made questionnaire. Data analysis was done using descriptive statistics and paired t-test, chi-square, and logistic regression analysis.

Results. Of a total cohort population of 993 in Ardakan and Meybod counties, 435 were assigned to the control group and 521 were assigned to the case group. The results of outcome analysis showed that 14.4% of the patients in the case group and 11.5% of

the patients in the control group died. According to the results of logistic regression analysis in COVID-19 patients, each one-year increase in age increased the risk of mortality by 6% ($HR = 1.06$, $p < 0.001$), each one-day increase in the hospital stay increased the risk of death by 8% ($HR = 1.08$, $p < 0.001$). Moreover, the presence of cardiovascular disease, chronic neurological disease, and chronic pulmonary disease increased the risk of death. The patients who underwent mechanical ventilation had 85% less chance of survival ($HR = 0.15$, $p < 0.001$).

Conclusions. The results showed a higher mortality rate in the elderly patients as well as those with underlying diseases. Attention should be paid to at-risk and elderly patients in terms of ensuring a healthy diet, improving their self-care practices, and providing long-term medical and healthcare facilities.

Introduction

Despite advances in laboratory sciences and medicine, epidemics are still a great challenge threatening the lives of millions. A series of unexplained cases of pneumonia were reported from Wuhan, China in the December 2019. On January 12, 2020, the WHO temporarily named this new virus as Coronavirus Disease 2019 (COVID-19). The WHO officially announced COVID-19 as the name of this new disease on 11 February 2020 [1] and identified it as a public health emergency on 30 January 2020 [2].

This virus has a high infectivity rate and incubation period (2-14 days), which increase its prevalence and hinder prevention and control [3].

This virus easily transmits from one person to another through respiratory droplets and direct contact with virus-containing body secretions via the eyes, mouth, and nose [4].

The mortality rate is high in COVID-19 patients requiring mechanical ventilation due to severe pulmonary injuries [5]. No specific antiviral drug has proven effective for severe COVID-19 and treatment is mainly

supportive, including maintain the vital signs, oxygen saturation level, and blood pressure and decreasing the complications like secondary infections and organ failure [6].

Early studies showed that patients with underlying diseases were at higher risk of complications and death from COVID-19. About 50% of the inpatients suspected of COVID-19 have other chronic diseases and 41% of inpatients with confirmed COVID-19 also suffer from cardiovascular or cerebrovascular disease. The researchers have also found a marked difference in mortality rate according to age group [7].

Despite global efforts to understand COVID-19, many issues are still unknown. The majority of the new studies are based on univariate comparisons. Moreover, most of the studies investigating the risk factors of mortality were conducted in confirmed cases in China and little information is available on the risk factors of death in other parts of the world. Furthermore, few studies have addressed the risk factors of this disease during the epidemic. Due to the fact that the risk factors of mortality in patients with covid-19 differ according to climatic and locational conditions and these risk factors cannot

be accurately generalized to all regions, therefore, this study was conducted in the center of Iran. Also, in this study, mortality risk factors have been investigated as a cohort study, which increases the reliability of the results by comparing the results in the cohort population.

Considering the above research gaps, this case-cohort study was conducted to evaluate the risk factors of mortality in COVID-19 patients.

Materials and Methods

STUDY DESIGN

This study was a case-cohort study. Such studies are used to investigate rare disease [8]. In these studies, the controls are selected from the at-risk population in the beginning of the follow-up time and these groups are selected using random sampling.

Population and research sample

The study was conducted in Ardakan and Meybod counties, Yazd Province. Considering cultural, geographic, climatic, and demographic conditions between these two counties and the relatively high prevalence of COVID-19 infection in these counties, population homogeneity, simultaneous onset of disease, and the similar origin of the population, the residents of these two counties were selected as the cohort population. The reference population was at suspected cases admitted to infectious and ICU wards of Ardakan and Meybod hospitals. The research sample was consistent with the reference population. The patients were selected by census. In this study, exposure was defined as a positive PCR test and survival or death was considered as the outcome of interest. All at-risk subjects that had direct contact with confirmed COVID-19 patients and had a positive PCR test for SARS-CoV-2 were selected as cases. The control group was selected randomly from at-risk subjects who have negative tested for SARS-CoV-2.

Data collection tool

The data collection tool was a researcher-made questionnaire based the data available in the COVID-19 data dashboard of Shahid Sadoughi University of Medical Sciences. The questionnaire included demographic, diagnostic, and clinical data of the patients such as age, sex, occupation, history of underlying diseases (cardiovascular disease, diabetes, renal disease, chronic neurological disease, and chronic pulmonary disease), length of hospital stay, history of mechanical ventilation, and final situation.

The follow-up time in case and control groups was three months starting from detecting the first case of COVID-19 in these counties (20 February 2020 to 20 May 2020). The COVID-19 data dashboard of Shahid Sadoughi University of Medical Sciences was used to collect the data of the subjects in case and control groups.

Statistical analysis

Frequency, percentage, mean, standard deviation, and median are used to describe the data. Independent t-test and chi square were applied to compare the variables between the two groups. Multiple logistic regression

analysis and binary logistic regression analysis with survival or death as outcome were used to evaluate the effect of each variable. All data were analyzed through SPSS.21 software.

Results

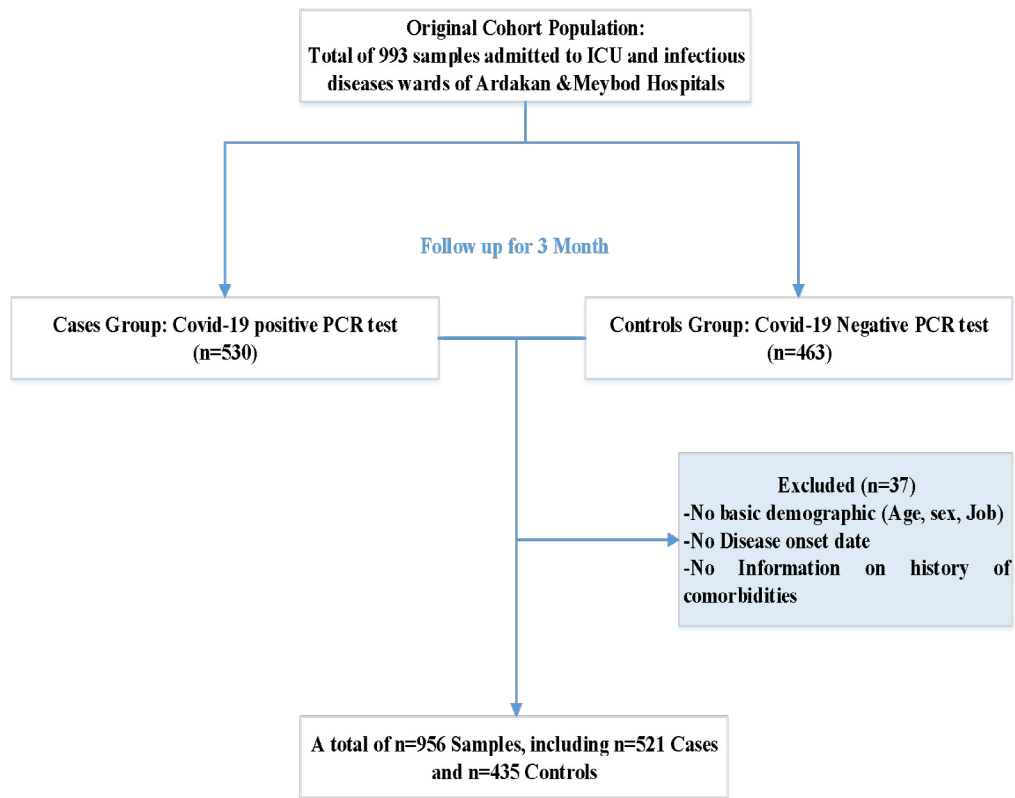
Of a cohort population of 993 in Ardakan and Meybod, 530 with positive PCR results were assigned to the case group as COVID-19 patients and 463 with negative PCR results were assigned to the control group. After applying the inclusion and exclusion criteria, 521 and 435 subjects were included in the case and control group, respectively (Fig. 1).

The results of chi square showed no significant difference in the distribution of age, sex, and occupation between the two groups ($p > 0.05$). No significant difference was also observed in the distribution of underlying diseases between case and control groups ($p > 0.05$) and both groups were similar in terms of having at least one underlying condition. Overall, 25.7% ($n = 246$) of the subjects had cardiovascular disease, 18.8% ($n = 180$) had diabetes, 9.2% ($n=88$) had chronic pulmonary disease, 4.1% ($n = 39$) had chronic neurological disease, 3.1% ($n = 30$) had renal disease. The results of outcome analysis showed that 14.4% of the cases ($n = 75$) and 11.5% of the controls ($n = 50$) died, indicating a significant difference ($p = 0.04$). Moreover, 12.9% of the cases ($n = 67$) and 12% of the controls ($n = 52$) were admitted to the ICU. The length of hospital stay was also significantly longer in the case group compared to the control group ($p = 0.001$) (Tab. I). The results show that the length of stay is longer in patients with a positive corona test and also in patients who have died (Fig. 2).

According to the results of logistic regression analysis in COVID-19 patients, each one-year increase in age increased the risk of mortality by 6% ($HR = 1.06$, $p < 0.001$) and each one-day increase in the hospital stay increased the risk of death by 8% ($HR = 1.08$, $p < 0.001$). Moreover, the presence of cardiovascular disease, chronic neurological disease, and chronic pulmonary disease increased the risk of death. The patients who underwent mechanical ventilation had 85% less chance of survival ($HR = 0.15$, $p < 0.001$) (Tab. II).

Discussion

The results of outcome analysis showed that 14.4% of the patients in the case group and 11.5% of the patients in the control group died, indicating a significant difference. A study in Wuhan, China reported that 28% of the COVID-19 patients died [9]. The mortality rate of COVID-19 was 10.5% and 6% in studies conducted by Shi [10] and Liu [11], respectively. The mortality rate was rather higher in the present study compared to the above studies. The difference in the mortality rate between different studies may be related to heterogeneity in the reported data, inclusion criteria for COVID-19

Fig. 1. Sample flow diagram detailing included subjects and exclusion criteria.

patients, and the conditions of health systems in different countries.

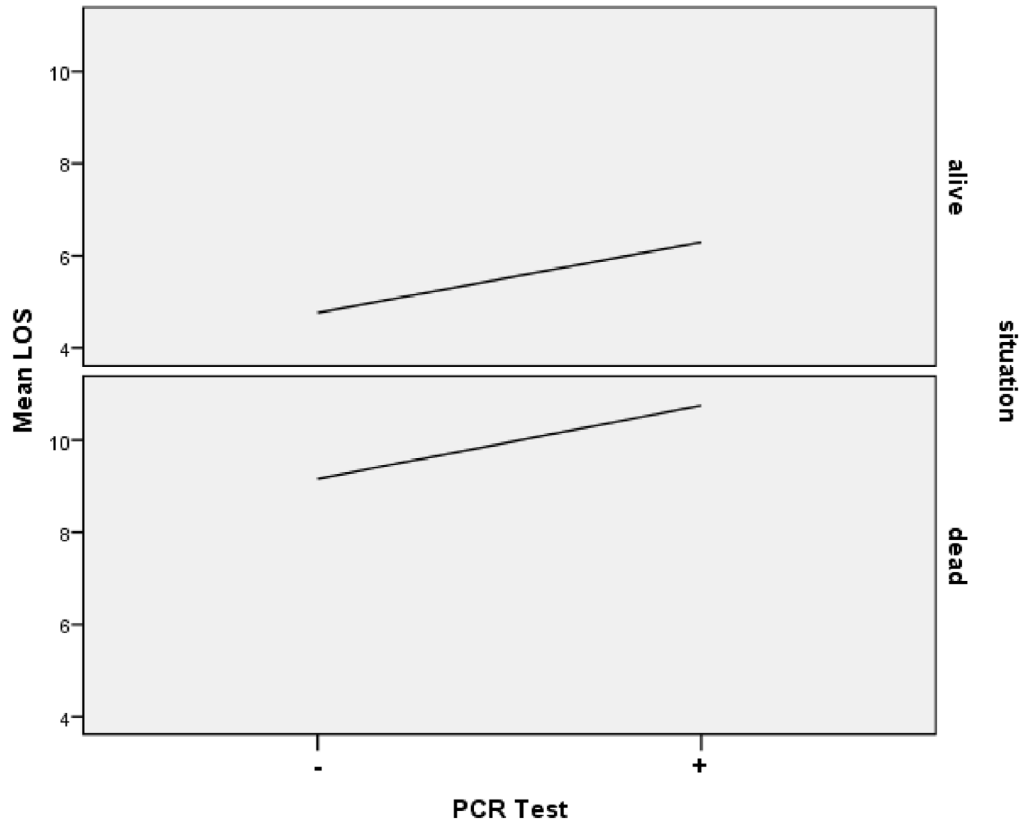
The results showed that the chance of death increased with age. Liu et al. also found a higher mortality percentage in the elderly patients [11]. The results of a study conducted in the U.S. showed that 80% of deaths occurred in patients aged above 65 years [12], which was similar to a study conducted in China that found that 80% of the mortalities occurred in people above

80 years [13]. COVID-19 is usually more severe in elderly patients and they often suffer from underlying diseases; therefore, they require better care and the risk of mortality is higher in this population.

According to the results of this study, the presence of cardiovascular disease, chronic neurological disease, and chronic pulmonary disease increased the chance of death in COVID-19 patients. According to the results of several studies, patients with cardiovascular diseases

Tab. 1. Baseline characteristics of study population.

Variables	Levels	All patients (n = 956)	Control (n = 435)	Case (n = 521)	p*
Age (years)	Mean \pm SD	57.79 \pm 18.02	57.08 \pm 19.64	58.29 \pm 16.43	0.29
Sex	Male	476 (49.8)	214 (49.2)	262 (50.3)	0.39
	Female	480 (50.2)	221 (50.8)	259 (49.7)	
Occupation	Hospital Jobs	21 (2.2)	13(3)	8 (1.6)	0.094
	Other Jobs	511 (53.4)	229 (52.6)	282 (54.1)	
	Unknown	424 (44.4)	193 (44.4)	231 (44.3)	
Chronic medical illness	Coronary heart disease	246 (25.7)	119 (27.4)	127 (24.4)	0.29
	Diabetes mellitus	180 (18.8)	77 (17.7)	103 (19.8)	0.45
	Chronic kidney disease	30 (3.1)	15(3.4)	15 (2.9)	0.71
	Chronic neurological disease	39 (4.1)	21(4.8)	18 (3.5)	0.32
	Chronic pulmonary disease	88 (9.2)	41(9.4)	47 (9)	0.91
LOS	Mean \pm SD	6.20 \pm 5.78	5.29 \pm 4.88	6.94 \pm 6.33	0.001
	Median, range	5 (1-53)	4 (1-41)	5 (1-53)	
Inpatient in ICU		119 (12.4)	52 (12)	67 (12.9)	0.37
Final Situation	Alive	831 (86.9)	385 (88.5)	446 (85.6)	0.04
	Dead	125 (13.1)	50 (11.5)	75 (14.4)	

Fig. 2. The length of stay depends on the patient's final situation and PCR test.

have the highest sensitivity to COVID-19 followed by patients with diabetes, chronic respiratory disease, hypertension, and cancer [3, 5, 14]. In a study by Zhang et al., the mortality rate was 41% higher in patients with a history of respiratory disease and 13% higher in

patients with a history of cardiovascular disease [15]. Shi et al. also found that the mortality rate was 9% and 11% higher in patients with a history of cardiovascular and pulmonary disease, respectively [10].

A one-day increase in the length of hospital stay

Tab. II. The effective epidemiological factors on Mortality of COVID-19 Patients.

Variable	Levels	Univariate			Multivariate		
		HR	95% CI	p	HR	95% CI	p*
Age	Year	1.066	1.046-1.086	<.001	1.061	1.036-1.087	<.001
LOS	Day	1.085	1.050-1.121	<.001			
Sex	Male	1	-	0.669			
	Female	1.113	.682-1.816				
Job	Hospital Jobs	1	-	0.999			
	Other Jobs	0	0.000-				
Coronary heart disease	Yes	2.942	1.768-4.898	<.001	2.211	1.118-4.371	0.023
	No	1	-		1	-	
Diabetes mellitus	Yes	1.462	0.825-2.591	0.193			
	No	1	-				
Chronic kidney disease	Yes	2.228	0.690-7.189	0.180			
	No	1	-				
Chronic neurological disease	Yes	5.206	1.984-13.659	0.001	3.955	1.179-13.259	0.026
	No	1	-		1	-	
Chronic pulmonary disease	Yes	2.541	1.271-5.079	0.008			
	No	1	-				
Mechanical Ventilation	Yes	1	-	<.001	0.090	0.032-0.252	<.001
	No	0.15	0.061-0.354				

HR: Hazard ratio; LOS: Length of Stay; CI: Confidence interval; * Logistic regression.
SD: Standard deviation; LOS: Length of Stay; * Chi square.

increased the risk of death by 8%. The mean length of hospital stay was longer in the case group compared to the control group such that the mean length of stay was 7 days in the case group. The results of a study conducted in Vietnam showed a higher mean length of hospital stay in COVID-19 patients (16). Studies performed in the U.S. [16, 17] and European countries reported a mean length of stay of 6-7 days for COVID-19 [18, 19]. Differences in the results may be related to differences in strategies employed by different countries for disease prevention and treatment, timing of the incidence and peak, and treatment facilities offered by hospitals.

According to the results, the risk of death was 85% higher in patients receiving mechanical ventilation. A meta-analysis by Taylor et al. also showed a mortality rate of 72% in patients under mechanical ventilation [20]. Similar studies have also found a longer hospital stay in patients requiring mechanical ventilation [21-24]. Patients that need mechanical ventilation are admitted to the ICU. They usually suffer from acute respiratory problems and therefore require more care than other patients do. The mean length of hospital stay and mortality rate is higher in these patients [25-26].

Conclusions

This study showed a higher mortality rate in cases compared to controls. Moreover, the disease was more lethal in elderly patients and those with underlying diseases. Since these patients have a weaker physical condition and immune system, they are more vulnerable to infectious diseases and acute respiratory syndrome. As for social factors, the elderly face social isolation in many societies, which impairs their self-care and immunity. Therefore, to reduce the mortality rate of COVID-19, especially in at-risk subjects, attention should be paid to early patients and those with underlying diseases. Moreover, it is necessary to develop long-term care facilities to control and contain disease progress. Since COVID-19 is a global threat, more in-depth analyses and studies are required.

Strengths and limitations

In this study, the effects of different risk factors and variables were compared between cases and a sample of the cohort population as controls, which provide more accurate information compared to other epidemiologic studies. However, the effects of many variables were not evaluated since their data were not available. It is recommended that these variables, especially clinical and laboratory variables, be compared in future studies.

Declarations

Ethics approval and consent to participate:
The article's proposal was approved by the ethics

committee of Shahid Sadoughi University of Medical Sciences with the ID of IR.SSU.REC.1399.194. Due to the retrospective nature of the study, no study specific consent form was used. However, patients admitted to our hospital are asked to sign a general consent upon admission, which covers the collection of patient data and publication of these results. Therefore, the individual's informed consent was waived by the above ethics committee. We received administrative permission from (Secretary of University/Regional Research Ethics Committee Shahid Sadoughi University of Medical Sciences) to access and use the data. Data used in the study were anonymized. The ethics committee approved this procedure with the above ethical code. The present study was conducted in terms of the principles of the revised Declaration of Helsinki, which waived requirement for informed consent.

Consent for publication

Not applicable.

Conflict of interest statement:

All authors report no conflicts of interest relevant to this article.

Funding

The authors sincerely thank Shahid Sadoughi "University of Medical Sciences" for all supports. This study was supported by grants from the Research Committee in Shahid Sadoughi University of Medical Sciences.

Availability of data

The data-sets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Authors' contributions

MMi and AD have designed the study and supervised the thesis. MR and MJF collected the data and analyzed it. They also prepared the first draft of the manuscript. MD, MMa and SM. HP has edited and finalized the manuscript; methodology: MB; performed a search of literature: MMi, AD, MM; editing MM. All authors read the manuscript and approved it.

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Received on September 26, 2023. Accepted on October 4, 2023.

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How to cite this article: Mirjalili M, Raadabadi M, Dehghani M, Aliabad MB, Mansouri M, Martini M, Dehghani A. Analysis of death risk factors among COVID-19 patients in Yazd, Iran: A case-cohort study. *J Prev Med Hyg* 2023;64:E304-E310. <https://doi.org/10.15167/2421-4248/jpmh2023.64.3.3098>

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HEALTH PROMOTION

Every cockroach is beautiful to his mother's eyes"? A multicentric study on the perception of child's health status according to the parent

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Keywords

Obesity • Health promotion • Children BMI

Summary

Introduction. Childhood obesity is a social health problem in the Western World and an important goal is to analyze and correct risk factors. However, part of the problem could be determined by a different perception of the weight.

Material and methods. In October 2019, we conducted a cross-sectional study in which a questionnaire was administered to the parents of primary and secondary school children in South-East Tuscany, Italy. The aim was to determine the association between children's Body Mass Index (BMI) and the parent's perception.

Results. Analysis was carried out on 1,405 complete questionnaires. We found that most parents wrongly perceive the weight of

their children. 88.3% of parents with obese children believe that their children are of normal weight or only "a little overweight". 67.6% of parents who have overweight children think that their children are of normal weight ($p < 0.001$).

Conclusions. Our results show a misperception of the weight of the children in the parents eyes. The acquisition of healthy behaviour during childhood is extremely important for health in adulthood and for avoiding the onset of associated diseases. Therefore, food education becomes a crucial objective. Children and parents need to increase consciousness of the correct weight and diseases resulting from bad nutrition.

Introduction

Obesity was described by World Health Organization (WHO) as the worst "non-infectious epidemic" in history [1]. Globally, in recent years the prevalence of obesity among children and adolescents has been increasing, and the trend continues to grow for the coming years [2, 3].

In Italy, it is estimated that 24.7% of children between 6 and 17 years of age are overweight (average data for the years 2015-2016), 28.6% of boys and 20.5% of girls. Consumption of adequate amounts of fruit and vegetables among children and young people is still low, with 12.9% of 3-17-year-olds consuming at least 4 portions of fruit and vegetables per day in 2016 [4].

Excess body weight in childhood and adolescence is associated with a higher risk of developing diseases such as diabetes at a younger age, breathing disorders and paediatric hypertension [5-7].

Individual and societal costs related to overweight and obese conditions are numerous, including reduced quality of life, healthcare costs, decreased productivity, and premature mortality [7, 8].

It is essential to know eating habits because it can be helpful in creating healthy eating practices in children. Therefore, many studies and policies have been carried out to improve eating habits [9, 10].

Childhood is a critical period to establish eating habits that influence the future risk of cardiometabolic diseases [9], so

prevention among school-age children has become critical. Diet and lifestyle play a central role in determining a healthy life, as they contribute to causing or preventing the onset of these chronic diseases [11, 12].

Schools, due to the large number of students that are present, can be an important setting to promote a healthy lifestyle with health promotion interventions [13], for example, including nutrition education in the curriculum and promoting healthy food choices during meals (e.g., presence of fresh fruit and absence of sweet fizzy drinks and sweet or salted snacks).

It is important to carry out health promotion and lifestyle modification activities in schools to improve young people's lifestyles, eating and drinking habits and, indirectly, to raise parents' consciousness of these issues through student activities.

The aims of this study are: i) to investigate student habits and the prevalence of obesity and overweight; ii) to assess the level of agreement between the children weight and the parents perception.

Materials and Methods

This descriptive research with analytical component is derived from the "sCOOL FOOD for a remarkable future" program, a broader study promoted by the Monte dei Paschi Foundation, designed to develop global citizenship skills, education on food and nutrition, well-

Tab. I. Students' weight status and relative percentage by gender.

	Numbers (%)	Female	Male
Underweight	35 (2.5)	24 (68.6%)	11 (31.4%)
Normal weight	947 (67.4)	493 (52.1%)	454 (47.9%)
Overweight	312 (22.2)	153 (49.0%)	159 (51.0%)
Obese	111 (7.9)	41 (36.9%)	70 (63.1%)

being, healthy lifestyles and motor/sport education among young people. The project arises from the need to promote in young people correct eating habits and lifestyles, and behaviours oriented towards sustainability, from an economic, social and environmental point of view, through one hour of lessons per week during school hours.

In October 2019, we administered 4,324 questionnaires to parents (one parent per child) of children of primary and secondary schools in South-East Tuscany (Italy). The questions concerned eating habits, biometric data, their children's lifestyle, and their perception of their child's weight. Before the administration of the questionnaire, parents were asked for their consent to processing personal data, and the confidentiality of all data collected and stored was guaranteed. Parents had one month to return the filled questionnaires. The ethics committee also approved the study.

The exclusion criteria were the absence of the child's personal or biometric data, partial filling of the questionnaire and the absence of consent to personal processing data.

Body Mass Index (BMI) and weight status were classified according to the World Obesity Federation's gender-specific cut-off points for BMI [14].

Statistical analysis

The association between the variables was carried out using the Chi-square test (χ^2). The weighted Kappa coefficient was calculated to measure the agreement between the parent's perception of the child's weight status based on BMI and the parent's perception of the child's food intake and the child's weight status. Parents' perception was paired with their child's actual weight status, and any disagreement between the two was considered as misperception. Data were collected and organized using Microsoft Excel, and statistical analysis was carried out using STATA SE/14.0 (StataCorp LLC, Texas USA). Differences were considered at a statistically significant level of 95% ($p < 0.05$).

Results

We received back 1,696 questionnaires, 39.2% of those sent; 275 returned without filling any field, 7 were incomplete and 20 were submitted twice or more times; for the latter we used the most recent ones. The final analysis was carried out on 1,405 questionnaires completed by parents.

There were 694 (49.4%) males children and 711 (50.6%) females. Mean age was 8.7 (SD 1.56) years in a range 5-12 years.

Students' weight status and relative percentage by gender are presented in Table I.

Out of 1,405 complete questionnaires, 947 (67.4%) children had normal weight, 312 (22.2%) were overweight, 111 (7.9%) were obese and 35 (2.5%) children were underweight. However, when comparing the BMI range with the gender of the children, there was a significant difference, particularly with regard to obesity, which was higher in boys (70 children, 63.0%) than in girls (41 children, 36.9%) and with regard to underweight, which was higher in girls (24 children, 68.6%) than in boys (11 children, 31.4%) Table I.

Asking parents what was their perception of the children's weight, we found that 1 out of 4 had a different perception compared to the real weight; the following parents' opinions on children were recorded: 78.3% normal, 13.5% a little bit overweight, 7.3% underweight and only 1% overweight (Tab. II).

For parents with obese children (111), 55.0% believed that their children were only "a little overweight", 33.3% considered their children being at a normal weight, and only 11.7% had the perception of their child's obesity. Furthermore, we found that 67.6% of parents with overweight children believed that their children were normal weight, 32.1% were aware that their child was overweight, and only 1 parent considered his child to be underweight. However, no parents thought their children were obese. Among normal-weight children, 9.7% of parents believed that their children were underweight and 3.0% that the children were a little overweight. Among underweight children, 74.3% of parents believed

Table II. Child's BMI compared to the parental perception of the child weight status.

Perceived BMI		Real BMI			
		Underweight	Normal weight	Overweight	Obese
Underweight	102 (7.2%)	9 (25.7%)	92 (9.7%)	1 (0.3%)	-
Normal weight	1,100 (78.3%)	26 (74.3%)	826 (87.2%)	211 (67.6%)	37 (33.3%)
Overweight	1,89 (13.5%)	-	28 (3.0%)	100 (32.1%)	61 (55.0%)
Obese	14 (1.0%)	-	1 (0.1%)	-	13 (11.7%)

Table III. Child's BMI compared to parental perception of child food intake.

Perception of food intake		BMI			
		Underweight	Normal weight	Overweight	Obese
Eat little	157 (11.2%)	9 (25.7%)	139 (14.7%)	6 (1.9%)	3 (2.7%)
Eat normal	1,148 (81.7%)	26 (74.3%)	794 (83.8%)	256 (82.1%)	72 (64.9%)
Eat too much	100 (7.1%)	-	14 (1.5%)	50 (16.0%)	36 (32.4%)

that their children were normal weight (Table II).

Questioning parents what their perception was about the children's weight, we found that most of them do not realize the child's wrong weight. For example, 28.6% of parents underestimated the child's weight, thus believed that their children were into the lower BMI range than the real one ($p < 0.001$), while 3.9% overestimated the child's weight. In particular, if the child was overweight or obese, their parents tend to underestimate it ($p < 0.001$); if the child is underweight, parents tend to overestimate the real weight ($p < 0.001$).

Therefore, among parents who have their children obese or overweight (423) only 113 (21.7%) of them have a real perception of the child's condition, while 310 (78.3%) underestimate the weight. Of all parents, only 67.5% have a true perception of their child's weight status, one parent out of 3 has an incorrect perception of their child's weight: 3.9% overestimate it while 28.6% underestimate it.

We also asked the parents to quantify how much their children eat. The results are shown in Table III. The majority, 64.9% of the parents of obese children, stated that their children eat "the right amount", 32.4% "too much" and 2.7% "too little". When parents of overweight children were asked the same question, 82.1% of them said their children eat "the right amount", 16.0% "too much" and 1.9% "too little". As for parents with underweight children, according to 74.3% their child eats "the right amount", according to 25.7% they eat "too little".

Discussion

Obesity is becoming a growing economic and social problem. Our study found overweight and obesity rates in line with the national and international average [15, 16]. Diet and lifestyle play a central role in determining a healthy and balanced life, as they help to cause or, conversely, prevent the onset of some of the most severe and widespread chronic diseases [17]. Eating habits play a key role, especially in preventing obesity and overweight, which are now considered two of the most critical health factors.

As shown by our results and other studies in the literature, parents tend to underestimate their children's weight status, especially among overweight children; this is worrying because parents play a crucial role in influencing positive behaviour and thus influencing future lifestyles [18]. One motivation is social desirability: parents are reluctant to label their child as "obese" and "overweight" because of prejudice and the

negative connotation associated with the words [19, 20]. The stigmatisation of obesity is often related to fear of fatness, anti-fat attitudes, low self-esteem, negative body image and poor quality of life among overweight and obese children [21]. On the other hand, the increasing prevalence of overweight or obese children has caused a change in society's attitude towards healthy weight, such that obesity is the new norm [22, 23].

Our study is similar in the findings to others [22, 24, 25], but it is the first conducted in Italy with such a large court of children (5-12 years old) that measures the misperception of the parents with the real weight of their children. A previous investigation in 2006 by Lazzeri [26] showed a correct perception of the nutritional status of the children and because of this our results raise an alarm considering that after 13 years we are witnessing a change, for the worse, in the perception of nutritional status. It may mean that proper health promotion campaigns have not been carried out in recent years.

Good eating and behavioural habits during the early years of life are decisive for health in childhood and adolescence and for health and quality of life in later life. How we did it, health promotion programmes need to be conducted on children first because interventions are more likely to lead to lasting changes in health behaviours. In addition, parental involvement in health interventions can be a key factor in their success and they are considered the most important influence on obesogenic health behaviours among children, as parents regulate the quality of food consumed in the household and active participation of the parent is important to allow habits to change [27-29]. Our results show that there is a lack of knowledge about the importance of proper nutrition within the family context, which could therefore negatively affect the child's future health status. However, there are many causes that make the onset of obesity multifactorial. One of the causes of the increase in obesity and overweight is linked to changes in society. Changes in the overall 'way of life' of people (always in a hurry and with less time to eat or eating properly) are manifested in an increase in the average amount of calories consumed, the emergence of nutritionally unbalanced eating patterns and a significant reduction in the time devoted to physical activity [3].

Currently, there is easier access to processed foods, refined sugars and fats, oils and meats, and consumption styles characterized by an increase in eating out and the use of pre-packaged [30, 31]; this, together with commercially available portions that are not exaggeratedly large (e.g., packaged snacks) but contain a high caloric content, could cause parents to perceive the amount of food intake as "low", as we found in our results. All this shows the

need to guide future consumers toward healthier eating habits and lifestyles through nutrition education. Another problem is cultural, as several studies report, because thinness is associated with poor health, and malnutrition is seen as a worse threat than obesity [32, 33]. Also for this problem, it is important to carry out measures that make school education accessible to all. This study has some limitations: weight and height were reported by the parent and not directly measured to avoid creating discomfort or competition among the children, which may have led to BMI estimates that may not be true due to parental errors; moreover, although the final number of questionnaires analysed was not small, 1,405, most of those sent, 67.5%, did not return; this could hide some selection BIAS; despite this, other studies have also had this problem [22, 24] and we believe that the results obtained are noteworthy.

Conclusions

Nutrition and lifestyle are essential determinants of health, and interventions in eating habits can influence the prevention of overweight and obesity and associated health problems. The dietary profile during childhood is critical in developing health status in adulthood, and schools could become an important agent for health promotion in this respect. Nevertheless, starting with a correct perception of one's nutritional status and weight is an essential element in understanding whether intervention is necessary. Our study shows that many parents do not have this perception of their children. Ours is the first Italian study that shows a parent's scattering of their child's nutritional status: our results show that among overweight children there is a parent's misperception of the child's weight to his or her actual BMI, consistent with the data in the literature. Having healthy behaviour during childhood is extremely important for the state of health of adulthood and avoiding the onset of associated diseases. Also, having correct eating habits and lifestyles means having behavior oriented towards sustainability in economic, social and environmental terms. Currently, there is still too much ignorance about proper nutrition, so nutrition education must become a crucial objective for our country's future and an essential goal is to create educational strategies to increase consciousness of the meaning of food, as evidenced by our study

Funding

SCOOL FOOD program was financed by the Monte dei Paschi Foundation. The authors did not receive any personal funds for the research.

Informed consent statement

The consent to the processing of personal data was asked to every parent before starting the questionnaire and

the confidentiality of all data collected and stored was guaranteed.

Conflict of interest statement

sCOOL FOOD program was financed by the Monte dei Paschi Foundation. The authors did not receive any personal funds for the research. Monte dei Paschi Foundation had no role in the test design, data collection or analysis, decision to publish, or preparation and discussion of the test results in the manuscript.

Authors' contributions

SC performed the analytic calculations and wrote the manuscript. MG, NN verified the analytical methods, supervised the findings of this work and revised the final manuscript. MD supervised the project and conceived the original idea of the program. All authors provided critical feedback and helped shape the research, analysis and manuscript.

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Received on February 6, 2023. Accepted on October 20, 2023.

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How to cite this article: Salini C, Messina G, Messina D, Nante N. "Every cockroach is beautiful to his mother's eyes"? A multicentric study on the perception of child's health status according to the parent. *J Prev Med Hyg* 2023;64:E311-E315. <https://doi.org/10.15167/2421-4248/jpmh2023.64.3.2859>

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The effect of cognitive-behavioral counseling on maternal-fetal attachment among pregnant women with unwanted pregnancy in Iran: A randomized clinical Trial

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Keywords

Cognitive-behavioral • Counseling • Maternal-fetal • Attachment • Unwanted Pregnancy

Summary

Background. Unwanted pregnancy is an important public health concern that can have significant health, social, and economic effects on the mother, the baby and her family. The establishment and enhancement of maternal-fetal attachment (MFA) play a role in the promotion of emotional communication between the mother and the child in the future. This study aimed at investigating the effect of cognitive-behavioral counseling on maternal-fetal attachment among pregnant women with unwanted pregnancy.

Methods. In this randomized clinical trial, 60 eligible pregnant women with unwanted pregnancy and gestational age of 22-28 weeks who had referred to health centers in Mashhad, a city in the northeast of Iran, were selected and they were through random block assignment divided into two groups of counseling with the cognitive-behavioral approach ($n = 30$) and the control group ($n = 30$). In addition to the routine pregnancy care, the cognitive-behavioral counseling group received four group counseling sessions on a weekly basis, while the control group only received the routine pregnancy care from healthcare providers. Maternal-fetal

attachment before and after intervention in the two groups was assessed through Cranley's Maternal-Fetal Attachment Scale. Comparison of mean scores within and between the two groups was performed using SPSS 21 through independent and paired *t*-tests.

Results. At the end of the study and after the intervention, the mean scores of maternal-fetal attachment in the intervention and control groups were 94.06 ± 11.73 and 80.16 ± 10.09 , respectively, and the difference between the groups was significant. Although the difference between the mean scores of each group at the beginning and the end of the study was significant, this difference between the two groups was also noticeable (21.56 ± 12.16 vs 7.40 ± 12.39) and statistically significant.

Conclusions. Cognitive-behavioral counseling can be effective in enhancing the maternal-fetal attachment in unwanted pregnancies; therefore, it is recommended to be integrated into pregnant women's healthcare programs.

Introduction

While a wanted pregnancy is a happy and enjoyable event for the family [1], unwanted pregnancy is an important public health concern in low- and middle-income countries that can have significant health, social, and economic effects on the mother, the baby and her family [2].

About 121 million unplanned pregnancies occur annually, accounting for about 48% of all pregnancies among women aged 15-49 years worldwide [3]. The prevalence of unwanted pregnancy in Iranian women was 27.9% until 2017 [4]. Unwanted pregnancy is considered as a high-risk pregnancy [5]. Unwanted pregnancy is associated with dangerous consequences for the mother including physical, emotional and financial problems, depression during pregnancy and postpartum, suicidal thoughts, exposed to physical violence, unsuccessfulness in breastfeeding, mother's low self-esteem, reduced the

receipt of adequate antenatal care, pregnancy-related problems, increases maternal deaths [6-8]. Moreover, unwanted pregnancy increases the likelihood of low birth weight, premature birth [9, 10], small for gestational age, neonatal mortality [10], mortality of infants and children, delay in growth and social character, and behavioral and psychological disorders of children [8]. The anger of mothers during unwanted pregnancies is suppressed and hidden and has impacts on the baby and the mother, and mothers with unwanted pregnancies attend less to their babies compared to mothers who are happy and joyful during their wanted pregnancies [11].

Maternal-fetal attachment (MFA) is a term used to describe the emotional bond between the mother and the fetus [12]. Emotional attachment to the unborn baby is created from the beginning of pregnancy, reaching its peak in the second trimester, when the mother perceives the first movements of the fetus [13], and continuing until postpartum. MFA is promoted through eye contact,

olfactory and touch sense of the mother and the baby [14, 15]. The emergence of maternal-fetal attachment plays a significant role in mother's engagement in prenatal health practices and behaviors [16], as well as in the acceptance of parental identity [17]. Maternal-fetal attachment can be a predictor of the attitude and mother's performance after delivery, mother and baby interaction, and postpartum attachment patterns [18]. The maternal-fetal attachment has a close relationship with the mother's emotional state and the relationship between mother and child in the future. A mother who is attached to her fetus during pregnancy is ready to make a happy connection with the baby after childbirth [19, 20]. Maternal-fetal attachment is an effective factor in the motor development and physical growth of infants during pregnancy and after birth [17, 21].

With higher maternal-fetal attachment, the mother tends more to apply health behaviors during pregnancy, such as abandoning smoking and alcohol, proper nutrition, exercise, continuing prenatal care, desire to know the fetus and participating in childbirth preparation classes, increasing maternal-neonatal attachment and neonatal nutrition with breastfeeding. All these behaviors lead to a satisfactory outcome of pregnancy and to the promotion of maternal and neonatal health [22]. Maternal-fetal attachment can be affected by issues such as social support, mental status, gestational age, maternal age, number of births, income, education, family ties, support and acceptance of pregnancy, unwanted pregnancy, high-risk pregnancy, abortion history, and fetal or neonatal death [18]. Brockington and colleagues (2006) reported that in unwanted pregnancies, mother-baby bonding is delayed due to feelings of fear, anxiety, and depression [23].

Since in Iran abortion is illegal and religiously banned, unwanted pregnancies are more likely to continue compared to other countries. Considering the adverse effects of unwanted pregnancy complications on maternal adaptation during pregnancy and maternal-fetal attachment, and since such adaptation can predict postpartum adjustment and, as a result, maternal and neonatal relationships, it is essential to provide supportive and counseling services to mothers with unwanted pregnancies.

Cognitive-behavioral counseling is a psychological approach and it is one of the highly effective short-term treatments that purpose of which is to identify and challenge irrational behaviors and thoughts so as to bring the individual to general mental health [24]. Cognitive-behavioral approach, which is a combination of cognitive and behavioral approach, helps a person to recognize and change his distorted thinking pattern and ineffective behaviors. In order to change these distorted and ineffective thoughts, targeted sentences are used, as well as the presentation of detailed and organized behavioral assignments [25].

Therefore, considering the importance of unwanted pregnancies and the need for intervention to help improve the health of women who choose to continue pregnancy, and since little attention has so far been

paid to implementing counseling programs to increase maternal and fetal attachment in unwanted pregnancies, the aim of this study was to determine the effectiveness of midwifery counseling with a cognitive-behavioral approach on maternal-fetal attachment in unwanted pregnancies.

Methods

STUDY DESIGN

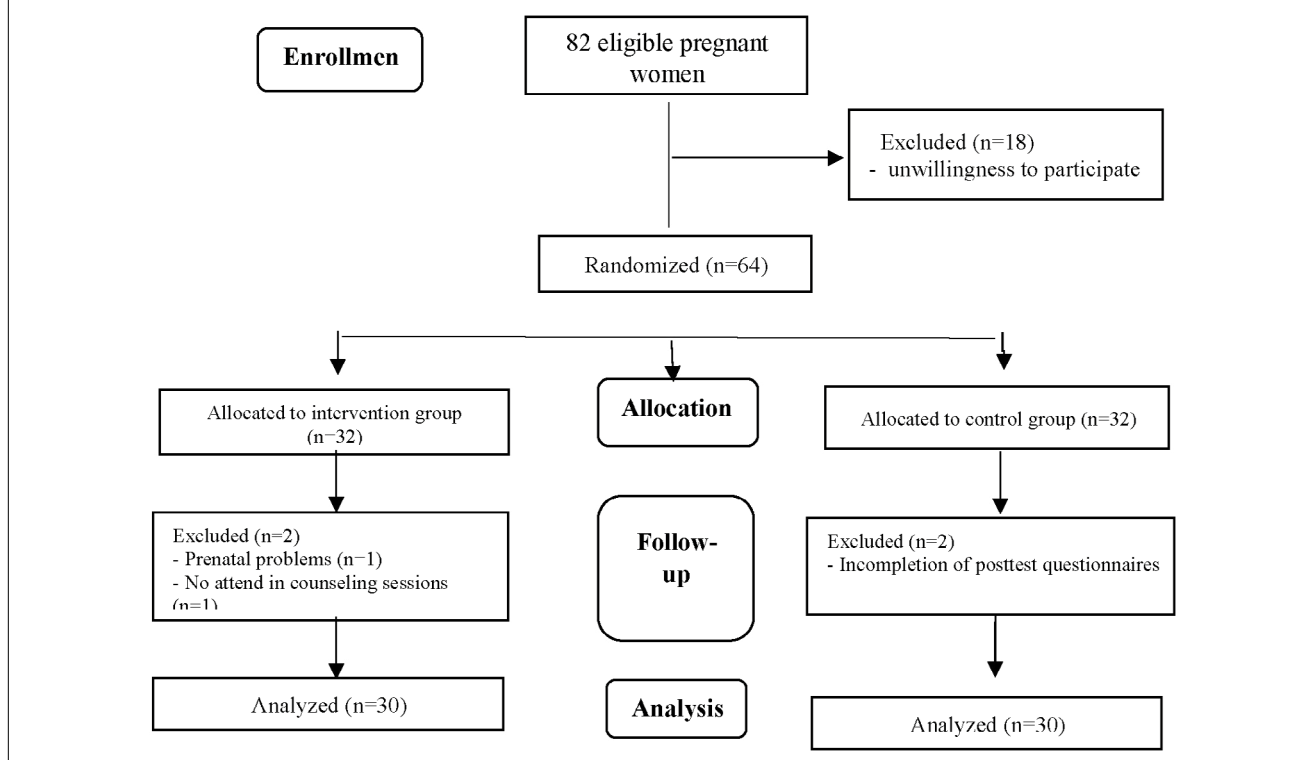
This is a randomized, double-blind clinical trial with two groups of intervention and control. It was conducted from September 2016 to March 2017 in Mashhad, Iran. The study protocol was approved by the Ethics Committee in Shahrood University of Medical Sciences, Shahrood, Iran (IR.SHMU.REC.1395.22) and registered in the Iranian Clinical Trial Center on 1 August 2017 (IRCT2016092930048N1). This clinical trial has been reported based on the CONSORT 2010 checklist [26].

PARTICIPANTS AND SETTING

Pregnant women referring to health centers in Mashhad, Iran, were selected for this study. Inclusion criteria for the study were: unwanted pregnancy; low-risk pregnancy; reading and writing literacy at least; gestational age of 22-28 weeks; singleton pregnancy; and no history of stillbirth, abortion, or mental illness. Exclusion criteria also were: lack of constant presence in counseling sessions; mothers' unavailability when completing the post-test questionnaire; occurrence of pregnancy problems; and severe stress.

SAMPLE SIZE AND RANDOMIZATION

Sample size was calculated based on the formula of difference of means in two independent groups and according to the mean and standard deviation of post-intervention attachment score (64.6 ± 3.6 and 61.1 ± 5.1) in a similar study (27) and considering a confidence level of 95% ($\alpha = 0.05$) and a test power of 80% ($\beta = 0.20$); 25 people were calculated in each group, that considering 25% drop, the size of each group was determined to be 32. Among the five health centers of Mashhad city, three centers were selected through cluster sampling. Each of these health centers includes several comprehensive health service centers. From each of these centers, three comprehensive health service centers were selected through cluster sampling. Subsequently, using the registry notebook of mothers, 112 women with unwanted pregnancies were listed, from whom 82 women were eligible to enter the study. These women were contacted, and 64 pregnant women were willing to participate in the study. Then, based on randomized block of four, 32 women were assigned to the intervention group and 32 women were assigned to the control group. Of these, two women in the intervention group (one due to prenatal problems and one because of reluctance to attend the counseling sessions for personal reasons) and two women in the control group (due to the lack of completion of post-test questionnaires) were excluded from the study (Fig. 1).

Fig. 1. Flowchart of participants in the clinical trial.

MEASURES

The instrument for collecting information was a questionnaire consisting of two parts. The first part included demographic characteristics and the second part included the Cranley's Maternal-Fetal Attachment Scale (MFAS). The Cranley's Maternal-Fetal Attachment Scale has 24 Likert items on a five-point scale ranging from 1 to 5 (Definitely yes: 5, Yes: 4, Not sure: 3, No: 2, Definitely no: 1), and only in the item 22, the scoring is done in reverse. The total score on the scale can range from the minimum 24 to the maximum 120. A higher score indicates more attachment [28]. The reliability of its English [28] and Persian [29] version has been confirmed in previous studies. The scale was administered to the participants in the two groups prior to the intervention and two weeks after it.

INTERVENTION

The participants who were eligible based on the inclusion criteria entered the study. Upon entry, participants in both groups completed the Cranley's Maternal-Fetal Attachment Scale. Then, the intervention group, in addition to routine healthcare, received attachment counseling sessions. Along these lines, based on their convenience for attendance, the intervention group members were divided into 3 groups of group counseling (one 10 and two 11 member groups) based on the proposed time to attend counseling sessions. Four weekly one-hour cognitive-behavioral counseling sessions were held for each group in health care centers by one of the researchers (a master's student) who was

a trained midwife in counseling, while the control group received only routine health care in these centers. It should be noted in order to prevent the transmission of information in the intervention group and the control group, it was planned that the control and intervention group were invited on different days to avoid contact. Two weeks after the intervention, the Cranley's Maternal-Fetal Attachment Scale was completed again for the two groups. To maintain the blindness in the study, the outcome (maternal-fetal attachment) on two weeks after the intervention, was measured by another midwife who was unaware of the allocation. The content of cognitive-behavioral counseling sessions is presented in Table I.

DATA ANALYSIS

The collected data were analyzed using SPSS 21. To determine the homogeneity of quantitative and qualitative variables between two groups, respectively t-test and Chi-square were used. Paired t-test and independent t-test were used to compare the maternal-fetal attachment changes between and within the groups. The significance level of the tests was set at less than 5%.

Results

In this study, the age range of the of participants was between 15 and 42 years, and no significant difference was observed between the groups. Other characteristics of the participants are shown in Table II. According to the results of Table II, there was no significant difference

Tab. I. Content of cognitive-behavioral counseling sessions.

First session
1. Welcoming
2. Knowing the group members and introducing the counselor, and the purpose, length, and number of sessions
3. Emphasizing the importance of participation in counseling sessions and of doing the homework assignments
4. Briefly describing the developed counseling program
5. Presenting the discussion on thoughts, and feelings
6. Discussing unwanted pregnancy and its complications
7. Knowing the reasons for considering a pregnancy as unwanted and providing appropriate counseling
8. Discussing the maternal-fetal attachment and its benefits
9. Determining homework assignments
Second session
1. Reviewing the previous session's main points and checking and discussing homework assignments
2. Introducing cognitive-behavioral counseling approach
3. Introducing cognitive and behavioral concepts
4. Group training based on previous homework assignments
5. Talking about misconceptions about pregnancy and fetus and correcting them
6. Teaching how to focus on the fetus and recognizing it as an independent entity, touching the abdomen by the pregnant mother, and recognizing and guessing the position of the fetus, counting the movements of the fetus from the abdomen, imagining a positive shape of the fetus, calling the fetus with a nickname, talking with the fetus, looking at the abdomen and paying attention to fetal movements, imagining hugging and breastfeeding the baby and giving a checklist for recording daily attachment behaviors
Third session
1. Reviewing the main points of the previous session and checking homework assignments
2. Introducing the relaxation technique
3. Problem-solving training
Fourth Session
1. Reviewing previous sessions and checking homework assignments
2. Summarizing

between the intervention and control groups in terms of age, occupation, education, number of pregnancies, sexual preferences and the use of contraceptive methods. In beginning of the study and before the intervention, mean scores of maternal-fetal attachment in cognitive-behavioral counseling and control groups were 72.58 ± 8.63 and 72.76 ± 9.13 , respectively, and there was no significant difference between the two groups ($p = 0.91$). At the end of the study and after the intervention, the mean maternal-fetal attachment scores in the intervention and control groups were 94.06 ± 11.73 and 80.16 ± 10.09 , respectively, and results of the independent t-test showed a significant difference between the two groups ($p < 0.0001$). Results of the paired t-tests also indicated that there was a significant difference between the mean maternal-fetal attachment scores of each group at the beginning and at the end of the study ($p < 0.0001$ for the intervention group, and $p = 0.003$ for the control group). In other words, the mean maternal-fetal attachment score of the intervention group after the counseling, and the control group at the end of the study, increased significantly. Although the difference between the mean scores of

each group at the beginning and the end of the study was significant, this difference between the two groups was also noticeable (21.56 ± 12.16 vs 7.40 ± 12.39) and statistically significant ($p < 0.0001$) (Tab. III).

Discussion

The purpose of this study was to assess the effect of cognitive-behavioral midwifery counseling on maternal-fetal attachment among women with unwanted pregnancy. Since, based on previous studies, the maternal-fetal attachment in unwanted pregnancies was significantly lower than that in wanted pregnancies, so these pregnancies need more counselling and intervention [19, 30].

The findings of this study showed that the maternal-fetal attachment in the intervention group was significantly higher than that in the control group. This could be due to the effect of cognitive-behavioral counseling techniques on maternal-fetal attachment in unwanted pregnancies. Cognitive approach helps a woman to change the way she thinks about herself, her baby, and her pregnancy, and in turn increases her ability to be emotionally responsible

Tab. II. Comparison of demographic and midwifery characteristics of the participants in two groups.

Variable		Intervention group (n = 30) Number (%)	Control group (n = 30) Number (%)	p-value ^a
Age (years)	Under 25 25-30 Over 25	8 (26.6%) 11 (36.6%) 11 (36.6%)	11 (36.6%) 9 (30%) 10 (33.4%)	0.53
Education	Below diploma Diploma Higher than diploma	13 (43.3%) 13 (43.3%) 4 (13.4%)	13 (43.3%) 15 (50%) 2 (6.67%)	0.69
Job	Housewife Employed	20 (66.6%) 10 (33.4%)	19 (63.4%) 11 (36.6%)	0.99
Number of pregnancies	1 2 ≥ 3	9 (30%) 7 (23.4%) 14 (46.6%)	8 (26.7%) 8 (26.7%) 14 (46.6%)	0.88
Sex preference	Girl Boy No difference	7 (30%) 14 (23.4%) 9 (46.6%)	11 (36.6%) 17 (56.7%) 2 (6.67%)	0.06
Use of contraceptive methods	Yes No	13 (43.3%) 17 (56.7%)	18 (60%) 12 (40%)	0.15

^a Significance level: $p < 0.05$.**Tab. III.** Comparison of maternal-fetal attachment scores before and after intervention in two groups.

Groups	N	Beginning of the study	End of the study	Difference	Paired T- test ^a	
Intervention	30	72.50 ± 8.43	94.06 ± 11.73	21.5 ± 12.16	T = 9.7	P < 0.0001
Control	30	72.76 ± 9.13	80.16 ± 10.09	7.40 ± 12.25	T = 3.28	P = 0.003
T-test ^a		T = 0.11	T = 4.92	T = 4.47		
		P = 0.91	P < 0.0001	P < 0.0001		

^a Significance level: $p < 0.05$.

for her baby [31]. Pregnancy training programs can be a good way to resolve pregnancy problems by teaching pregnant women about the issues they need, such as teaching attachment behaviors.

Studies on the effect of education and different methods of counseling on attachment style of pregnant women have produced controversial results.

Some studies showed that after various psychological interventions, there is a significant increase in maternal-fetal attachment [13, 15, 27, 29, 31]. Abbasi et al. (2008) [32] and Toosi et al. (2011) [27] concluded that training and performing some attachment behaviors increased maternal-fetal attachment. Increase in the maternal-fetal attachment in their studies is in line with the results of the present study. A study by Kim et al. (2004), showed that teaching maternal-fetal attachment behaviors, such as speaking and touching the fetus from the abdomen, in primiparous mothers can increase maternal attachment in the intervention group compared with the control group, which is consistent with the our findings [33]. In this study, the reasons that this psychological counseling significantly improved the MFA score were the training of the following behaviors: teaching how to focus on the fetus and recognizing it as an independent entity, touching the abdomen by the pregnant mother, recognizing and guessing the position of the fetus, counting the movements of the fetus from the abdomen, imagining a positive shape of the fetus, calling the fetus with a nickname, talking with the fetus,

looking at the abdomen and paying attention to fetal movements, imagining hugging and breastfeeding the baby.

Azogh et al. (2018) also stated that cognitive-behavioral training increases maternal-fetal attachment in pregnant women with a history of stillbirth, which is in line with the result of this study [34].

As the results of the current study indicate, although the mean maternal-fetal attachment score after the counseling showed a noticeable increase in the intervention group, the control group also gained an increase in the mean attachment score, although this increase in the control group is much lower than the intervention group. The increase in the score in the control group could be due to the increase in the gestational age. This finding is consistent with the studies of Salibury et al. (2003) and Ustunsoz et al. (2010), who mentioned that with the increase in the gestational age, the maternal-fetal attachment also increases [12, 19].

In the study of Sastad et al. (2011), educational intervention among mothers did not increase maternal attachment to the fetus, which is not consistent with the results of the present study [35]. Ahern & Ronald (2003), who studied the effect of fetal touching on mother attachment behaviors found that there was no significant difference between the two groups after the intervention [36].

Therefore, it can be seen that there are different results regarding the effect of training and a variety of counseling

methods on attachment style in pregnant women. Salisbery et al. (2003) also mentioned that the amount of maternal-fetal attachment might be different in different training programs, which could be due to differences in counseling and training procedures, location, length or the onset time of the training in pregnancy [12].

One of the strengths of this study was that group counseling encouraged mothers to share experiences. Since the pregnancy was unwanted, the participants were less inclined to attend counseling sessions and to reduce this limitation, it was tried to emphasize the importance of maternal-fetal attachment and the possible benefits of counseling for women, and to encourage them to take part in the following sessions. Another limitation was the lack of follow up of mothers to postpartum and the lack of investigation of the effect of intervention on the attachment of mother and child after birth due to time constraints.

Conclusions

The results of the present study showed that midwifery group counseling with a cognitive-behavioral approach at the end of the second trimester of pregnancy increases the maternal-fetal attachment. Since, based on previous studies, maternal-fetal attachment is a very important and influential indicator in the physical growth and motor development of children during pregnancy and after birth [21, 37]; therefore, it is recommended that midwifery group counseling with a cognitive-behavioral approach is used as an easy, inexpensive and non-invasive method to increase maternal-fetal attachment especially among women with unwanted pregnancies.

Ethics Approval

Before embarking upon the study, approval was obtained from the Ethics Committee of Shahroud University of Medical Sciences (IR.SHMU.REC.1395.22); the study was registered in the Iranian Registry of Clinical Trials (Code IRCT2016092930048N1), and finally, a written permit was obtained from the concerned authorities to produce it to the research environments. Then, written informed consents were obtained from all participants and they were briefed on stages of the study and the procedures for their admission and participation in counseling sessions.

Acknowledgments

This study was the result of a master's thesis in midwifery counseling in Shahroud University of Medical Sciences. Hereby we express our gratitude to the Research Deputy of Shahroud University of Medical Sciences, who financially supported the implementation of this project. We are also grateful to Health Deputy of Mashhad, who cooperated with the researchers in implementing the

plan. We also owe a word of gratitude to all pregnant mothers who participated in this research.

Funding

This study was supported by Shahroud University of Medical Sciences.

Informed consent statement

Informed consent was obtained from all participants.

Conflict of interest statement

There is no conflict of interest in this study.

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Received on April 17, 2023. Accepted on September 15, 2023.

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How to cite this article: Ghasemi Nasab Z, Motaghi Z, Nazari AM, Keramat A, Hadizadeh-Talasaz F. The effect of cognitive-behavioral counseling on maternal-fetal attachment among pregnant women with unwanted pregnancy in Iran: A randomized clinical trial. *J Prev Med Hyg* 2023;64:E316-E322. <https://doi.org/10.15167/2421-4248/jpmh2023.64.3.2930>

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HEALTH PROMOTION

Addressing childhood obesity through policy: A cross-sectional study in Malta

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Keywords

Paediatric obesity • Health policy • Obesogenic environment • Intersectoral collaboration

Summary

Introduction. Childhood overweight and obesity are major public health challenges, with Malta having one of the highest prevalences among European countries. The COVID-19 pandemic may further worsen this epidemic. The food and physical activity environments impact children's behaviours. This study looks at barriers to maintain a healthy weight, responsibility to address obesity, and assesses parental support for 22 policies aimed at addressing childhood obesity. Public support for policy is key because it influences which policies are adopted and their success.

Methods. A cross-sectional, paper-based, quantitative survey was conducted amongst parents of primary school-aged children in Malta in 2018-2019. Ethical approval was obtained. Statistical analysis was performed using SPSS.

Results. 1,169 parents participated. The food environment was

more commonly identified as a barrier to maintain a healthy weight than the physical activity environment. Parents were least supportive of taxation policies, and most in favour of increasing spaces available for safe physical activity (94.0%), followed by providing free weight management services for children (90.8%). The level of support varied significantly by various socio-demographic/economic characteristics; parents with a higher educational level were significantly more supportive of most policies. Most findings were consistent with the international literature.

Conclusions. Most policies supported are trans-sectoral; a health-in-all policies approach is needed to address the obesogenic environment. The strong public support identified for several policies should embolden policymakers to consider policy options that were not previously considered.

Introduction

Overweight and obesity in children is a major public health challenge in many developed countries, with Malta being no exception. The COVID-19 pandemic may further worsen the childhood obesity epidemic through a worsening obesogenic environment characterised by school closures, home confinement resulting in physical inactivity and altered food intake behaviours, thus addressing childhood obesity has become a top priority for policymakers [1]. Maltese children and adolescents were amongst the most overweight and obese from the World Health Organisation (WHO) European Region countries that participated in the 2018/2019 Childhood Obesity Surveillance Initiative (COSI) study [2] and the 2017/2018 'Health Behaviour in School-Aged Children' (HBSC) survey [3]. A local study which measured the weight and height of students showed that 42.1% of boys and 37.1% of girls in primary schools were overweight or obese and highlighted significant inequality around their socio-economic status; children in State (non-fee paying) schools were the most obese, while children in fee-paying Independent schools were the least obese [4]. Childhood overweight and obesity are likely to track into adulthood [5]. In the 2019 European Health Interview Survey, Malta reported the highest proportions of overweight and obesity in the EU (64.8%), with 28.7% of adults being obese [6]. Obesity affects the physical, psychological and social health of the individual [5] and

causes a substantial economic burden on society through direct and indirect costs [7, 8].

It is likely that an overall 'obesogenic environment' is driving the childhood obesity epidemic [9]. In Malta, children's behaviours are affected by easy access to processed, energy-dense food and beverages (F&B), coupled with a built environment that offers limited opportunities for active transport or play [10].

Interventions that target individual physical activity (PA) and dietary behaviours are increasingly being recognised as having limited effectiveness, hence a multi-level environmental approach is needed to address the obesity epidemic [11]. The EU Action Plan on Childhood Obesity 2014 -2020 called for a shared commitment of member states to address childhood obesity by setting out priority areas for action [12]. In Malta, a number of initiatives to address the obesity problem were launched in the past decade, focusing mainly on the school setting with the 'Whole School Approach to a Healthy Lifestyle: Healthy Eating and Physical Activity Policy' published in 2015 establishing a curriculum on healthy eating and PA [13]. However, most schools cater for much less than 1 hour of PA per day, the daily recommended amount of PA for 5 to 17 year old children and adolescents by the WHO [14]. In August 2018, subsidiary legislation on the 'Procurement of Food for Schools Regulations' was enacted [15] in an effort to improve the quality of food available in schools. A national obesity strategy was launched in 2012 [16], however thus far action outside

the school setting in Malta has been limited despite an increase in the prevalence and burden of obesity. Public support for policy is key because it influences which policies are adopted and makes policy implementation more effective [17]. Some policy options are more acceptable to the public than others. The dominant narrative around who is responsible for addressing obesity is also an important consideration when determining policy. Although responsibility for addressing obesity is often attributed to the individual or family unit, the narrative of collective societal responsibility – where the government, schools and the food industry are also regarded as key stakeholders – is increasingly gaining more support [17].

The aim of this cross-sectional study was to assess the level of support expressed by the parents or guardians of a representative sample of primary school-aged children for a range of policies that could address childhood overweight and obesity in the Maltese Islands, with attention given to variations by socioeconomic background and other characteristics. It also explores what barriers parents face in trying to maintain a healthy weight in children, and their views on who is responsible for addressing the obesity epidemic. The researchers felt that parents in particular were the ideal population to target because they have a large impact on children's lifestyles, and their support for policy measures is therefore likely to make policy implementation more successful and effective. Such information is invaluable for the development of context-specific recommendations for policies and strategies to address childhood obesity.

Methods

RESEARCH DESIGN AND SAMPLING METHOD

A cross-sectional study was conducted between 2018 and 2019. Paper questionnaires were distributed to a stratified random sample of parents/guardians of 1,880 primary school-aged children aged between 5 to 11 years (school Year 1-6). Maltese and English language versions of the questionnaire were distributed in 4 State schools (public; non-fee paying), 2 Church schools (run by religious organisations; subsidised) and 1 Independent school (private; fee-paying) in Malta and Gozo, which ratio is representative of the number of children attending each type of school. Questionnaires were distributed to approximately 50 students per year (*i.e.* Year 1-6; six years in total) in each participating school. Siblings were given only one copy of the questionnaire per family. Parents unable to communicate in Maltese or English were excluded from this study. To enhance geographic regional representation, one primary school was randomly selected from each of the six 'Nomenclature of Territorial Units for Statistics (NUTS)' 'Local Administrative Units (LAU)' (Districts) [18], with an additional school selected from the Western district, being the largest NUTS unit with a variety of the three different school types.

THE RESEARCH TOOL AND DATA COLLECTION

The questionnaire used to collect data was based on the 'Public attitudes to reducing levels of overweight and obesity in Scotland' questionnaire developed by NHS Health Scotland in conjunction with ScotCen [17]. Permission to use the questionnaire was sought and received. Contextual translation of the English questionnaire to Maltese was done. Questions were culturally adapted to the Maltese context in consultation with local experts (consultant paediatricians, Public Health Medicine consultants with interest in policy, nutritionists, and experts from the Ministry for Education). Following this, both questionnaires were reviewed by another bilingual professional who ensured that the questions in Maltese retained the meaning of the questions in English. Psychometric evaluation of the research tool was done. Face validity of the questionnaire was performed, followed by test-retest reliability testing. A pilot study was carried out in two schools, following which minor adaptations were made, producing the final research tool. The questionnaire collected personal demographic and socio-economic data; information about respondent's experiences of barriers to maintaining a healthy weight; explored attitudes about responsibility for addressing obesity, recognition of the consequences of obesity and assessed support for 22 policy options. These 'upstream' policy options were selected as these had not yet been introduced in Malta, and most of them had been listed as potentially actionable measures in the Health Weight for Life Strategy [16]. Thus, policies related to children's education on healthy eating and regulating unhealthy F&B within schools were not assessed, because these have already been addressed locally. A 5-point Likert scale was used for most questions except for the section on responsibility for obesity, for which a multiple tick-box option was used. In addition, self-reported weight and height measurements of participating parents and their children were collected to enable calculation of Body Mass Index (BMI).

5-point Likert scales were grouped into 3 categories, so that scores "1" (strongly disagree) and "2" (disagree) were grouped together as "Disagree", and scores "4" (agree) and "5" (strongly agree) were grouped together as "Agree", while "3" (neither agree or disagree) was left as neutral. Weight status was categorised using BMI cut-off points established by the WHO [19]. The 'type of job' variable was coded according to the International Standard Classification of Occupations (ISCO-08) codes, which were then grouped into 4 categories.

ETHICAL CONSIDERATIONS

Ethical approvals to conduct this study were obtained from the Research Ethics Committee of the University of Malta, the Research and Innovation Unit of the Ministry for Education and Employment, the Secretariat for Catholic Education, college principals and the head of each participating school. The questionnaire was anonymous and no personal identifiers were collected.

DATA ANALYSIS

R Statistical Software (v3.5; R Core Team 2018) was used to assess representativeness of the children of the respondent sample compared to the actual population of primary schoolchildren for sex and type of school. Data analysis was carried out using SPSS® version 25. Univariate analysis was performed to assess the association between the dependent (22 policy options) and independent (children's and parents' characteristics) variables using Chi-squared test and Fisher's Exact Test. P-values that could be rounded down to 0.05 or lower were considered to be statistically significant. The 22 policy options were then grouped into four policy factor domains (each having Eigenvalue higher than 1) using Principal Component Analysis (PCA) with Varimax rotation which were then used in the regression analysis:

- Factor Domain 1: Restriction policies;
- Factor Domain 2: Taxation policies;
- Factor Domain 3: Enabling/ Incentive policies;
- Factor Domain 4: Food Regulation policies.

Policy options with factor loadings that rounded to 0.5 and above were included in the domains. The mean support of all the policies that loaded on the respective factor domain was calculated, ranging between 1 and 5 (where a higher mean represents higher support, with '3' signifying neutral level of support). Support for the four factor domains was treated as a continuous variable. As the Shapiro-Wilk test indicated that the four factor domains had a non-normal distribution, the Mann-Whitney U test, Kruskal-Wallis test and Spearman's rank correlation coefficient test were used to assess the influence of the independent variables (children's and parents' characteristics, and barriers) on support for each policy factor domain. The independent variables that were significantly associated with support for any of the four factor domains were used to create models using multivariate linear regression with a forward stepwise approach (results in Tab. III).

Results

A total of 1,169 completed questionnaires were returned, giving a response rate of 62.2%. There were no statistically significant differences for sex ($p = 0.860$) and school type ($p = 0.994$) between the children of the respondent sample and the actual population of primary schoolchildren (based on the latest data from Malta's National Statistics Office) [20].

SOCIO-DEMOGRAPHIC CHARACTERISTICS

Table I summarises the socio-demographic characteristics of participants and their children. The participants' median age was 37.9 years (age range 22-66 years).

BARRIERS TO MAINTAINING A HEALTHY WEIGHT

The food environment was more commonly identified as being a barrier to maintaining a healthy weight than the PA environment (Fig. 1). Cheap fast food being too easily available was the most common barrier identified

(92.6%; 95% Confidence Interval (CI): 90.9-94.1%), whereas PA being too expensive was the least common barrier identified (24.6%; 95% CI: 22.1-27.1%).

RESPONSIBILITY FOR ADDRESSING THE OBESITY PROBLEM

As shown in Figure 2 and 3, parents were overwhelmingly identified as having a key role to play in addressing the obesity epidemic (94.4%; 95% CI: 93.1-95.8%), but children themselves were also thought to be responsible for their overweight status by a third of respondents. The majority of respondents (85.7%; 95% CI: 83.7-87.8%) chose one or more of the options denoting individual responsibility (*i.e.* parents, relatives, healthcare professionals, children) as well as one or more of the options denoting collective responsibility (*i.e.* schools, media, government, food and drink manufacturers, local sports centres or supermarkets).

Most respondents (78.6%; 95% CI: 76.2-81.0%) were in favour of immediate governmental action to address the childhood obesity problem. Only 5.6% (95% CI: 4.2-7.0%) were in opposition.

RECOGNITION OF THE CONSEQUENCES OF OVERWEIGHT AND OBESITY

The majority of participants (92.0%; 95% CI: 90.4-93.6%) believed that childhood overweight and obesity increases the risk of health problems. 72.9% (95% CI: 70.3-75.5%) of respondents were aware that excess weight in childhood does not go away by itself.

SUPPORT FOR POLICY TO ADDRESS OBESITY

The support level for each of the 22 policy options is shown in Figure 4. Policies that facilitate healthy behaviour, referred to as 'enabling or incentive policies', received the most support. In order of decreasing popularity, these included increasing safe spaces for PA (94.0% in favour; 95% CI: 92.6-95.4%), followed by providing free weight management services for overweight children (90.8%; 95% CI: 89.1-92.5%) and increasing PA to at least one hour daily during school hours (89.9%; 95% CI: 88.2-91.6%) as can be seen in Figure 4. Taxation policies were the least supported overall, with fewer than half of the participants in favour and almost a third who were neutral. However, the level of support increased if taxation were to be ring-fenced. The level of parental support for the different policy options varied significantly ($p < 0.05$) by various child and parental socio-demographic characteristics as seen in Table II. In this Table, the 22 policy options are grouped into 8 categories based on the literature review that was conducted. Compared to parents with a low level of education, parents with a higher educational level were the most significantly supportive of most of the proposed policies, but were significantly less supportive of offering free healthy meals at schools ($p = 0.019$), and measuring children's weight in schools and sending health report card with the child's weight status to parents ($p < 0.001$). The parents' income, employment status and type of job also influenced the level of support for many policy

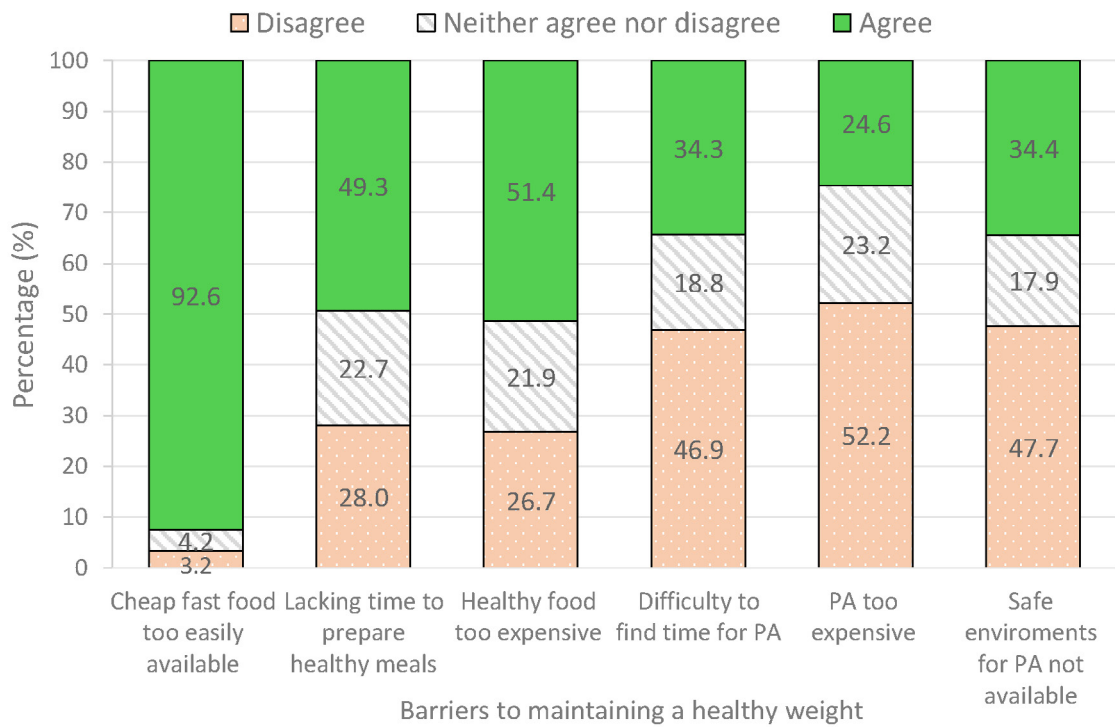
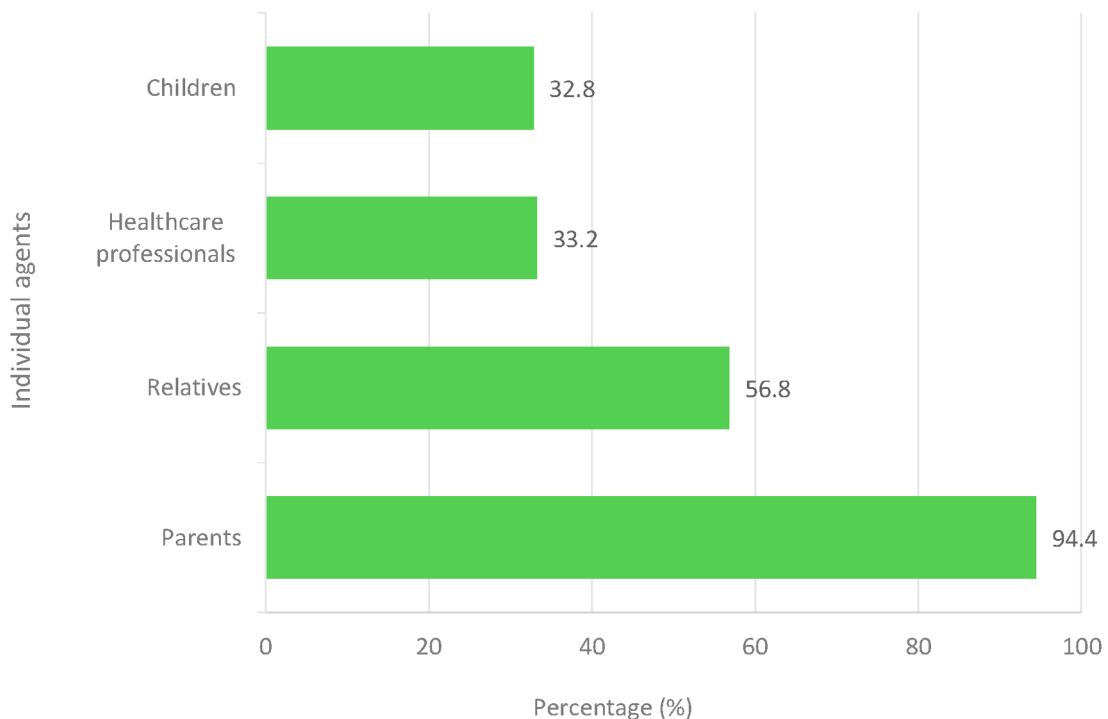
Tab. I. Socio-demographic characteristics of participants and their children.

Characteristics	Variable	Category	Frequency (n)	Percentage (%)
Children’s characteristics	Sex (n = 1 169)	Boy	596	51.0
		Girl	573	49.0
	Type of school (n = 1 169)	State	655	56.0
		Church	352	30.1
		Independent	162	13.9
	Self-reported BMI (n=836)	Underweight	32	3.8
		Normal	457	54.7
		Overweight	153	18.3
		Obese	194	23.2
Parents/Guardians’ characteristics	Age group (n = 1 169)	20-29	87	7.4
		30-39	645	55.2
		40-49	409	35.0
		≥ 50	28	2.4
	Gender (n = 1 169)	Male	197	16.9
		Female	972	83.1
	Region of residence (LAU) (n = 1 169)	Southern Harbour	210	18.0
		Northern Harbour	193	16.5
		South Eastern	173	14.8
		Western	213	18.2
		Northern	212	18.1
		Gozo	168	14.4
	Country of birth (n = 1 169)	Not Malta	115	9.8
		Malta	1 054	90.2
	Relationship status (n = 1 169)	Lives with partner	1 053	90.1
		Does not live with partner	116	9.9
	Highest level of education achieved (ISCED level) (n = 1 166)	Primary (0-1)	5	0.4
		Secondary (2-3)	392	33.6
		Post-secondary/vocational (4-5)	342	29.3
		Tertiary (6)	295	25.3
		Postgraduate (7-8)	132	11.3
	Employment status (n = 1 155)	Not gainfully employed	283	24.5
		Gainfully employed	872	75.5
	Type of job (ISCO code) (n = 926)	Professionals and managers (1-2)	414	44.7
		Associate professionals (3)	148	16.0
		Clerks, services & sales, armed forces workers (4,5,0)	312	33.7
		Manual and craft workers (6-9)	52	5.6
	Monthly household income (€) (n=881)	< 1 000	82	9.3
		1 000-1 599	205	23.3
		1 600-2 299	180	20.4
		2 300-3 299	219	24.9
		≥ 3 300	195	22.1
	Self-reported BMI (n=999)	Underweight	28	2.8
		Normal	427	42.7
		Overweight	341	34.1
		Obese	203	20.3

options. Parents suffering from obesity and parents of children suffering from obesity were significantly less supportive of providing more safe spaces for PA than parents with a normal weight and those having normal weight children.

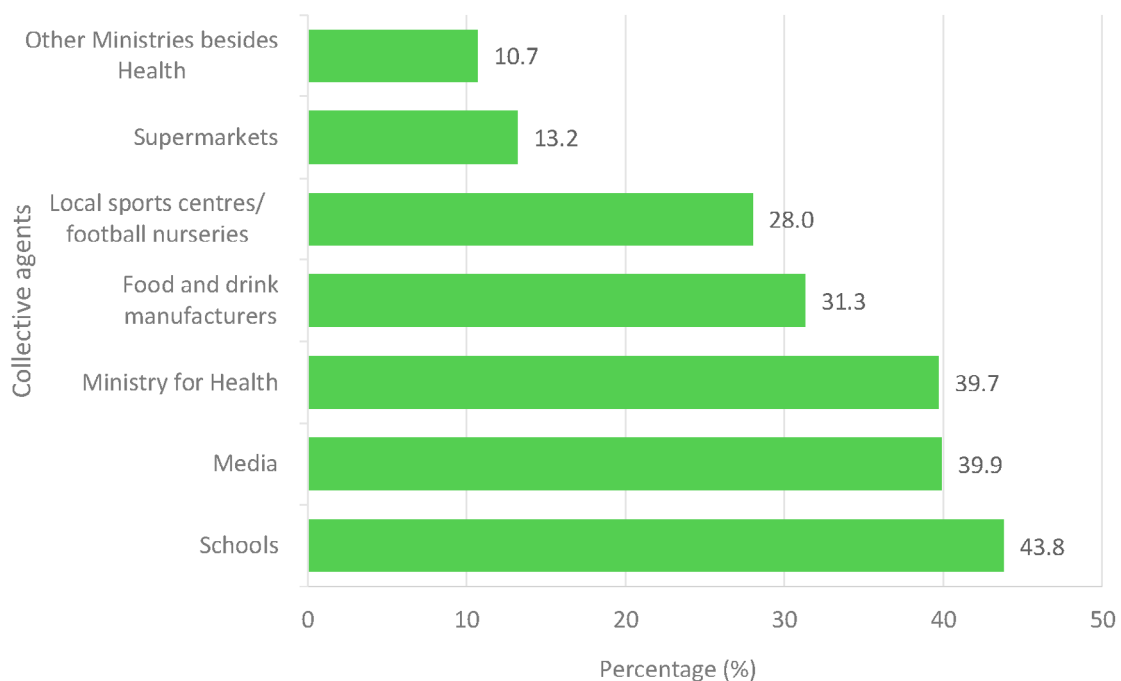
When the 22 policy options were grouped into four policy factor domains using PCA Varimax rotation, Enabling/Incentive policies received the most support

(mean 4.37 out of 5; 95% CI 4.34-4.40), while taxation policies received the least support (mean 3.28; 95% CI 3.21-3.34) (Tab. III). Socio-economic variables had a statistically significant effect on the level of support for most policy domains (level of education, income, employment status and type of job), though some lost their significance following multivariate linear regression as shown in Table III. Parents working as professionals

Fig. 1. Barriers to maintaining a healthy weight in children.**Fig. 2.** Individual responsibility to tackle childhood obesity..

(ISCO codes 1-3) were significantly more supportive of food regulation policies, and manual and craft workers (ISCO codes 6-9) were significantly less supportive of Taxation policies; parents whose children attended Independent fee-paying schools were significantly more

supportive of taxation policies; parents with a higher level of education (ISCED levels 6-8) were significantly more supportive of Restriction policies as shown in Table III. Other variables whose effect remained statistically significant following multivariate analysis

Fig. 3. Collective responsibility to tackle childhood obesity.

include parental age, children's self-reported BMI and country of birth. Parents who perceived that cheap fast food was too easily available was a barrier to maintain a healthy weight were significantly more supportive of all four policy factor domains (Tab. III).

Discussion

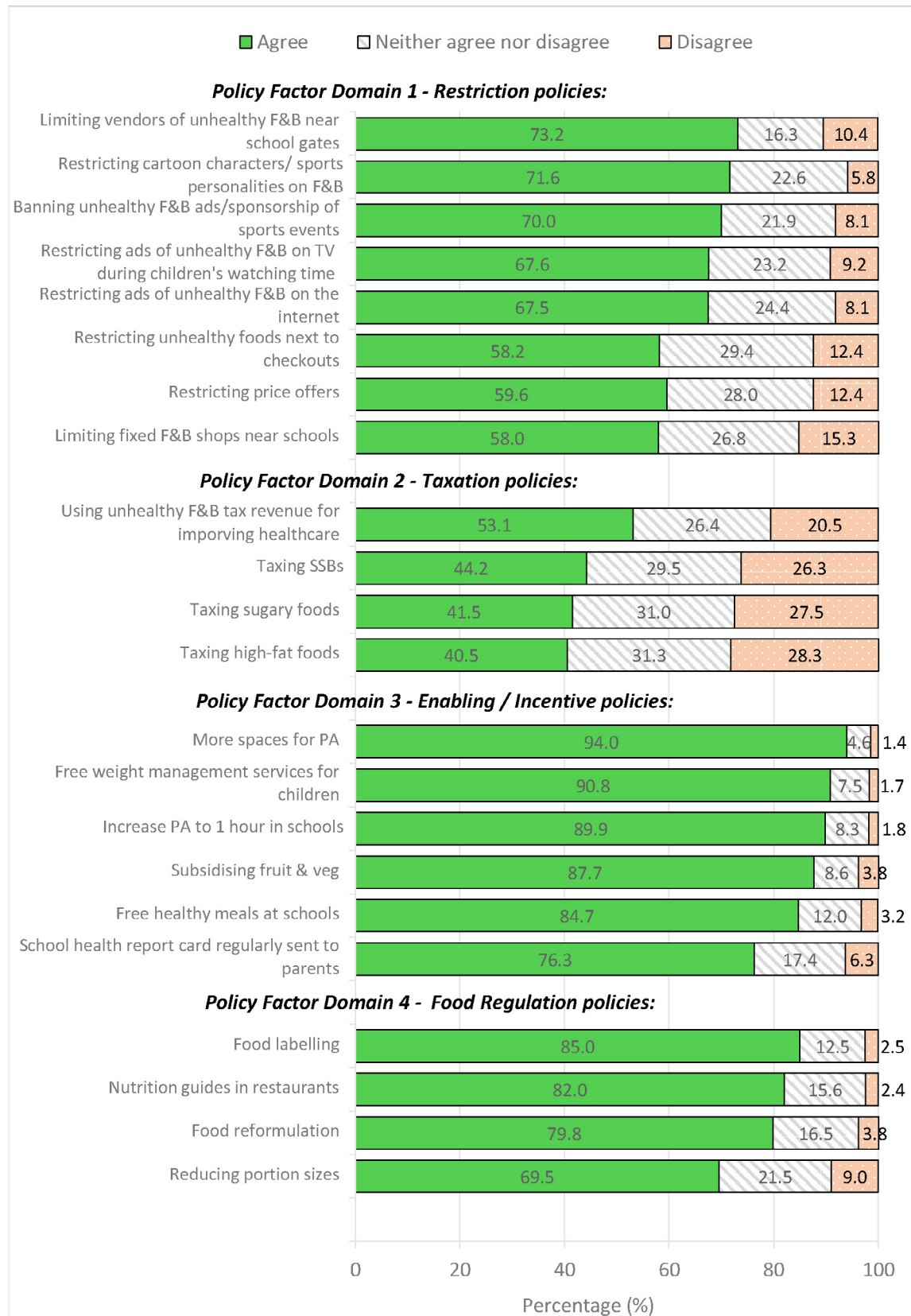
Children are vulnerable because their behaviour is impacted by others, especially parents, since they are unable to make autonomous decisions [21]. Similar to an American study, over 90% of participants attributed responsibility to address childhood obesity to parents (94.4% in our study; 90.7% in the American study) [22] and the public is now highly aware of obesity-related health threats facing adults and children. RTI International sponsored a representative survey of U.S. households ($n = 1,047$). At the same time, most respondents also felt that responsibility should be shared by the individual and society, rather than solely focusing on individual responsibility as in previous literature [23] obesity has for decades been defined as an individual issue with strong moral dimensions. Studies tend to show that obese people are viewed as selfish, impotent, lazy and unattractive; they are stigmatized in every aspect of their life, from their work to their education or health. The medicalization process that occurred in a very thorough way since the 1950s has not changed that fact that obesity continues to carry a lot of symbolic and cultural dimensions that have a lot to do with the cultural promotion of beauty in our modern societies. From a

qualitative analysis led in two countries (England and France).

The majority of participants felt that cheap fast food was too easily available (92.6%). This was also identified as the biggest barrier by 91% of Scots in a study by the NHS Health Scotland. This Scottish study (2017) similarly found that the food environment (cost, time, availability) was a bigger barrier to maintaining a healthy weight than lack of time and cost of PA [17]. Our study identified a dissonance between the most common barriers identified, which relate mainly to the food environment, and the policies which received most support, which primarily relate to the PA environment. It is possible that the most popular policies were those that entail the least inconvenience and do not require major changes to the family unit's lifestyle or behaviour, however it is clear that policymakers and politicians will need to take bold, possibly politically controversial decisions – such as introducing ring-fenced taxes – to mitigate the barriers faced by the population in accessing healthy food while addressing the over-abundance of cheap, unhealthy food. Participants generally felt that the cost of healthy food is too high, rather than identifying the cost of PA as a barrier. In the current local context of increasing food prices, due in part to supply chain disruptions caused by the COVID-19 pandemic [24] and the Russia-Ukraine conflict [25], it might be more desirable and politically acceptable to subsidise healthy food from revenue generated by taxing unhealthy F&B instead of subsidising PA.

Similar to the situation described in the international literature, support was lowest for taxation policies [17,

Fig. 4. Support for policy options to tackle childhood overweight/obesity.



26-28] with percentage support being within the previously described ranges of 21.6% in an American study [26] to 62% in a Scottish study [17], although

fewer than a third of respondents expressed outright disagreement with these policies. Furthermore, support increases if the revenue generated were to be ring-fenced

Tab. II. Significant associations between children’s and parents’ characteristics and support for different policy options.

Independent Variables		Children's characteristics			Parents' characteristics									
		Sex	Type of school	Self-reported BMI	Gender	Age group	Region of residence (LAU)	Relationship status	Country of birth	Education level	Employment status	Type of job	Monthly household income	Self-reported BMI
Nutritional Information*	Food labelling									0.021		0.037	0.030	
	Nutrition guides in restaurants					0.039				0.012				
Marketing, advertising & sponsorship policy*	Restricting cartoon characters/ sports personalities on F&B			0.053		0.027			0.036	0.028	0.003		0.045	
	Banning unhealthy F&B ads/ sponsorship of sports events		0.049							0.013	0.035			
	Restricting unhealthy F&B adverts on TV during children's screen time		0.016			0.016	0.026			0.005	0.038	0.001	0.005	
	Restricting unhealthy F&B adverts on the internet					0.006	0.022					0.008		
Community & Consumer food environment*	Reducing portion sizes						0.003					0.007		
	Restricting price offers									0.054	0.007			
	Restricting unhealthy foods next to checkouts													
Food reformulation*										< 0.001	0.001	< 0.001		
Free weight management services for children*												0.049		
Built environment policy*	More spaces for PA			0.047		0.046	0.008			0.018		< 0.001	0.002	0.023
	Limiting fixed F&B shops near schools									0.002	0.006			
	Limiting vendors of unhealthy F&B near school gates		0.016						0.048	0.002	0.003		0.028	
School policy*	Free healthy meals at schools					0.048				0.019				
	Increase PA to 1 hour in schools					0.039	0.010			0.013		0.025		
	Schools send health report cards with weight	0.028	0.013			0.017			0.024	< 0.001		0.049		
Fiscal policy*	Taxing high-fat foods		0.005	< 0.001	0.008		0.020			< 0.001	0.003	0.004	0.030	
	Taxing sugary foods		< 0.001	< 0.001						< 0.001	< 0.001	0.001	0.003	
	Taxing SSBs		< 0.001	0.012			0.014			< 0.001	0.002	0.004	< 0.001	
	Tax revenue to improve healthcare services			0.011								0.003		
	Subsidising fruit & veg								0.011					

* Numbers in each cell represent p-values; empty cell = no statistically significant difference (p > 0.05); p-values displayed in bold are highly significant (< 0.01).
BMI: Body Mass Index; F&B: Food and Beverages; PA: Physical Activity; SSBs: Sugar-Sweetened Beverages

for healthcare service provision, although the percentage in favour of such policy locally (53.1%) was lower than that in France (72.7%) [29], but higher than that in Australia (41.4%) [28]. While 98% of the countries in the WHO European region have fiscal policies on alcoholic beverages, only 23% have such policies on Sugar-Sweetened Beverages (SSBs) and even lower for foods high in fat, sugar and salt (HFSS) (6%) [30]. Unsurprisingly, enabling policies such as providing more spaces for safe PA, subsidising fruit & vegetables, *etc.*, received the most support, given that these are not associated with a cost burden (*e.g.* taxation) that directly impacts families’ financial outlay. Around 5% of the countries in the WHO European region subsidise healthy foods, but no country has both food taxes and subsidies together in place [30]. Creating more spaces where PA can be safely performed was enthusiastically supported (94.0% in favour), reflecting growing local concern about overdevelopment and increasing advocacy for public open spaces [31] and active transport [32]. Parents with obesity and parents of children with obesity are the least supportive of more spaces for safe PA; this situation should not be overlooked when developing policy, as those who stand to benefit most from such spaces might use them least.

Around schools’ perimeter, policies that restrict vendors, in particular mobile vendors, from selling unhealthy foods near school gates and directly targeting children should be prioritised given the considerable support this received, with only one-tenth of parents disagreeing with such a measure, compared to 15.3% disagreeing with limiting fixed F&B shops near schools. This was substantially different from results obtained in an American study, where support for restricting convenience stores within close distance to schools was low (37% in favour), and may be due to the local cultural context [33]. The school setting is an important place where children can be physically active. During the initial phase of the COVID-19 pandemic, the school setting was hugely impacted with many countries going into lockdown and closing schools [34], possibly further widening inequality gaps [35]. Increasing daily PA during school hours across all types of schools would probably be welcomed by parents given the high support this policy received. Restricting audiovisual media advertising of unhealthy F&B to children is another area of interest. Watching television (TV) increases sedentary behaviour, encourages snacking, and exposes viewers to F&B

adverts [36]. A majority of TV advertisements aimed at children are for unhealthy foods [37]. Children regularly ask their parents to buy food products that they see advertised [38]. Initiatives that regulate adverts of unhealthy food targeting children on TV have been found to be cost-effective [39]. Support for restricting unhealthy food adverts during children’s TV programmes/channels was slightly higher in America and Germany, with three-quarters, and four-fifths of respondents in favour respectively [22, 40, 41], compared to two-thirds locally. Around two thirds of countries in the WHO European region have mandatory policies targeting HFSS foods and beverages marketing on children, while 32% have voluntary policies [30]. It would be beneficial if action in this sector is taken at the EU level, since many children nowadays watch international children’s channels rather than local TV channels. Regulation of unhealthy F&B advertising on media popular with children should also be considered, given the popularity of engaging with social media, watching online programmes and videos, or playing games online and the significant impact such marketing has on different diet-related outcomes. Since a person’s eating behaviours are usually established at a young age and then maintained [42], it is important to optimise the food environment that

influences food preferences as early as possible. Around 80% of Malta’s food supply is imported [43], hence international action on mandatory standardised front-of-pack food labels (FOPLs) and food reformulation would undoubtedly benefit Malta and other countries, with respondents being highly supportive of both policies in this study. FOPLs have been recommended by the WHO as a ‘best-buy’ to prevent non-communicable diseases [44], with participants from 12 countries across different continents being most in favour of multiple traffic lights labels [45]. Optimising nutrition labels of foods/ beverages was highly supported in other countries as well including Germany (86.7%) [41], Australia (85%) [46], five countries in the Asia Pacific region (86.3%) [48], but slightly less in the US (63%-65%) [26, 47]. Food reformulation is also supported by the public in Scotland (82%), and 5 countries in the Asia Pacific region (79.3%) [48]. Adoption of FOPL policies vary across countries – 26% of WHO European region Member States have mandatory policies while 15% have voluntary policies [30]. Additional pressure can be exerted at the international level, such as at EU level, if agreement between Member States around issues such as food reformulation, food packaging regulations on unhealthy foods targeting children, and stricter audio-

visual media advertising is reached. The EU online consultation on the revision of Food Information to Consumers regulation including food labelling is an encouraging step forward [49].

Our observation that parents with a higher level of education were significantly more supportive of several policies than those with a lower educational level was similar to findings of studies conducted in America, Scotland and Turkey [17, 22, 26, 27]. The link between higher levels of education and support for policy might be mediated by parental health literacy. Thus, investing in health literacy, for example through health promotion campaigns on food labels and other initiatives targeted towards those with a lower level of education, might empower parents (and the voting public in general) to be more supportive of demonstrably effective regulatory interventions. Education campaigns should also address misconceptions such as the belief that obesity in children goes away by itself as children grow (a quarter of respondents were not aware). Furthermore, despite over 90% of respondents being aware that childhood obesity can lead to comorbidities, one must also factor in parental optimism, with parents being more likely to believe that their own child is at a lower chance of developing health problems related to obesity than they would for a typical child [50].

This study was limited by a low response by males which could have led to a Type 2 error; significant differences for support by parental gender were only found for one policy (taxing high-fat food). The cross-sectional nature of this study and the use of a paper-based questionnaires could have given rise to the usual limitations of such studies, including recall bias.

Conclusions

Most of the policies assessed in this study were well supported, with policies that received the highest support (increasing spaces for safe PA, followed by free weight management services for children, increasing PA to 1 hour daily in schools, and subsidising fruits & vegetables) being more likely to be effective if implemented. It is vital that the observed socioeconomic differences in the level of support do not foil the implantation of effective policies to address obesity, as inaction further compounds the existing inequality gaps surrounding childhood obesity. Addressing the different aspects of the obesogenic environment has a central role in providing potential solutions.

It is encouraging that most parents are aware that a collective approach is needed to support the individual to address obesity, as this may embolden policymakers and politicians to be less reluctant to introduce regulatory measures that might go against industry demands such as food reformulation, food advertising regulations or licensing restrictions of food stores near schools.

Stronger policy responses to address childhood obesity are needed. To be able to introduce and enforce several of the actions assessed in this study, an inter-sectoral

and whole of government approach is needed, both at national and international levels, as the impact of several policies such as restricting audio-visual advertising and marketing of HFSS foods and SSBs, food reformulation and mandatory standardised FOPL would be felt in many countries. Addressing childhood obesity has become more urgent than ever given that the obesity situation was already worsening prior to the COVID-19 pandemic and is expected to be further negatively impacted by the pandemic [1, 35].

Acknowledgments

This study was financially supported by the Tertiary Education Scholarship Scheme (TESS) administered by the Ministry for Education, Malta. TESS had no role in the design, analysis or writing of this study.

Ethical approval

This study was approved by the Research Ethics Committee of the University of Malta (Reference: FRECMDS_1718_056), the Research and Innovation Unit of the Ministry for Education and Employment (Reference: RI2018/093), the Secretariat for Catholic Education, college principals and the head of each participating school.

Conflict of interest statement

None of the authors declare any conflict of interest.

Authors' contributions

MB, DC and CG conceptualised the study and designed the methodology. MB collected the data. MB and NC analysed the data. MB, DC and NC interpreted the results. MB drafted the initial version of the manuscript. MB, DC, CG and NC contributed to the final manuscript.

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Received on May 1, 2023. Accepted on October 23, 2023.

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How to cite this article: Borg M, Cauchi D, Gauci C, Calleja N. Addressing childhood obesity through policy: A cross-sectional study in Malta. *J Prev Med Hyg* 2023;64:E323-E336. <https://doi.org/10.15167/2421-4248/jpmh2023.64.3.2938>

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Supplementary material

Tab. III. Significant influence of parents' and children's characteristics and barriers on support for the four Policy Factor Domains at univariate and multivariate analysis, and change in mean support for the statistically significant categorical variables at multivariate linear regression.

Policy Factor Domains	Parents'/children's characteristics**	Univariate Analysis		Multivariate Analysis	
		Mean support (95% CI)	Unadjusted p-value	Mean support (95% CI)	Adjusted p-value*
Factor Domain 1: Restriction policies (Mean support 3.86 out of 5; 95% CI 3.81-3.90) Barriers statistically significant (adjusted p-value): • Cheap fast food too easily available (< 0.001) • Healthy food too expensive (0.023)	Parents' age group (years)		0.049		0.007
	20-29 (Reference)	3.64 (3.47-3.82)		3.69 (3.49-3.88)	
	30-39	3.88 (3.82-3.95)	0.007	4.00 (3.94-4.06)	0.002
	40-49	3.87 (3.79-3.95)	0.012	4.04 (3.96-4.12)	0.001
	≥ 50	3.68 (3.30-4.07)	0.490	3.94 (3.61-4.25)	0.189
	Education level (ISCED)		< 0.001		0.001
	Primary & Secondary (0-3) (Reference)	3.70 (3.62-3.79)		3.78 (3.65-3.90)	
	Post-secondary/vocational (4-5)	3.83 (3.75-3.91)	0.102	3.81 (3.68-3.93)	0.184
	Tertiary (6)	4.00 (3.91-4.09)	< 0.001	4.01 (3.88-4.12)	0.001
	Postgraduate (7-8)	4.03 (3.89-4.17)	< 0.001	4.03 (3.88-4.18)	0.001
	Region of residence		0.019		
	Employment status		0.001		
	Type of job		0.001		
	Child's Type of School		< 0.001		0.004
Factor Domain 2: Taxation policies (Mean support 3.28 out of 5; 95% CI 3.21-3.34) Barriers statistically significant (adjusted p-value): • Cheap fast food too easily available (0.005)	Independent (Reference)	3.57 (3.39-3.74)		3.61 (3.34-3.88)	
	State	3.22 (3.13-3.30)	< 0.001	3.15 (3.00-3.31)	0.001
	Church	3.25 (3.14-3.36)	< 0.001	3.21 (3.03-3.39)	0.006
	Child's self-reported BMI		0.014		0.041
	Underweight/Normal (Reference)	3.20 (3.10-3.30)		3.17 (3.02-3.32)	
	Overweight	3.50 (3.33-3.67)	0.004	3.40 (3.17-3.63)	0.045
	Obese	3.35 (3.21-3.49)	0.203	3.40 (3.17-3.63)	0.049
	Type of job (ISCO code)		0.002		0.004
	Professionals and managers (1-2) (Reference)	3.41 (3.31-3.52)		3.48 (3.34-3.62)	
	Associate professionals (3)	3.38 (3.21-3.56)	0.887	3.62 (3.39-3.84)	0.274
	Clerks, services & sales, armed forces workers (4,5,0)	3.26 (3.15-3.38)	0.209	3.40 (3.21-3.59)	0.482
	Manual and craft workers (6-9)	2.83 (2.51-3.15)	0.001	2.80 (2.40-3.21)	0.001
	Region of residence		0.043		
	Education level		0.001		
	Employment status		0.006		
	Monthly household income		0.004		

(continues)

Tab. III (follows). Significant influence of parents' and children's characteristics and barriers on support for the four Policy Factor Domains at univariate and multivariate analysis, and change in mean support for the statistically significant categorical variables at multivariate linear regression.

Factor Domain 3: Enabling/Incentive policies (Mean support 4.37 out of 5; 95% CI 4.34- 4.40) Barriers statistically significant (adjusted p-value): <ul style="list-style-type: none"> • Cheap fast food too easily available (<0.001) • Healthy food too expensive (<0.001) • Parents lack time to prepare healthy meals (0.002) • Safe environments for PA not available (0.029) 	Country of birth		0.031		0.034
	<i>Malta (Reference)</i>	4.38 (4.03-4.72)		4.39 (4.35-4.42)	
	<i>Not Malta</i>	4.27 (3.22-5.00)	0.031	4.28 (4.18-4.38)	0.034
Factor Domain 4: Food Regulation policies (Mean support 4.06 out of 5; 95% CI 4.02- 4.10) Barriers statistically significant (adjusted p-value): <ul style="list-style-type: none"> • Cheap fast food too easily available (0.002) • Parents lack time to prepare healthy meals (0.030) 	Type of job (ISCO code)		< 0.001		0.001
	<i>Professionals and managers (1-2) (Reference)</i>	4.20 (4.15-4.26)		4.23 (4.17-4.29)	
	<i>Associate professionals (3)</i>	4.15 (4.06-4.23)	0.313	4.18 (4.07-4.28)	0.358
	<i>Clerks, services & sales, armed forces workers (4,5,0)</i>	3.96 (3.89-4.04)	< 0.001	4.04 (3.97-4.12)	< 0.001
	<i>Manual and craft workers (6-9)</i>	3.84 (3.63-4.06)	0.001	3.93 (3.73-4.12)	0.003
	Region of residence		0.019		
	Education level		< 0.001		
	Monthly household income		0.005		

* Empty cells under multivariate analysis category adjusted p-value = no statistically significant difference ($p > 0.05$); Category p-values displayed in bold are highly significant (<0.01). ** Only Child's Type of School and Child's self-reported BMI in Factor Domain 2 relate to Children's Characteristics; all other characteristics relate to Parents' Characteristics. BMI: Body Mass Index; CI: Confidence Interval; PA: Physical Activity.



HEALTH PROMOTION

Integrating one health: exploring the global dialogue on bioethics

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Keywords

One health • Bioethics • Public health • Animal ethics • COVID

Summary

Unesco's World Bioethics Day, whose theme this year is the protection of future generations, reveals the centrality of the concept of one-health, as the main way to guarantee a future for the planet seen as the common home of all living beings. The recent pandemic has sufficiently shown how animal health is linked to human health and how only the balance of the entire planet guarantees both. Living on earth as human

beings, no longer blinded by the Anthropocene's arrogance, but conscious of having a fundamental responsibility for the health care and well-being of every species is the imperative that should guide scientific research, education and social life. Thus, a renovating of the education system is essential to break down rigid boundaries between disciplines and promote complex and critical thinking.

Introduction

This year as well, on October 19th, 2023, the World UNESCO Day will be celebrated as part of commitment of RM Institute of science and technology and World Bioethics Day Department of International Chair in Bioethics, WMA Cooperating Centre, to proliferate the awareness and practice of Bioethical principles documented in the UNESCO Universal Declaration on Bioethics and Human Rights 2005.

The chosen theme for this year's celebration is "Protecting Future Generations", inspired by Article 16 of the UNESCO Universal Declaration on Bioethics and Human Rights. This theme encompasses multiple dimensions, aiming to create an environment that ensures the physical, mental, psychological, social, and moral well-being of future generations.

As highlighted by UNESCO, one of the most urgent risks for future generations is the environmental crisis, which requires strong efforts to reduce carbon emissions, protect biodiversity, conserve natural resources, and develop sustainable technologies.

The worsening of devastating phenomena, such as those caused by uncontrolled urbanization, climate change, global warming, and over-consumption of natural resources (some of which are non-renewable), has long since revealed the fragility of the traditional logic of indiscriminate exploitation of nature. This logic is based on the principle that anything technically possible can be done to maximize productivity and profit [1].

In this context, Heidegger's reflection on technology becomes particularly relevant, as it appears to have betrayed the original meaning of Greek *techné* as the disclosure of being in contemporary society. Instead, it has become a form of "provocation" (*Herausfordern*)

"by which nature is required to provide an energy to be extracted and accumulated" [2].

The consequences of these phenomena have led to a growing recognition that the traditional approach is unsustainable and detrimental to both the environment and human well-being [3]. The idea that natural resources are limitless and can be exploited without consequence has been shattered by resource depletion, loss of biodiversity, and intensity of natural disasters.

The rising awareness has highlighted the necessity of a paradigm shift towards a more sustainable and holistic approach that takes into account the interconnectedness of ecological systems and human activities. Such an approach acknowledges that the health and well-being of both the environment and human beings are intertwined and depend on each other [4].

To address the urgent challenges we face, it is essential to adopt practices that promote conservation, restoration, and responsible use of natural resources. This involves embracing principles of ecological balance, resource efficiency, and the preservation of biodiversity.

The concept of One Health and its relevance in the context of the pandemic.

The recent pandemic caused by the SARS-CoV-2 virus, as well as previous viral emergencies such as HIV, SARS, swine flu, Ebola, and others, have also highlighted the importance of considering health as a "circular" concept, where issues of human, animal, and environmental health are closely interconnected.

This concept is now widely represented by the expression "One Health", on which interest has been growing recently. It clearly shows how our own health depends on ecological balance and the well-being of animals and the environment, prompting us to reflect on the impact of our actions on ecosystem's balance and all species' health [5-7].

Among the different fields where the need for this paradigm is particularly felt, there are food safety, the fight against antibiotic resistance and climate change, as well as the control of zoonoses, considering the devastating impact that zoonotic diseases can have on whole planet's public health [7, 8].

As custodians and wise administrators of this planet, we have the responsibility to consider the long-term effects that our actions have on what Pope Francis emblematically defines as the "common home" and to take care of it and its most vulnerable members, belonging to different species, races, cultures, and religions [9].

This commitment requires expanding the horizon of care beyond the boundaries of a mere anthropocentric view to all living beings depending on the health of our "common" planet.

And it is precisely this approach, able to go beyond a narrow vision of the present, that calls for a new individual and collective responsibility transcending the daily time horizon to take into account the long-term impact that our actions can have. This is a real way of ensuring a healthy and sustainable world for future generations.

One Health ethics is based on fundamental ethical values such as justice, equity, sustainability, and responsibility. The reference to these principles implies that humans belong to a broader community including both other living beings and inanimate things. Furthermore, it considers Earth as a subject and not like a pool of resources for unrestricted and indiscriminate human use. Furthermore, valuing the concept of One Health pushes us to overcome individualistic thinking and to acknowledge the importance of a collective action, since – as Edgar Morin reminds us – our life is inextricably linked to our planet and we cannot but be in solidarity with the Earth [11, 12].

Health is a complex concept that can be interpreted differently depending on cultural, social, and individual contexts. Questioning the true meaning of what it means to be healthy is an important philosophical inquiry that can also lead to a critical reevaluation of our beliefs and value [13].

The traditional definition of health, provided by the World Health Organization (WHO), is a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity. More recently, health has been defined as the ability to adapt and self-manage in the face of physical, emotional, and social challenges [14]. However, even this new definition, which is more open and dynamic compared to the traditional one, may not fully reflect the complexity and diversity of people's health experiences.

A broader philosophical perspective can lead us to question the social, economic, political, and environmental influences on people's health. We could examine how structural inequalities, limited access to healthcare resources, and social determinants contribute to health disparities among different populations. Additionally, we could challenge our beliefs about the hierarchy of living beings and reconsider our relationship with other human beings and non-human animals [15-17].

A rational view of nature implies a more inclusive

perspective, where health is considered a common good that we should strive to promote for all individuals, regardless of their species.

Aiming to an equitable health requires a collective commitment to address inequalities and create a fair and accessible healthcare system [18].

In this context, it is crucial to reconsider the traditional boundaries between disciplines, sectors, and interests, and work together to address emerging challenges in an interdisciplinary manner and a long-term vision.

By connecting knowledge from different disciplines, ethical reflection can help us in addressing the complex challenges we globally face. In fact, an ethics of responsibility on a global scale invites us to consider the moral implications of our actions and decisions, to recognize our interconnectedness and interdependence, and to urge an awareness of our common destiny and the need to act in ways that promote the well-being of all life [19].

Through interdisciplinary dialogue and ethical reflection, we can develop a deeper understanding of the ethical dimensions of our choices and create guidelines that steer us towards sustainable and just practices. This ethical reflection helps us navigate the complexities of our world, addressing urgent issues such as environmental degradation, social inequality and the protection of human rights [20].

Conclusions

TOWARDS A NEW PARADIGM IN EDUCATION

These considerations prompt reflections on the need for a profound rethinking of current university education, which is still firmly anchored in a clear separation between scientific and humanistic training [21-23]. In this regard, the great mathematician Whitehead's affirmation on the dangers of specialization seems more relevant than ever, as "the training of professionals in the specializations of knowledge increases the sum of knowledge in specific fields, but this success negatively affects the realm of knowledge [24].

Whitehead's insight highlights the potential drawbacks of over-specialization, as it might lead to a fragmented understanding of the world and hinder the development of a holistic perspective. The compartmentalization of knowledge may limit our ability to grasp the interconnectedness and complexity of real-world challenges.

To address the pressing issues that we face as a global community, it is crucial to foster interdisciplinary approaches that bridge the gap between scientific and humanistic disciplines. By integrating different forms of knowledge, we can gain a more comprehensive understanding of complex problems and explore innovative solutions beyond narrow disciplinary boundaries.

An education system that encourages interdisciplinary collaboration and cultivates a broad range of skills, including critical thinking, creativity, and ethical reasoning, is essential in preparing students to face the complex challenges of the modern world [25]. By nurturing a holistic perspective and promoting a synthesis of knowledge, we can overcome the limitations of specialization and

cultivate a more integrated and interconnected approach to education and problem-solving [26].

The complexity of the issues requires a different organization of knowledge, which, echoing Morin once again, entails a “form of thinking aimed not only at separating for knowing but also at interconnecting what is has been separated by disciplines’ fragmentation: the human beings, the nature, the cosmos, the reality” [11].

Financial support

This research did not receive any specific grant from funding agencies in the public, commercial, or notforprofit sectors.

Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

All authors conceived the study and contributed to the preparation of the manuscript related to their sections and approved the final version to be submitted.

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Received on July 6, 2023. Accepted on July 27, 2023.

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How to cite this article: Ciliberti R, Schiavone V. Integrating one health: Exploring the global dialogue on bioethics. *J Prev Med Hyg* 2023;64:E377-E339. <https://doi.org/10.15167/2421-4248/jpmh2023.64.3.3021>

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The specter of cholera in Libya and North Africa: Natural disasters and anthropization threaten human health during recent years

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Keywords

Libya • cholera • Natural disaster • Public health anthropization • Environmental ethics

Summary

Introduction. According to data from the World Health Organization (WHO), in the last year cholera has re-emerged in various areas of the planet, particularly in Africa. The resurgence of this disease is closely linked to poor hygiene, which is sometimes the result of wars or environmental disasters, as in Lebanon and Syria since autumn 2022 and today in Libya.

Discussion. The spread of cholera is chiefly caused by the presence of contaminated water, in environments with inadequate hygiene and sanitation. Another cause, however, is the lack of access to adequate vaccination and treatment campaigns.

Method. In this short paper, the authors highlight the possibility of a resurgence of epidemic cholera in Libya, especially in light of the consequences of the devastating cyclone Daniel and the simultaneous collapse of two dams upstream of the city of Derna. They also highlight the concern that cholera and other infec-

tious diseases may also spread in Morocco, which was hit by a severe earthquake on 8 September last. The focus of the paper is the awareness that the spread of epidemic diseases is very often linked to human actions, which may trigger or exacerbate the effects of natural disasters.

Conclusions. Since these events have devastating effects both on the environment and on people and their psychophysical balance, it is evident that we need to devote greater attention to the health of the planet, to which the health and survival of the human species is strictly and inextricably linked. Indeed, disasters related to phenomena of anthropization facilitate the spread of infectious diseases, placing a heavy burden on local and global health organizations and the health of entire populations. A change of course is therefore essential, in that human actions must be aimed at limiting rather than aggravating the spread of diseases.

Fig. 1. Barry Commoner* - The proper use of science is not to conquer nature but to live in it.



* Barry Commoner (May 28, 1917 – September 30, 2012) was an American cellular biologist, college professor, and politician. He was a leading ecologist and among the founders of the modern environmental movement.

Introduction

In September 2023, Northern Africa was struck by two huge natural disasters. On September 8, a devastating 6.8 magnitude earthquake hit the High Atlas Mountain range, killing over 2,800 people and injuring thousands more. Two days later, between 10 and 11 September, Cyclone Daniel hit the eastern coasts of Libya, bringing torrential rain and winds of up to 180 km/h and causing devastation.

The damage caused by Cyclone Daniel was frighteningly aggravated by the fact that the storm caused the simultaneous collapse of two dams upstream of the city of Derna, in Cyrenaica. Over 33 million cubic metres of water burst from the reservoirs, flooding large areas and killing thousands; around 6,000 perished in the city of Derna alone, and 10,000 people are still missing.

In addition, almost 40,000 people in the north-east of the country have been left homeless. However, the final balance will not be drawn up for a long time yet, in view of the scenes of bodies piled up in the streets, corpses continually washed up by the sea and entire areas swept away by the fury of the water.

Morocco was hit by an unpredictable natural disaster, destroying the ancient buildings, which had not been

constructed to withstand an earthquake. In the case of Libya, by contrast, the disaster can be ascribed both to climate change, which is disrupting Mediterranean weather patterns, and to anthropization, which determined, among other things, the construction of reservoirs dangerously close to a city; in the event of the collapse of the dams, the inhabitants would have no escape, as unfortunately happened.

Health policies and public health strategies in a global context: the emergence of diseases such as cholera

As the Worldwide Fund for Nature has pointed out, “Cyclone Daniel was the killer, but the instigators of the devastating floods that caused thousands and thousands of victims in Libya (shocking figures) are climate change, bad or non-existent land planning and the lack of warning systems” [1, 2]. The country’s unstable political situation also hinders the implementation of adequate and effective preventive health policies and, in the event of necessity, results in shortages of relief services, with the real possibility of being unable to prevent the spread of deadly epidemics.

Just a few months ago, we outlined the risk of cholera in Syria, which in February 2023 was also hit by a destructive earthquake; this exacerbated the difficult social and health situation of the country, which has been racked by a bloody war for 12 years [3]. Both the war and the earthquake have caused the displacement of large masses of the population, who live in refugee camps where the hygiene situation is totally out of control. Indeed, in Syria (excluding the north-west), 103,123 cases of cholera were recorded from 1 January to 5 August 2023 [4].

Like Syria, Lebanon also reported to the World Health Organization a cholera epidemic which, within a few weeks at the end of 2022, had reached significant numbers, mainly affecting children under the age of 5 years [5].

Between October 2022 and June 2023, 8,007 cases of cholera were recorded in Lebanon [6].

The situation of Pakistan should also be remembered: from 2022, due to earthquakes and severe drought, the cholera outbreak is overwhelming what remains of the provinces of Sindh, Belucistan e Punjab.

confirmed cases of cholera are currently 290, while the suspected cases are over 2000, only in the first 5 months of the year, when outbreaks in the three regions were confirmed.

Certainly, it is a country where cholera is endemic but the rapid increase in cases of cholera requires a careful surveillance in particular in province of Sindh where many cases of disease have been recorded: 234, into the area there is the largest city of Pakistan called Karachi, a very important crossroads for maritime and air transport so there is a high probability of spread of the disease to other countries [7].

Cholera came back in Haiti after the previous epidemic of 2016, the hurricane “Matthew” was devastating and caused a strong spread of cholera.

“Between 2 October and 6 December last year, the Ministry of Public Health and Population of Haiti reported a total of 13.672 cases of suspected disease of cholera, (including 283 death) (the mortality rate was 2,05%) from all ten departments of the country” [8].

After years of steady decline, cholera is re-emerging in various areas of the planet. Indeed, according to WHO data, “28 countries have reported cases since the beginning of 2023”. During the same period in 2022, 16 countries reported cases [9].

“The WHO African Region remains the most severely affected, with 16 countries reporting cholera cases since the beginning of 2023. The outbreaks in many Southeast African countries, including Burundi, Malawi, Mozambique, South Africa and Zimbabwe, appear to have stabilized in recent weeks. In the Democratic Republic of the Congo, the number of cases is plateauing at over 950 cases each week at the national level, with some regional variations, with the majority of cases concentrated in North Kivu, South Kivu, and Tanganyika” [10, 11] (Figs. 2-3).

There are many of these states that has also been a resurgence of other infectious diseases in recent months, such as poliomyelitis, which returned to Africa after the WHO declared Africa polio-free on 25 August 2020 [12, 13].

In this scenario, the Libyan tragedy has significantly exacerbated the risk of outbreaks of cholera and other infectious diseases, as well as of dehydration and malnutrition. Indeed, in the areas hit by the cyclone and the flood, corpses and animal carcasses still litter the streets, while others are buried under meters of mud. Most infrastructure and hospitals are impracticable and access to safe water is extremely limited. Moreover, the practice of burying large numbers of corpses in improvised mass graves can also lead to serious problems, owing to the possible contamination of groundwater. Thus, the priorities today are to provide shelter, food and clean water, primary medical care, and also psychological assistance. There is also a serious risk that the number of victims could more than double.

Cholera is an acute intestinal infection caused by consuming the bacterium *Vibrio cholera* which can be present in contaminated food or water.

Cholera is due to water-related diseases caused by undrinkable water and lack of hygiene, and there are villages where people have no choice, in fact cholera transmission is closely linked to inadequate access to clean water and sanitation facilities.

Cholera also causes an extremely virulent disease, and it is a very aggressive disease; it can cause severe diarrhea, dehydration and even death. Clean water and good hygiene are important to prevent it. In order to control cholera epidemics and reduce the number of deaths, it is essential to careful monitoring hygienical conditions in the communities, the access to clean drinking water and

Fig. 2. Cholera cases reported by WHO between early 2022 and 15 August 2023 in some countries in the African region (Source: WHO. Multi-country outbreak of cholera, External situation report #6 - 6 September 2023).

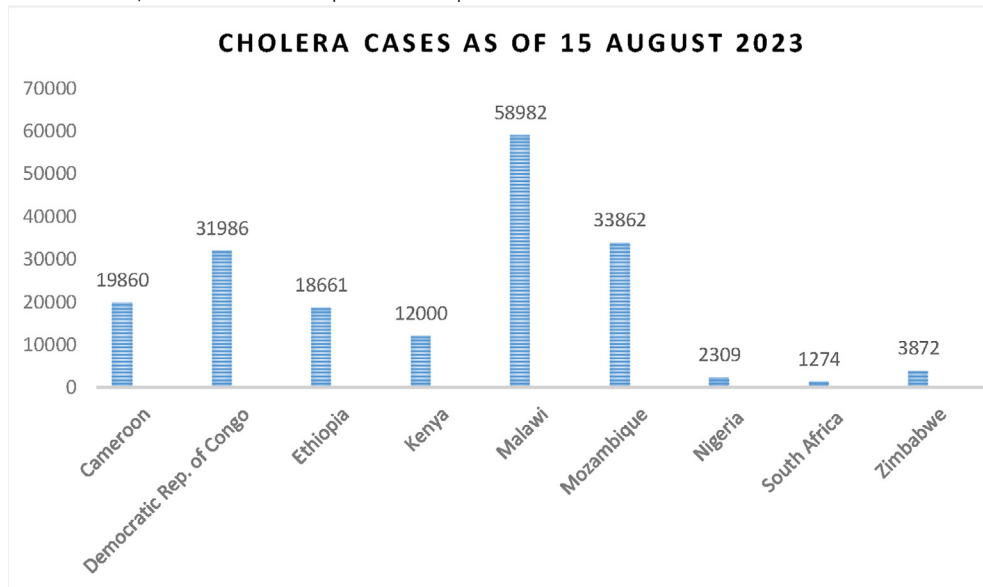
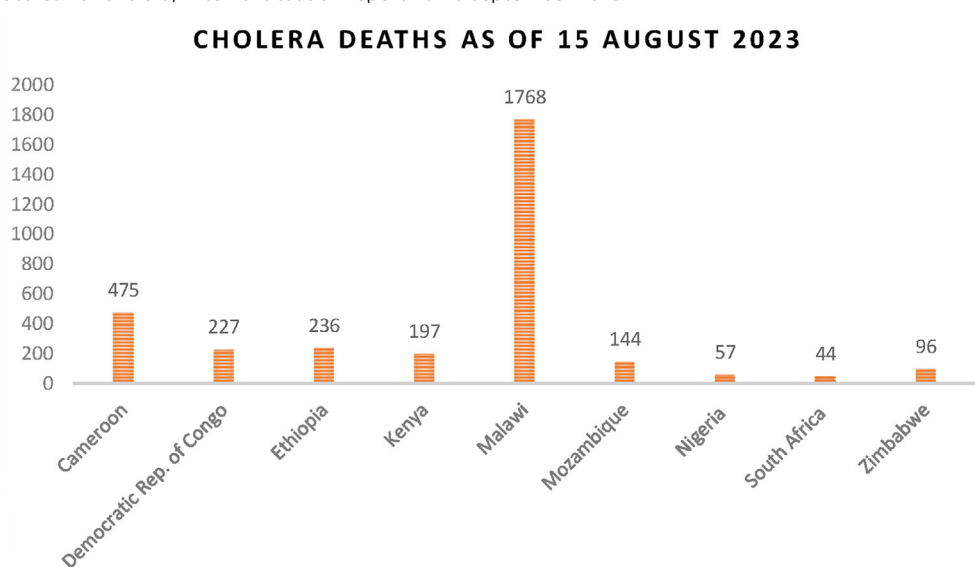


Fig. 3. Cholera deaths reported by WHO between early 2022 and 15 August 2023 in some countries in the African Region (Source: WHO. Multi-country outbreak of cholera, External situation report #6 - 6 September 2023).



strengthen and spread treatment and vaccines against cholera. Furthermore, an interdisciplinary approach is recommended in health surveillance of life and work environment.

A cholera epidemic would make this situation even more dramatic, overwhelming the survivors of this enormous tragedy, the causes of which lie not only in the force of nature but also in man's improper management of the territory and resources.

Earthquakes are natural phenomena that leave us shocked and helpless. But events like the disaster in Derna are often aggravated by "human factors".

Libya is one of the most arid countries in the world; only

5% of its territory receives at least 100 millimetres of rain per year. Hence, 95% of Libya's water supply comes from underground aquifers. Moreover, the ongoing civil war only exacerbates this situation of vulnerability. Indeed, water distribution networks have been partly destroyed and waste management has been practically paralysed, significantly increasing the risk of water-borne diseases, including cholera [14].

As has been pointed out, "66% of the population living in Libya is subject to water stress – that is, a temporary or prolonged condition of lack of water – while more than 10% of the population does not have access to safe drinking water and sanitation services" [15];

understandably, this situation has negative repercussions in terms of public health.

For this reason, back in 2020, UNICEF raised the alarm regarding the increased probability of outbreaks of cholera and other infectious diseases linked to the shortage of water [16], especially among those displaced by inter-ethnic fighting and among the migrants imprisoned in detention camps.

Ethics, environmental prevention and human behaviour: a long obstacle course

The need to reverse the trend in human behaviour, both of individuals and populations, is evident.

As regards the public health programme and the social impact the efforts of government and health authorities must focus on improving access to clean water, adequate sanitation facilities, strengthening the surveillance and control system for these diseases. In some cases, they are complemented by systematic early identification of different cases and needs, resolution and best solutions of most common problems.

All this has already been established and planned by current “Ending Cholera Road Map” of 2017.

“Ending Cholera-A Global Roadmap to 2030 operationalizes the new global strategy for cholera control at the country level and provides a concrete path toward a world in which cholera is no longer a threat to public health. By implementing the strategy between now and 2030, the Global Task Force on Cholera Control (GTFCC) partners will support countries to reduce cholera deaths by 90 percent. With the commitment of cholera-affected countries, technical partners, and donors, as many as 20 countries could eliminate disease transmission by 2030” [17, 18].

At the same time, we must safeguard our planet and tackle the risks associated with the specific features of certain areas, in order to ensure the safety of the people who live there. But to do so, it is above all necessary for man to reappraise and correct his way of relating to and “using” our planet, which is the only one we have. Understanding this simple but fundamental reality should prompt us to adopt lifestyles that are environmentally sustainable.

Human health, too, depends on the health of the planet, its animals and plants. By taking care of the Earth, we take care of ourselves and other people.

Environmental disasters, whether caused or exacerbated by human actions, expose the limits of our capacity for prevention and treatment. Indeed, when hospitals and healthcare facilities are destroyed, when enormous masses of people migrate in search of safer places to live, when prevention campaigns cannot be implemented, when clean water, basic hygiene, medicines, and healthcare personnel are in short supply, it becomes extremely difficult to respond effectively to multiple and simultaneous epidemics. And the repercussions on populations are enormous.

- Firstly, there is the risk of contracting one of the infectious diseases that appear during the various disasters.
- Secondly, those people who are already ill see their treatment interrupted.
- Thirdly, normal prevention programmes break down.
- And finally, psychological problems afflict those who are hardest hit or weakest.

Conclusions

In light of our brief reflection, we believe it is essential to propose a focus on these problems, which mainly involve the environmental sphere, but which also have repercussions on public health as a whole. This chain of events must be broken, as far as this lies within human capabilities. Man needs to change his behaviour, his building techniques, and his territorial and environmental planning activities. Such modifications would certainly improve our ability to manage the health of populations and to deal with complex emergencies.

“Like music and art, love of nature is a common language that can transcend political or social boundaries”.
(Jimmy Carter)**

Fig. 4. James Earl Carter Jr., Jimmy Carter** – Plains, 1^o October 1924.



** Jimmy Carter served as the 39th President of the United States from 1977 to 1981. He was awarded the 2002 Nobel Peace Prize for work to find peaceful solutions to international conflicts, to advance democracy and human rights, and to promote economic and social development.

[The biography for President Carter and past presidents is courtesy of the White House Historical Association].

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

DO; designed the study; DO: conceived the study; DO and MM: drafted the manuscript; DO, MM and CM: critically revised the manuscript. DO and CM: performed a search of the literature; furthermore: MM: methodology; DO and CM: validation and data curation; CM: formal analysis; MM and CM: final editing. All authors critically revised the manuscript. All authors have read and approved the latest version of the paper for publication.

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Received on September 27, 2023. Accepted on October 9, 2023.

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How to cite this article: Martini M, Minet C, Orsini D. The specter of cholera in Libya and North Africa: natural disasters and anthropization threaten human health during recent years. *J Prev Med Hyg* 2023;64:E340-E344. <https://doi.org/10.15167/2421-4248/jpmh2023.64.3.102>

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NON-COMMUNICABLE DISEASES

Body weight changes and diabetes mellitus incident: A cohort study from the Middle East

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Keywords

Diabetes mellitus • Body mass index • Weight

Summary

Objective. Obesity is a known risk factor for diabetes, but the effect of weight changes on the incidence of diabetes is not yet determined. This study aims to evaluate the long-term effects of weight change [based on body mass index (BMI)] on the incidence of diabetes mellitus (DM) in a middle eastern population.

Method. In the Isfahan Cohort Study (ICS) 6504 adults equal or greater than 35 years of age were recruited at 2001 and were followed until 2013. Absolute BMI changes (Δ BMI) were calculated by subtracting the baseline BMI from the BMI measured at follow-ups. To compare participants with different baseline BMI easier, relative changes in BMI were quantified as the percentage of changes from baseline. DM was assessed based on standard definitions. Multivariable Cox regression was used to determine the association between Δ BMI and the incidence of diabetes.

Results. During follow-ups, 261 new cases of diabetes were recorded, with an IR of 3401.29 per 100,000 P-Y. The highest number of new cases of type 2 DM belongs to participants with overweight and obesity who had minimal BMI changes (less than 5% of their baseline BMI limits; 42 and 38 new cases, respectively). Participants who were obese at baseline and had lost more than 10% or gained 5-10% of baseline BMI were in the groups with the highest IR [360.05 - 95% CI (239.3-541.8) and 322.39 - 95% CI (178.5-582.1) respectively]. There was no significant association between BMI changes and the incidence of DM in the participants with normal BMI, overweight, and obesity at baseline in crude and adjusted models.

Conclusions. This study showed there was no significant association between diabetes mellitus incidence and BMI changes.

Introduction

Diabetes mellitus (DM) is a chronic disease characterized by increased blood glucose concentration and is known as a major risk factor for cardiovascular diseases (CVD) and a higher risk of mortality and morbidity [1, 2]. The prevalence of DM is rapidly increasing over the world, such that the number of diabetic patients has doubled over the last 30 years [3], estimates show that the prevalence of diabetes and mortality and morbidities associated with diabetes will continue to increase across the globe [1]. Genetics and acquired risk factors with insulin resistance pathology play an important role in the pathogenesis of DM. Obesity is one of the acquired factors that are widespread in the world today and has a specific role in the incidence of diabetes [4]. In the Middle Eastern obesity has one of the highest ranks in the world, a review study done in 2011 shows the prevalence of overweight and obesity to be 50-80% among adults in the Middle East [5]. Another study covering 52 countries worldwide shows adults in the Middle East

have the highest mean BMI after the USA [6]. BMI is a measurement derived from the mass (weight) and height related to the extent of obesity. In the field of obesity and diabetes, some studies show BMI > 30 kg/m² compared to normal BMI (BMI < 25 kg/m²) is associated with a 3-10 times greater risk of developing diabetes [7]. Other than BMI measured at a single time point, the BMI increase (weight gain) has shown to be a risk factor for diabetes [8].

A Scientometrics study in the Middle East shows between 1990-2013 number of obesity/overweight studies has had an increasing trend [9]. Although the association between obesity and the prevalence of diabetes is definite, studies on long-term BMI changes and the incidence of diabetes are limited and inconsistent. Some studies have shown moderate weight loss (7-10%) results in a significant reduction of incidence of diabetes (> 40%) among high-risk groups [10-15]. Some studies suggest almost any amount of weight gain is associated with an increased risk of incident diabetes [16, 17]. Other observational studies show inconclusive or contradictory results about

the association between long-term BMI change and the risk of DM [18-21]. Accordingly, this epidemiologic survey aims to evaluate the effect of long-term BMI changes on the incidence of diabetes in the Isfahan Cohort Study, a cohort in the Middle East region.

Method

STUDY POPULATION

The Isfahan Cohort Study (ICS) is a population-based study with a representative population of 6504 adults equal to or older than 35 years of age, living in urban and rural areas of three counties (Isfahan, Arak, and Najaf Abad) in central Iran [22]. Subjects were participants in the baseline survey of the Isfahan Healthy Heart Program (IHHP), a community trial for CVD. Recruitment started from January 2nd to September 28th, 2001, and subjects were followed for 13 years. Participants were selected by multistage random sampling for subject enrolment to reflect age, sex, and urban/rural distribution of the community [23]. After recruiting, subjects were followed in 2005-2006 and 2010-2011. The interview and attendance to clinical examination response rates were 98% and 95% respectively. For this study, participants without a history of DM at baseline who were present until the fifth follow-up (2013) were included. The study's ethical approval was contained by the Ethical Committee of Isfahan Cardiovascular Research Center, a WHO collaborating center.

BMI MEASUREMENT

Height and weight measurements were conducted by a secured metal ruler barefoot and a calibrated scale in light clothing. BMI was calculated as weight (kg) divided by height squared (m^2). Participants were divided into three groups "under or normal weight" ($BMI < 24.9 \text{ kg}/m^2$), "overweight" ($BMI: 25-29.9 \text{ kg}/m^2$), and "obese" ($BMI > 30 \text{ kg}/m^2$) as Health Canada's Guideline for Body Weight Classification [23]. Absolute changes in BMI (ΔBMI) were calculated by subtracting the baseline BMI from the BMI measured at follow-ups. To compare participants with different baseline BMI easier, relative changes in BMI were quantified as the percentage of changes from baseline. The magnitude of ΔBMI was further classified into "minimal" ($\pm 5\%$), "moderate" ($\pm 5-10\%$), and "large" ($> \pm 10\%$).

DIABETIC CASE DEFINITION

Subjects with fasting plasma glucose (FPG) greater than 126 mg/dl (7.0 mmol/L) or a 2-hour post-challenge glucose value of more than 200 mg/dl (11.1 mmol/L) or being on anti-diabetes medication were defined to have diabetes [24].

OTHER VARIABLES

Based on risk factors recorded for DM [25], variables are further assessed in this study. Collecting data was carried out using questionnaires by trained health

professionals [26]. The quality of diet was assessed based on a validated 48-item food frequency questionnaire (FFQ) [27]. Participants have reported the frequency of consumption of any of the food items, on a daily, weekly, and monthly basis. Data on physical activity was obtained based on 4 activity domains of job-related activity; transportation-related activity; housework and house-maintenance activity; and sports and leisure time activity. Information about the frequency, time spent, and intensity of these activities was gathered [28]. Smoking status and parental DM history also were assessed.

STATISTICAL ANALYSIS

Data are reported as mean \pm SD for continuous and number (percent) for categorical variables. Kolmogorov-Smirnov test was used for testing the normality assumption. ANOVA with post-hoc test and chi-square test was used for comparing mean and frequency between groups respectively. The percentage of changes was calculated as the difference between two values divided by baseline multiple 100. The incidence rate is a measure of the frequency with which diabetes occurs over 13 years of follow-up when the denominator is the product of the person-time of the at-risk population. Crude and adjusted Cox regression models were used to evaluate the relationship between occurring diabetes and risk factors. Also, a hazard ratio with a 95% CI interval was reported. StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP. was used for analyzing data. A p-value less than 0.05 are considered significant.

Results

In this population-based study, 771 women and 786 men (a total of 1,557 participants) with a mean age of 47.11 were included. Table I reports the demographic health and lifestyle factors of study participants at baseline according to BMI categories. As shown in Table I, the mean age in all groups is almost the same. Over 77% of female and 56% of male participants are either overweight or obese which makes a total of 74.5% of all participants not being in the normal range. To compare overweight and obese participants, individuals with normal BMI are more physically active and have a healthier diet. The majorities of smokers (current or former smokers) have normal BMI and are overweight and then obese participants are less likely to have a smoking history.

In follow-up period, both women and men with normal BMI had the greatest mean changes ($13.37 \pm 17.72\%$ and $7.17 \pm 12.35\%$ weight gain respectively). On average, participants in normal and overweight groups experienced weight gain and obese individuals experienced weight loss ($0.84 \pm 11.11\%$ for women and $2.72 \pm 12.29\%$ for men). The majority of participants (both men and women) had minimal BMI changes ($\pm 5\%$ of their baseline BMI limits) after follow-up (38.0% women, 40.2% men). Besides minimal changes, those

Tab. I. Demographic health and lifestyle factors by baseline body mass index (BMI) categories.

Variables	Normal/underweight < 25 kg/m ² n = 513	Overweight 25-29.9 kg/m ² n = 648	Obese ≥ 30 kg/m ² n = 396
Age (year) Mean (SD)	47.33 (9.8)	47.37 (9.57)	46.39 (8.19)
Sex Mean (%)			
Male	340 (66.3%)	334 (51.5%)	112 (28.3%)
Female	173 (33.7%)	314 (48.5%)	284 (71.7%)
Smoking status Mean (%)			
Current smoker	137 (26.8%)	88 (13.6%)	39 (9.8%)
Former smoker	34 (6.6%)	38 (5.9%)	12 (3.0%)
Never	341 (66.6%)	521 (80.5%)	345 (87.1%)
Physically active Mean (SD)	1018.85 (595.61)	941.66 (555.55)	828.16 (522.08)
Healthy eating index Mean (SD)	0.99 (0.26)	0.94 (0.26)	0.89 (0.29)
Parental history of diabetes (%)	28.1%	37.6%	34.3%

who have gained more than 10% of their baseline BMI (24.3% women, 23.0% men) and then who have gained 5-10% of baseline BMI (17.8% woman, 16.4% men) are the majority of the study population. Only 11.2% of women and 9.2% of men lost more than 10% of baseline BMI, and 8.8% of women and 11.2% of men lost 5-10% of their baseline BMI (Tab. II).

After 13 years of follow-up, a total of 261 new cases of DM were identified out of 9926.7 per year (P-Y), with an incidence rate (IR) of 3401.29 per 100,000 P-Y. Table III shows the highest number of new cases of type 2 DM belongs to participants with overweight and obesity who had minimal BMI changes (less than 5% of their baseline BMI limits; 42 and 38 new cases, respectively). Participants with normal BMI who had lost 5-10% and more than 10% of their baseline BMI had the lowest number of new cases of DM. Participants who were obese at baseline and had lost more than 10% or gained 5-10% of baseline BMI were in the groups with the highest IR [360.05 - 95% CI (239.3-541.8) and 322.39 - 95% CI (178.5-582.1) respectively]. The lowest IR belongs to participants who had normal BMI at baseline and 5-10% loss [97.01-95% CI (24.3-387.9)]. Since the

majority of the population study had minimal changes (1030.1, 1816.9, 1028.7 P-Y in normal, overweight, and obese groups respectively) it might explain the higher number of new DM cases in the mentioned groups. It would appear from the high IR in the obesity group and the low IR in the group with normal BMI at baseline, that baseline BMI has had a great role on the incidence of DM (Tab. III).

When estimating the association of BMI changes and the incidence of DM in the total study population, participants with normal BMI, overweight, and obesity at baseline, had no significant relation either with no adjustments, adjustment with age and sex and adjustment with age, sex, parental history of diabetes, smoking status, healthy eating index, and physical activity (Tab. IV).

Discussion

In this study, no significant relations between weight changes and incidence of DM in all categories of normal BMI, overweight, and obese of the Isfahan Cohort Study population were seen. The mean age for each

Tab. II. Body mass index (BMI) change from the baseline (Δ BMI).

ΔBMI	Baseline BMI and 2013 survey			
	Women N = 771		Men N = 786	
ΔBMI (absolute, kg/m²) by baseline BMI category				
Normal/underweight	-2.82 ± 3.69		-1.55 ± 2.64	
Overweight	-1.07 ± 3.26		-0.42 ± 2.72	
Obese	0.33 ± 3.73		0.92 ± 4.06	
ΔBMI (relative, %) by baseline BMI category				
Normal/underweight	-13.37 ± 17.72		-7.17 ± 12.35	
Overweight	-3.97 ± 12.25		-1.61 ± 10.10	
Obese	0.84 ± 11.11		2.72 ± 12.29	
Relative ΔBMI category	Proportion (%)	Baseline BMI (kg/m²)	Proportion (%)	Baseline BMI (kg/m²)
> 10% loss	11.2%	31.21 ± 4.65	9.2%	28.49 ± 4.46
5-10% loss	8.8%	30.44 ± 3.79	11.2%	26.96 ± 3.83
± 5%	38.0%	29.07 ± 4.19	40.2%	26.14 ± 3.61
5-10% gain	17.8%	27.79 ± 4.35	16.4%	25.34 ± 3.27
> 10% gain	24.3%	25.70 ± 4.62	23.0%	24.09 ± 3.66

Tab. III. Incidence rate (IR) of diabetes (per 100,000 person) by baseline BMI categories and BMI change (Δ BMI) categories.

Δ BMI categories	Between baseline and 2013 survey								
	Normal/underweight (< 25 kg/m ²) n = 513			Overweight (25-29.9 kg/m ²) n = 648			Obese (\geq 30kg/m ²) n = 396		
	#cases	IR	95% CI	#cases	IR	95% CI	#cases	IR	95% CI
> 10% loss	3	148.03	47.7-459.0	9	241.02	125.4-463.2	23	360.05	239.3-541.8
5-10% loss	2	97.01	24.3-387.9	14	249.30	147.6-420.9	12	285.47	162.1-502.7
\pm 5%	20	161.78	104.4-250.7	42	192.62	142.3-260.6	38	307.84	224.0-423.1
5-10% gain	10	144.54	77.8-268.6	27	272.94	187.2-398.0	11	322.39	178.5-582.1
> 10% gain	20	125.33	80.9-194.3	20	244.28	157.6-378.6	10	248.69	133.8-462.2

group at baseline was 47.33, 47.37 and 46.39 years which indicate that the majority of the study population has been middle-aged, conducting similar surveys in younger population studies might show different results. The overall IR of diabetes mellitus between the three categories of Normal BMI, Overweight, and Obese was the highest in Obese (≥ 30 kg/m²) participants and the lowest in those with Normal BMI (< 25 kg/m²). Based on BMI categories, participants with minimal BMI change ($\pm 5\%$) and normal BMI at baseline, 5-10% weight gain and overweight at baseline, and obese subjects at baseline with more than 10% weight loss showed the highest IR (non-significant) for DM after 13 years follow up. When assessing the relationship between BMI changes and the incidence of DM, a specific pattern was not seen after analysis, and the hazard ratio (HR) does not show a significant positive or adverse effect on any of the categories or subgroups.

In the current study, the majority of women were in overweight and obese groups (40.7% and 36.8%) while the majority of men were in normal and overweight groups (43.3% and 42.5%) at baseline. Participants with normal BMI were more likely to be smokers, more physically active, and have healthier diets. After follow-up, the mean BMI changes for participants with normal BMI and overweight were positive, meaning weight gain for these groups, and for participants with obesity, the mean changes were negative, meaning weight loss for this group. Mean BMI changes in the obese group were greater for men than women ($2.72 \pm 12.29\%$ compared to $0.84 \pm 11.11\%$). Overall, the majority of the study population (both men and women) experienced minimal BMI changes ($\pm 5\%$). In a similar study of Alberta's Tomorrow project cohort, the demographic features of the study population are similar to the current study, in which the majority of current smokers are in the normal BMI group (15.7% compared to 12.9 and 11.6), although the results for former smokers is the opposite (40.5% in the obese group compared to 35.1% and 28.1% for overweight and normal BMI). Also, participants with normal BMI are more physically active (52.7%) and have healthier diets. In the mentioned study, BMI had increased in participants with overweight and obesity at baseline it showed to be associated with an increased risk of diabetes incident, and BMI decreased associated with decreased risk of diabetes incident. On the other hand, BMI changes in participants with normal BMI show no significant relation with the risk of diabetes

incidents [29].

In another study of the 20-year China Health and Nutrition Survey risk of DM, the incidence was increased in participants with weight gain compared to minimal BMI change, especially with rapid and significant weight gain rather than moderate weight gain [30]. Another study of the Japanese population showed an increase of BMI by 1 kg/m² is associated with a 25% increase in the risk of diabetes incidence, even for participants with normal BMI at baseline [31]. Similar results were reported in a cohort study by Oguma et al., which demonstrated weight gain as a risk factor for diabetes, even in individuals with normal BMI at baseline [20]. The study of Koh-Banerjee et al., on US men, demonstrated every 1 kg of weight gain increases the risk of diabetes by 7.3% [32]. The study of MY Health Up Study done by Kaneto et al., demonstrated that long-term weight gain in adults is an indicator of developing diabetes in the future, even weight gain within the limits of normal BMI is associated with an increased risk of diabetes [18]. The meta-analysis of Kodama et al. suggested weight gain as a predictor of developing type 2 diabetes, especially in early adulthood in comparison to middle or late adulthood [33]. The same results, conducted from other studies such as Colditz et al., and French et al., demonstrated weight gain as a predictor of diabetes incidence. In the current study, although not statistically significant, moderate weight gain (5-10% of baseline body weight) in overweight participants is associated with the highest incidence rate of diabetes in that group [8, 21].

On the other hand, some studies showed weight loss can have a protective effect on developing diabetes, such as the study by Wing et al., after 2 years of interventions on diet and exercise [14]. In the meta-analysis of Karla et al., after pooling 63 studies into the meta-analysis, it is shown that even a small reduction of weight is associated with reduced risk of diabetes, (every 1 kg of weight loss is associated with lowering the odds of diabetes by 43%) [34]. In the trials of Kosaka et al., Long et al., Penn et al., Knowler, et al., and Lindstro et al., similar results are conducted [10-13, 15]. In a nationwide Korean study undertaken by Kim et al., no significant relations between increased BMI and incident diabetes was seen, however, weight loss was significantly associated with lower risk of diabetes [35].

Some studies suggest weight changes even weight loss is a risk factor for developing chronic diseases such as

Tab. IV. Association between BMI changes (Δ BMI) and incidence rate of diabetes: results from multivariable Cox regression.

Total participants n = 1557	*Model 1 HR (95% CI)	**Model 2 HR (95% CI)	***Model 3 HR (95% CI)
Δ BMI (absolute) Per kg/m ²	1.00 (0.99-1.01)	1.00 (0.99-1.00)	0.99 (0.99-1.00)
Δ BMI (relative) Per 10%	1.00(0.99-1.01)	1.00(0.99-1.00)	0.99(0.99-1.00)
Relative ΔBMI (category)			
> 10% loss	0.96 (0.63-1.46)	0.95 (0.62-1.45)	0.93 (0.61-1.41)
5-10% loss	1.11 (0.75-1.64)	1.05 (0.70-1.55)	1.14 (0.76-1.69)
\pm 5%	1 (-)	1 (-)	1 (-)
5-10% gain	1.05 (0.74-1.49)	1.08 (0.76-1.54)	1.13 (0.80-1.61)
> 10% gain	0.77 (0.55-1.09)	0.77 (0.55-1.09)	0.83 (0.59-1.17)
Subgroup 1: Normal/underweight at the baseline n = 513			
Δ BMI (absolute) Per kg/m ²	0.99 (0.97-1.01)	0.99 (0.97-1.01)	0.99 (0.97-1.01)
Δ BMI (relative) Per 10%	0.99(0.97-1.01)	0.99(0.97-1.01)	0.99(0.97-1.01)
Relative ΔBMI (category)			
> 10% loss	0.47 (0.11-2.01)	0.51 (0.11-2.19)	0.55 (0.12-2.38)
5-10% loss	0.89 (0.26-3.03)	0.72 (0.21-2.48)	0.77 (0.22-2.66)
\pm 5%	1 (-)	1 (-)	1 (-)
5-10% gain	0.89 (0.41-1.91)	1.02 (0.47-2.21)	1.08 (0.49-2.36)
> 10% gain	0.75 (0.40-1.40)	0.76 (0.41-1.44)	0.80 (0.43-1.51)
Subgroup 2: overweight at the baseline n = 648			
Δ BMI (absolute) Per kg/m ²	0.99 (0.97-1.01)	0.99 (0.97-1.00)	0.99 (0.97-1.00)
Δ BMI (relative) Per 10%	0.99(0.97-1.01)	0.99(0.97-1.00)	0.99(0.97-1.00)
Relative ΔBMI (category)			
> 10% loss	1.21 (0.66-2.23)	1.18 (0.64-2.17)	1.14 (0.62-2.09)
5-10% loss	1.20 (0.58-2.48)	1.05 (0.49-2.21)	1.02 (0.48-2.18)
\pm 5%	1 (-)	1 (-)	1 (-)
5-10% gain	1.28 (0.78-2.09)	1.32 (0.81-2.17)	1.36 (0.83-2.23)
> 10% gain	1.15 (0.67-1.96)	1.18 (0.69-2.03)	1.22 (0.71-2.10)
Subgroup 3: obese at the baseline n = 396			
Δ BMI (absolute) Per kg/m ²	0.98 (0.97-1.00)	0.98 (0.96-1.00)	0.98 (0.96-1.00)
Δ BMI (relative) Per 10%	0.98(0.97-1.00)	0.98(0.96-1.00)	0.98(0.96-1.00)
Relative ΔBMI (category)			
> 10% loss	0.78 (0.40-1.50)	0.77 (0.39-1.49)	0.78 (0.40-1.53)
5-10% loss	0.85 (0.50-1.44)	0.78 (0.45-1.33)	0.91 (0.53-1.58)
\pm 5%	1 (-)	1 (-)	1 (-)
5-10% gain	1.13 (0.58-2.23)	1.27 (0.64-2.50)	1.29 (0.65-2.56)
> 10% gain	0.81 (0.40-1.64)	0.90 (0.44-1.81)	0.96 (0.47-1.96)

*Model 1: Rare analysis, no adjustments; **Model 2: Adjusted with age and sex; ***Model 3: adjusted with age, sex, parental history of diabetes, smoking status, healthy eating index and physical activity.

diabetes type 2. In the study of Higgins et al., weight loss is shown to be associated with reducing the risk of high blood pressure and cholesterol but does not decrease the incidence of diabetes [19]. In the Cohort of Kaneto et al., weight gain has a significant effect on diabetes incidence, but a weight loss of more than 2 kg does not show any significant relations with diabetes incidence compared to moderate weight loss [18]. Conflicting

results are also seen in the study of Oguma et al., although in this study weight gain is associated with an increased risk of diabetes, weight loss in early adulthood is not significantly related to diabetes incidence [20]. Also in the Iowa Women's Health Study done by French et al., BMI change is associated with an increased risk of chronic diseases such as diabetes, and even weight loss can increase the risk of developing diabetes [21]. In

this study although not statistically significant, weight loss of more than 10% of basal body weight in obese participants is associated with an increased incidence rate of diabetes. These results are almost consistent with the findings of our study. Although most of the mentioned studies showed a direct link between weight gain and DM incidence, the paradoxical role of weight loss or its ineffectiveness cannot be ignored. The justification for these contradictions can be explained by the baseline weight and BMI, the patient's age, and the presence of other risk factors [21].

Conclusions

This cohort study in the Middle East region showed that there was no significant association between diabetes mellitus incidence and BMI changes. This survey also indicated that there was no specific pattern in weight changes and diabetes outbreaks.

Acknowledgments

The authors thank Dr. Rahil Ghahramani for her cooperation in ICS and critically reading the manuscript.

Funding

Thesis, Isfahan University of Medical Sciences.

Informed consent statement

The study's ethical approval was contained by the Ethical Committee of Isfahan Cardiovascular Research Center, a WHO collaborating center, and informed consent has been obtained from all participants.

Conflict of interest statement

None.

Authors' contributions

RSM, MKA: conceptualization; RSM, MKA, MS: methodology; RSM, AS: investigation and literature search; MT, MKA, MS, HR: data curation; RSM, AS: writing-original draft; MKA, MS: writing-review and editing.

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Received on June 24, 2023. Accepted on July 18, 2023.

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How to cite this article: Salesi R, Kermani-Alghoraishi M, Sadeghi A, Roohafza H, Talaei M, Sarrafzadegan N, Sadeghi M. Body weight changes and diabetes mellitus incident: A cohort study from the Middle East. *J Prev Med Hyg* 2023;64:E345-E351. <https://doi.org/10.15167/2421-4248/jpmh2023.64.3.2650>

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NON-COMMUNICABLE DISEASES

Oral health and nicotine dependence in tobacco users visiting a Dental Institution in North India

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Keywords

Tobacco Users • Nicotine Dependency • Hygiene • Dental Caries • Gingivitis

Summary

Objective. The cross-sectional study was intended to evaluate the oral health and nicotine dependence among tobacco users.

Material & Methods. Fagerstorm Test for Nicotine Dependence estimated nicotine dependence and clinically oral examination was performed in recording the dentition status, oral hygiene, gingivitis and periodontal health. Descriptive statistics was computed using mean, percentage and standard deviation. Association was estimated using Independent T Test. Binary logistic regression and multiple regression analysis was used in inferential statistics.

Results. In general, 55.3% had dental caries, followed by 92.6%

having gingivitis and 7.4% had clinical attachment loss. Mean DMF was 2.60 (\pm 3.88) and the subjects mean oral hygiene score was 3.49 (\pm 1.11). The mean DMF score of tobacco users worsened with increasing age. Current smokers were 1.07 times more predisposed to get dental caries than former smokers and smokeless tobacco chewers had higher odds of 1.060 times to fall susceptible to dental caries than those smoking tobacco. Dependence on tobacco substantially worsened oral hygiene.

Conclusions. Tobacco cessation practices shall be effectively enforced to minimize the burden of nicotine dependence.

Introduction

India is the second largest producer of Tobacco [1]. The worldwide health implications of tobacco have been relentlessly emphasized time and again, still tobacco consumption persists with 28.6% consuming tobacco in smokeless and smoke form [2]. The current rate of progression of tobacco usage is projected upto 8 million as anticipated by 2030 [3]. In India the consumption of smokeless tobacco is more rampant owing to low cost. Promotion of tobacco products through surrogate advertisements is condemnable and adds the cumulative increase in consumption of smokeless tobacco [4]. Irrespective of the form in which tobacco is consumed it is source of lung cancer, oral cancer, cancer of nasal cavity, pharynx, oesophagus, urinary bladder and myeloid leukemia [5]. Smoking practice is prevalent in India since ancient times and is consumed in multiple forms such as beedis, cigarettes in smoking form and large fragment of population consume smokeless tobacco (SLT) mixed with different concoctions for example pan masala, gutkha, khaini, zarda etc. One out of 4 individuals are hooked to smokeless tobacco which is cheap and readily available. Substantially 199.4 million adults consume tobacco in smokeless form and 0.35 million Indians succumb to death every year due to this habit [6]. Illness arising due to consumption of tobacco affect the productivity, raise out of pocket expenses spent on health care and contribute to non-communicable diseases (NCD's) [7, 8]. Tobacco addiction with advancing age increases susceptibility of muscular illness, cognitive decline, hearing loss, vision

changes and dementia [7]. Commendable measures have been introduced for instance 'Cigarettes and Other Tobacco Products Act (COPTA) act, banning sale of loose cigarettes in certain states, displaying pictorial health warnings labels on packets and forbidding the usage of plastic to pack tobacco products [6, 9]. Despite the fact that tobacco control laws have been imposed there are several shortcomings such as imposition of tax on tobacco products, monitoring sale of tobacco to minors and pushing the legal age to purchase tobacco up to 21 years [6]. Smoking cigarette also poses environmental threat due to release of toxins for example microplastics raising concern of plastic pollution and carbon footprint added out of production of tobacco [10, 11]. Even though the National Tobacco Control Programme has been operational but the ground reality of tobacco epidemic requires consistent awareness from grassroot level involving multiple stakeholders such as academicians, members from civil society, NGO's and assistance from trained social health workers [12]. The National Tobacco Control Programme (NTCP) is also offering Tobacco Cessation services by training health workers who could help in offering assistance, empathy and support to those who are willing to quit tobacco [12]. From the latest National Family Health Survey-5 in the state of Himachal (NFHS-2019-20) there has been an upward rise in tobacco consumption with 32.3% of men consuming tobacco in some form [12] and sustainable action plan need to be formulated to decelerate the dependency of tobacco. The bulk of research is exploring knowledge attitude and perception towards tobacco usage targeting

adolescents and school-going children [13] and there is limited literature accounting oral health of those addicted to tobacco in Himachal. Hence, a study is demanded to evaluate the oral health of tobacco users and to estimate the nicotine dependence among tobacco users [14].

Material & Methods

A cross-sectional study was conducted for a period of 4 months after obtaining ethical approval from Institutional Ethical Committee with protocol number-BDC/C-10/1260-A dated 20th December 2022. Considering margin of error at 5%, confidence level set at 95%, with expected response distribution of 34% and considering 10% dropout the final sample size was rounded to 380. The investigator who collected the data was calibrated and trained. The inter-rater reliability obtained using cohen's kappa statistics was $\kappa = 0.81, 0.74, 0.86$ and 0.82 for dental caries, oral hygiene, gingival condition and periodontal health. A pre-tested Fagerstorm Test for Nicotine Dependence was used to estimate nicotine dependency and the scale reliability was assessed before beginning the study with Cronbach's alpha 0.95 which was strongly acceptable.

Subjects who were 18 years of age and above were enrolled in the study and written informed consent was obtained from those who were ready to participate. Those who suffered from systemic conditions such as diabetes mellitus and hypertension were excluded from the study. Subjects who were dependent drug abusers and alcohol users were kept out from the study. Patients visiting OPD were enquired about smoking habit and evaluated using pre-tested Fagerstorm Test for Nicotine Dependence [15, 16]. Subjects were asked questions pertaining to smoking status and duration of habit by doing face-to face interview using close-ended Fagerstorm Test for Nicotine Dependence. Depending upon the literacy status of participants the FTND questionnaire was used in English and a translated version of FTND in Hindi language was deployed. The Fagerstorm Test for Nicotine Dependence is a standardized tool based on ordinal scale that consists of six items in evaluating the consumption of tobacco, the obsession to use and the severity of addiction to tobacco. During scoring of Fagerstorm Test for Nicotine Dependence the scores from all items are summed up and greater score corresponds to severe physical dependence to nicotine. The subjects were further stratified into low nicotine dependence and significant nicotine dependence on basis of judgement by Fagerstorm Test for Nicotine dependence [15, 16]. Smokers were likewise segregated into current smokers and former smokers on basis of classification given by Centre for Disease Control and Prevention [17]. Smokers oral health was judged clinically by recording their dentition status, oral hygiene, gingival health and periodontal health using DMF Index, Oral hygiene Index simplified OHI(s), Loe and Silness Gingival Index and Community Periodontal Index [18-20].

STATISTICAL ANALYSIS

Data curation and statistical analysis was done using statistical package for social sciences version 21.0, Armonk, NY: IBM Corp [21]. Descriptive statistics was computed using mean, percentage and standard deviation. Comparison was estimated using Independent T Test and P Value less than 0.05 was treated statistically significant. Inferential statistics was computed by estimating binary logistic regression and multiple regression analysis.

Results

The mean age of subjects was (34.7 ± 11.27) years and the median duration of tobacco chewing was 10 years (IQR: 4-19) 98.2% were males and just 1.8% constituted females 44.2% ($n=168$) were smokeless tobacco users, 40.2% ($n=153$) smoked tobacco and 15.6% ($n=59$) were dual users that is they smoked and chewed tobacco. Four-fifth (88.2%) were current smokers and less than one-fifth (11.8%) were former smokers. 21.5% most commonly smoked beedi and 18.6% smoked cigarette. Most commonly chewed (SLT) product was (36.3%), zarda followed by gutka (27.9%) and rest consumed products such as paan, supari and khaini. Around half of the subjects 53.9% showed significant nicotine dependence and 46.1% were having low to moderate dependence on nicotine. 58% smoking tobacco (ST) had significant nicotine dependence and rest 42% smoking tobacco (ST) had low to moderate dependence to nicotine. Among smokeless tobacco users (SLT) 45.8% were having significant nicotine dependence and 54.2% SLT users showed low to moderate dependence to nicotine. Unusually 64% dual users had significant nicotine dependence. Advancing age additionally influenced nicotine dependency with three-fourth (75%) in age range of 45-70 years having significant nicotine dependency and notably half of tobacco consumers (48.9%) in age range of 18-44 years had significant nicotine dependence. The mean Fagerstorm Test Nicotine Dependence Score (FTND) in 15.6% of dual users was (7.50 ± 3.63) , followed by (5.30 ± 3.29) in those who smoked tobacco (40.2%) and concurrently (3.75 ± 2.75) was the mean score amongst those chewing tobacco (44.2%).

55.3% had dental caries, followed by 92.6% having gingivitis and 7.4% had clinical attachment loss. 83.4% had fair oral hygiene and 16.6% comprised poor oral hygiene. Mean DMF score of tobacco consumers was $2.60 (\pm 3.88)$ and the subjects mean oral hygiene score was $3.49 (\pm 1.11)$ which was interpreted poor. $0.93 (\pm 0.21)$ was the total mean gingival score. The mean DMF score of tobacco users worsened with increasing age and smokeless tobacco users had less DMF score $2.19 (\pm 3.67)$ in comparison to mean DMF of smokers $2.98 (\pm 4.30)$. Nicotine dependent subjects had non-significant relationship with mean DMF score except with a smaller number of retained teeth seen in those with significant dependence to nicotine (Tab. I).

Tab. I. Comparing Dental Caries status and Oral Hygiene among Nicotine Dependent using Independent T Test.

Nicotine Dependence	Decayed Teeth Mean (\pm SD)	F Value	P value	Mean (\pm SD)-Debris Index-DI (s)	F value	p value
Low to Moderate Dependence	1.46 (\pm 1.87)	.087	0.86	0.82 (\pm 0.39)	18.046	0.01*
Significant Dependence	1.42 (\pm 1.94)			0.94 (\pm 0.48)		
	Missing Teeth Mean (\pm SD)	18.994	0.00*	Mean (\pm SD) Calculus Index-CI (s)	18.994	0.00*
Low to Moderate Dependence	0.49 (\pm 1.06)			1.24 (\pm 0.31)		
Significant Dependence	1.34 (\pm 3.96)			1.35 (\pm 0.39)		
	Filled Teeth Mean (\pm SD)	.295	0.76			
Low to Moderate Dependence	0.16 (\pm 0.68)					
Significant Dependence	0.13 (\pm 0.76)					
	Total Mean DMF			OHI(s)-Mean (\pm SD)		
Low to Moderate Dependence	2.13 (\pm 2.40)	15.873	0.00*	0.16 (\pm 0.68)	.295	0.00*
Significant Dependence	3.00 (\pm 4.70)			0.13 (\pm 0.76)		

Comparison of mean oral hygiene (OHIs) scores between significantly dependent nicotine users and moderately dependent nicotine users clearly stated poor oral hygiene which was statistically significant ($p < 0.00$) (Tab. I).

The mean number of decayed teeth and filled teeth had non-significant comparison between current smokers and former smokers however mean number of missing teeth were more predominant in former smokers than current smokers with significant association ($p < 0.00$). (Tab. II) Comparison of gingival inflammation showed that mean Gingival index scores between significant dependent nicotine users and moderate dependent nicotine users were non-significant and like-wise non-significant difference was observed in gingival scores obtained between current smokers and former smokers. (Tab. III).

There was non-significant association drawn in comparing oral hygiene and gingival inflammation between current smokers in addition to former

smokers. (Tab. III). The multiple regression was run to predict DMF score from smoking status and nicotine dependence. The variables significantly predicted DMF score, $F, (2, 377) = 6.842, p < 0.05, R^2 = 0.03$. Binary logistic regression showed the odd's ratio of 1.078 (that is, current smokers were 1.07 times more pre disposed to get dental caries than former smokers) and smokeless tobacco chewers had higher odds of 1.060 times to fall susceptible to dental caries than those smoking tobacco (Tab. IV). None of the interviewed participants solicited advise for tobacco cessation.

Discussion

In the above study 40.2% smoked tobacco and the prevalence rate was higher with previous studies involving tobacco consumers [22, 23], but was slightly less in comparison with study from north-central India [24].

Tab. II. Dental caries and Oral Hygiene of Current smokers vs Former smokers using Independent T Test.

Nicotine Dependence	Decayed Teeth Mean (\pm SD)	F Value	P value	Mean (\pm SD)-Debris Index-DI(s)	F value	p value
Smokers	1.45 (\pm 1.93)	0.57	0.81	0.88 (\pm 0.44)	.110	0.31
Former smokers	1.40 (\pm 1.75)			0.95 (\pm 0.45)		
	Missing Teeth Mean (\pm SD)	39.319	0.00*	Mean (\pm SD) Calculus Index -CI(s)	.195	0.27
Smokers	0.76 (\pm 2.15)			1.31 (\pm 0.36)		
Former smokers	2.37 (\pm 6.42)			1.24 (\pm 0.34)		
	FilledTeeth Mean (\pm SD)	1.880	0.17			
Smokers	0.13 (\pm 0.72)					
Former smokers	0.22 (\pm 0.79)					
	Total Mean DMF			OHI(s)-Mean (\pm SD)		
Smokers	2.41 (\pm 3.40)	11.655	0.01*	2.18 (\pm 0.74)	.183	0.93
Former smokers	4.00 (\pm 6.31)			2.19 (\pm 0.74)		

Tab. III. Comparing Gingival Inflammation of Current smokers vs Former smokers and Nicotine Dependents using Independent T Test.

Gingival Index	Mean (\pm SD)	F value	p value
Smokers	0.92 (\pm 0.43)	1.092	0.22
Former smokers	1.00 (\pm 0.37)		
Low to Moderate Dependence	0.92 (\pm 0.36)	14.346	0.72
Significant Dependence	0.94 (\pm 0.47)		

Tab. IV. Binary Logistic Regression.

Group	Wald	B	p value	Odds Ratio
Current smokers	5.782	.076	0.01	1.078
Smokeless tobacco	3.420	.058	0.06	1.060
smokers	3.260	-.246	0.07	.782

55.9% (n= 127) had a strong urge not to give up the first cigarette smoked early in morning which was slightly lower than study from South India [25] and 44.2% of tobacco users chewed tobacco but the prevalence was smaller to previous studies [22, 23] involving smokeless tobacco users. Significant dependence to nicotine was observed and the prevalence was comparable with a study reported from north India [26] but the prevalence escalated in comparison with earlier studies [22, 27]. Dental caries rate was less in tobacco users [14] because smoking raises thiocyanate level in saliva which has the property to curb dental caries, nevertheless decrease buffer capacity of saliva and increased levels of streptococcus mutans may aggravate dental caries [28]. 48.6% smoked 11-30 cigarettes which was lower when compared smoking rate from Nepal and South India [25, 29]. Alarming 60.4% smoked tobacco immediately within waking up after 6-30 minutes which is disturbing trend contrary to GATS India Report 2016-17 [8]. Quarter of subjects (27.5%) placed their dip within 6-30 minutes which was in agreement with tobacco chewing practices from South-east Asia [29] but contrary to study from North western India [30] and 46.4% used to chew more frequently during first few hours after awakening [30]. 14.6% intentionally swallowed tobacco juice and this observation was concurrent with findings from South-east Asia study [29]. More than one-third SLT users consumed zarda and gutka which was comparable with a recent study [31] but barely one-fourth (24.5%) chewed more than 3 pouches/week of (SLT) which was significantly less than previous studies [25, 32]. Around one-fifth (26.8%) had the urge to chew tobacco when they were unwell and bedridden. In smokers 58% had significant dependence to nicotine which was equivalent to study conducted in Nepal [28] and 70% found it strenuous to refrain from smoking in public places correlating with previous literature [26]. More than two-third (75%) in the age-group of 45-70 years had significant nicotine dependence and this corresponded with earlier study [23]. 75% of those who consumed tobacco for greater than 40 years were helpless towards nicotine dependence and crucially 58.3% consuming tobacco for more than 20 years were also significantly dependent on nicotine.

Thus, raised nicotine dependence commensurate with smoking duration.

Overall half (45.8%) of smokeless tobacco users and those smoking tobacco had significant dependence on nicotine despite twin imposition of ban and punishment on sale of both smokeless tobacco and loose beedis [33]. The limitations of our study involved change in mind-set of those responding because some of them may have suppressed the information culminating into social desirability bias. It is a natural tendency that we intend to alter our response when interviewer ask questions which are socially unacceptable. Another constraint in our study was that we did not explore the association of smoking with other Non-Communicable Diseases (NCD's).

Recommendations

Concerted measures practically applied can be such as raising price of purchase of SLT which could effectively reduce the demand and affordability of SLT. Another novel measure which may curtail the demand of both smoked products and SLT would be enforcement of retail licensing which will restrict the number of tobacco vendors selling tobacco products [6]. We need to further assess how far tobacco companies are complying with Food Safety and Standard Authority of India (FSSAI) by not blending tobacco with ingredients such as spices, sweeteners, flavouring agents and scents in making tobacco products palatable and pleasant [6].

Given the high burden of disease and out of pocket health expenses arising from consumption of tobacco introspection is required to check how committed the government is in reducing the prevalence of tobacco by 30% achievable before 2025 [34]. Social media should also be utilized to sensitize the youth about the harms of tobacco [34, 35]. It is need of hour to scale up tobacco-cessation campaigns to reduce the burden of tobacco consumption.

Conclusions

Approximately half of the subjects had significant dependence to nicotine. Pronounced dependence to nicotine worsened oral hygiene of individuals and likewise dental caries weakened with marked dependency to nicotine. Thus, oral health of tobacco users was neglected.

Funding

The study was self-funded by the authors.

Informed Consent Statement

Informed Consent was obtained from participants before commencement of study.

Conflicting interest statement

Authors declare no conflict of interest.

Authors' contribution

AA: study conception and design, acquisition of data, drafting of manuscript.

AA, KA: analysis and interpretation of data, critical revision.

Acknowledgements

The study was self-funded by the authors. No financial support was received for this research from Bhojia Dental College & Hospital. The authors gratefully acknowledge the people who participated in their research.

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Received on April 11, 2023. Accepted on October 2, 2023.

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How to cite this article: Avasthi A, Avasthi K. Oral health and nicotine dependence in tobacco users visiting a Dental Institution in North India. *J Prev Med Hyg* 2023;64:E352-E357. <https://doi.org/10.15167/2421-4248/jpmh2023.64.3.2924>

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Understanding conflicts of interest in rational drug prescription in a developing country: A stakeholder analysis, healthcare guidelines and ethical public health issues

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Keywords

Conflicts of interest • Rational drug prescription • Developing country • Stakeholder analysis • Ethical public health issues • Health policy

Summary

Background. Rational drug prescription (RDP) is one of the main components of the healthcare systems. Irrational prescribing can bring about numerous negative consequences for the patients and governmental agencies. This study aims to analyze the involvement of stakeholders in rational drug prescribing, their position (opponent or proponent), and the rationale behind it.

Methods. This was a qualitative study conducted in 2019. Semi-structured face-to-face interviews were conducted with 40 stakeholders. Purposive and snowball sampling techniques with maximum heterogeneity were adopted to select the interviewees. Data was analyzed by MAXQDA software using thematic approach.

Results. Iranian Food and Drug Administration employs the highest authority on the rational prescribing policy. Although the Ministry of Health and Medical Education, the Social Security

Organization as one of the main health insurance organizations, pharmaceutical companies, and the Medical Council of the Islamic Republic of Iran, are among agencies that have great authority to improve rational prescribing, they fail to act professionally as they have conflicting interests. Remarkably, the Iran Food and Drug Administration, insurance organizations, family physicians, and patients, highly support the rational prescribing policy while the pharmaceutical companies display the least support for it.

Conclusions. To make the prescription and using drugs more rational, policy makers should focus on different sources of conflicts of interest that different actors have. They should devise legal, behavior and financial policies accordingly to lessen or at least neutralize these conflicting interests, otherwise achieving RDP would be impossible in short and long terms.

Background

“The irrational use of drugs is a major problem throughout the world. According to the WHO estimations, more than half of all medications are prescribed, dispensed or sold inappropriately, and that half of all patients fail to take them correctly” [1-3]. In rational drug prescribing, the appropriate drug should be prescribed for the patient in appropriate doses for an effective treatment period according to the individual's clinical condition. Simultaneously the rational drug prescription (RDP) should also strive to impose the lowest cost possible

on the patient and the community [4]. Altogether, these objectives can be met only if the various steps for drug prescription including the diagnosis of the disease, determining efficient and safe treatment(s), choosing the right drug, dose, and duration of treatment are considered. And to provide the necessary information to the patient and to evaluate the patient's response to the treatment [5]. Irrational drug prescribing can render adverse consequences for the patients and also can lead to patient dissatisfaction, prolonging the duration of treatment, exacerbation of the diseases, severe side effects, hospitalization, as well as undermining the

doctor-patient relationship, and ultimately increasing the treatment costs for the patients in particular and for the government agencies and financial organizations in general [6, 7].

Medications account for 20 to 40 percent of health budgets in many developing countries and 10 to 20 percent in developed countries [8]. One of the issues concerning drug prescription in Iran is non-adherence to the principles of rational drug prescribing. Note that the issue is not particular to Iran, but one of those pertaining to pharmacotherapy worldwide [9]. Studies show that economic factors, *i.e.* the financial association between the physician and the patient, are one of the contributing factors that have exacerbated the irrational prescription of drugs in Iran. Apparently the payment system can affect this relationship which has been proved by other studies in Taiwan and the American states of California and Pennsylvania [6, 10-12]. Payment methods such as fee for service which encourages health care providers to provide more services can also interfere with prescribing drugs rationally. This is the most common payment method in Iran [13].

The financial structure in the Iranian health system and the way of providing health care services have created different sources of conflicting interests which have made it difficult to move towards rational prescription of drugs. The conflicts of interest in the health care system forces actors to behave in favor of their own benefits rather than being faithful to the medical and professional standards such as rational drug prescription [14]. Thus, identifying all related actors interested in prescribing, using, and classifying drugs according to their position (opposing or supporting), and defining their resources mobilized for affective implementation. Importantly, the reasons behind their opposition, supporting or opposing RDP, and identify their potential resistance sources should be understood [15, 16]. This understanding can help health policy makers to advise proper strategies and policies to change the opposing opposition of actors. The present work aims at revealing interests that different actors have in the current chain of drug usage in Iran. The findings may serve in providing policymakers with further insights into rationalizing drug prescribing.

Methods

It is qualitative research that is part of a more extensive work on "Analysis of policies of drug rational prescription and providing policy options for Iran". In our work, we applied stakeholder analysis method for identifying the major policy players and actors of drug rational prescription, and their relationships, position, interest, power sources, and their impact on the implementation of RDP (Tab. I) [17].

Semi-structured interviews were used as the main method to collect the data. We attempted to recognize all the main stakeholders as much as possible and selected stakeholders with the highest variation from various organizations [18]. Different stakeholders, including

Tab. I. Descriptions for defining stakeholders' interest, position, and power.

Interest	The degree of positive or negative influence of policy change on stakeholders, the disadvantages and advantages of the policy implementation for stakeholders or their organization
Position	Stakeholders' understanding regarding the policy and their position about the proposed policy reform: Supporting, opposing or neutral?
Power	Potential resources and capacity, including authority, money, knowledge, political power, <i>etc.</i> for influencing policy decisions

Food and Drug Administration (FDA), Ministry of Health and Medical Education (MoHME), Social Security Organization, Medical Council, Iran Health Insurance Organization, Medical Records Organization, pharmaceutical companies, medical universities, Family physicians and specialists, pharmacists, and patients were chosen for interview. From these stakeholders, key informants with relevant experiences, education, and research in the field, were selected using purposive sampling technique. Another snowball sampling technique was used to identify other stakeholders and informants during the initial interviews. Information was extracted from the interview analysis and document reviews.

In total, 40 face-to-face interviews were conducted, which were continued until no more key stakeholder and informant were specified, and saturation was obtained. The questions were asked depending on the experience of the interviewees, so that the practical and most detailed information could be obtained. At the beginning of each interview, the interview purpose was explained. Confidentiality of the interview content was ensured and anonymity was preserved. Interviews were then taped by two sound recorders. The average length of each interview was 75 min. Meanwhile, while interviews were done, some notes were also taken in addition to the recording.

The transcribed interviews were analyzed and indexed using two researchers. For this purpose, thematic analysis was used by MAXQDA12 software. The following items were used for assessing information concerning the actors' influence and interest both ranging from high to low as well as their positions (supporting, opposing, or neutral) (Tab. III): responses of interviewees on their status and roles of the other stakeholders; the quality of reactions of actors appeared in reports, analysis of relevant documents, and finally the judgment and interpretation of authors.

Results

In this study, the main agencies of rational drug prescription were analyzed. The agencies included the Ministry of Health and Medical Education, the Iran Food and Drug Administration, health insurance organizations (the Iran Health Insurance Organization and the Social

Tab. II. List of key stakeholders and their roles in rational drug prescribing.

No.	Organization	Involvement
1	Ministry of Health and Medical Education	Responsible for policymaking, preparing clinical guidelines including guidelines to manage the prescription of drugs (expensive drugs, drugs with high consumption etc.), health care provision, and supervision in the health system including drug section
2	Food and Drug Administration	The chief policymaker in devising, implementing, and supervising the application of rational drug prescribing policies
3	Health insurance organizations	Policymaking, setting basic benefit packages including drugs to be covered for patients, Preparing a list of covered drugs, paying for drugs under coverage, Responsible for strategic purchasing in the health system Supervising physicians' prescriptions and Adopting legislations in this respect
4	Pharmaceutical companies	Producing adequate, high-quality and affordable drugs
5	Family physicians	Treating patients and prescribing drugs which are under coverage of Family Physician Program
6	Specialists	Treating patients and prescribing drugs
7	Medical Council	Devising rational drug prescribing policies and preparing clinical guidelines
8	Pharmacists	Delivering drugs to patients, Interacting with physicians and providing valid information to prevent drug interactions, Educating patients about the correct application of drugs
9	Patients	Using and paying for drugs

Tab. III. The interest, positions and influences of key stakeholders of rational drug prescription in Iran.

	Organization	Interests ^a	Positions ^b	Influences ^c
1	Ministry of Health and Medical Education	High	Moderate Support	Moderate
2	Food and Drug Administration	High	High support	High
3	Insurance organizations	High	High support	Moderate
4	Pharmaceutical companies	High	Low support	High
5	Family physicians	Low	High support	Low
6	Specialists	High	Moderate Support	Low
7	Medical Council	High	Moderate Support	Moderate
8	Pharmacists	Moderate	Moderate Support	Low
9	Patients	High	High support	Low

^a Degree to which stakeholders likely to be affected by policy change; ^b Understanding of stakeholders about the policy issue and their position regarding the proposed policy reform: support, oppose, or neutral?; ^c Potential capacity and resources including money, authority, political power, and knowledge to influence policy decisions.

Security Organization), pharmaceutical corporations, family physicians and specialists, pharmacists, the Medical Council of the Islamic Republic of Iran, and patients. The role, power, position and conflict of interests that each of these actors has regarding prescribing drugs rationally, would be explained in detail as follows.

The involvement and role of key stakeholders of rational drug prescribing in Iran.

Before addressing each stakeholder individually, the roles that each actor has regarding the prescribing drugs rationally in Iran have been provided in Table II. This helps understanding the power, position and conflict of interests of actors better.

MINISTRY OF HEALTH AND MEDICAL EDUCATION

According to the Iranian constitution, the MoHME is responsible for policymaking, health service provision, and supervising the quality of health services and the performance of health care providers in the health sector. The MoHME is also responsible for medical education and training health workforces in different fields. MoHME legally has the authority to implement policies

and arrangements for the rational prescription of drugs in Iran. However, some interviewees believe that the conflicts of interest within the MoHME prevent it from exercising this authority in this regard, as M6 says, “*One of the issues we have in the country is that the positions are not clear. Conflict of interests is integrated in the MoHME as it devises and implements policies produce medicine, sell them, and buy them at the same time. When all of these conflicting duties gather together, conflict of interests would be unavoidable*”.

IRAN FOOD AND DRUG ADMINISTRATION

The Secretariat of the National Committee for Rational Prescribing of Drugs is established within the Iran Food and Drug Administration. The committee comprises of members actively involved in the development of drug policies. The headquarters of Iran Food and Drug Administration is located within the MoHME. One of nine deputies of Medical Universities is Food and Drug Administration which work as its provincial branches. Committees exist within medical schools nationwide, which happen to be similar to the national committee

with the very structure. *"We stated in the bylaws of the national committee that the medical universities should also have a committee for rational prescribing of drugs, and the university deputies of medical universities should attend in the committee. The representative of the health insurance schemes and the provincial medical council, four specialist including internal medicine, gynecology, surgery, pediatrics, and one pharmacist should also be present in the committee"* said M10.

HEALTH INSURANCE ORGANIZATIONS

Health insurance organizations have a legal authority in terms of rational drug prescribing and usually can use this power to force physicians to consider principles of rational drug prescriptions. They can cancel their contract with the health care providers or avoid reimbursing the drugs, which have not been prescribed rationally. Arguably, insurance organizations hold a significant authority in rational drug prescribing. *"Our physician training is not protocol-based so that we could prepare protocols [for rational drug prescribing]. The only place where the protocols seem to work is through the force of Social Security Organization and IHIO, which says 'I won't pay your due (if you don't practice according to the rational drug prescription), you have to prescribe drugs this way,'"* said M6.

One of the reasons that prevent policymakers from efficiently exercising their authority to prescribe drug rationally is the conflict of interests. One of the interviewees believed that a lack of transparency in the mission statement as an influential factor. That is, an individual's rank within the system is relevant here.

M13 says, *"There are inconsistencies in the health system have made it a bit difficult to control irrational drug prescription. If you are going to sell and supervise the sales of something (drug) yourself, supervision will definitely become an issue. On the one hand, the Social Security Organization says 'I have to sell my drugs because 60% of drugs in the country are produced by me; on the other hand, it says that physicians should not prescribe too much drug for patients'"*

PHARMACEUTICAL COMPANIES

The mission of pharmaceutical companies is to cure patients mainly by producing adequate, high-quality, and affordable drugs. Many of the interviewees stated that the role of pharmaceutical companies has been now more commercialized as their main concern is to focus on earning more profits despite their organizational mission and commitment.

"The profit of pharmaceutical companies is in selling more and they don't care much about the health of people. To be honest, I am working in a pharmaceutical company too, but companies prefer to sell the drugs and their sales are important. Pharmaceutical companies are not so concerned about it (rational drug prescription)" said M26. According to some of the interviewees, making some wrong policies in the Ministry of Health and Medical Education has caused many pharmaceutical companies to deviate from their main commitments and to focus on their sale market instead.

"What have the times brought on? When the Ministry of Health says that price of the drug x should not exceed 100 Tomans for the consumer; and at the same time the company allege that producing this drug cost the least 120 Tomans. Instead, MoHME asks pharmaceutical companies 'earn your profit from selling other drugs.' Pharmaceutical companies should be able to gain their profits from every drug they produce" mentioned M8.

FAMILY PHYSICIANS

The family physician program was implemented in rural areas of Iran in 2003 to reduce inequalities in using health care services, to enhance universal health coverage and to promote social justice. This program has been influential in improving the health status of population, particularly in rural and urban areas with populations of fewer than 20,000 individuals. According to the most of interviewees there is no financial relationship between family physicians and patients. FPs are paid a fixed amount of money monthly (per capita) regardless of the number of people they treat, health care services they provide or the amount of drugs they prescribe. Because of these reasons, interviewees believed that FP program can help to follow and achieve the goals of rational drug prescription. Prescribing more drugs for patients does not lead to more financial resources for the FPs. In other words, physician's lack of dependence on patient satisfaction for income leads to rational drug prescription. *"Other family physicians and I who work in the clinic do not care much about the financial aspects at all because we receive a fixed salary"* M27 said.

SPECIALIST DOCTORS

According to many interviewees, physicians logically agree with rational drug prescription to treat patients. Some financial and cultural considerations force them to take into account irrational requests of patients for prescribing drugs in order to maintain patient's satisfaction and keep the flow of patients in the long run, which normally will lead to irrational drug prescribing. *"In practice, we all like to prescribe drugs rationally, but as we work [as professionals], we have to prescribe drugs in a way to satisfy the patients as well. Generally speaking, the physicians support rational drug prescribing but some irrational prescribing goes for the sake of keeping patients"* M15 mentioned.

MEDICAL COUNCIL OF THE ISLAMIC REPUBLIC OF IRAN

Medical Council of the Islamic Republic of Iran is an independent and union organization that advocates for doctors and patient rights, respectively. The role of Medical Council in rational drug prescribing is mainly consultative by participating and giving advice in the relevant meetings and committees. As the Secretariat for Rational Drug Prescribing is located within the Food and Drug Administration, the role of the Medical Council of the Islamic Republic of Iran and Hospital Affairs Deputy of MoHME concerning rational drug prescribing is not considerable in practice. *"The role*

of Medical Council is negligible now, although the Medical Council is responsible for implementing the law of medical council. The Medical Council could play a more influential and serious role in improving rational drug prescription but I believe this is mostly because the rational drug prescribing secretariat is not within the Medical Council” says M4.

The target population of Medical Council is medical doctors. They have a high legitimacy in the society and enjoy strong lobby and power in the MoHME. Because of that, even Medical Council cannot force them to work within some restrictive frameworks or impose some policies which may restrict their autonomy and practice. “The Medical Council has yet to persuade doctors that if you want to see a patient, you must write your prescription electronically, not on a piece of on paper just like that” said M4.

The main duties of pharmacists are provision of drug consultation for the patients. Financial issues and payment methods can create a situation which may impede pharmacists to consider principles of rational drug prescription. At times, emerging circumstances such as lack of economic recognition and support from policymakers combined with the absence of legislation in this regard lead to conflicts of interest that alter the professional and ethical commitments of pharmacists and jeopardize the interests of patients. Regarding this concern, one interviewee said that: “But there are several economic concerns (which may hinder pharmacists moving towards rational prescribing). For instance, a pharmacist can prevent many [of unnecessary drug consumption] uses, but why a pharmacist should do that? Who would pay pharmacists if they reduce the consumption of a drug? How about the financial incentives when it comes to selling drugs? There are drugs that if I were to instruct you on how to take them, it would take at least half an hour. Well, who reimburse me for that? Why physicians are paid for their visits and consultations but not the pharmacists? What do you pay for when doctors examine you? For their time and knowledge, right? Why don't you pay the pharmacists for these?” M8 said.

Pharmacists have a critical role in the clinical process of patients in the health system. The pharmacists can accelerate the process of treatment of patients and help treating physicians to cure patients effectively by supervising pharmaceutical procedures and proposing the best pharmaceutical recommendations which can result in rational prescription. This requires a close and interactive relationship between physicians and pharmacists. Interviewees believed that currently this kind of relationship does not exist between them in Iran. “The problem is that the relationship between doctors and pharmacists are not strong enough” M15 said.

Pharmacists can influence rational drug prescription differently depending on whether they own pharmacy and get bonus for selling more drugs. Hence, it can be said that their impact on rational prescription is moderate. “Generally, the position of pharmacists regarding the rational drug prescribing is not favorable; they are not

really interested in rational prescribing. Remember that it depends on whether they are the owner of the pharmacy or not. Pharmacists who work as technical officers for the owners of pharmacies do not have a share in the pharmacy's profit and do not care much about the drug sales. I (as a technical officer) sign a contract and receive a fixed payment monthly. Pharmacy owners are obliged to pay my monthly salary regardless of the amount of pharmacy's sales” M 23 said.

Collusion among a small portion of physicians and pharmacies is undeniable and some of physicians refer their patients to some specific pharmacy to get their drugs. Sometimes, this collusion occurs between pharmaceutical companies, doctors and pharmacies. These companies attempt to increase their sales by suggestion of paying commissions to physicians and pharmacies to sell their drugs, an act that leads to increasing the health care expenditures for health insurance companies, the whole health system, and patients, and ultimately imperils the health of community. “Sometimes we see pharmacists colluding with pharmaceutical companies or even doctors by paying commission to prescribe their proposed drugs or sending patients to their pharmacies” said M25.

PATIENTS

Rational drug prescription or prescribing proper drugs for the patients considering their socioeconomic status and medical condition by the doctor will cure the diseases in the shortest period of time with imposing the least amount of cost possible on patients and the health system and simultaneously will lead to patient satisfaction as well as reduce adverse drug reactions and negative side effects among patients.

“Of course we all like to receive affordable prescriptions that will cure us soon enough once we refer to a doctor,” M40 agreed.

Table III indicates that the family physicians receive the least impact from the rational drug prescribing program unlike other stakeholders, as family doctors receive a certain monthly salary with no financial relationship between the patient and the doctor and prescribing more medications to will not render more income for the doctor. According to this table, the Iran Food and Drug Administration, insurance organizations, family physicians and patients display the highest support for rational drug prescribing policy while pharmaceutical companies display the least support for this issue.

The Iran Food and Drug Administration exerts the highest impact on this policy, while the Ministry of Health, insurance companies, and the Medical Council of the Islamic Republic of Iran also hold a high authority in this regard, but do not act efficiently due to conflicts of interests.

Discussion

The Iran Food and Drug Administration was the chief stakeholder of Iran's rational drug prescription policies

and programs. The responsibility for rational drug prescription must be put in the hands of the Ministry of Health, and all other actors within the health system, including health insurance schemes should work in line with MoHME' policies. Various legal solutions have been envisioned for the efficacy of medical expenses, but collaboration and empathy of all healthcare system components are needed to fulfill the aims and render optimal use of resources at the end. Due to establishment of the Secretariat of the National Committee for Rational Prescribing of Drugs in the FDA, the main duties regarding the RDP are expected from this organization and the role of other actors including the Deputy of Treatment and Education of Ministry of Health is limited to attend in the meetings despite their potential capacity for playing a greater role. The MoHME as the main actor for making health policies and responsible for health governance, is expected to act more strongly and force other deputies and influential actors to collaborate with FDA more closely for rational prescribing of drugs. Meanwhile, international health studies and reports, including documents published by the World Health Organization indicate that health promotion interventions requires coordinated efforts by all relevant individuals and institutions from outside and inside of health system, including public and private actors, NGOs, industries, and the media [19].

Improving rational drug prescribing programs in Iran needs the strengthening of the stewardship function of the MoHME by reorganizing its structure and responsibilities. As seen in the healthcare systems of developed countries such as Germany and Japan, the responsibilities of the Ministry of Health must be limited to supervision, monitoring of the quality and standards of healthcare services, and regulating the relations between various actors and institutions within the healthcare system, even those with conflicting interests including health insurance schemes and pharmaceutical companies [20].

The next influential stakeholder affecting the RDP in Iran was health insurance organizations. Health insurance organizations review the drug prescription behavior of both general and specialist physicians and send their prescription behavior profile to them as one of the main effective health expenditures control mechanisms. These feedbacks can help physicians to be aware of their prescription behavior and compare their practice with the average prescription in the country and their peers with the same specialist. By following more rational drug prescription behaviors, this can lead to improving the quality of health care services, accelerating recovering from diseases sooner, reducing side effects of irrational drug prescription, and reducing unnecessary costs for patient and community costs.

Health insurance companies are the main financier in the health system and are the main payer to reimburse the costs of prescribed drugs. Health insurance experts review the medical claims of hospitals and do not cover drugs which have not been prescribed rationally. As a result, health insurance organizations could

reshape the behavior of physicians and rationalize their prescription, and move towards optimizing drug expenditures. According to the findings of the current study, the health insurance organizations have failed to use their potential power and authority effectively and efficiently to step forward making drug prescription more rational despite having control on financial resources as one of the major levers to reform health system and modify the behavior of physicians. A study by Sinot's designated that health insurance companies can impact the prescribing behavior of physicians and reduce their prescriptions [16].

Doctors are among the most powerful stakeholders in the country who can affect the rational drug prescribing policies and programs directly. Accordingly, doctors can be separated into specialists and general practitioners. Specialist physicians and a group of general practitioners working in the private sector may have to not to consider the principles of rational drug prescription strictly, because patients' satisfaction is affected by the number of drugs that doctors prescribe in a single prescription or the patients may insist on prescribing some specific drugs which may not appropriate for them. Doctors know that "money follows the patient in the private sector" means that they oblige to violate the principles of rational drug prescription as they have to make their patients satisfied if they want to have a constant flow of patients and money in the long run. When a patient refers to a pharmacy, the pharmacists usually are forced to prescribe medication based on what the patients believe is appropriate for them which can lead to irrational drug prescribing [18]. In many developing countries, antibiotics are often prescribed irrationally. For instance, hospital-based studies show that more than half of the treated patients receive antibiotics [19].

In the current health system in Iran, a patient may visit several specialists in a day to treat a particular disease as they can go to different specialists without limitation (family physician and following referral system is implemented in rural areas and at the moment, although it still suffers from many operational challenges and the regulations are often being violated by patients and family physicians). The same drugs may be prescribed by different physicians for the patients and they may also contradict and usually there is no checking the history of drugs prescribed by other physicians or drugs that patients may use currently. So there is no efficient and effective system to supervise or monitor the health care services and drugs prescribed by the providers at the time of prescription. This lack of integration causes many problems in the health system, for instance there is no adequate control over the health centers and patients regarding drugs they get which leads to a substantial waste of financial resources of the government and health insurance organizations and at the same time will increase the out-of-pocket expenditures of patients. The lack of controlling mechanisms creates a situation in which a part of providers and pharmacists prescribe extra drugs irrationally for the patients in order to gain more money.

In 2021, an online electronic system was introduced for prescribing and dispensing drugs and the physicians were obliged to use this new system for prescription. As many clinical rules have been embedded in the electronic system, most of common medication errors, irrational prescriptions and common contradictory medication prescription would be eliminated. This can lead to improving rational prescription by warning doctors not to prescribe some specific drugs for patients with specific conditions and warning physicians whenever a common wrong prescription or contradiction is happening. So besides rational drug prescription, electronic prescription system increases staff productivity and improves accuracy in providing medical services such as drug prescription by physicians, and saving financial resources. Another reform implemented by the IHIO in August 2019 was introduction a new online system for reviewing claims. This online intelligent system can also help health insurance organizations to move towards automatic implementation of rational prescriptions. For instance, this system warns and informs the health insurance experts when number of drugs prescribed for the patients violates the predetermined limits. This also informs physicians and nurses to be aware of rational prescriptions principles entered in the system. Similar systems are being establishing in other basic health insurance organizations.

The second group of stakeholders includes physicians serving within the government system as rural family physicians. Arguably, the rural family physicians prescribe drugs more rationally given that they receive a certain monthly salary from the system, their income does not depend on patients, and are now required not to prescribe more than a certain average of drugs in each prescription. It's worth mentioning that some experts believe that the restricted number of drugs that family physicians are allowed to prescribe for patients sometimes contradict with the rational prescription principles because seasonal illnesses, the rise of regional diseases, *etc.* do not seem to be reflected in FP' guideline. In fact, regional needs and diseases, as well as the patient's circumstances affect the items prescribed by the physician and no particular number or amount could be predetermined.

Recently the Office for Health Technology Assessment, Health Standards and Tariffs of MoHME in cooperation with specialized clinical groups has focused on developing clinical guidelines for medications, health services and diagnosis examinations which can lead to rational prescription and using health services. Guidelines recommend the most reliable clinical path for health provision but currently there are no reliable mechanisms to implement all guidelines which have been developed until now. It is health insurance experts who have financial incentives in some cases to use these guidelines not to reimburse drugs not prescribed according to the guidelines standards.

Incentive payment to physicians funded by the savings made via rational drug prescribing and taxing physicians based on their income can be efficient strategies for

rationalizing drug prescribing. In the end, laws are needed to render accountability and efficiency for relevant organizations concerning their particular commitments to actualize rational drug prescribing in addition to the necessity for a solid authority to devise and enforce macro policies. Successful implementation of mandatory policies can help reduce disadvantages and improve prevailing strengths.

The most convenient strategy to attain RDP is to implement a rural insurance program in the form of a family physician referral system. The approval of Article 91 in the Fourth Economic, Social, and Cultural Development Plan of the Islamic Republic of Iran is also an emphasis on the establishment of healthcare insurance with a focus on family physicians and the referral system. In the family physician program and referral system, the general practitioner and his or her team are fully responsible for the well-being of the individuals and families under their care and remain so for the follow-up of the patient's aftermath once the patient has been referred to the specialized levels. Accordingly, one of the most crucial duties of a family physician is to provide primary healthcare assistance and services, without which the application of the "family physician" term is inappropriate to imply a mere provision of medical services. Furthermore, all healthcare services included in the family physician program are actively provided to the population under care.

Another major strategy in attaining RDP is the use of media, including the Islamic Republic of Iran Broadcasting (IRIB) organizations. Media play an important role in promotion of RDP by broadcasting informative programs regarding the necessity of following rational prescription. IRIB media draws the attention of health policymakers and individuals within society towards the irrational drug prescribing issue and its consequences. Therefore, health policymakers must establish an close and strong relationship with the media and influence the content and form of the information conveyed via media outlets [21-23].

Conclusions

Conflict of interest in some influential organizations, including the Ministry of Health, Medical Council of the Islamic Republic of Iran, and the Social Security Organization, have caused these organizations not to exercise their potential authority and means to move towards RDP as efficiently as expected. The Ministry of Health is obliged to implement a strategic and comprehensive program for the RDP in the country and establish adequate collaboration and harmony with all health stakeholders through participation. Improving the state of drug prescribing in the country necessitates the implementation of multi-sectoral policies with the participation of all organizations and stakeholders involved in this regard. The effective response to this issue also demands the political commitment of policymakers, high-ranking officials and the healthcare system.

Ethical aspects

Ethical approval was obtained from the Kermanshah University of Medical Sciences (IR.IUMS.REC.1397.1060).

Acknowledgments

This study was supported by Kermanshah University of Medical Sciences.

The researchers would like to thank the Clinical Research Development Unit of the Educational Treatment Center of Imam Reza (PBUH). We are also thankful to those who participated in our study and agreed to put their precious time to interview and enrich our data by their valuable statements.

Conflict of interest statement

The authors declare no conflicts of interest.

Authors' contributions

FM, HS, and FS participate in conception or design of the work. FM collected the data. FM, MB, AS, ME, SE, MS, RH, MB, MM participated in data analysis and interpretation, drafting the article. FM, MB, ME, and RH contributed in critical revision of the article. All named authors approved the final approval of the version to be submitted.

Consent for publication

Not applicable.

Availability of data and materials

All transcriptions and data generated during the current study are in Persian and not publicly available as it is not allowed by the Ethics Committee, but would be available from the corresponding author on reasonable request.

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Received on July 18, 2023. Accepted on July 27, 2023.

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How to cite this article: Moradi F, Bazyar M, Soroush A, Seyedin H, Soleymani F, Etemadi M, Ezadi S, Salimi M, Behzadifar M, Martini M, Hussain R. Understanding conflicts of interest in rational drug prescription in a developing country: A stakeholder analysis, healthcare guidelines and ethical public health issues. *J Prev Med Hyg* 2023;64:E358-E366. <https://doi.org/10.15167/2421-4248/jpmh2023.64.3.3036>

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History of primary health care in Iran

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Keywords

Primary health care • Iran • History of Public health • Health policy • Equitable health

Summary

Background. *The history of the primary healthcare system in Iran portrays a journey of strategic development and implementation that has resulted in significant advancements in healthcare access and overall population well-being. Starting in the early 1980s, Iran embarked on a comprehensive approach to health care delivery prioritizing universal access, equity, and community participation.*

Introduction. *The foundation of this system was established during the Alma-Ata Conference in 1978, which placed a strong emphasis on the role of primary health care in attaining health for all.*

Iran's unwavering commitment to this approach led to the creation of an extensive network of rural and urban health centers designed to offer essential health services and preventive care to all citizens.

Discussion. *Over the years, the expansion of Iran's primary healthcare system has yielded noteworthy accomplishments. Maternal and child mortality rates have seen substantial declines, attributed to improved access to maternal care and immunization services. The effectiveness of the system in reaching diverse populations has been enhanced through community*

engagement and the integration of traditional medicine. Furthermore, Iran's focus on health education and disease prevention has resulted in heightened public awareness and the adoption of healthier lifestyles. Despite these achievements, challenges continue to persist. Disparities in the quality and accessibility of services between urban and rural areas remain a concern. Moreover, the ongoing necessity for infrastructure development, training of the health workforce, and efficient resource allocation underscore the continuous efforts required to strengthen the primary healthcare system.

Conclusions. *The history of Iran's primary health care system is marked by progress and achievements, underscored by an unwavering commitment to providing comprehensive, community-based care. Iran's journey serves as an exemplary model, highlighting the positive impact of prioritizing primary health care in achieving better health outcomes for its population. As Iran continues to evolve its health system, addressing challenges and building upon successes, the history of its primary health care system serves as a valuable lesson in the pursuit of accessible and equitable health care for all.*

Introduction

Primary Health Care (PHC) is a fundamental component of healthcare systems, characterized by its universal accessibility, community-based nature, comprehensiveness, and provision at the initial level of the healthcare system [1]. It is widely acknowledged as the bedrock of a well-functioning healthcare system, aiming to address the health requirements of both individuals and communities across their lifespan [2]. PHC takes a holistic approach to health and well-being, extending beyond medical care to encompass the social, economic, and environmental determinants of health [3].

Primary Health Care possesses several key characteristics

1. **Accessibility:** PHC aims to ensure unfettered access for all individuals, regardless of their social or

economic standing. This objective is accomplished through community-based services and strategically positioned health centers, facilitating convenient proximity to the population [4].

2. **Comprehensiveness:** The range of healthcare needs is comprehensively covered by PHC services, encompassing preventive, promotive, curative, and rehabilitative elements. This comprehensive framework enables individuals to sustain good health and curtail the onset of diseases effectively [5].

3. **Coordination:** PHC emphasizes effective coordination and integration of various healthcare services, including medical, dental, mental health, and preventive care. This coordinated approach ensures a well-rounded provision of care that addresses every facet of an individual's health [6].

4. **Community Involvement:** PHC fosters active participation from the community in the planning, execution, and evaluation of healthcare services. This collaborative engagement allows for the

customization of services following the specific needs and cultural contexts of the population [7].

5. *Health Promotion and Disease Prevention:* PHC places significant emphasis on educating individuals and communities regarding healthy lifestyles and disease prevention. This proactive approach reduces the burden of illness and diminishes the necessity for complex and expensive treatments [8].
6. *Early Detection and Management:* PHC focuses on early detection and management of health issues. By addressing health problems in their early stages, PHC can often prevent the progression of diseases and complications [9].

Importance of PHC

1. *Universal Access:* PHC ensures the availability and accessibility of basic health services to all individuals, irrespective of their socioeconomic background. This is paramount in achieving health equity and reducing health disparities [10].
2. *Cost-Effectiveness:* By emphasizing prevention and early intervention, PHC can minimize the need for expensive medical interventions and hospitalizations. This generates cost savings for individuals, communities, and the healthcare system as a whole [11].
3. *Population Health Improvement:* The focus of PHC on health promotion and disease prevention contributes to the enhancement of overall population health. Healthy individuals are more productive and can make positive contributions to society [12].
4. *Reduced Health Inequalities:* PHC addresses the social determinants of health, thereby helping to bridge health outcome disparities between different population groups [13].
5. *Stronger Health Systems:* A robust PHC system forms the foundation of a well-functioning healthcare system. It establishes a referral pathway for specialized care when necessary and prevents the overwhelming of hospitals and specialized clinics [14].
6. *Emergency Preparedness:* Effective PHC systems can respond more efficiently to public health emergencies and disease outbreaks by promptly identifying and managing cases at the community level [15].

PHC is a fundamental approach to healthcare delivery that promotes health, prevents diseases, and provides essential services to communities. It plays a critical role in ensuring equitable access to healthcare, improving population health, and building resilient health systems [15].

The Alma-Ata Conference, also known as the International Conference on PHC, was a historic event held in Alma-Ata (now Almaty), Kazakhstan, in September 1978 [3]. The conference brought together representatives from various countries, international organizations, and health experts to discuss and endorse a groundbreaking approach to health care known as PHC [5]. The Alma-Ata Conference

marked a significant turning point in global health policy by emphasizing the importance of PHC as a fundamental strategy for achieving health for all [15]. The conference's declaration and strategy laid out a comprehensive and holistic approach to health care that went beyond the traditional medical model and focused on addressing the underlying social, economic, and environmental determinants of health [6].

Key Principles and objectives of the Alma-Ata Conference

1. *Equity and Social Justice:* The conference underscored the imperative of providing fundamental healthcare services to all individuals, regardless of their socioeconomic status. This approach aimed to mitigate health inequalities and disparities among various population groups [8].
2. *Comprehensive Care:* The PHC approach emphasizes the significance of delivering a broad spectrum of health services, encompassing preventive, promotive, curative, and rehabilitative care. It aimed to address the majority of health needs within a community [10].
3. *Community Participation:* The Alma-Ata Declaration acknowledged the significance of engaging communities in the planning, implementation, and evaluation of healthcare services. This community involvement ensured that health services were culturally sensitive and customized to local needs [9].
4. *Intersectoral Cooperation:* PHC stressed the importance of collaboration among diverse sectors, such as health, education, agriculture, and social welfare, to tackle the broader determinants of health and foster overall well-being [1].
5. *Health Promotion and Disease Prevention:* The conference underscored the importance of health promotion and disease prevention as integral components of PHC. This entailed educating individuals and communities about healthy behaviors and lifestyles [16].
6. *Access to Essential Medicines:* The Alma-Ata Declaration emphasized the vital role of ensuring access to essential medicines as a cornerstone of primary healthcare services [12].

The Alma-Ata Declaration culminated in the adoption of the "Health for All" goal, which sought to enable every individual to lead a socially and economically productive life by attaining a certain level of health [12]. The declaration called upon governments and international organizations to prioritize the establishment and development of PHC systems as a means to achieve this objective. While the Alma-Ata Conference and the PHC approach received widespread support and recognition, implementing PHC proved to be challenging in many contexts due to various barriers, including limited resources, political obstacles, and competing health priorities [2]. However, the principles laid out in the Alma-Ata Declaration continue to influence global health policies and strategies,

emphasizing the importance of a comprehensive, community-based, and equitable approach to health care delivery [12].

Health system in Iran

The health system in Iran is characterized by a combination of public and private sectors, aiming to provide universal access to healthcare services for its population. The Iranian healthcare system comprises public and private healthcare providers, with the public sector being predominant [16]. This sector includes government-funded hospitals, clinics, and health centers. Although the private sector also contributes to healthcare provision, the majority of the population relies on the public sector for their healthcare needs. Iran places significant emphasis on primary healthcare, considering it a fundamental building block of its healthcare system. To cover a large portion of the population, Iran operates a national health insurance system called the Islamic Republic of Iran Health Insurance Organization. This system provides coverage for various health services, such as hospitalization, outpatient care, and prescription medications. The country has made considerable investments in developing a robust healthcare infrastructure, which includes hospitals, clinics, and medical facilities. This infrastructure is intended to facilitate the delivery of healthcare services across the country [17].

Medical education and training in Iran are well-established, with several reputable medical universities and institutions that educate medical professionals, including doctors, nurses, and allied health workers. In addition to conventional medicine, Iran has a rich history of traditional and complementary medicine [18].

Traditional Persian medicine continues to be practiced and integrated into the overall healthcare system. Iran also has a domestic pharmaceutical industry that produces a diverse range of medications. The government has taken steps to encourage domestic pharmaceutical production and reduce dependency on imported drugs. Like many countries, Iran faces various health challenges, including non-communicable diseases, infectious diseases, and disparities in access to health care services, particularly in rural and underserved areas [19].

PHC in Iran and its evolution over the years

In the years following World War II, mobile teams were established in Iran to combat diseases such as malaria, tuberculosis, and leprosy. These teams primarily consisted of individuals with 6 to 12 years of formal education, who had completed specialized courses. Over time, these individuals were also trained in diagnostic and vaccination practices.

In 1049, the “Tarbit Behdar” project was initiated in Mashhad, to supply manpower to rural areas. After

completing a four-year program that encompassed theoretical, practical, and internship training, these individuals would serve in villages and departmental centers.

However, in the 1960s, the *Tarbiat Behdar schools* ceased their operations, and graduates gradually enrolled in Parashki colleges. Following completion of their rural service, these graduates pursued a minimum of three years of additional training to become doctors.

Since 1964, the health law has been implemented in Iran. According to this law, medical school graduates, graduates of related fields, and a select number of high school graduates who are surplus to the requirements of the army, are mandated to serve in the Ministry of Health. Under the supervision of physicians, diploma graduates are deployed in rural areas to provide medical treatment and ensure public health. Despite the positive impact of these health workers, challenges have arisen due to their unfamiliarity with village culture, incomplete deployment, and inconsistent workforce size. Consequently, the full potential of these health workers has not been fully realized.

In 1972, a research project was implemented in cooperation with the World Health Organization (WHO), the Faculty of Health at the University of Tehran, in West Azarbaijan province, Iran. The project aimed to develop medical and health services by establishing a system for providing services and utilizing non-physician personnel in peripheral units. Concurrently, other similar projects were carried out in different regions of the country. For instance, the village welfare education project at Shiraz University was implemented in Fars Kovar, along with projects by the Social Services Organization in Fars and Tehran, and in Al Shatar, Lorestan.

By 1980, the health and treatment indicators were discouraging. The infant mortality rate stood at 104 per thousand live births, life expectancy was 57 years, and access to clean water and sufficient caloric intake were significantly lower compared to many other countries. However, in the aftermath of the Islamic revolution, the government formulated fundamental policies for health, treatment, and medical education programs. The formation of the first parliamentary government in the middle of 1980 led to the establishment of the Program and Organization Review Council in 1981.

This council, which consisted of several specialized committees, presented its initial report on policies and priorities to the Council of Deputy Ministers in 1982. Despite the imposed war between Iraq and Iran, and despite the heavy bombings of cities, all the necessary rules and relationships required for organizing the components of the network system were explained in detail during the Council of Deputy Ministers meeting. The information was compiled into a book titled “Attitude towards Health, Treatment, and the Training of Medical Manpower” by two diligent experts from the Ministry. This book later became the basis for compiling plans for the expansion of healthcare networks in the country. In this book, the selection of the city as an administrative-geographical scale for the expansion

of healthcare networks was emphasized, and with the efforts of these two experts and with the help of the patient and hardworking employees of the provinces, expansion plans were prepared for each city of the country until 1984.

In March 1984, the Islamic Council granted the Ministry of Health a credit equal to 2,500,000,000 Rials to set up a health and treatment network in one city of each province. In order to spend this credit and actually expand the health and treatment networks, the Ministry of Health, Treatment and Medical Education established a unit called the Headquarters for the Development of the Health-Treatment Networks of the country, which continues to operate after many years.

Principles and criteria in the expansion of healthcare networks in Iran

The expansion of the network system in healthcare is guided by several general principles and rules, which are outlined below:

1. *Geographical Access:* The aim of ensuring geographical access is to provide all members of society with convenient access to the nearest healthcare unit, regardless of their location. The objective is to limit the maximum distance individuals need to travel to reach a healthcare facility to a one-hour walk. Moreover, healthcare units should be strategically positioned to align with natural patterns of population movement.
2. *Cultural Access:* The expansion of healthcare networks should strive to promote inclusivity and minimize ethnic, cultural, and religious conflicts. The objective is to ensure that all designated populations can avail themselves of the services offered by healthcare units in a harmonious manner.
3. *Proportional Resource Allocation:* Maintaining a balance between the volume of healthcare services and the availability of trained manpower is crucial. This is important to prevent healthcare providers from being overwhelmed by client demand, while also ensuring that clients do not experience long wait times. Striking an appropriate balance will contribute to controlling service costs as well as preventing service provider unemployment.
4. *Affordable Service Costs:* The cost of healthcare services should be designed in a manner that is affordable for individuals, families, and society as a whole. Encouraging people's active participation, promoting the shared utilization of resources, and harnessing the expertise of multi-professional teams are effective strategies to reduce costs.
5. *Service Leveling:* Service leveling refers to the provision of healthcare services in a connected and streamlined manner. This approach significantly reduces the cost of service provision. For instance, in a manufacturing analogy, producing an intricate computer device does not necessarily require thousands of highly skilled engineers. Instead,

the process can be simplified and broken down into manageable steps, allowing individuals with appropriate training at each stage to contribute their services efficiently and in a shorter time frame. What is certain is that the design of the service process is the responsibility of the highest specialized ranks. In this way, the heavy costs of education can be reduced. Currently, in the network system, a part of medical science is leveled; the required force is used at each level.

On the other hand, when one of the referrals from the environmental units requires more specialized services, the environmental unit can direct the individual to higher levels of care. For instance, in the fight against malaria, responsibilities at the first level include blood slide preparation, spraying, larvicide application, health education, and patient follow-up. The second level is responsible for slide testing, diagnosis, and treatment initiation, while the third level focuses on epidemiological investigations and environmental improvement.

Currently, in the PHC network system, health centers serve as the first level of service provision in both rural and urban areas, with medical centers occasionally available in cities. It is essential that every population falls within the ambit of the first level, which caters to a specific population. Urban and rural health centers constitute the second level of service provision, while hospitals and specialized polyclinics make up the third level. Some consider academic hospitals offering super-specialized services to be the fourth level.

The delivery of services occurs through a referral system. As highlighted in the section on service provision levels, if the first level encounters cases that require specialized services beyond its capabilities, the unit will refer the client to the second level.

If necessary, the second level will then refer the patient to the third or fourth level for specialized and super-specialized services. This chain of service delivery, starting from the first level and moving to higher levels, is known as the referral system.

Health House

The Health House is a unit primarily located in a village, often covering several other villages known as *Qamar* villages. Each health center typically serves an average population of 1500 individuals. The health center staff is composed of male and female nurses who play a significant role in ensuring optimal coverage. Key factors for achieving this include the native background of health workers, their constant communication with the community, accurate health information recording, and continuous monitoring of health center activities.

The primary objective of the health center is to provide essential healthcare services to the covered population. The center is responsible for a range of crucial tasks, including:

1. conducting an annual census of the population within their coverage area;
2. educating the population and encouraging their active participation in various aspects of healthcare.
- C. Providing family health services, such as:
 - *care during pregnancy, childbirth, and breastfeeding;*
 - *care for children under five years old;*
 - *provision of healthcare for school students;*
 - *offering services related to family planning;*
 - *administering vaccinations;*
 - *conducting home visits to follow up on cases of abandonment or delayed referral.*

In addition, the health center performs services related to disease control, which include:

1. diagnosis of diseases, implementation of prevention standards, and monitoring the treatment of affected cases, such as tuberculosis, leprosy, malaria, among others;
2. preparation of blood slides from patients suspected of having malaria, monitoring larvicide spraying, and improving the environment to combat disease;
3. provision of first aid and symptomatic treatment, particularly for specific illnesses like acute respiratory infections and diarrheal diseases.

Furthermore, the health center engages in environmental health activities, such as:

- visiting the places of preparation, distribution, storage and sale of food and consumables;
- school environment health;
- hygiene of the workshop environment;
- suggesting basic improvements to the environment;
- attention to the collection of solid waste materials and sanitary disposal of waste;
- chlorination of drinking water;
- participation in the implementation of improvement projects and their maintenance.

In Iran's service delivery system, the health house serves as an environmental unit managed by community health workers known as health workers. To ensure cultural adherence and efficient service provision, each health house is staffed with both a female nurse and a male nurse. The female nurse primarily oversees internal health house operations, such as client reception, care for covered individuals, vaccination procedures, maintaining vaccination records, providing primary treatment, and administering medication. On the other hand, the male nurse assumes responsibility for tasks outside the health house, including patient follow-up for infectious diseases, diagnosis, environmental health monitoring, and vaccination efforts.

However, it should be noted that this division of responsibilities does not restrict female health workers from considering home visits as part of their core duties, nor does it prevent male health workers from accepting and caring for clients within the health house. Ideally, health workers should be chosen from the same rural area where the health house is located. In cases where this is not possible, individuals from neighboring areas should be considered.

Rural health center

The rural health center is a village-based unit that encompasses one health center located within the same village, as well as multiple health centers from neighboring villages. Within the rural health center, a team composed of doctors, associates, and technicians specializing in family health, disease control, environmental health, oral and dental health, and laboratory work collaboratively. This team, led by a doctor, also includes paramedics and administrative staff.

The primary responsibility of the rural health center is to provide support to health houses, monitor their operations, accept referrals, and establish effective communication with higher-level medical facilities. In addition to their core functions, rural centers are also expected to perform the following tasks:

- A. *treating outpatients and individuals referred by health centers;*
- B. *determining treatment plans for infected cases and providing guidelines for follow-up care in health centers;*
- C. *monitoring the activities of health centers in the areas of family health, disease prevention, and environmental health;*
- D. *offering services related to oral and dental health, blood pressure, and diabetes management in selected health centers;*
- E. *undertaking basic environmental improvements and conducting water sampling;*
- F. *participating in the implementation and supervision of health projects;*
- G. *assisting health centers with the procurement of materials, tools, and medications.*

Urban health center

The Urban Health Center is a facility located in urban areas, serving an average population of approximately 12,000 individuals. In comparison to rural health centers, urban centers often include additional staff members, such as assistants or radiography technicians. The primary objective of the urban health center is to provide essential healthcare services to the covered population and, when necessary, facilitate patient referrals to hospitals. The center's responsibilities encompass a wide range of duties, including:

- a) *Outpatient care:* This involves diagnosing illnesses, identifying cases requiring specialized attention or care, and offering health education to patients.
- b) *Oral hygiene and dental services.*
- c) *Family health:* This entails education on health-related matters, such as pre-marriage care, antenatal and postnatal care, breastfeeding guidance, children's spacing, performing pap smears, and, if necessary, intrauterine device (IUD) placement. The center also takes care of children under the age of five, provides student support, offers specialized care for vulnerable groups like children and mothers, administers vaccinations,

conducts home visits to address cases of abandonment or delayed referrals, and provides therapeutic aids.

d) *Disease prevention*: The center actively promotes health education and implements programs to combat diseases outlined in the national plan. Close monitoring of patients with conditions that require continuous visits and treatment control, such as malaria [20], tuberculosis, and leprosy, is a crucial task [20-23]. Additionally, the center ensures the enforcement of preventive measures concerning environmental cleanliness and the individuals surrounding those affected by infectious diseases. The well-being of students is also an area of focus.

e) *Environmental health, food hygiene, and sanitation*: Through health education initiatives, the center conducts inspections of public spaces, as well as the preparation, distribution, storage, and sale locations of food and consumables. Regular food and water sampling is carried out to ensure safety standards are met.

The center also monitors the cleanliness of school environments, evaluates the sanitation practices of workshops and factories, measures hazardous factors in work environments, assesses occupational safety factors, paying attention to the sanitary disposal of waste, performing medical diagnostic tests, cooperation in the field of medical manpower training, collecting, sorting, and classifying preliminary investigations and maintaining information and statistics, and preparing reports.

Currently, Iran boasts an extensive network of over 24,000 healthcare facilities, encompassing houses health, urban, and rural health centers. The health system structure in Iran is illustrated in Figure 1 [24].

Iran's PHC network has made significant strides in healthcare delivery. Firstly, it has vastly improved

access to essential health services, particularly in remote and underserved regions, leading to better healthcare equity [25]. Secondly, the PHC network has contributed to a substantial reduction in communicable diseases through widespread vaccination and disease prevention programs. Additionally, it has played a pivotal role in promoting community engagement and health education, fostering a culture of preventive healthcare. Lastly, the network's emphasis on early detection and treatment has positively impacted health outcomes and life expectancy across the nation. Overall, Iran's PHC network stands as a model for effective healthcare system development [26].

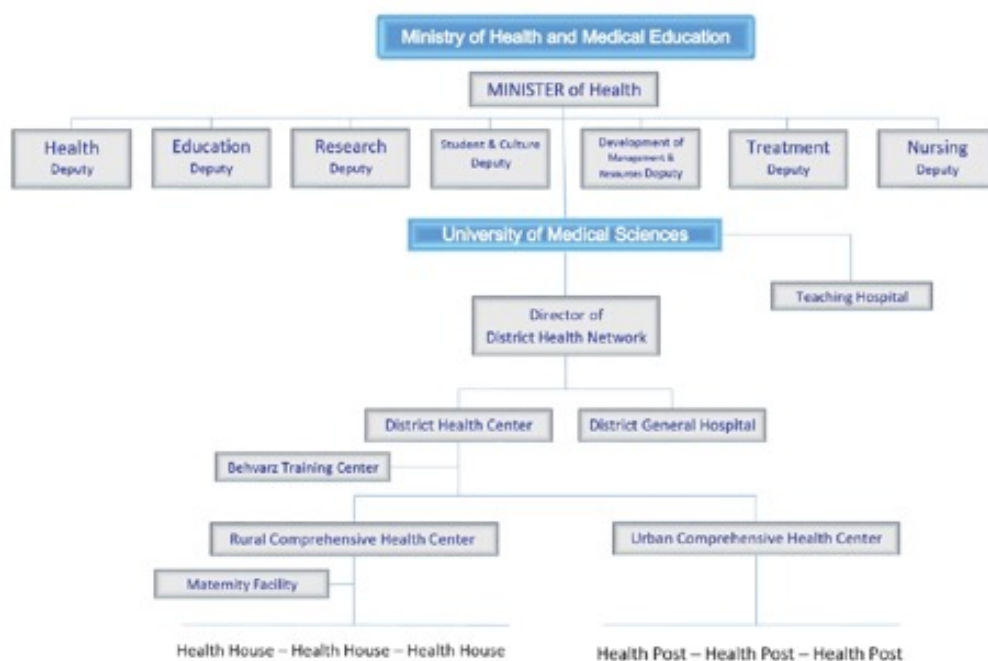
Conclusions

Iran has made remarkable advancements in the development of its PHC system. By establishing an extensive network of healthcare facilities in both rural and urban areas, the country has successfully enhanced the availability of crucial healthcare services for its citizens.

This expansion has led to improved coverage of preventive care, health education, and fundamental medical treatments. Noteworthy achievements include a decrease in maternal and child mortality rates, increased vaccination rates, and more effective disease prevention initiatives.

The involvement of the community and the integration of traditional medicine have played crucial roles in the success of this expansion. Nevertheless, certain challenges such as disparities in service quality and

Fig. 1. Health system structure in Iran.



access between urban and rural regions still persist, demanding continuous efforts to ensure equitable and comprehensive healthcare delivery.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

Informed consent statement

Not applicable.

Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

AR and MB designed the study; MB and MM conceived the study; AR, BDT and MB drafted the manuscript; AR, BDT, MM, MB critically revised the manuscript. AR, SJE, MM performed a search of the literature; furthermore: BDT, SJE: methodology; BDT and SJE: validation and data curation; AR, BDT and SJE: formal analysis; MM and MB final editing. All authors critically revised the manuscript. All authors have read and approved the latest version of the paper for publication.

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Received on September 6, 2023. Accepted on September 18, 2023.

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How to cite this article: Aboutorabi A, Darvishi Teli B, Rezapour A, Ehsanzadeh Sj, Martini M, Behzadifar M. History of primary health care in Iran. *J Prev Med Hyg* 2023;64:E367-E374. <https://doi.org/10.15167/2421-4248/jpmh2023.64.3.3081>

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ERRATA CORRIGE

Journal of Preventive Medicine and Hygiene 2023;64:E178-E187. <https://doi.org/10.15167/2421-4248/jpmh2023.64.2.2902>

Errata, p. E178

Use of medicines to alleviate negative emotional states among adolescents attending Special Education Centres

Corrige

Use of medicines to alleviate negative emotional states among adolescents attending Special Education Centers in one line

Errata, p. E180

Other psychosocial variables

- Impulsivity vs self-control: an abbreviated version of the Barratt Impulsivity Scale (BIS-11), consisting of 7 statements related to diligence in task planning, ability to concentrate and deliberate, inconsiderate behaviour and difficulty in concentrating, with responses ranging from “1” = “never or rarely” to “4” = “almost always or always.” [28, 29]. The internal consistency of this scale was acceptable (Cronbach’s $\alpha = 0.70$).

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Errata, p. E180

Sociodemographic factors in the regression model were coded as follows:

- gender (1 = girls, 2 = boys);
- type of centre (1 = YSC, 2 = YCC);
- family composition (1 = both parent family, 2 = single parent family).

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Therefore, it became interesting to see how the prevalence of medicine use among adolescents in SEC differs from the prevalence among of adolescents from “regular” schools.

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Errata, p. E180

Data on the families of students from “regular” schools, on the other hand, indicate that the majority of these adolescents (approximately 77%), live with both parents [37].

Corrige

Data on the families of students from “mainstream” schools, on the other hand, indicate that the majority of these adolescents (approximately 77%), live with both parents [37].

Errata, p. E182

Fig. 1. Summary of the medicine use prevalence among SEC students (younger group 12-15-year olds) and among the 2016 Mokotów Study respondents (medicine use at least 1-2 times in the last 30 days, in percents).

Corrige

Fig. 1. Summary of the medicine use prevalence among SEC students, younger group 12-15-year olds (results on the left) and among the 2016 Mokotów study respondents (results on the right). Medicine use at least 1-2 times in the last 30 days.

Errata, p. E184

The questionnaire completed by study participants included a question on the narcotics use, among which “psychotropic, sedative, tranquilizers and sleep-inducing medicines” were listed in addition to substances like cannabis, NPS and amphetamines.

Corrige

The questionnaire completed by study participants included a question on the illegal drug use, among which “psychotropic, sedative, tranquilizers and sleep-inducing medicines” were listed in addition to substances like cannabis, NPS and amphetamines.

Errata, p. E184

The question on narcotic substances refers to the last year, while the questions on medicine use refers to the last month.

Corrige

The question on illegal drugs refers to the last year, while the questions on medicine use refers to the last month.

Errata, p. E187

How to cite this article: Pisarska A, Ostaszewski K. Use of medicines to alleviate negative emotional states among adolescents attending Special Education Centres. *J Prev Med Hyg* 2023;64:E178-E376. <https://doi.org/10.15167/2421-4248/jpmh2023.64.2.2902>

Corrige

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