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Telemedicine for Outpatients: A Case Study of the First Experience with Diabetic Patients in the Local Health Authority of Modena

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Keywords: Telemedicine; tele-visit; outpatient; ambulatory care; diabetes mellitus
Parole chiave: Telemedicina; televisita; specialistica ambulatoriale; diabete mellito

Abstract

Background. *During the COVID-19 pandemic, telemedicine had the opportunity to demonstrate its potential. In Italy, after an initial period of mistrust, it became clear that remote medicine can provide significant benefits for both healthcare professionals and patients. In the Local Health Unit of Modena (Emilia Romagna region, Northern Italy), great importance was placed on developing, promoting, and managing all telemedicine activities. In particular, it was decided to prioritize the activation of tele-visit services in accordance with the guidelines of the Emilia-Romagna region.*

Study Design. *This case study aims to illustrate the activities planned and developed at the Local Health Authority of Modena for the implementation of the first service of this kind, the tele-visit service for outpatients suffering from type 1 diabetes mellitus, and to analyze data from the first 12 months of activity (from May 2023 to April 2024) to share reflections on the strengths and critical points encountered.*

Method. *For the activation of tele-visits at the Local Health Authority of Modena, a dedicated working group was established with the mandate to manage all clinical, organizational, and IT aspects. Before starting the service, various preliminary activities were carried out, including selecting the clinical specialty to be activated, defining patient inclusion criteria, implementing IT systems, assessing clinical risks, preparing and distributing information materials, training healthcare personnel, and planning outpatient activities.*

Results. *During the first year of experimental activation of the service (May 2023–April 2024), a total of 72 patients were enrolled in the project, with 103 tele-visits provided. The patients were predominantly women (67%), and the most represented age groups were 30–39 (26%) and 40–49 (21%). Half of the specialists in the Diabetology Service (9/19) participated in the initiative by providing tele-visits, most of whom were young and all of whom were women. The main issues identified through regularly scheduled meetings with professionals, to which the working group is seeking the most appropriate solutions, include poor adherence by many patients who still have doubts about this modality, the habit of many patients rescheduling appointments multiple times, a habit not diminished by this visit method, the non-uniform adherence of professionals, and uneven territorial diffusion of the service. Lastly, professionals reported various IT difficulties. Although the number of tele-visits was not high, the initiative has sparked*

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the interest of several specialists, some of whom have already proposed activating other telemedicine services, with some even suggesting innovative new projects. The next steps will involve extending diabetes monitoring to pregnant women with gestational diabetes and developing tele-visit services for endocrinology, neurology, hematology, and gastroenterology.

Conclusions. *Implementing a tele-visit service in a Local Health Unit is a complex process. A thorough evaluation of the issues that emerged during the development phases and the initial delivery period can help us to act proactively to prevent the failure of future projects. Our evaluations suggest a need to act on two fronts: on one hand, we must organize further activities to promote telemedicine to both patients and healthcare providers, while on the other hand, we must work to resolve IT issues.*

Background

The World Health Organization defines telemedicine as "the delivery of health-care services where distance is a critical factor, by all healthcare professionals using information and communication technologies for the exchange of valid information for diagnosis, treatment, and prevention of disease and injuries, all in the interests of advancing the health of individuals and their communities" (1).

Digital medicine is used worldwide for multiple purposes. For example, there are projects aimed at patients with diabetes (2-4), cardiac pathologies (5,6), oncology patients (7,8), and patients with chronic (9-11) or multiple pathologies (12,13). Various initiatives are also dedicated to health promotion (14-16), the prevention of oncological diseases (17,18), and even caregiver support (19,20).

In Italy, telemedicine has been discussed for over a decade, as the first national guidelines were published in 2012 (21) and several experimental projects began across the country (22). However, most of these activities did not transition into routine practice.

During the COVID-19 pandemic, Italian healthcare professionals' attitudes towards telemedicine changed: after an initial period of confusion, necessity led them to set aside doubts and leverage the potential offered by remote services (23-25).

This shift towards telemedicine was reinforced in 2020 with the publication of Italian guidelines for the provision of telemedicine services (26). This document outlines the characteristics, reporting methods, and pricing of services that can be provided via telemedicine, ensuring uniformity in the initiatives developed across various Italian regions. As emphasized in the guidelines, telemedicine services must not be considered merely IT activities to be implemented on personal computers; these are healthcare services that must be integrated into the patient's care journey, aligned with their needs to ensure appropriateness, effectiveness, efficiency, and safety.

The National Recovery and Resilience Plan (PNRR) (27) represents a strategic blueprint to support the digitalization of healthcare systems. It aims to revitalize the national economy and strengthen public services in the aftermath of the COVID-19 pandemic. A significant focus of the PNRR is on transforming the Italian healthcare system, with telemedicine emerging as a cornerstone of this transformation. The PNRR highlights the necessity for a robust technological infrastructure and digital literacy. Investments have been made to improve broadband connectivity across the country, ensuring that telemedicine services are reliable and accessible, and to develop training programs for healthcare professionals and patients to maximize the benefits of telemedicine. Furthermore, the "Piattaforma Unica per la Telemedicina", a unified telemedicine platform initiative, has been established to consolidate and streamline telehealth services nationwide.

To develop, promote, and manage telemedicine activities, in early 2023, the Local Health Authority (LHA) of Modena (Emilia-Romagna region, Northern Italy) formalized a steering committee aimed at coordinating all organizational telemedicine projects, according to the guidelines of the Emilia-Romagna region (28). The committee decided to prioritize the activation of tele-visits dedicated to chronic patients who do not require physical examinations. The first service made available in the LHA was the tele-visit service for patients with type 1 diabetes mellitus. The steps taken to activate the service are described here, along with the ongoing evaluation results from the first year of the tele-visit service's implementation (May 2023 - April 2024).

Case Report

1. Setting

The Local Health Authority (LHA) of Modena covers the entire provincial territory of Modena (Emilia-Romagna region, Northern Italy), and is divided into seven health districts: Carpi, Castelfranco Emilia, Mirandola, Modena, Pavullo, Sassuolo, and Vignola (Figure 1). The physical configuration of the Modena provincial territory is characterized by a plain area in the north (48% of the overall territory), a hilly area (17%), and a mountainous southern part (35%) (29). With a population of 700,000, the province of Modena is the second largest province by population in the Emilia-Romagna region.

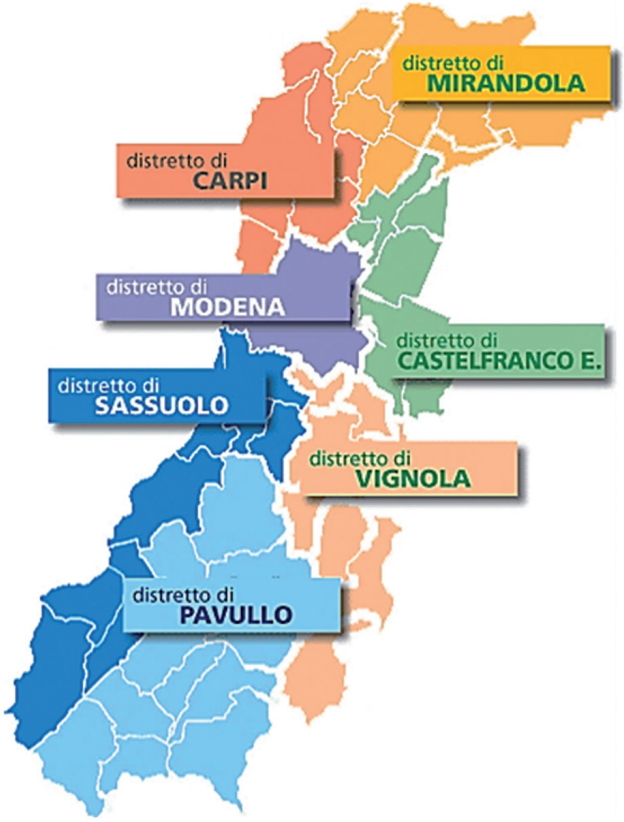

Figure 1 - Health districts of the Local Health Authority of Modena

2. Steering committee and the working group for tele-visits

In February 2023, a steering committee was formalized with the role of coordinating all telemedicine projects. The steering committee set priorities and organized specific working groups for each area of development (tele-visits, tele-consultation between professionals, and tele-monitoring of vital parameters). These working groups were given the authority to manage their activities independently and report their progress during general meetings, which were scheduled monthly.

The specific working group for tele-visits is composed of:

- Clinical specialists
- Outpatient Management Service
- Clinical Governance and Health Technology Assessment Service
- Risk Management Service
- Data Protection Officer (DPO)
- Communication Service
- Information & Communication Technology (ICT) Service
- Clinical Engineering Service.

This working group met at least monthly and was responsible for managing all clinical, organizational, and technical aspects related to the implementation of tele-visit services, in accordance with current regulations, the indications provided by the national guidelines of 2020 (26), and the deliberations of the Emilia-Romagna Region (30-32). Once all necessary activities were defined, a company procedure was written (Figure 2).

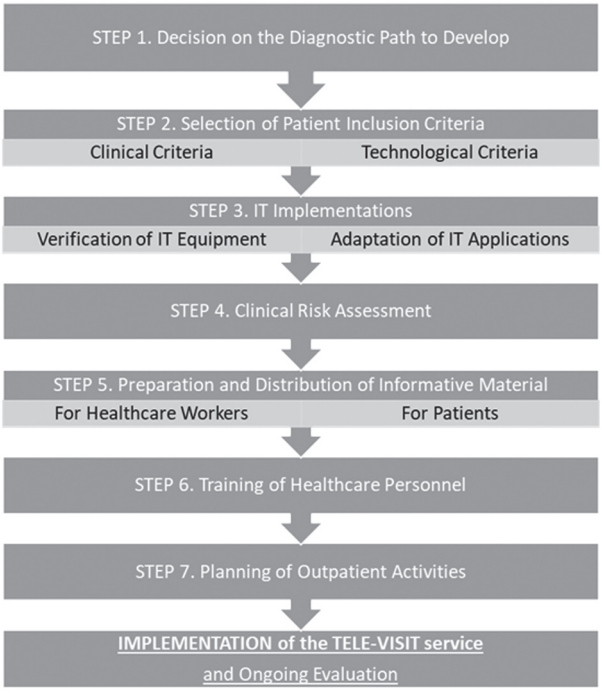

Figure 2 - Schematic flow of the activities for development of tele-visit services

3. Steps of the tele-visit service activation

Step 1. Decision on the diagnostic path to develop

It is estimated that 6% of the population of the province is affected by diabetes (approximately 44,000 patients, 56% male) with an estimated incidence of the disease equal to 3,500 new cases each year (33). The committee, therefore, decided to begin planning tele-visit activities with the Diabetology Service, this service is a single territorial service distributed across the province of Modena that manages adult patients with type 1 diabetes mellitus (juvenile diabetes) and type 2 diabetes mellitus (adult diabetes). The service consists of 9 clinics located in all 7 districts of the province, and the 19 specialists working within the service operate in multiple districts to ensure uniformity across the provincial territory.

In 2023, the Diabetology Service provided more than 26,000 visits, including over 7,000 first visits and almost 19,000 follow-ups.

In agreement with the working group, the diabetologists decided to begin with patients suffering from type 1 diabetes mellitus. This cohort consists primarily of younger individuals who are able to manage home therapy, generally do not require physical examinations, and are typically able to use digital devices.

Step 2. Selection of patient inclusion criteria

Patients eligible for this project had to have both clinical and technological requirements.

The diabetologists identified the following clinical criteria for patient selection:

- Patient with type 1 diabetes mellitus
- Patients already being followed by the professionals involved in the tele-visit services
- Clinical stability
- Good adherence to injection therapy.

The working group defined the technological criteria as follows:

- Availability of a device capable of connecting to the internet and with a webcam (computer or smartphone)
- Good IT skills, or having a caregiver who can assist
- An active email address
- A stable Internet connection
- An activated electronic health record (Fascicolo Sanitario Elettronico, FSE).

Step 3. It implementations

Both hardware and software availability had to be carefully assessed before starting the tele-visit service. An evaluation of the IT equipment in the medical offices was carried out, and some computers that lacked webcams were provided with them. Regarding software, while awaiting the implementation of the "Piattaforma Unica di Telemedicina," IT applications made available by the Emilia-Romagna region for healthcare units were used. In particular, the regional platform for tele-visits (C4C Meeting) was selected, as it provides a "virtual room" where the patient and specialist can conduct a video call and securely exchange data (34). Local applications were used for reporting the visit and consulting previous information, and they were updated by adding:

- The IT connection between the company applications and C4C Meeting;
- A specific field for the collection of informed consent for this remote modality;
- A tool to assist doctors in filling out the additional fields required in the tele-visit report. Indeed, Regional legislation requires that the medical report for tele-visits include additional information about the people present during the visit (relatives, caregivers, or healthcare workers) and the quality of the visit itself.

Step 4. Clinical risk assessment

Before starting the tele-visit service, a proactive clinical risk assessment was conducted to identify potential critical issues and possible areas of human error, and to provide timely remedies. The tool used for this analysis was the FMECA method (Failure Mode and Effect Criticality Analysis).

The most critical issues identified were:

- The incorrect identification of the patient and consequent reporting on the wrong patient. To address this problem, specialists received instructions to verify the patient's identity before starting the visit by asking for personal information (surname, first name, and date of birth).
- The failure to integrate data recorded by glucometers with the applications used by professionals. All patients with type 1 diabetes mellitus use glucometers capable of transmitting recorded data to the cloud. Unfortunately, diabetologists are unable to access this information directly. To correct this problem, a guide was created to instruct patients on how to make this information available to specialists. The guide must be emailed to patients before the tele-visit.

Following the FMECA results, other minor corrective actions were also implemented. Subsequently, as required by the FMECA, the risk

was reassessed to ensure that the corrective actions led to risk mitigation.

Step 5. Preparation and distribution of informative material

The working group focused on preparing informative materials for both operators and patients.

Two types of documents were designed for operators. The first set of documents provided general information on telemedicine and on tele-visits, while the second set included IT guides for use during tele-visits.

The material for patients was developed with health literacy principles in mind. In particular, the patient materials were reviewed jointly with a group of citizens.

The materials for patients were made available on an internet page (www.ausl.mo.it/televisita), and a printable version (in PDF format) was prepared and provided to professionals in case patients requested it. The informative materials for healthcare workers were made available on an intranet page, thus accessible only within the company network.

Step 6. Training of healthcare personnel

After completing all the preliminary activities, the committee proceeded with training doctors and nurses. Two online training events were organized (ECM accredited) to ensure the highest possible participation. During these meetings, information was provided on the entire process, including regulatory and IT issues.

Step 7. Planning of outpatient activities

The committee decided to involve all 19 professionals active in the provincial service on a voluntary basis, rather than starting with a "pilot district." The duration of the tele-visits was intended to be the same as that of in-person visits, approximately 30 minutes. Diabetologists chose not to allocate specific hours or days exclusively for the tele-visit service. Therefore, each diabetologist could independently schedule tele-visits according to their own and the patient's needs.

4. Implementation of the tele-visit service and on-going monitoring

Final verification tests were carried out in April 2023 and yielded positive results. Therefore, the diabetes tele-visit service of the Modena LHA officially began in May 2023.

Regular ongoing monitoring of tele-visit provision was conducted during the first year of the service to evaluate the numbers and characteristics of both patients and diabetologists involved in telemedicine visits, as well as to identify potential critical issues or strengths emerging during service provision.

From May 2023 to April 2024, a total of 72 patients were enrolled in the project (Table 1). The majority of patients were female (67%), with the most represented age groups being 30-39 years (26%) and 40-49 years (21%). Patients came from across the provincial territory, although districts located at the far ends of the province, such as Mirandola and Pavullo, were underrepresented. Seven patients residing outside the province were also included in the tele-visit service, as they were followed by professionals from the Carpi and Vignola districts.

Table 1 - Socio-demographic characteristics of patients adhering to the tele-vist sercive, Local health authority of Modena

	Total Sample (N=72)	**%**
Age		
Mean (SD)	48.2 (20.2)	
20-29	12	17%
30-39	19	26%
40-49	15	21%
50-59	5	7%
60-69	4	6%
70-79	9	13%
80-89	8	11%
Gender		
M	24	33%
F	48	67%
District of Residence		
Carpi	13	13%
Castelfranco Emilia	6	8%
Mirandola	-	0%
Modena	14	19%
Pavullo	2	3%
Sassuolo	14	19%
Vignola	16	22%
Outside the province	7	10%

A total of 103 tele-visits were provided. Most patients (55, or 76%) received only one tele-visit, 11 patients (15%) received two visits, and 6 patients (8%) received three or more tele-visits.

As shown in Figure 3, tele-visits were not carried out regularly and uniformly across all seven districts of the LHA. However, an overall increasing trend

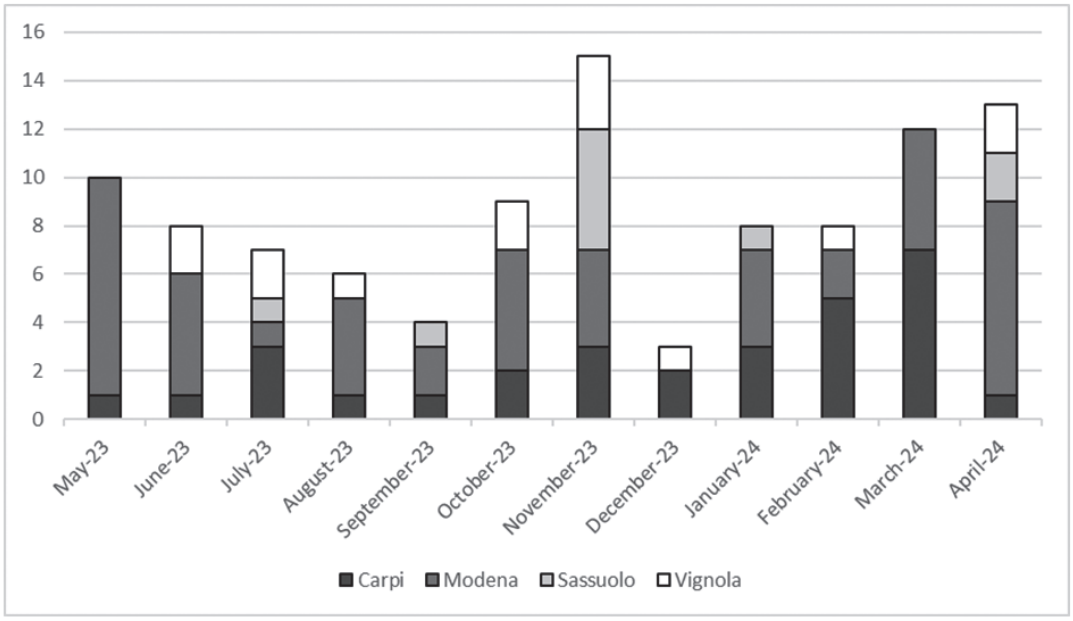

Figure 3 - Distribution of the tele-visits provided (total: N° 103 tele-visits)

can be observed, particularly after the summer, until December 2023, when the LHA experienced a cyber-attack that disrupted the use of all IT applications for several days in the health facilities throughout the province of Modena. Following this critical interruption, the tele-visit trend restarts to increase, reaching in April 2024 a number similar to the highest number recoded in November 2023.

Among the 19 specialists (2 men and 17 women) in the Diabetology Service, half of them provided telemedicine services. The active specialists, all female, tended to be younger (40-49 years) than their non-adhering colleagues.

Even after the service began, the working group for tele-visits remained available to support the specialists' activities. Additionally, official meetings were scheduled every two months to assess the progress of the service and address any critical issues.

Actions implemented to mitigate the critical issues identified during the FMECA analysis proved effective, as no errors in patient identification or failures in integrating glucometer data were reported. However, the scheduled meetings were crucial in identifying other potentially critical issues that might have otherwise remained unnoticed. For instance, diabetologists reported that many patients were hesitant about this modality, preferring in-person visits. Additionally, it was found that many patients habitually rescheduled their appointments multiple times, with no improvement observed using the tele-visit service. Finally, professionals noted that using different IT applications was troublesome from an IT perspective.

Discussion

The analysis of the process of developing the first tele-visit service at the LHA of Modena, along with the evaluation of the initial monitoring data on the volume and main characteristics of the activities provided, can be very useful for planning and developing additional telemedicine services within this or similar Local Health Authorities. Several potentially critical issues emerged during both the planning and implementation phases of the service. However, various solutions were identified and implemented to improve the service.

1. Working group planning activities

Before starting a new tele-visit service, clinical, organizational, IT, and regulatory assessments and evaluations need to be carefully conducted to identify potential system critical issues and possible areas of human error, and to provide timely and proactive remedies. Thorough and accurate planning and development are crucial to setting up an effective

and efficient service, as integrating telemedicine into healthcare activities requires the collaboration of multiple professional skills.

Furthermore, to reduce potential critical issues when implementing a telemedicine service in an LHA for the first time, it is important to carefully choose the type of service and the patient group to start with. At the LHA of Modena, we chose to begin with the Diabetology Service because it covers the entire provincial area and manages clinically stable patients over a long period. Additionally, this service uses more IT applications than other disciplines, which helps reduce problems in IT implementation.

The definition of the clinical inclusion criteria was also straightforward, as professionals are familiar with their patients and found it easy to identify the group that would benefit most from tele-visits.

The activity that most engaged the working group was the clinical risk assessment. Several close meetings were necessary to draft the specific FMECA for tele-visits in diabetology. Once the specific document was prepared, a "standard FMECA" was developed, which will be used for implementing tele-visits in other disciplines.

Finally, according to our experience, external communication needs to be addressed with particular attention. It is important to promote the service from the start and provide enrolled patients with all necessary information. Therefore, the working group made both printable material and a dedicated website page available. However, after several months of experience, the group decided to review the information material, reducing the content of printed materials and increasing the information available on the website. On the other hand, as patients and/or caregivers are familiar with using technology, printed materials are likely to be superfluous.

2. Patients features

As expected, most patients adhering to the tele-visit service are under 50 years old (46 out of 72, or 64%). However, some older patients were also able to benefit from the tele-visit service, thanks to the support of a caregiver. In particular, the 8 patients over 80 years of age who participated in the tele-visit service are patients treated at home by diabetes specialists. This highlights the importance of including caregivers and/or home care specialists in the process to avoid excluding older patient groups from telemedicine services, as physically going to the clinic can be challenging for them.

Seven patients residing outside the province of Modena utilized tele-visits. However, when analyzing the patients' districts of residence, we observed poor adherence among patients (2 patients) residing in districts located at the far ends of the province. This finding is puzzling, especially considering that this type of service is known for its potential to reach patients who are far from health services or have physical or logistical difficulties in traveling. This phenomenon cannot be attributed to poor promotion of the service by the professionals working in these districts, as they also work in neighboring districts showing higher adherence. Further evaluations are needed to better understand this issue and find effective solutions.

Most patients (76%) participated in only one tele-visit. This data is not surprising and is not considered a dropout from the service. Given that these patients are characterized by clinical stability (as per the inclusion criteria) and the short period examined (as these patients generally undergo checks annually or even less frequently), we believe this feedback is normal. When data from a longer period are available, it will be possible to verify whether patients enrolled will prefer this modality again. Of the 72 patients enrolled, six patients (8%) had three tele-visits or more. These are patients who were stable at the time of the initial proposal, but the need for more frequent checks subsequently emerged.

Finally, it is interesting to note that most patients (67%), as well as all of the professionals participating in the project, are female.

3. Use of technology

Several IT issues can act as barriers during the implementation and expansion phases of tele-visit services. For all telemedicine services, a stable connection capable of supporting data exchange is essential. In Italy, high-speed internet is available in only 44.2% of households (35). Additionally, the province of Modena includes 35% mountainous terrain (29), where connections do not always meet the required standards, especially during adverse weather conditions. When selecting patients, it is necessary to consider the quality of the internet service, which inevitably limits the pool of potential enrollees. Unfortunately, this issue affects the most disadvantaged areas where telemedicine could be most beneficial for ensuring access to healthcare.

Furthermore, it is important not to overestimate the IT skills of both patients and professionals. The digital divide, which primarily affects elderly or underprivileged patients (36), poses a significant

obstacle to the spread of telemedicine. In the LHA of Modena, we chose to start with a project involving mainly younger patients; however, future projects cannot exclude the portion of the population with the greatest health needs.

IT skills of caregivers also need to be addressed. Even among healthcare professionals, there are high levels of digital illiteracy (37-39). While all professionals use digital devices in their daily practice, their expertise often pertains only to specific tasks. Therefore, considerable effort must be devoted to creating informational materials, both online and in print, and organizing multiple training sessions. Many specialists have reported discomfort with using various IT applications. For instance, diabetologists must use four different IT applications simultaneously during visits for analyzing and recording parameters, drafting medical reports, and compiling treatment plans. Additionally, for tele-visits, they need an extra application for video calls, which they find cumbersome.

This issue is expected to be resolved by the new IT applications and the regional telemedicine platform, which will be implemented soon. All new IT applications are designed to integrate telemedicine services effectively.

4. Adherence of specialists and tele-visit Volumes

Despite efforts to promote adherence among professionals, only half of the diabetologists (9 out of 19) began performing tele-visits. This indicates that there is still much work to be done to address the existing doubts about telemedicine. In addition to the previously discussed IT issues, other factors could explain this phenomenon and need to be carefully investigated in future monitoring. During the first official meetings scheduled emerged that, first of all, despite the experience gained during the COVID-19 pandemic, skepticism about the potential of telemedicine still remains. This is especially true for older specialists, who tend to have a generally low propensity for change. Additionally, there is a widespread fear among specialists of having and overload of activities due to need to repeat visits in case of troubles with communication and relationship with patients.

A non-proactive attitude among doctors could also explain why many eligible patients are reluctant to use this delivery method, preferring in-person visits instead. The volume of tele-visits provided over the 12-month period was likely less than expected, even though no minimum volume targets had been set. Unfortunately, performance was affected by a cyberattack on the LHA in December 2023, which rendered tele-visit services unavailable for approximately 15-20 days, interrupting the positive trend observed in October and November.

Since this service was new to the organization, the working group was unable to estimate the number of tele-visits to schedule. Consequently, specialists decided not to allocate specific days for telemedicine activities. This decision proved to be prudent, as it helped avoid periods of unused time due to a lack of patients.

Tele-visits were conducted in only four districts of the province. However, this can be partly justified by the fact that specialists work across multiple districts and had the flexibility to schedule tele-visits where they prefer. This flexibility is in line with the purpose of telemedicine: to provide services to patients who are far away from healthcare facilities.

Regarding potential enrollment issues, unfortunately, we have not tracked proposals for tele-visits, so we cannot currently calculate the refusal rate. This aspect will be thoroughly addressed in the next monitoring evaluation. The working group is also working on identifying different process indicators that are essential for a comprehensive and effective evaluation of the service, such as the percentage of specialists involved, the number and percentage of patients enrolled, and the number and percentage of refusals or patients who switch back to in-person visits after their initial tele-visit.

Even though the number of tele-visits was not high, interest in this type of service has grown among other specialists, some of whom have already proposed new telemedicine services and innovative projects. The working group has begun exploring new areas that could benefit from telemedicine, such as providing services to prisons, which are often situated in particularly challenging contexts.

Upcoming actions will also include expanding diabetic check-ups to pregnant women with pregnancy-related diabetes and developing tele-visits in endocrinology, neurology, hematology, and gastroenterology.

Conclusions

Implementing a tele-visit service for the first time in an LHA is not an easy process. Several critical issues can emerge during both the planning and implementation phases of the service, but these should

not deter the improvement of existing services or the development of new telemedicine initiatives. In fact, a thorough and in-depth evaluation of these critical issues can enable proactive measures to prevent known problems from leading to the failure of future projects.

Our evaluation suggests that we need to focus on two main areas: first, it is essential to organize additional activities to promote telemedicine to both patients and healthcare professionals; second, it is crucial to address IT issues, including the integration of IT systems.

Riassunto

Telemedicina nell'ambito della specialistica ambulatoriale: case study della prima esperienza con i pazienti diabetici presso l'Azienda USL di Modena

Introduzione. Durante la pandemia da COVID-19, la telemedicina ha avuto l'opportunità di mostrare il suo potenziale. In Italia, dopo un primo periodo di diffidenza, si è compreso che la telemedicina può rappresentare un valido vantaggio sia per gli operatori sanitari che per i pazienti.

Nell'Azienda Unità Sanitaria Locale di Modena (Regione Emilia-Romagna), è stata data grande importanza allo sviluppo, alla promozione e alla gestione di tutte le attività di telemedicina, in particolare si è deciso di dare priorità all'attivazione di servizi di televisita, in linea con le linee guida regionali.

Disegno dello studio. Questo *case study* ha lo scopo di illustrare le attività pianificate e sviluppate presso l'Azienda USL di Modena per l'implementazione del primo servizio di questa tipologia attivato, il Servizio di televisita per pazienti ambulatoriali affetti da diabete mellito di tipo 1, e di analizzare i dati dei primi 12 mesi di attività (da maggio 2023 a aprile 20214) allo scopo di condividere riflessioni sui punti di forza e di criticità riscontrati.

Metodi. Per l'attivazione delle televisite presso l'AUSL di Modena è stato istituito uno specifico gruppo di lavoro con il mandato di gestire tutti gli aspetti clinici, organizzativi e informatici. Prima dell'avvio del servizio sono state svolte diverse attività preliminari, quali la scelta della specialità clinica da attivare, la definizione dei criteri di inclusione dei pazienti, le implementazioni informatiche, la valutazione del rischio clinico, la predisposizione e distribuzione del materiale informativo, la formazione del personale sanitario e la pianificazione delle attività ambulatoriali.

Risultati. Durante il primo anno di attivazione sperimentale del Servizio (maggio 2023-aprile 2024) sono stati arruolati nel progetto complessivamente 72 pazienti per un totale di 103 televisite erogate. I pazienti erano prevalentemente donne (67%) e le fasce d'età più rappresentate erano 30-39 (26%) e 40-49 (21%).

Metà degli specialisti del Servizio di Diabetologia (9/19) ha aderito all'iniziativa erogando televisite, questi erano perlopiù giovani e tutte donne.

Le principali criticità rilevate dagli incontri regolarmente programmati con i professionisti, alle quali il gruppo di lavoro sta cercando di trovare le più adeguate soluzioni, sono state la scarsa adesione di molti pazienti che nutrono ancora dubbi su questa modalità, l'abitudine di molti pazienti di riprogrammare più volte l'appuntamento, che non risulta diminuita con questa modalità di visita, la non uniforme aderenza dei professionisti e diffusione a livello territoriale del servizio. Infine, i professionisti hanno segnalato diverse difficoltà di tipo informatico-tecnologico.

Anche se il numero delle televisite non è stato elevato, l'attività ha suscitato l'interesse di diversi professionisti e alcuni hanno già proposto di attivare altri servizi di telemedicina, alcuni addirittura proponendo nuovi progetti innovativi. Le prossime azioni riguarderanno l'estensione dei controlli diabetologico alle donne incinte con diabete gestazionale e lo sviluppo di televisite endocrinologiche, neurologiche, ematologiche e gastroenterologiche.

Conclusioni. Implementare un'attività di televisite in un'Azienda Sanitaria è un processo complesso. Una valutazione accurata e approfondita delle criticità emerse nelle fasi di sviluppo e nel periodo iniziale di erogazione può consentire di agire proattivamente per evitare che i problemi possano portare al fallimento dei progetti futuri. Dalle nostre valutazioni emerge la necessità di agire su due fronti: da un lato occorre organizzare ulteriori attività per promuovere la telemedicina rivolte sia ai pazienti che agli operatori, dall'altro occorre lavorare anche per risolvere le problematiche informatiche.

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Predicting the risk of type 2 diabetes: Standardized diabetes risk score among the Khmer ethnic minority in Vietnam

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Keywords: Khmer people; Tra Vinh (province); Modified diabetes risk score; type 2 diabetes; Vietnam
Parole chiave: Popolo Khmer; Tra Vinh (provincia di); punteggio di rischio di diabete modificato; diabete di tipo 2; Vietnam

Abstract

Background. *Predicting the risk of progression to type 2 diabetes, as well as identifying the factors that increase this risk, helps the population adjust the modifiable risk factors, improve quality of life, and reduce the disease burden.*
Subjects and methods. *A cross-sectional study was conducted on 918 ethnic Khmer minority people aged 40 and above in Vietnam who had never been diagnosed with type 2 diabetes.*
Objective. *To predict the 10-year risk of type 2 diabetes, the Finnish Diabetes Risk Scoring Scale, adjusted for the Asian population with modification of the waist circumpherence and Body Mass Index Cut-Offs, was used.*
Results. *The 10-year predicted risk of progression to type 2 diabetes in ethnic Khmer people aged 40 years and older in southern Vietnam, using the Asian-modified Finnish Diabetes Risk Scoring Scale, resulted 10.54% in the total population study, females have a higher risk at 12.62% compared to 8.01% of males. Among the items that make up the Finnish Diabetes Risk Scoring Scale, age, waist circumference, BMI, family history of diabetes, history of high blood glucose, and use of blood pressure medication were the most accurate predictors, with the area under the Receiver operating characteristic (ROC) curve at 0.83, 0.81, 0.77, 0.75, 0.74 and 0.73 respectively. The optimal cut-off score to identify progression to tipe 2 diabetes was 13.5 points (Se = 1.00, Sp = 1.00, $p < 0.001$). The multivariable logistic regression model shows that factors associated with high risk of type 2 diabetes progression in 10 years are age, gender, occupation, economic status, education level and regular alcohol consumption ($p < 0.05$). The study results provide a basis for proposing potential solutions to reduce modifiable risk factors for type 2 diabetes in the population. These include providing culturally appropriate health education and changing behavior to address alcohol consumption.*
Discussion and conclusions. *The use of the Asian-modified Finnish Diabetes Risk Scoring Scale to predict the risk of progression to type 2 diabetes and as a screening tool for undiagnosed type 2 diabetes is appropriate for the Vietnamese Khmer population.*

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Introduction

Type 2 diabetes (T2D) is a non-communicable disease that is increasingly common globally. According to the International Diabetes Federation in 2021, there are 537 million adults (aged 20-79) worldwide, and more than 3 out of 4 adults with diabetes live in low- and middle-income countries (1). According to the 2021 STEPS (STEPwise approach to Surveillance) national survey on risk factors for non-communicable diseases, Vietnam has approximately 15.1 million adults with hypertension (23.3%) and 4.5 million with T2D (7.3%), and 17% have prediabetes (2); the estimated undiagnosed T2D cases are 50%. Prolonged chronic hyperglycemia can lead to metabolic disorders and result in damage to various organs, such as the heart, blood vessels, kidneys, eyes, and nerves (3,4). While there is no specific treatment for the disease, it can be prevented if people actively address the risk factors, especially during the prediabetes stage. Therefore, identifying individuals in the prediabetes stage is crucial for preventing disease progression or reducing severe complications of T2D (3). The main factors for T2D are environmental, genetic, obesity, and physical inactivity, all of which are increasing at a high rate (5,6).

The Finnish Diabetes Risk Score (FINDRISC) scale assesses the risk of progressing to T2D based on 8 factors, including age, Body Mass Index (BMI), waist circumference, daily physical activity, consumption of fruits and vegetables, use of blood pressure-lowering medication, history of elevated blood glucose, and family history of diabetes (7). The total score ranges from 0 to 26, with a higher score indicating a higher risk of developing Type 2 Diabetes. The FINDRISC scale has been adapted to use Asian-specific BMI and waist circumference cut-off points. The highest cut-off for waist circumference is based on the Asian standard (90 cm for men and 80 cm for women) instead of the European standard (102 cm for men and 88 cm for women) used in the original FINDRISC. The BMI classification is also specific for the Asian population. According to the World Health Organization (WHO), the risk of T2D and cardiovascular disease increases in Asians with a BMI ≥ 25 kg/m^2, and the classification is as follows: BMI < 18.5 kg/m^2: underweight; 18.5 kg/m2 – 23 kg/m2: acceptable risk; 23 kg/m2 - < 27.5 kg/m2: increased risk; ≥ 27.5 kg/m2: high risk (8). The scoring for each item is presented in Table 1.

Table 1 - The FINDRISC scale evaluates the risk of diabetes for Asians

Item	Standard		Score
1. Age, years	< 45		0
	45 - 54		2
	55 - 64		3
	> 64		4
2. BMI, kg/m²	< 23		0
	23 - < 27,5		1
	≥ 27,5		3
3. Waist circumference, cm	Male	Female	
	< 82	< 72	0
	82 – 90	72 - 80	3
	> 90	> 80	4
4. Physical activity ≥ 4 hr/week	Yes		0
	No		2
5. Daily consumption of vegetables, fruits	Yes		0
	No		1
6. Use of blood pressure medication	No		0
	Yes		2
7. History of high blood glucose	No		0
	Yes		2
8. Family history of diabetes	No		0
	Yes, 2nd degree relative		3
	Yes, 1^{sd} degree relative		5

The Khmer people are an ethnic minority group, representing 1.4% of the total population in Vietnam. Tra Vinh province has the largest Khmer population, accounting for 32% of the province's residents (9). The Khmer people are primarily farmers (engaged in rice cultivation), hired laborer and small-scale merchants in local markets. They face economic difficulties, and their educational attainment is relatively low (in the study sample, 12.9% were illiterate, and 59.0% had only completed primary education, 1-5 years of schooling). As a result, they have limited knowledge of disease prevention, understanding of the consequences of diseases, and access to healthcare services. Economic challenges are the biggest obstacle for them in affording screening and treatment services. Therefore, a cost-free tool is needed for local healthcare workers to estimate the risk of T2D in the Khmer population, provide early notification, and facilitate their access to diagnosis and treatment. The assessment of the 10-year risk of diabetes among the Khmer population aged 40 and above in Tra Vinh has not been reported in previous studies. FINDRISC is a non-invasive and feasible tool to predict the risk of T2D in high-risk undiagnosed individuals (7).

Materials and methods

1. Study Design

This cross-sectional study was conducted from June to September 2023 in the community of Tra Vinh province, which is a province in the Mekong Delta region of southern Vietnam. It aimed to estimate the risk of developing T2D mellitus over the next 10 years (2033) among Khmer adults aged 40 and above, who had the cognitive capacity and communication ability, had not been previously diagnosed with diabetes, and consented to participate in the study.

2. Sample size

The sample size was calculated using the following formula:

$$n = Z^2_{1-\alpha/2} \frac{p\,(1-p)}{d^2};$$

where, n is the smallest sample size to be achieved in the study; p is the predicted 10-year T2D rate of 16.7% (based on a previous study in Da Nang, Vietnam in 2017 (10)); d is the absolute error of 5%, and Z(1-α/2) is the Z-statistic for a 95% confidence level. A design effect of 1.5 was applied. The minimum sample size calculated using the formula was 896 people. In practice, when creating the sample, we collected an excess sample, totaling 950 questionnaires, to account for potential sample errors. After removing subjects with incomplete data, the final number of questionnaires collected was 918, and we used it for the analysis.

3. Data collection

The study used a population proportionate to size (PPS) sampling method (Figure 1), following these 4 steps:

1) From the total of 106 communes/wards in Tra Vinh province;

2) 30 communes/wards were selected based on the

No.	Ward/Commune name	N. of Khmer people ≥ 40 ys	Cumulative size	N. associated
1	Cầu Ngang	169	169	0 - 169
2	Mỹ Long	18	187	170 -187
3	Mỹ Long Bắc	32	219	188 - 219
4	Mỹ Long Nam	14	233	220 - 233
5	Mỹ Hòa	1,217	1,450	234 - 1450
6	Vĩnh Kim	24	1,474	1,451 - 1,474
7	Kim Hòa	2,103	3,577	1,475 - 3,577
8	Hiệp Hòa	1,789	5,366	3,578 - 5,366
9	Thuận Hòa	1,618	6,984	5,367 - 6,984
10	Long Sơn	2,250	9,234	6,985 - 9,234
11	Nhị Trường	3,107	12,341	9,235 - 12,341
12	Trường Thọ	2,440	14,781	12,342 - 14,781
13	Hiệp Mỹ Đông	32	14,813	14,782 - 14,813
14	Hiệp Mỹ tây	29	14,842	14,814 - 14,842
15	Thạnh Hòa Sơn	2,273	17,115	14,843 - 17,115

1. Compiled a list of 106 clusters (wards/communes) in Tra Vinh province, Vietnam.
2. Purposively selected 30 communes out of 100 communes, based on the size of the Khmer population aged over 40 years in each cluster.
• The cluster interval k = 129,202/30 = 4,306
• A random number x = 201 (satisfying the condition $1 \leq x \leq 4,306$)
• The first cluster: chosen with the order number in the list as x = 201, at cluster 3, around cluster 188 - 219.
• The next cluster: x + k, x + 2k, ..., x + (n - 1)k. The total number of clusters is 30.
3. Sample size in each cluster: survey at least 30 Khmer people over 40 years old in each cluster.

Figure 1 -The procedure for implementing the Probability Proportional to Size (PPS) sampling method (Presenting the first 15 clusters out of the total 106 clusters).

size of the Khmer population aged 40 and above;

3) A list of Khmer individuals was compiled, and systematic random sampling was used to select participants based on the population proportion in those 30 communes;

4) Local health officials invited the selected individuals (who consented to participate) to the commune health stations for medical examination and interviews.

4. Contents and Data Collection Methods

1) Participants' information and anthropometric measurements were collected through direct interviews using the WHO STEPS questionnaire (Vietnamese version) (11). For Khmer participants who only spoke the Khmer language, only the interviewers who were proficient in the Khmer language conducted the interviews in Khmer.

2) Participants were asked about their history of antihypertensive medication use, history of dysglycemia, and family history of diabetes.

3) The FINDRISC score was calculated using BMI and waist circumference cut-offs for the Asian population. The highest cut-off was for the Asian waist circumference standard (90 cm for men and 80 cm for women), instead of the European standard (102 cm for men and 88 cm for women) used in the original FINDRISC. BMI categories were also based on the WHO Asian classification: BMI <18.5 kg/m2: underweight; 18.5-23 kg/m2: acceptable risk; 23-<27.5 kg/m2: increased risk; ≥27.5 kg/m2: high risk (8).

4) The 10-year T2D risk was estimated using the FINDRISC-Asia scoring system: <7 points, low risk (1/100); 7-11 points, slightly elevated risk (1/25); 12-14 points, moderate risk (1/6); 15-20 points, high risk (1/3); >20 points, very high risk (1/2) (7).

5. Statistical analysis

Data analysis was performed using Stata software version 17.0. The distribution of study variables was described using chi-square tests. Independent variables associated with the prediction of 10-year T2D risk were identified through univariate analysis, and those variables were then selected for inclusion in a multivariate logistic regression model. Receiver operating characteristic (ROC) curves were used to evaluate the predictive value of the items in determining the 10-year diabetes risk. A statistical significance level of $p < 0.05$ was chosen.

Results

The total number of survey participants was 918, with 418 males and 500 females. Their average age was 67.5 years, with the youngest being 40 and the oldest 82. The majority of the participants, 63.4%, were engaged in agricultural occupations, while 13.3% were small-scale market vendors and hired laborers, and 23.3% were retired or had other occupations. 14.4% of the participants were living alone, and 12.9% were illiterate.

The risk of developing T2D is presented in Table 2, with the percentages for the risk levels of Low Risk, Moderately Low Risk, Moderate Risk, and High Risk being 28.8%, 36.9%, 16.0%, and 18.3% respectively. There were no cases in the Very High Risk category.

The optimal cut-off value of the FINDRISC scale was 13.5 to assess the 10-year risk of T2D in the Khmer community aged over 40 (Sensitivity = 1.00 and Specificity = 1.00, $p < 0.001$). The predictive performance of the FINDRISC scale items is represented by the ROC Curve. Among the factors, age (Area Under the Curve (AUC)) = 83%; the optimal cutoff value was 66 years old) has the highest value, followed by Waist circumference (AUC = 81%; cutoff value = 81.5), BMI (AUC = 76.7%; cutoff value = 22.95), having a family member with diabetes (AUC = 74%), a history of high blood glucose (AUC = 74.6%), and having previously been prescribed blood pressure medication (AUC = 72.7%); having physical activity of 4h/week is considered a protective factor against risk (AUC = 27.3%). The factors that have less value in distinguishing the high-risk level of progression to diabetes are gender (AUC = 67.8%) and daily consumption of vegetables and fruits (AUC = 59.2%) (Figure 2*)*.

We selected 9 determining factors for the Asian FINDRISC score and incorporated them into a multiple regression model to identify independent factors that increase or decrease the Asian FINDRISC score in the Khmer community aged 40 and above (Table 3). The equation is as follows: Asian FINDRISC score = -18.68 + 0.14*Age - 1.72 *female + 0.27*BMI + 0.17* Waist circumference -1.96*Physical activity ≥ 4 hours/week - 1.26*Daily consumption of vegetables, fruits + 2.12*Use of blood pressure medication + 1.82*History of high blood glucose + 3.68*2*2nd degree relative + 4.94*3*1st degree relative (for individuals without a specific variable in the equation, the value of that variable is set to 0). The results are as follows: for every 1 year increase in age, the score increases by 0.14 points; females have a decrease of

Table 2 - Predicting the risk of diabetes in males and females using the Asian FINDRISC

FINDRISC		n (%)				Prediction of T2D risk		
		Total	Male	Female		Total	Male	Female
<7	Low risk	264 (28.8)	114 (27.3)	150 (30.0)	1/100	0.29	0.27	0.30
7-11	Low-moderate risk	339 (36.9)	181 (43.3)	158 (31.6)	1/25	1.48	1.73	1.26
12-14	Moderate risk	147 (16.0)	95 (22.7)	52 (10.4)	1/6	2.67	3.78	1.73
15-20	High risk	168 (18.3)	28 (6.7)	140 (28.0)	1/3	6.10	2.23	9.33
>20	Very high risk	0 (0.0)	0 (0.0)	0 (0.0)	1/2	0	0	0
Mean, SD *(min, max)*		9.2 ±4.2 *0 - 19*	8.8 ±3.9 *0 - 19*	9.6 ±4.4 *3 – 19*		p < 0.001		
Total		918 (100)	418 (100)	500 (100)		10.54	8.01	12.62

n: frequencies, (%): Column percentage, SD: standard deviation, T2D: Type 2 diabetes

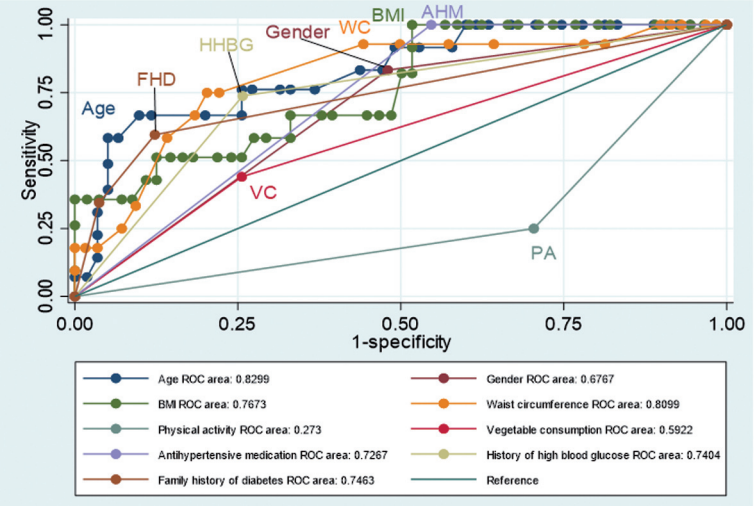

Figure 2 - Display the ROC curve between the Asian FINDRISC and the individual items of the scale
FHD: Family history of diabetes; HHBG: History has been found of high blood glucose; WC: Waist circumference; BMI: Body mass index; AHM: History of taken antihypertensive medication; PA: Physical activity; VC: Vegetable consumption.

Table 3 - The multiple regression equation for the 8 items of the Asian FINDRISC scale

Item	Coefficient	Std. err.	t	95% CI	p-value
Age, 1 year	0.14	0.004	36.54	0.13 – 0.14	< 0.001
Gender, male	-1.73	0.088	-19.69	-1.90 - -1.55	< 0.001
BMI, 1 kg/m²	0.27	0.018	14.83	0.23 – 0.30	< 0.001
Waist circumference, 1 cm	0.17	0.006	29.16	0.16 – 0.18	< 0.001
Physical activity ≥ 4 hr/week	-1.96	0.092	-21.40	-2.14 - -1.78	< 0.001
Daily consumption of vegetables, fruits	-1.26	0.081	-15.62	-1.42 - -1.10	< 0.001
Use of blood pressure medication	2.12	0.094	22.54	1.94 – 2.31	< 0.001
History of high blood glucose	1.82	0.101	18.10	1.62 – 2.02	< 0.001
Family history of diabetes					
Yes, 2nd degree relative	3.68	0.112	32.71	3.46 – 3.90	< 0.001
Yes, 1sd degree relative	4.94	0.136	36.39	4.67 – 5.20	< 0.001
Constant	-18.68	0.544	-34.37	-19.75 - -17.62	< 0.001

Std. err.: standard error, CI: confidence interval

1.72 points; every 1 unit increase in BMI is associated with a 0.27 point increase; every 1 cm increase in waist circumference corresponds to a 0.17 point increase; having physical activity ≥ 4 hours/week and a daily consumption of vegetables and fruits decrease the score by 1.96 and 1.26 points respectively; the use of blood pressure medication and a history of high blood glucose increase the score by 2.12 and 1.82 points respectively; having a first-degree relative with diabetes increases the score by 4.94 points, while having a second-degree relative increases the score by 3.68 points. The sum of the component scores is the Asian FINDRISC score, which predicts a high risk of progressing to T2D if the Asian FINDRISC score is > 13.5.

In the univariate logistic regression analysis, 7 variables were found to be statistically significant and were included in the multivariate logistic regression model (Table 4). This model selection approach increases the power to detect and avoid omitting any confounding variables or covariates, which could lead to biased estimates and incorrect conclusions. Each additional year of age increased the odds ratio (OR) of T2D by 1.3 (OR = 1.3, 95% CI 1.3-1.4, p < 0.001). Females had a 24-fold higher risk of developing T2D compared to males (OR = 24.0, 95% CI 18.8-65.3, p < 0.001). Small-scale vendors and hired laborers had a 2.8-fold higher risk compared to farmers (OR = 2.8, 95% CI 1.1-7.2, p = 0.026). The poor (as confirmed by the government) had a 2.7-fold higher risk compared to the non-poor (OR = 2.7, 95% CI 1.2-6.4, p = 0.022). Individuals with more than 12 years of education and the illiterate had a 40.6-fold (OR = 40.6, 95% CI 12.6-130.7, p < 0.001) and 7.3-fold (OR = 7.3, 95% CI 3.4-15.6, p < 0.001) higher risk, respectively, compared to those with 1-12 years of education. Frequent alcohol consumption was associated with a 3.4-fold higher risk compared to non-drinkers (OR = 3.4, 95% CI 1.6-7.6, p = 0.002).

Discussion

The predicted 10-year risk of progression to T2D among ethnic Khmer individuals aged 40 and above in southern Vietnam, using the adapted Asian FINDRISC scale, is 10.54% for the total population. Females have a higher risk at 12.62% compared to 8.01% for males. This figure is higher compared to studies in Thua Thien Hue province in central Vietnam in 2020, where the projected 10-year T2D progression risk in the community was 4.24%; similar to our study,

Table 4 - Multivariable logistic regression analysis of demographic factors and risk of T2D over the next 10 years (n = 918)

Values	Risk of T2D		Univariate analysis		Multivariate analysis	
	High (n = 168)	Low, Moderate (n = 750)	OR 95% CI	p-value	OR 95% CI	p-value
Age, mean (SD), years (min – max)	67.5 (±8.7) *(52 - 82)*	56.8 (±10.6) *(40 - 77)*	1.2 (1.1-1.2)	< 0.001	1.3 (1.3-1.4)	< 0.001
Gender, n (%)						
Male	28 (6.7)	390 (93.3)	1		1	< 0.001
Female	140 (28.0)	360 (72.0)	5.4 (3.5-8.3)	< 0.001	24.0 (8.8-65.3)	
Occupation, n (%)						
Farmer	60 (10.3)	522 (89.7)	1		1	
Small business, hired laborer	30 (24.6)	92 (75.4)	2.8 (1.7-4.6)	< 0.001	2.8 (1.1-7.2)	0.026
Retirement, others	78 (36.5)	136 (63.5)	5.0 (3.4-7.3)	< 0.001	0.9 (0.4-1.9)	0.728
Economic status, n (%)						
Not poor	138 (20.1)	550 (79.9)	1	0.018	1	0.022
Poor	30 (13.0)	200 (87.0)	0.6 (0.4-0.9)		2.7 (1.2-6.4)	
Marital status, n (%)						
Single	54 (40.9)	78 (59.1)	1	< 0.001	1	0.682
Married	114 (14.5)	672 (85.5)	0.3 (0.2-0.4)		0.8 (0.4-1.9)	
Using alcohol and beer, n (%)						
No	124 (25.7)	358 (74.3)	1		1	
Yes	44 (10.1)	392 (89.9)	0.3 (0.2-0.5)	< 0.001	3.4 (1.6-7.6)	0.002

n: frequencies, (%): row %, CI, confidence interval; OR, odd ratio

females were predicted to have a higher risk at 8.18% compared to 4.91% for males (12). The higher disease prevalence and risk in females compared to males have also been reported in many previous studies (13). Women appear to bear a greater burden of risk factors at the time of T2D diagnosis (14). Pregnancy can lead to metabolic abnormalities resulting in gestational diabetes, which is also a major risk factor for the subsequent development of T2D in women (15,16). Additionally, the increasing prevalence of obesity during the menopausal period (17), is also a strong risk factor for T2D (18).

The optimal cutoff value of ≥ 13.5 on the Asian FINDRISC scale has the highest discriminative power to diagnose high risk of developing T2D within 10 years in the study population (with Sensitivity at cutpoint: 1.00 and Specificity at cutpoint =1.00). Our cutoff point is higher compared to a 2016 study in Norway, which found the Asian FINDRISC cutoff with the best predictive value for T2D to be 11 points (19), or a study in Madrid, Spain that reported ≥ 13 points (20); while the initial recommendation for the scale was ≥ 15 points (7). Clearly, different study populations may yield slightly varying results. If the ≥ 15 point cutoff was applied to this study population, it would have significantly underestimated the 10-year diabetes risk compared to the actual risk. In general, more recent studies have consistently shown a lowering of the Asian FINDRISC cutoff point for assessing T2D risk compared to earlier recommendations.

Age is an important factor in the risk of progressing to T2D. The age of onset for diabetes is typically over 40 years old, with the disease often developing silently and being difficult to detect. In our study, the threshold of 66 years old was assessed to be at high risk (Sensitivity at cutpoint: 0.67, Specificity at cutpoint: 0.90). Age is directly proportional to the risk of developing T2D due to the progressive deficiency in insulin secretion with aging (21) and the increasing state of insulin resistance due to metabolic changes (22). Occupation is also related to a higher risk of progressing to T2D. Sedentary occupations such as small-scale trading and freelance work have a higher risk compared to farmers, which is closely related to higher levels of physical activity. The farmers in this context mainly grow rice using manual labor, without modern machinery or mechanization in agriculture.

In Vietnam, individuals who are truly poor will be officially recognized as such by the government. This study found that the poor have nearly a 3-fold higher risk of developing T2D compared to the non-poor. Similarly, a study by Chih-Cheng Hsu in China (23), showed that compared to those with average incomes, the poor have around a 50% higher risk of developing T2D. Additionally, we can also observe that the poor are less likely to receive regular health check-ups and glucose tests as recommended. Maintaining a healthy lifestyle and diet when experiencing blood glucose dysregulation is also more challenging for low-income groups.

Frequent alcohol consumption has a 3.4-fold higher risk of progressing to T2D (in this study, frequent use was defined as consuming at least 6 alcohol units at least once a week). Moderate alcohol intake (16g of pure alcohol per day) has a protective effect for non-drinkers, but high consumption (50g) no longer provides a protective factor (24,25). Alcohol affects the hormonal balance of blood glucose, specifically insulin. Excessive alcohol consumption can slow down or disrupt the production of insulin (26,27).

Conclusion

The 10-year diabetes risk forecast according to the Asian FINDRISC scale is 10.54%, with a risk of 8.01% for males and 12.62% for females. The optimal cut-off point for predicting a high risk of progression to type 2 diabetes on the scale is 13.5. The items of the Asian FINDRISC scale effectively measure accuracy, except for the item related to daily fruit and vegetable consumption. Using the Asian FINDRISC scale to predict the risk of progression to type 2 diabetes and to screen for undiagnosed cases is appropriate for the Khmer Vietnamese population.

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Ethical approval: The research was approved by the Biomedical Research Ethics Committee of Can Tho University of Medicine and Pharmacy (Decision No. 23.013.NCS/PCT-HĐĐĐ15.6/23). Participants' information was kept confidential and used only for research purposes. The survey did not cause any harm to the participants, and they were free to withdraw from the study at any stage. The study was approved by the Department of Health, the District Health Center, and the local Health Stations where the study participants resided in Tra Vinh province.

Authors Contributions: T.T.H. Nguyen designed the details of the study. T.T.H. Nguyen and L.P. Duong investigated the data and ensured accurate and strict exclusions according to the study crite-

ria. The analysis was carried out by T.T.H. Nguyen interpreted the analysis and wrote the paper. L.P. Duong contributed to the critical evaluation and revision of the manuscript. T.T.H. Nguyen and L.P. Duong approved the final version of the article.

Availability of data and material: The data sets during and /or analysed during the current study are available from the corresponding author on reasonable request.

Conflict of Interests: All authors declare no conflicts of interest in this paper.

Riassunto

Previsione del rischio di diabete di tipo 2: punteggio standardizzato di rischio di diabete tra la minoranza etnica Khmer in Vietnam

Contesto. Prevedere il rischio di progressione verso il diabete di tipo 2, nonché identificare i fattori che aumentano tale rischio, aiuta la popolazione a "migliorare" i fattori di rischio modificabili, a promuovere la qualità della vita ed a ridurre il carico di malattia.

Obiettivo. Prevedere il rischio di diabete di tipo 2 a 10 anni utilizzando la Scala finlandese di rischio del diabete di tipo 2, adattata per la popolazione asiatica con modifiche della circonferenza toracica e modifiche dei Cut-Offs dell'Indice della massa corporea.

Soggetti e metodi. Studio trasversale condotto su 918 persone appartenenti alla minoranza etnica Khmer di età pari o superiore a 40 anni in Vietnam che non avevano ricevuto in precedenza una diagnosi di diabete di tipo 2. È stata utilizzata la scala Scala finlandese di rischio del diabete di tipo 2 adattata, con modifiche alla circonferenza della vita e diversi limiti dell'Indice di Massa Corporea, adattati per la popolazione asiatica.

Risultati. Il rischio di progressione verso il diabete di tipo 2 previsto a 10 anni nelle persone di etnia Khmer di età pari o superiore a 40 anni nel Vietnam meridionale, utilizzando la Scala finlandese di rischio del diabete di tipo 2 modificata per l'Asia, è del 10,54% nella popolazione totale, mentre le femmine hanno un rischio più elevato al 12,62% rispetto all'8,01% degli uomini. Tra gli elementi che compongono la Scala finlandese di rischio del diabete di tipo 2 - età, circonferenza della vita, BMI, storia familiare di diabete, storia di glicemia alta e uso di farmaci per la pressione sanguigna - sono stati i predittori più accurati, con l'area sotto la curva Receiver operating characteristic (ROC) rispettivamente a 0,83, 0,81, 0,77, 0,75, 0,74 e 0,73. Il punteggio di cut-off ottimale per identificare la progressione verso il diabete di tipo 2 era di 13,5 punti (Se = 1,00, Sp = 1,00, $p < 0,001$). Il modello di regressione logistica multivariata mostra che i fattori associati ad un rischio elevato di progressione del diabete di tipo 2 in 10 anni sono età, sesso, occupazione, stato economico, livello di istruzione e consumo regolare di alcol ($p < 0,05$). I risultati dello studio forniscono una base per proporre potenziali soluzioni per ridurre i fattori di rischio modificabili per il diabete di tipo 2 nella popolazione. Questi includono fornire un'educazione sanitaria culturalmente e contenutisticamente appropriata e cambiare comportamento per affrontare il consumo di alcol.

Conclusioni. L'uso della scala FINDRISC per predire il rischio di progressione verso il diabete di tipo 2 e come screening per il diabete di tipo 2 non diagnosticato è risultato appropriato per la popolazione vietnamita di etnia Khmer.

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Exploring the gap between notified and diagnosed cases of Foodborne Diseases: evidence from a time-trend analysis in Italy

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Keywords: Foodborne Diseases; Notification of Infectious Diseases; COVID-19 pandemic.
Parole chiave: Malattie Trasmesse da Alimenti; Notifica di Malattie Infettive; Pandemia di COVID-19.

Abstract

Background. *Foodborne diseases are a major global public health concern, causing significant morbidity and mortality worldwide. The COVID-19 pandemic has had widespread effects on various aspects of life, including the food supply chain, potentially impacting the incidence of foodborne diseases. This study aims to analyze the differences between notified and diagnosed cases and investigate the potential impact of the COVID-19 pandemic on foodborne diseases in the metropolitan area of Bologna, Italy.*
Study Design. *A retrospective time trend analysis from two databases was conducted.*
Methods. *The Local Health Authority of Bologna collected data re/Emilia-Romagna Region on the infectious disease reporting system over a six-year period (2017-2022), which included three years of the COVID-19 pandemic. This data was compared with information collected during the same period at the microbiology laboratory serving the entire metropolitan area of Bologna. Statistical methods included percent change calculations, binomial tests, annual averages, gender and age stratification, and trend analysis with regression.*
Results. *An increase (+34.4%, P-value ≤0.01) in notified cases during the pandemic - compared to the pre-pandemic period - was found. However, no differences were observed in diagnosed cases when comparing the two periods. The year 2021 saw a significant increase in reported cases of foodborne diseases among schoolers (+300.0%) and workers (+133.3%) compared to 2020. On the other hand, diagnosed cases decreased significantly in 2020 (-19.1%, P<0.01) and increased in 2021 (+21.9%, P<0.01). In absolute terms, a stark difference was observed between notified and diagnosed cases across all the study years (2017–2022).*
Conclusions. *This study highlights the discrepancy between notified and diagnosed cases of foodborne diseases and how the COVID-19 pandemic has increased reporting without affecting transmission. These findings contribute to the ongoing discussion on improving foodborne disease reporting systems.*

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Introduction

Foodborne diseases pose a significant threat to global public health, causing a substantial burden of morbidity and mortality worldwide (1-3). According to the World Health Organization (WHO), foodborne diseases affect almost one in ten people worldwide, resulting in approximately 600 million cases and 420,000 deaths annually (4). These illnesses are caused by various pathogens, including bacteria, viruses, parasites, toxins, and chemicals that can contaminate food at any stage of production, processing, and distribution (5).

The COVID-19 pandemic has impacted many aspects of our lives, including the food supply chain (6, 7). The impact of the pandemic on food systems has been extensive, with disruptions in food production, distribution, and consumption, leading to changes in demand and altered consumer behavior. These changes may have affected the incidence of foodborne diseases, potentially increasing risks or altering transmission patterns, but the extent and nature of this impact are not yet fully understood (8).

Accurate reporting is crucial, as it allows for identifying and tracking outbreaks, enabling public health agencies and authorities to implement appropriate control measures (9). Additionally, it enables researchers to study the epidemiology of foodborne diseases, leading to a better understanding of their causes and risk factors (10). However, the reliability of this data depends heavily on the consistency and completeness of reporting, which may have been compromised during the pandemic due to various factors, such as overwhelmed healthcare systems and shifts in public health priorities.

To address these uncertainties, we conducted a time-trend analysis in the Local Healthcare Authority (LHA) of Bologna, which is located in the north of Italy, has a population of over 870,000 inhabitants and extends over an area including 45 municipalities (11). To evaluate any underreporting of potentially foodborne transmitted diseases, we conducted a comparative analysis between SMI (*Sorveglianza malattie infettive* [Reporting System for Infectious Diseases]) and MU (*Microbiology Unit – IRCCS Azienda ospedaliero-universitaria di Bologna*). The SMI system collects data from cases notified by doctors in the region whenever a case is diagnosed. The MU database contains the data of each patient after carrying out the laboratory diagnosis.

This study aimed to report epidemiological trends in foodborne diseases in Bologna over six years, including three years marked by the COVID-19 pandemic. Specifically, the study aimed to detect potential discrepancies between cases notified by the doctors to the LHA and those diagnosed by the microbiological laboratory. Additionally, we wanted to understand whether the COVID-19 pandemic affected the reporting of foodborne diseases. Ultimately, this study seeks to highlight potential gaps in the current reporting system and propose strategies to enhance the accuracy and reliability of foodborne disease surveillance in the post-pandemic era.

Methods

Data for this retrospective study were collected through the SMI and MU. The SMI system is a central notification system that collects data from cases reported by medical doctors in the region of Emilia-Romagna upon diagnosis (12, 13). The MU (microbiology metropolitan laboratory serving as the primary local laboratory) database contains data for each patient after a diagnosis.

Our data covered the period from January 1, 2017 to December 31, 2022 (six years). The SMI labeled the specific types of foodborne diseases that we collected data on as *Salmonella* infections, *Shigella spp.*, *Norwalk* virus, *Campylobacter spp.*, *enteropathogenic Escherichia coli* (EPEC), *Yersinia enterocolitis*, or *Shigella sonnei*.

Percent changes in cases of foodborne disease in 2020–2022 relative to the previous three-year period (2017–2019) were calculated as $(x_t - x_{t-1}) \times 100 / x_{t-1}$. Assuming the simplest comparative situation in which the denominators are equal and indefinitely large, the statistical significance of the change was assessed using a conditional binomial probability test based on the fact that if $x = x_{t-1} + x_t$, where x_{t-1} and x_t are independent Poisson random variables, then $x_t | x \sim$ Binomial (x; 0.5). This means that x_t was tested as a proportion of $x = x_{t-1} + x_t$ against a Binomial (x; 0.5). Exact *P*-values were computed based on the binomial distribution (14). Cases notified to the SMI and diagnosed by the MU were summarized as annual averages and analyzed separately. Analyses were also stratified by gender and age group, that is, preschoolers (0–5 years), schoolers (6–18 years), workers (19–65 years) and retirees (>65 years).

In a secondary analysis, we used the same approach to estimate the percentage change in annual cases of foodborne disease. Lastly, the time trend in the annual percentage of notified cases over-diagnosed cases

was assessed using a linear regression model with variance-weighted least squares (15).

The pandemic years were defined in line with the WHO, considering the 2017–2019 period as non-pandemic and the 2020–2022 period as pandemic (16). All data were analyzed using Stata 17 (StataCorp. 2021. *Stata Statistical Software: Release 17.* College Station, TX: StataCorp LLC). The significance level was set at 0.05, and all tests were two-sided.

Emilia-Romagna's health administrative data are pseudonymized at the regional statistical office before analysis. Each individual is assigned a unique patient identifier, eliminating the possibility to trace the patient's identity or access other sensitive data. According to Article 9 of the General Data Protection Regulation (EU Regulation 2016/679), pseudonymized administrative data can be used without specific written informed consent when patient information is collected for healthcare management, quality evaluation, and improvement. Moreover, because the elaborations presented in this work are part of the surveillance activities of a public health institute, no institutional review board approval was required.

Results

We observed 436 notified cases (source: SMI) between 2017 and 2022 and 2,482 diagnosed cases (source: MU) over the same period.

Table 1 summarizes the comparative analysis between 2017–2019 and 2020–2022, which showed an increase in the total number of foodborne diseases reported in the LHA of Bologna despite the lack of differences in diagnosed cases. During the COVID-19 pandemic years, there was a significant 34.4% increase in overall notified cases (P-value≤0.01). When examining gender differences, only males exhibited a statistically significant change, with an increase of 52.6% (P-value≤0.001); the change in reported cases among females, on the other hand, was negligible (+14.6%, P-value>0.05). Analysis stratified by age group revealed statistically significant changes in reported cases in the working-age and preschool populations, with increases of 71.8% (P-value≤0.01) and 52.9% (P-value≤0.05), respectively. MU data did not confirm these changes.

Table 2 provides a comprehensive overview of the annual notified cases of foodborne disease in the LHA of Bologna from 2017 to 2022, stratified by age group. A substantial increase of 300.0% (P-value≤0.001) was observed in schoolers aged 6–18 years in 2021, compared to 2020. Conversely, a significant decrease in notified cases (−77.8%, P-value≤0.001) was observed in the same population in 2020 relative to 2019. The category of *workers* witnessed a statistically significant increase in 2021 compared to the previous year (+133.3%, P-value≤0.05).

Discrepancies between notified and diagnosed cases were observed in all years, as shown in Table 1 and Table 3. The only significant change in SMI-reported cases was in 2021, with an increase of 60.7% (P-value≤0.01), while there were statistically significant results in 2020 (−19.1%, P-value≤0.01)

Table 1 - Average Annual Cases of Foodborne Disease Notified to the SMI in the Local Healthcare Authority of Bologna and Diagnosed by the Microbiology Unit in 2017–2019 vs. 2020–2022, Overall and by Gender and Age Group.

	SMI Notified Cases				MU Diagnosed Cases			
	2017/19	2020/22	Δ%	*P*-value	2017/19	2020/22	Δ%	*P*-value
All	62.0	83.3	+34.4	0.002	427.7	399.7	−6.5	0.096
Gender								
Male	32.3	49.3	+52.6	0.001	236.3	225.3	−4.7	0.390
Female	29.7	34.0	+14.6	0.385	191.3	174.3	−8.9	0.131
Age group, y								
Preschoolers (0–5)	17.0	26.0	+52.9	0.022	113.0	103.7	−8.3	0.290
Schoolers (6–18)	15.0	15.7	+4.4	0.917	88.7	90.7	+2.3	0.829
Workers (19–65)	13.0	22.3	+71.8	0.008	132.7	117.0	−11.8	0.093
Retirees (>65)	17.0	19.3	+13.7	0.566	93.3	88.3	−5.4	0.549

Abbreviations: SMI, *Sorveglianza Malattie Infettive* (Reporting System for Infectious Diseases);
MU, *Microbiology Unit (IRCCS Azienda Ospedaliero-Universitaria di Bologna).*

Table 2 - Annual Cases of Foodborne Disease Notified to the SMI in the Local Healthcare Authority of Bologna from 2017 to 2022, by Age Group.

Year	Preschoolers (0–5 y)		Schoolers (6–18 y)		Workers (19–65 y)		Retirees (>65 y)	
	n	Δ%	*n*	Δ%	*n*	Δ%	*n*	Δ%
2017	14	—	6	—	8	—	19	—
2018	21	+50.0	12	+100.0	17	+112.5	14	−26.3
2019	16	−23.8	27	+125.0*	14	−17.6	18	+28.6
2020	24	+50.0	6	−77.8***	12	−14.3	19	+5.6
2021	21	−12.5	24	+300.0***	28	+133.3*	25	+31.6
2022	33	+57.1	17	−29.2	27	−3.6	14	−44.0

* Significant at the 5% level.
** Significant at the 1% level.
*** Significant at the 0.1% level.
Notes: Percentage changes are calculated relative to the previous year.
Abbreviations: SMI, *Sorveglianza Malattie Infettive* (Reporting System for Infectious Diseases).

and 2021 (+21.9%, *P*-value≤0.01) for MU-diagnosed cases.

Lastly, a positive linear trend with an annual change of +2.2% (P-value≤0.001) was observed in the percentage of SMI notified cases relative to the number of positive MU tests (Figure 1), the only notable exception being the year 2020.

Discussion

The data analyzed in this study reveal a steady uptrend in the incidence of reported foodborne illnesses over the years. An anomaly was observed in 2020 when there was a noticeable decline in such cases. This deviation has been corroborated by the findings of Ray et al., 2020 (8). Subsequent data highlight a marked resurgence in cases the following year, aligning with the observations documented in the EU One Health 2021 report (17). Despite this positive trend in notified cases, the significant difference in absolute terms between lab-diagnosed and doctors' reported cases during 2017–2022 underscores the limitations of current reporting mechanisms.

Recent reports from the European Center for Disease Prevention and Control (ECDC) enable us to compare the data from this study with the European data from 2022. In 2022, several countries reported a stable trend in Campylobacteriosis cases compared to 2021, albeit lower than pre-pandemic levels (18). The number of confirmed cases of Hepatitis A in 2022 was like those in 2020 and 2021, significantly lower than in pre-COVID-19 years (19). Additionally, the number of reported Listeriosis cases in 2022 reached the maximum since observation began in the EU/EEA (20). While an increase in Salmonellosis cases

Table 3 - Annual Cases of Foodborne Disease Notified to the SMI and Diagnosed by the Microbiology Unit in the Local Healthcare Authority of Bologna from 2017 to 2022.

Year	SMI Notified Cases			MU Diagnosed Cases		
	n	Δ%	*P*-value	*n*	Δ%	*P*-value
2017	47	—	—	391	—	—
2018	64	+36.2	0.128	441	+12.8	0.089
2019	75	+17.2	0.396	451	+2.3	0.763
2020	61	−18.7	0.265	365	−19.1	0.003
2021	98	+60.7	0.004	445	+21.9	0.005
2022	91	−7.1	0.663	389	−12.6	0.057

Notes: Percentage changes are calculated relative to the previous year.
Abbreviations: SMI, *Sorveglianza Malattie Infettive* (Reporting System for Infectious Diseases); MU, *Microbiology Unit (IRCCS Azienda Ospedaliero-Universitaria di Bologna)*.

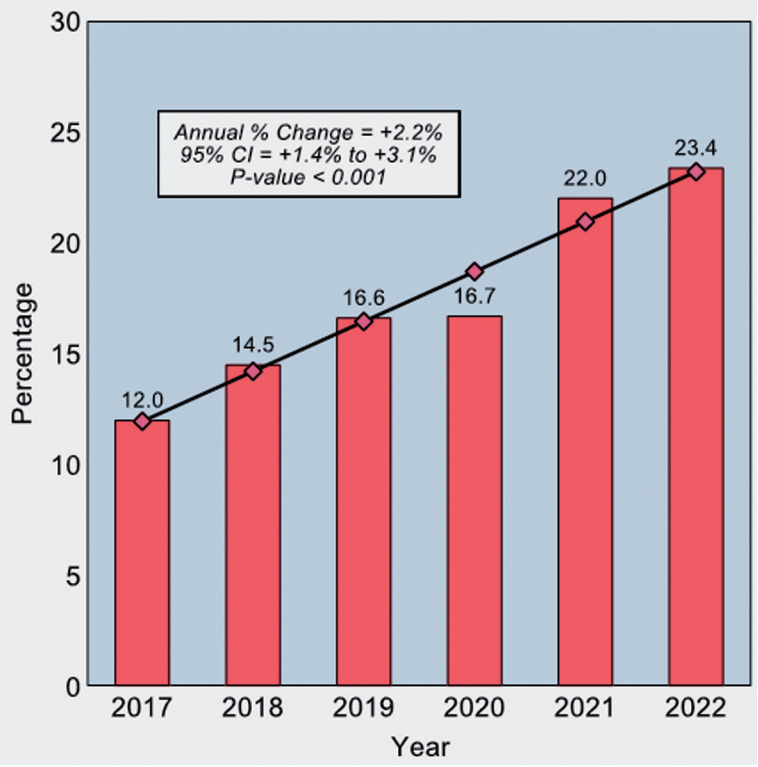

Figure 1 - Foodborne Diseases Notified to the SMI over the Number of Positive Laboratory Tests in the Local Healthcare Authority of Bologna between 2017 and 2022.
Notes: The time trend was assessed using a linear regression model with variance-weighted least squares.
Abbreviations: SMI, *Sorveglianza Malattie Infettive* (Reporting System for Infectious Diseases).

was recorded compared to the previous year of 5.4%, it marked a 16.8% decrease from pre-COVID levels in 2019 (21). Moreover, 2022 witnessed a 25% rise in Shiga toxin-producing Escherichia coli (STEC) infections in EU/EEA countries compared to the previous year (22). The cases of Shigellosis have been progressively increasing from 2020 to 2022, approaching the levels seen before the COVID-19 pandemic. However, there was a significant decrease in reported cases in 2020 and 2021 related to previous years (23). Furthermore, there was a 22.2% increase in reported cases of Yersiniosis in 2022, surpassing the numbers seen before the COVID-19 pandemic in 2018–2019 (24).

As previously reported, the three-year pandemic from 2020 to 2022 requires an in-depth analysis to explain the observed inconsistent trends. The scientific literature provides numerous examples of a decline in reporting infectious diseases during the COVID-19 pandemic (25-29). Several potential explanations could be considered, such as the impact of the pandemic on data collection and reporting systems and the use of non-pharmaceutical measures implemented from 2020 onwards. Furthermore, the closure of workplaces, schools, and restaurants caused by the stay-at-home policy may have contributed to a limited spread of these diseases (8, 30-32). Additionally, the observed 34.4% increase in reporting to the LHA during the pandemic, contrasted with a slight decline in laboratory diagnosis data, suggests that heightened focus on infectious disease reporting during COVID-19 may have influenced healthcare workers' reporting behavior, potentially leading to an increased propensity to report cases.

To significantly reduce bureaucracy and streamline the reporting process, it is imperative to establish a direct reporting mechanism where laboratories communicate infectious disease data directly to LHAs. By eliminating unnecessary intermediaries, this approach will ensure that critical information flows swiftly from the point of data generation to those responsible for public health decision-making. This direct line of communication would not only cut down on the time delays typically associated with multi-step reporting processes but also reduce the risk of data distortion or loss that may occur when information

passes through multiple channels.

With laboratories reporting directly to LHAs, the process would become more efficient and less prone to bureaucratic slowdowns. This efficiency allows public health officials to respond more rapidly to emerging threats, receiving real-time data without the administrative bottlenecks that often plague traditional reporting systems. Moreover, this streamlined approach would enable a more agile response to outbreaks, where timely data can be the difference between containment and widespread transmission.

Implementing direct laboratory-to-LHA reporting also fosters greater accountability. Laboratories would be responsible for the accuracy and promptness of the data they provide, knowing that any delays or inaccuracies have immediate implications for public health. This accountability would drive improvements in the quality of data reported, further enhancing the overall effectiveness of the public health surveillance system.

Foodborne diseases pose a significant public health concern, and physicians should be well-versed in diagnosing and managing them (33, 34). Vigilance against these illnesses is crucial, given their potential for severe complications, especially among susceptible populations (35), such as the elderly (36).

Further research is needed to understand the reasons behind the gap between notified cases and diagnoses and to determine whether this trend is present in other regions of Italy or the world (37).

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Ethics approval: This study complies with the Declaration of Helsinki. According to Article 9 of the General Data Protection Regulation (EU Regulation 2016/679), pseudonymized administrative data can be used without specific written informed consent when patient information is collected for healthcare management, quality evaluation, and improvement. Moreover, because the elaborations presented in this work are part of a public health institute's surveillance activities, no institutional review board approval was required.

Riassunto

Esplorare il divario tra casi notificati e diagnosticati di Malattie Trasmesse dagli Alimenti: evidenze da un'analisi dell'andamento temporale in Italia

Introduzione. Le malattie trasmesse da alimenti rappresentano un grave problema di salute pubblica a livello globale, causando una significativa morbilità e mortalità in tutto il mondo. La pandemia di COVID-19 ha avuto effetti su vari aspetti della vita, compresa la catena di approvvigionamento alimentare, con un potenziale impatto sull'incidenza delle malattie di origine alimentare. Questo studio si propone di analizzare le differenze tra casi notificati e casi diagnosticati e di indagare il potenziale impatto della pandemia di COVID-19 sulle malattie trasmesse da alimenti nell'area metropolitana di Bologna, Italia.

Disegno dello Studio. È stata condotta un'analisi retrospettiva dell'andamento temporale usando due fonti informative.

Metodi. L'Azienda USL di Bologna ha raccolto i dati attraverso il sistema di segnalazione delle malattie infettive dell'Emilia-Romagna nell'arco di sei anni (2017-2022), compresi tre anni di pandemia di COVID-19. Questi dati sono stati confrontati con le informazioni raccolte nello stesso periodo presso il laboratorio di microbiologia che serve l'intera area metropolitana di Bologna. I metodi statistici includono variazioni percentuali, test binomiali, medie annuali, stratificazione per genere ed età, e modelli di regressione.

Risultati. È stato riscontrato un aumento (+34,4%, P≤0,01) dei casi notificati durante la pandemia rispetto al periodo pre-pandemico. Tuttavia, non sono state osservate differenze nei casi diagnosticati confrontando i due periodi. L'anno 2021 ha visto un aumento significativo dei casi segnalati di malattie trasmesse da alimenti tra la popolazione in età scolare (+300,0%) e in età lavorativa (+133,3%) rispetto al 2020. D'altra parte, i casi diagnosticati sono diminuiti significativamente nel 2020 (-19,1%, P<0,01) e aumentati nel 2021 (+21,9%, P<0,01). È stata riscontrata una netta differenza, in termini assoluti, tra i casi notificati e quelli diagnosticati in tutti gli anni di studio (2017-2022).

Conclusioni. Questo studio evidenzia la discrepanza tra i casi notificati e quelli diagnosticati di malattie trasmesse dagli alimenti e di come la pandemia di COVID-19 ha incrementato le notifiche senza influenzare la loro trasmissione. Questi risultati contribuiscono alla discussione in corso sul miglioramento dei sistemi di segnalazione delle malattie trasmesse dagli alimenti.

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How outdoor and indoor green spaces affect human health: a literature review

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Keywords: Green spaces; biophilia; restorativeness; human health; forest therapy; ecosystemic services
Parole chiave: Spazi verdi; biofilia; restorativeness; salute umana; terapia forestale; servizi ecosistemici

Abstract

***Background**. The analysis of the complex interactions between outdoor or indoor greenness and the health of individuals and ecosystems is a topic of current and growing interest.*
***Study design.** This review aims to examine and summarise the results of studies conducted to evaluate the effects of exposure to greenness on various aspects of human health and the natural environment.*
***Methods.** For this purpose, in April 2024 we searched PubMed, Web of Science, and Scopus databases, Google Scholar and specialised books.*
***Results.** Evidence gathered demonstrates a remarkable correlation between exposure to outdoor and indoor greenness and the improvement of mental health, including the reduction of stress, anxiety, and depression. Contact with greenness is also associated with improvements in physical health, such as reductions in blood pressure, heart rate, and inflammation, as well as in cognitive abilities, concentration, and overall recovery.*
These benefits are recognisable both in outdoor spaces, such as urban parks, oases, and public gardens, and in indoor spaces, through the introduction of plants and nature-evoking elements in living and working environments. The presence of vegetation in indoor environments, such as offices, schools, healthcare facilities, prisons, and others, can contribute to improving the quality of social spaces, fostering communication, and collaboration, and attenuating aggressiveness and inequalities, thereby increasing employee satisfaction and work efficiency. The combination of outdoor/indoor green spaces and the well-being of the living environment includes exposure to greater biodiversity, mitigation of extreme weather events, absorption of atmospheric pollutants, attenuation of urban background noise, and increased privacy. The presence of vegetation in urban areas has a positive impact on social cohesion, promoting interpersonal interaction and facilitating the development of more cohesive and inclusive communities, thus supporting a sense of belonging and collective identity.
Conclusions. *In conclusion, these results underline the importance of considering contact with greenness as a fundamental element in promoting the psychophysical health and well-being of individuals and ecosystems, suggesting the adoption of nature-based therapies and interventions in public health policies and urban planning practices.*

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Introduction

In recent years, interest in green spaces, both indoors and outdoors, has increased rapidly. Research in the field demonstrates a growing interest in the positive effects of such spaces on human health, the urban ecosystem, and the natural environment in general. However, it is crucial to delve deeper into analyses to fully understand the impacts and maximise the benefits of this relationship between humans and nature, particularly in light of ongoing climate changes.

Climate change appears to induce a broad spectrum of adverse effects on public health, along with an increase in the risk of infectious diseases, psychiatric disorders, cancer and other diseases (1). Moreover, in recent years, extreme climate has induced a decline in greenness (2,3). Specifically, since the beginning of the century, a total of 243 large-scale vegetation decline events have been identified (2). Furthermore, the current trend highlights a simultaneous burgeoning process of global urbanisation. It is estimated that by 2050, there will be a 68% increase in urbanised areas accompanied by a rise of 2.2 billion urban residents, primarily concentrated in Africa and Asia (4). With the anticipated urbanisation surge, the importance of outdoor and indoor green spaces emerges as an updated tool for designing healthier and more habitable environments to promote more resilient and sustainable urban communities.

Nevertheless, scientific literature reveals a lack of comprehensive classification and a clear definition of green space (5). This issue primarily stems from the complexity and diversity of green spaces, which can significantly differ in size, physical characteristics, functions, and management methods. In summary, the concept of urban greenness, both outdoor and indoor, is generally conceived as green environments with vegetation presence, including mainly urban public parks, non-built and/or open areas, tree-lined streets, or areas with herbaceous and shrubby vegetation suitable for recreational activities, as well as remnants of adjacent or internal city forests (6–10). Within certain disciplines in the context of natural and life sciences, a more specific meaning is attributed to the concept of green space, associating it with protected areas such as natural reserves, conservation areas, and national parks. Definition ambiguity is particularly evident when identifying private outdoor green spaces, such as urban gardens, historic parks, urban orchards, porches, courtyards, and loggias with mixed vegetation, botanical gardens, balconies, windows, and alleys adorned with green elements, vertical gardens, or green roofs, or tree-lined streets or private passages, as well as indoor urban greenness consisting of ornamental plants, a significant element of living environments which has not been fully understood, yet (11).

Terminological ambiguity occurs both within and among disciplines, and this ambiguity makes it difficult to find meaningful understanding in published literature (5). Complexity also arises in the analysis of interactions between humans and green spaces – primarily indoors – which are arranged with digital accessories, high-definition prints, or synthetic reproductions that simulate natural greenness. In this context, the qualitative and quantitative measurement of green spaces fluctuates within the methodology applied in various studies, adapting to the research scenario and objectives.

In light of this complexity, the availability of an overview concerning the effects on human health of urban outdoor and indoor green spaces is crucial for urban designers and health professionals. Considering all of the above, the primary objective of this narrative review is to analyse the extensive range of literature available on the potential benefits for human health and the ecosystem derived from the design and conservation of green spaces, both indoor and outdoor, in living and care environments. In addition to examining the impacts on residential comfort in urban areas, we will also focus on the importance of ecosystem services offered by such spaces in combating ongoing climate changes. Furthermore, the work aims to contribute to updating sustainable urban practices focused on collective well-being, suggesting a deeper exploration of forest therapy as support for health protocols.

Methods

Given the vastness of the topic and the diversity of relevant papers, we used a narrative approach to summarise the literature, searching the following databases in April 2024: PubMed, Web of Science, Scopus, and Google Scholar. The aim was to identify scientific publications, research articles, specialised books, and other relevant documents. This methodological approach involved the use of specific keywords such as “urban greenery”, “indoor and outdoor greenery”, “green spaces”, “natural space”, “green structures”, “forest therapy”, “biophilia”, “nature therapy”, “biogenic volatile organic compounds”, “ecosystem services”, “territorial planning”, “nature-based solutions”, “heatwaves”, “climate changes”, “health”,

"well-being", "mental health", "hospital admissions", "pollen allergies" and "restorativeness".

The selection of studies followed a procedure that included title screening, abstract reading, analysis of keyword presence in the full article, searching for relationships among keywords, examination of cited literature, and consultation of cited articles. During this phase, particular attention was paid to the relevance of keywords across various disciplinary domains. The diversity of study protocols and the resulting heterogeneity of results made statistical meta-analysis impractical.

Articles that were not peer-reviewed and those that did not meet the predefined inclusion criteria (e.g., molecular biology or chemistry studies, studies specifically investigating biodiversity conservation) were excluded from the study. Additionally, extensive use was made of paper and book resources available at the library system of the University of Camerino (Italy) to ensure a higher quality of the review.

Results and discussion

This review of the scientific literature was carried out to explore the interactions and complex interplay of relationships characterising indoor and outdoor greenness, in light of current climatic and anthropological dynamics. The aim was to investigate the interactions among these components and the health and well-being of individuals, as well as the integrity of urban and natural ecosystems.

The results derived from retrieved studies were qualitatively analysed and discussed to identify the primary interactions and emerging trends concerning the effects of green exposure on human health and the natural and built environment.

How Nature and Urban Greenness, both Outdoor and Indoor, can influence Living, Health, and Human Well-being

The interaction between the environment and human health is a complex topic, and still not fully understood to date, especially when attempting to synthesise and correlate data from various disciplines. Urban green space, both indoor and outdoor, can be defined as a setting characterised by the presence of vegetation or individual plants. Interactions with green space, and their effects on human health (direct and indirect), vary based on a diverse array of experiences and variables involving social, economic, environmental, spiritual, political, and behavioural aspects of specific individual or group dynamics (Table 1).

Urban green space, both outdoor and indoor, serves as a component bridging the anthropological with the ecological dimension, and it is within this context that humans form relationships and engage in various activities, occupying and inhabiting spaces.

In this context, architecture plays a pivotal role. Architecture is a discipline that shapes space to fulfil the diverse needs of humans; evolving continuously, buildings have primarily been conceived as abstract objects or formal compositions. However, Harry F. Mallgrave, a historian of American architecture, asserted that, based on neuroscientific discoveries such as those of mirror neurons, architecture is primarily an embodied experience that encompasses the entire mind-body-environment relationship (12). In support of this, a recent umbrella review suggests that acting on the built environment has a positive impact on mental health and social inclusion (13).

Perceiving spaces is defined as establishing an empathetic relationship with them, through which our psycho-physical and emotional apparatus aligns with environmental stimuli and is influenced by them. Individuals with easy access to natural environments near their living areas are overall healthier compared with others lacking this condition.

One of the proposed guidelines is the '3–30–300 rule' for urban forestry: at least 3 well-established trees in view from every home, school, and place of work, at least a 30% tree canopy in every neighbourhood; and less than 300 m to the nearest public green space from every residence (40). The long-term indirect impacts of nearby nature also include higher satisfaction levels with one's home, work, and life in general (41).

According to John Agnew's definition of place (42), any discussion involving green space should encompass at least three notions. The first is the placement of green space within physical space. The second involves the localisation and description of as much environmental information as possible, including flora, fauna, microbiota, air quality, soil conditions, drainage systems, microclimatic conditions, and artificial structures. The last, and most significant, notion encompasses all interactions between humans and green space, reflecting how humans can utilise green space and how green space can influence their lives (43).

In recent centuries, there has been an extraordinary disengagement of humans from the natural environment. Never before in history have individuals spent so little time in physical contact with animals and plants, and the long-term consequences of such behaviour

Table 1. Green spaces' direct and indirect factors leading to beneficial effects in humans.

Type of effect	Description	Key Publications
Direct		
Psychological Well-Being and Health Improvement	Improvement of mood, reduction of stress and anxiety, and enhancement of overall mental well-being through the presence and use of green spaces	(14–21)
Attentional restoration	Improved attention span and reduction of mental fatigue through exposure to natural environments	(22,23)
Biophilia	Innate and positive connection of humans with nature, enhancing the sense of belonging and aesthetic pleasure	(24,25)
Indirect		
Reduction of air pollution	Plants in green areas can absorb air pollutants, improving air quality and reducing the risks associated with respiratory diseases	(26–31)
Noise reduction	Green areas can function as natural barriers, attenuating ambient noise levels, improving sleep quality and reducing stress associated with noise	(32,33)
Increased physical activity	The presence of parks and green areas encourages outdoor physical activity, which contributes to the prevention of chronic diseases such as obesity and cardiovascular diseases	(34–36)
Temperature reduction	Green areas can mitigate the urban heat island effect, helping reduce local temperatures and improve thermal comfort	(37–39)

are unknown (44). Some research has already demonstrated that excessive artificial stimulation and an existence spent in purely man-made environments can lead to exhaustion and a decline in vitality and health. Modern society, by its very nature, isolates people from external environmental stimuli and regular contact with nature (45,46).

There are different types and indicators of green space. Vilcins and co-workers (47) provided an overview, classifying the exposure type in passive 'indirect' (e.g., view of greenness from a window), passive 'accidental' (e.g., walking past street trees) and active 'intentional' (e.g., visiting a park), and indicators in five groups, namely 'greenness', 'open space and parklands', 'quality of parklands or open space', 'vegetation cover', and 'biodiversity', underlining the complexity of such interaction and the importance of understanding it.

An ideal context for privileged contact with nature is the search for Soplicowo. Soplicowo is an imaginary term, described by the author Adam Mickiewicz (1798-1855), in the poem Pan Tadeusz. The term is connected to the environment of the great forests of Poland including that of Bialowieza, and identifies the "place" or "lived experience", referring to the moment of direct contact with nature through an imaginative empathic experience, an intimate and profound moment to experience and in which one can participate from the perspective of another (48). This idea, theorised by Professor Franco Pedrotti (botanist, Professor Emeritus at the University of Camerino, Italy), also explains that this contact seems possible in two different forms, but the emotions experienced are always the same in both cases. The first modality refers to contact with nature in places where it manifests itself in a grandiose and exceptional way, such as a large forest, a mountain range, a cliff along the ocean coast and other pristine environments and landscapes. The second mode refers to contact with nature where it appears in minor, even very limited aspects, such as an isolated tree, a hedge, a meadow, and so on. Minor but sufficient to evoke emotions, benefits, and interests.

Soplicowo can also be interpreted as the search for a mental state through a suitable congruous contact with nature: the famous Garden of Eden, present and fundamental for all human cultures which stimulates and reconciles the relationship with the whole, inspiring, relaxing the feeling towards nature or creation (48).

The fundamental point is to observe nature in all its manifestations. However, it is necessary to know how to do it, and observing it is the simplest and most direct means to derive enjoyment from it. Seeing animals and plants adds an extra dimension; nature is valued by simply observing it, creating awareness and empathy that are the foundations of the will to preserve it (49).

The presence of nature in inhabited places also represents a spiritual connection between humans and the natural environment in which they live. Traces of such interaction are manifold and are still visible in urban environments, as well as in isolated areas, where

small remnants of ancient nature such as patches of ancient forests or monumental isolated trees are still used today as retreats for prayer and meditation, near monasteries and hermitages (50). It is hard to historically identify when and how humans began to consider green space as an architectural element to design and inhabit according to their needs. In the Western World, since the 4th century, particularly in Europe, it is conceivable to place the first green space projects, with the function of refreshment and relief, near charitable structures (hospitium), where pilgrims, orphans, disabled individuals, elderly, wanderers, sick, and insane could find accommodation, care, and relief.

Another interesting relationship between humans and green spaces lies in the built environment, both indoor and outdoor. The increasing ability of humans to utilise natural resources as a source of research and design inspiration, as well as a source of natural materials, is indeed another form of tacit synergy and often assumes worrying distortions detrimental to human health and the urban ecosystem in general.

An example of this interaction lies in the 1900 Paris Exhibition, where the architect Renè Binet, for the construction of the Monumental Gate at the main entrance to the exhibition, sought inspiration from nature, inserting the vertebrae of a dinosaur, the cells from a beehive, rams, peacocks and poppies along with other stimuli from Ernst Haeckel's studies on radiolarian protozoa (51).

It has long been debated over whether nature is friendly and comforting or hostile and indifferent; however, the approach to well-being and human health in urban environments, both indoor and outdoor, requires a non-dualistic vision ideally based on ecological ethics and the evolution of multidisciplinary techniques and knowledge (52). It follows that when men suppress or destroy living forms, they dispose of things that are not theirs, they eliminate something that they had not given or produced and will never be able to return, thus transgressing a fundamental norm of biological ethics (52).

The fundamental objective of designing and revitalising anthropic environments is to ensure that health and well-being, in all their forms, are considered inspiring muses, thus promoting the increasingly relevant approach of biophilic design (53).

Lack of residential exposure to green space may result in premature mortality. A large study estimated the premature mortality burden due to lack of and unequal residential exposure to green spaces in 978 European cities and 49 greater cities, in 31 European countries (n = 169 134 322 residents aged ≥ 20 years old). A high mortality burden could be avoided if the WHO recommendation (54) for universal access to green space was achieved in these cities. In particular, estimates indicated that meeting the WHO recommendation of access to green space could prevent 42968 (95% CI 32296–64177) deaths annually using the normalised difference vegetation index (NDVI) proxy (20% [95% CI 15–30] of deaths per 100000 inhabitants-year), which represents 2.3% (95% CI 1.7–3.4) of the total natural-cause mortality. For the % of green area (GA) proxy, 17947 (95% CI 0–35747) deaths could be prevented annually. According to these data, expanding green space could avert a significant number of natural-cause fatalities in European cities each year. This emphasizes the need for policy interventions to improve the exposure of green spaces in cities and offer local estimates of the consequences. The registered green space distribution varied between cities and was not equally distributed within cities. Among European capitals, Brussels (Kingdom of Belgium), Paris (French Republic), Copenhagen (Denmark), Athens (Hellenic Republic), Budapest (Hungary), and Riga (Republic of Latvia) showed some of the highest mortality burdens due to the lack of green space. Urban interventions aiming to increase green space could promote better health and well-being while contributing to the development of sustainable and healthy cities (55).

Moreover, a meta-analysis of cohort studies highlighted an inverse association between surrounding greenness and all-cause mortality. Particularly, the pooled hazard ratio for all-cause mortality per increment of 0.1 NDVI within a buffer of 500 m or less of an individual's residence was 0.96 (95% CI 0.94–0.97) (18).

Restorativeness of Indoor and Outdoor Green Spaces on Health and Well-being

A key term, advocated by the Kaplan spouses and originating from environmental psychology, is 'restorativeness'. This term denotes the process of enhancing psycho-physical faculties derived from the environmental characteristics in which one finds themselves. Restorativeness identifies four fundamental elements: 'being-away', which pertains to the ability to psychologically and physically distance oneself from stress; 'fascination', whereby a place is rejuvenating if it does not require effort to be observed and presents pleasant stimuli from an aesthetic and acoustic standpoint; 'coherence', which promotes places that are familiar, welcoming, and comfortable; 'compatibility', which suggests that well-being is

enhanced in places one chooses to frequent.

According to Kaplan et al. (41) the concept of 'restorativeness' refers to the degree to which an experience, environment, or process contributes to the restoration of an individual's physical, cognitive, emotional, or social resources. This concept implies the capacity of an element or activity to promote renewal, refreshment, and individual well-being.

The association between restorativeness and natural environments has been the subject of numerous studies in the field of environmental and positive psychology (56). Within the realm of health and well-being research, several scientific studies have analysed the interactions between psychophysical health and indoor and outdoor green spaces, focusing on the restoration of health and improvement of well-being as crucial indicators to assess the effectiveness of such interactions. Contact with nature promotes health and well-being, and these benefits stem from multiple phenomena attributable partly to the visualisation of natural scenes and partly to being in close contact with natural environments (44).

Moreover, a meta-analysis provided evidence of greenness exposure's beneficial effects on cardiovascular health. In particular, the analysis showed that a 0.1 increase in NDVI was significantly associated with 2-3% lower odds of event, namely cardiovascular disease mortality [OR = 0.97 (95% CI 0.96–0.99)], ischemic heart disease mortality [OR = 0.98 (95% CI 0.96–1.00)], cerebrovascular disease mortality [OR = 0.98 (95% CI 0.97–1.00)], and stroke [OR = 0.98 (95% CI 0.96–0.99)] (57). However, the authors also claimed the need for further prospective and mechanistic studies to support their conclusions.

Furthermore, a meta-analysis showed that a high green space environment was significantly associated with a decreased diabetes mellitus prevalence [OR = 0.875 (95% CI 0.859–0.891; $p < 0.001$)] and mortality [Hazard Ratio = 0.917 (95% CI 0.904–0.930; $p < 0.001$)] (58). These findings corroborated results obtained in a previous systematic review, which found that higher exposure to green spaces reduces the risk of type 2 diabetes mellitus and the risk of being obese, and increases the likelihood of physical activity (59). However, there is the possibility that research tends to assume that the mere presence of nearby green spaces corresponds to an aware and active use of them (60).

Restorativeness and Psychological Well-being

Mental health is a multidimensional component that permeates various spheres of individual life, reflecting a rich and complex area of inquiry within specialist literature. This concept has traditionally been explored through various parameters such as mood, social relationships, autonomy, as well as the sense of belonging, unity, socialisation, and peer support. Additionally, significant is the role of safe and supportive environments, the promotion of individual freedom, and the process of recovery from mental disorders or psychological distress. The nature deficit disorder theory, proposed by the pedagogue and researcher Richard Louv, demonstrates that too little connection with nature impairs well-being, causing concentration difficulties, stress, anxiety, and depression (61). The global burden of such mental disorders has been estimated. In particular, 418 million disability-adjusted life years (DALYs) could be attributable to mental disorders in 2019 (16% of global DALYs). The global economic value associated with this burden is estimated at USD 5 trillion, and corresponds, at a regional level, to about 4% of gross domestic product in Eastern sub-Saharan African countries and 8% in North American countries (62).

Scientific studies have associated psychological improvement, along with reduced levels of stress and the ability to relax, with the enhanced well-being experienced from being in a natural environment (63). Furnass discovered that the experience of nature can help strengthen the activity of the right hemisphere of the brain and restore harmony in organ functions as a whole (64). An hour-long walk in nature (e.g., urban park, garden, etc.) attenuates the harmful effects of the urban environment, potentially reducing the risk of mental disorders, via a mechanism which involves a decrease in amygdala activation (65).

According to a study conducted by the National Research Council of Italy (CNR) and Club Alpino Italiano (CAI), pre-post percentage changes in synthetic indices of moods following forest therapy sessions were as follows: anxiety (–79%), depression (–74%), hostility (–77%), energy (+13%); effort (–45%) and confusion (–56%) (66).

In outdoor green-designed environments (e.g., therapeutic gardens, orchards, urban parks), psychological recovery is accentuated in areas perceived and identified as safe to visit – although people's feelings of social safety depend on the level of urbanisation (67) – through clear architectural identity, simple design with easily identifiable paths and entrances, capable of offering atmospheres regulated based on the activities to be carried out, thus providing either a more private environment or one more suitable for socialising (63). The sense of security is further

amplified by the presence of staff to support users or provide balanced support in the activities carried out in that environment, as well as the absence of dirt or the presence of adequate lighting. However, the quality of the environmental settings – which include, in addition to what was mentioned above, esthetics, walkability, biodiversity, or the availability of social activities – is still poorly explored in scientific literature, as pointed out by a recent systematic review analysing the effect of nature exposure on children's psychological well-being (68). In this review, in which most of the selected studies yielded statistically significant but weak to moderate effects, the authors also highlighted a need for further longitudinal studies, which typically provide more robust evidence of causality than cross-sectional designs.

Restorativeness and Stress Recovery

Scientific studies concerning the relationship between health and green spaces in parks or therapeutic gardens within healthcare settings reported positive outcomes in debilitated patients and caregivers. Individuals suffering from stress-related issues such as burnout, depression, and anxiety may experience shorter periods of illness, fewer symptoms of anxiety and depression, and a higher level of well-being and recovery if they spend time or work in outdoor environments as part of their treatment (63).

Psychophysiological stress recovery is facilitated by exposure to emotional stimuli derived from natural environments, through the enhancement of positive emotions, the reduction of anger, aggression and fear (69), as well as the restoration of strength and a decrease in confusion states (70).

Restorativeness in Healthcare Settings

Restorativeness, within the context of healthcare, pertains to the capacity of environments, interventions, or processes to contribute to the recovery and well-being of individuals. In healthcare settings, fostering restorative environments plays a crucial role in promoting patient healing and enhancing the well-being of healthcare professionals (71). A study demonstrated that even a short break in outdoor and indoor green areas (such as courtyard gardens, healing gardens, terraces, and green atria) reduces stress for healthcare staff, especially during extreme emergencies such as those encountered during the COVID-19 pandemic (70).

Contact with the natural cycle allows the mind to quieten, instilling a sense of calm (72). When engaging with nature (e.g., a garden, a natural landscape, the sight of trees and animals), sensory processes are triggered, aiding individuals in relaxation by distracting from inner thoughts, general stress, and concerns. They feel grounded in the environment, regain concentration (63), reduce fear, anxiety, or nervousness, muscle tension eases, and recovery improves, especially in cases of post-operative care (73).

The benefits derived from positive stimuli through contact with nature are integral parts of the fundamental mechanisms of optimal psychophysiological recovery. Ulrich, in his studies, argued that hospitalised patients had a more favourable recovery (shorter post-operative hospital stays, lower scores of post-surgical complications, fewer negative comments from nurses, and lower intake of strong analgesics) when their windows overlooked trees rather than a brick wall of a building (19,69). In the intensive care unit context, greenness and outdoor facilities are crucial not only to improve the well-being of critically ill patients, but also of their families and caregivers (74).

In hospital environments, interactions between patients and indoor and outdoor greenness have demonstrated beneficial effects, such as the reduction of aggressive behaviour (75), better pain control, reduced anxiety, and an increased level of patient satisfaction in accepting the care protocol. Also, in hospital settings, experiences involving distraction therapy with images and sounds of nature showed a significant reduction in the quality and intensity of pain in patients undergoing painful and invasive procedures, such as flexible bronchoscopy (76) or dressing changes in patients with burns (77).

Looking out the window and intercepting nature images (e.g., trees, cultivated fields, or parks) alleviate stress symptoms such as digestive disorders and headaches, with a consequent reduced need for assistance requests (78,79). Contact with nature has shown a positive impact on blood pressure and cholesterol, greater acceptance of treatments, reduced use of medications and nursing care, a peaceful view of life, reduced stress from highly anthropised environments, control of the spread of respiratory and mental illnesses, recovery from mental fatigue and severe stress (such as violence, mental illnesses, or addictions). In a public health and prevention context, in population health strategies, nature should be considered a fundamental health resource in disease prevention for urban populations worldwide (44).

The commissioning of increasingly significant research and scientific studies is verifying the role of forest therapy in human health. Forest therapy has proven effective in improving immune functions with

beneficial therapeutic effects on the physio-psychological health of urban residents through the lowering of blood pressure, alleviation of stress with reduced salivary cortisol (80) and a significant reduction in depression (81).

Forest therapy is now fully recognised among the many valuable ecosystem services offered by forests. Immersion in the forest produces direct and measurable effects with a broad-spectrum action that affects, among others, the psychological, neurological, cardiocirculatory, and immune spheres (66). Immersion in nature thus fosters a healthy detachment in the peace of green areas (e.g., gardens, orchards, natural parks, reserves, oases, etc.) that fascinate and soothe through colours, shapes, scents, and sounds where each element is in coherence with the others.

Restorativeness and Cognitive Development in Indoor and Outdoor Environments

Restorativeness is evident both indoors and outdoors. Incorporating elements of nature in indoor spaces and the availability of them in well-designed outdoor environments can have significant benefits for individuals' physical and mental health.

In work environments, interaction with green areas, combined with lighting control and sunlight penetration, mitigates the negative impact of work-related stress, reduces the intention to quit, and enhances overall well-being, positively influencing productivity (82). One study suggested that introducing foliage plants into the office environment can lead to improved health and a reduction in discomfort symptoms (–23%), particularly cough (–37%), fatigue (–30%), dry/hoarse throat and dry/itching facial skin (–23%) (83). Residential environments offering areas with abundant and diverse green components stimulate children positively, improving cognitive functions (84) and enhancing performance in tasks requiring attention and cognitive processing. Such conditions can also be achieved through listening to sounds and viewing images depicting natural environments (23,85), such as videos (86) or direct contact (e.g., excursions) (87). Moreover, when it comes to children, a study carried out in Spain (88) showed a beneficial association between exposure to green space and cognitive development, which was partly mediated by buffering against urban environmental pollutants.

Furthermore, research has highlighted that students with a view of nature from their room achieved higher scores in the test administered in the experiment compared with those with a non-natural view (89). These findings are corroborated by other works. A study conducted in Chile showed that higher school greenness was associated with improved individual-level academic outcomes among elementary-aged students, with associations of greater magnitude and strength for students attending public schools (90). Another work (in Brazil) found that greater exposure to green space surrounding schools is associated with higher academic performance, but the associations varied significantly depending on the type of greenness measures used (NDVI, distance from green spaces, and quantity of green spaces) (91). In particular, authors estimated that NDVI was positively associated with school-level academic performance, distance from green areas was negatively associated with academic performance, whereas the number of green areas gave mixed association results.

Three systematic reviews (92–94) confirm the beneficial effects of active or passive exposure to greenness and natural environments on youth development, neurodevelopment and various health outcomes. However, the authors agree that the great heterogeneity in methodologies and the diversity of domains within each outcome make it difficult to draw quantitative conclusions, calling for further longitudinal and mechanistic studies.

The positive effectiveness of interaction with nature seems to be helpful also in cases of immigrants, especially first-generation immigrants from rural backgrounds; by developing feelings of increased identity and integration (in addition to all the benefits described above), they were better able to tolerate the effects of detachment from their country of origin (44,95). Being in natural environments evokes a sense of 'oneness' with nature and the universe, and transcendental experiences have been reported, as well (96). An interest in scientific investigation is emerging regarding human testimonies that recount the relationship between the beneficial effects of care provided by certain plants in the recovery from severe psychophysical traumas (e.g., post-traumatic psychological disorders), with individuals attributing symbolic value to these same plants; this value is linked to the positive effect had in the trauma environment or to the general benefit obtained from contact with plants which are evocative of positive and regenerating memories (73).

When it comes to the elderly, a systematic review reported a moderate relationship between neighbourhood built environment (NBE) and cognition/dementia among older adults, highlighting the need for standardised and long-term NBE measures and high-sensitivity cognitive tests (97). Moreover, a

systematic review with dose-response meta-analysis provided some evidence of a slight inverse association between greenness and dementia at intermediate exposure levels (but not at high levels), underlining however that the available studies might have been affected by the lack of an adequate assessment of potential mediators and/or confounders (98).

The ecosystem services of the Indoor and Outdoor green spaces on the urban environment

Extensive experimental data and technical applications are found in the reviewed literature. However, as of yet, no generally accepted methods have been found that unequivocally establish the vital role that green spaces – in all of their forms – play in providing ecosystem services that benefit urban ecosystems and residential surroundings.

Indoor and outdoor green spaces are key in improving air quality by removing various air pollutants. While long-term exposure to airborne pollutants has been linked to a higher incidence of cardiovascular and respiratory diseases (99,100), neurodegenerative disorders (101) and birth defects (102), short-term exposure to ambient air pollution has been linked to exacerbated asthma that has led to an increase in hospital admissions (103). Exposure to a polluted air environment was also found to be statistically associated with a higher frequency of micronuclei (MN) in children (overall effect size = 1.57 [95% CI 1.39–1.78]), which is in turn potentially associated with several pathological states and a higher risk of developing chronic degenerative diseases (104).

Removing air pollutants also leads to an economic benefit. It has been estimated that the monetary benefit resulting from removing air pollutants such as PM_{10} in Ferrara (Northern Italy) amounts to about 2.12 million euros for 2019 and more than 47.000 euros for O_3 removal (105). In large cities, where air pollution is a frequent problem, careful planning of green spaces is crucial to not aggravate the weight of photochemical contamination (106).

During days of weather stability, with lack of ventilation, intense sunshine and specific humidity conditions (e.g., heat island effect), plants release to the atmosphere biogenic volatile organic compounds (BVOCs) that interact with nitrogen oxides (NO_X) from anthropogenic sources, contributing to the formation of atmospheric ozone. Ozone, peroxyacyl nitrates, aldehyde and ketones, hydrogen peroxide, secondary organic aerosol and particulate material can be formed by the photochemically driven reaction between NO_X, BVOC and anthropogenic VOC (AVOC) (106). Forests that emit isoprene near sources of NO_X pollution (such as metropolitan industrialized areas) can significantly contribute to O_3 formation and peak concentrations observed during the hot summer climate (107).

The creation of volatile organic compounds of anthropogenic origin (AVOC) and the rise in global temperatures are more significant factors contributing to the phenomena of photochemical smog pollution, which cannot be attributed to natural causes. Studies on the plant species best adapted to tolerate this kind of environmental stress may be found in scientific literature; this promotes a reduced atmospheric emission of BVOC (108).

In indoor environments, the main sources of volatile organic compounds (VOCs) come from a variety of sources such as cleaning products, building materials, furniture, cosmetics, deodorants, insecticides, heating devices, cigarette smoke, printers, photocopying machines, glues, paints, adhesives and various solvents. Among them, benzene and formaldehyde are the most dangerous compounds for human health. The associated risks are influenced by the individual's lifestyle and aggravated by the time spent in unhealthy environments; it has been estimated that an urban population typically spends more than 80–90% of its time inside buildings (109). Scientific studies conducted on common dwelling plants have demonstrated the effectiveness of a particular group of species in effectively reducing the concentration of pollutants such as VOCs, cleaning the indoor air and also playing a role in thermal regulation. Research conducted by the National Aeronautics and Space Administration (NASA) in the 1980s, as well as by other researchers (110), demonstrated the potential of plant systems to remove organic compounds (111,112). However, a review pointed out that some experimental conditions might not reflect those of real indoor environments. This may be caused by the dissimilarity between laboratory settings and real environments (e.g., air exchange rates, large volumes, and persistent VOC emissions) (113).

Also, the interaction between plant leaves and airborne microplastics has recently drawn researchers' attention. A recent study demonstrated that even small urban forests (less than 0.2 km^2) has the potential to accumulate more than 2 billion pieces of airborne microplastics per year, also suggesting that canopy leaves could be a long-term sink for this kind of pollutant (114).

Plants, by virtue of their physiology and their role in ecosystem dynamics, improve the quality of soil

and water by helping generate environments suitable for the survival of microorganisms, responsible for the main chemical reactions of decomposition of compounds of anthropic and biological origin (115). Vegetation, based on species-specific ecological adaptations, assumes the function of an environmental sentry capable of providing preliminary complex information on the ecology of a given area and also serves as a bioindicator in environmental monitoring (116).

The presence or absence of peculiar plant species suggests the possibility of being able to identify, in that area, the distribution of certain species of animals, the nature of the soil (alkaline or acidic), the water regime (dry or wet), the orientation of the slope (exposed to the South or the North), the hypertrophy of river waters or whether there are molecules that exceed the limit of tolerance of plants, producing toxicities which might be evident in the appearance of vegetation, the specific composition and the structure of plants (117). The stationary and fixed behaviour of vegetation offers an opportunity to obtain detailed, long-term data remotely, useful for developing models of prediction of water quality in relation to land use (118).

Vegetation has a positive influence on soil chemical and physical characteristics, and understanding the most suitable plant species is essential for effective planning of recovery and restoration of degraded environments. Natural forests have better vegetation characteristics and soil properties than plantation forests, so designing based on models that replicate natural ones would increase their effectiveness (119).

Significant positive interactions between the built environment and acoustic well-being are established in the properties of the vegetation to absorb or spread sound (120,121). Green facades, green walls and the soil on which plants are planted contribute to a dissipative function by destroying sound waves (122). In indoor environments, specific tests have confirmed that plants can absorb a significant amount of acoustic energy, especially in the presence of the soil substrate, which plays a predominant role in acoustical absorption. The barrier effect on the part of vegetation turns out to be a service capable of reducing the noise from point and linear sources (123). Moreover, field studies have demonstrated that thick trees and the regular arrangement of trees reduce the noise from a point source (123). The effects of environmental noise (e.g. noise from road, rail and air traffic and industrial buildings) on non-hearing health fall into the disturbance categories as well as sleep disorders, cardiovascular diseases and cognitive impairment in children; understanding workplace and environmental noise is therefore important for public health.

Moreover, indoor and outdoor green spaces play an important role in the conservation of animal and plant biodiversity, especially in highly urbanised areas. In this context, the habitat generated allows to accommodate animals that characterise the sound landscape of that green area (124). The barrier effect that develops from the presence of outdoor and indoor green areas, such as groves, areas dense with shrubs and trees or sieves, is also related to the search for domestic privacy or generally in open and often overcrowded environments. The presence of outdoor vegetation such as bushes and thick sieves also allows to moderate the microclimate, protecting both vehicles and structures from extreme weather events such as night frosts or excessive sunlight in the summer season.

When it comes to the reforestation of urban areas, researchers suggest the promotion of participatory approaches (citizens, local stakeholders, technicians and other experts) to address the primary needs of the local population concerning the social sphere (105). In order to bring about social change and enhance health outcomes, this type of approach emphasises the significance of forming relationships between investigators and the people for whom the research is primarily intended to be useful (125). They have been conducted on various populations, including young people and vulnerable communities, such as cancer patients (126–132). This approach may bring to an increased awareness and a deeper understanding of the contribution of ecosystem services to collective well-being. In a co-participating decision-making process, social interactions are promoted, strengthening the sense of belonging, participation and preservation. In addition, green spaces improve the quality of urban life by offering equally accessible opportunities for recreational activities and interaction with the natural environment.

This review has some limitations and strengths. The primary limitation of this analysis includes the potential presence of selection bias in the collected data and dependence on the availability and quality of consulted information sources, primarily stemming from the heterogeneity of study protocols, which may make it challenging to compare and synthesise results quantitively. For the same reasons, a systematic study quality assessment was not performed. Additionally, the retrospective nature of the included studies might constrain our understanding of causal relationships between greenness and health. Despite these limitations, this literature review provides a comprehensive

overview of the effects of greenness exposure on human health and the natural and built environment, underlining the importance of considering green as a fundamental element in promoting the psychophysical well-being of individuals and ecosystems, and suggesting the adoption of forest and nature-based therapies and interventions in public health policies and urban practices. Moreover, these results strongly open up new perspectives for nature and biodiversity conservation through the involvement of existing structures such as green areas, forests, nature parks, oases, and sites of conservation interest, and, given the potential for serious and irreversible adverse human health impacts of ecological degradation, closely connect ecosystems and human well-being in a One Health perspective.

Conclusions

In conclusion, several correlations were identified between green exposure and improvements in mental, physical, and overall health and well-being. The studies highlighted the benefits of both outdoor and indoor green spaces, which can positively contribute to individuals' psychological and physical well-being by providing a more relaxing, stimulating, and healthful environment, as well as increasing cognitive abilities, attention, and even stimulating creativity. The presence of vegetation can reduce stress, depression, and anxiety, as well as positively influence blood pressure and heart rate. Moreover, vegetation presence contributes to improving air quality and creating a healthier microclimate in both indoor and outdoor living environments.

Ecosystem services provided by forests and vegetation, such as water cycle regulation (e.g., the biotic pump theory (133)) and air purification, are essential for maintaining a healthy and sustainable urban environment, particularly in mitigating heat waves (134–137).

The presence of green areas in inhabited contexts can foster a sense of overall well-being in communities, promoting social engagement and reducing feelings of isolation by increasing the sense of belonging and stimulating spirituality. This encourages a more active and healthier lifestyle, encouraging people to spend more time outdoors and engage in physical activities. Furthermore, numerous studies have demonstrated that indoor and outdoor greenness has a positive impact on patient healing and recovery in healthcare settings. Practices such as forest therapy and nature contact should be increasingly adopted to enhance people's health and well-being, thanks to the beneficial effects of nature contact. Finally, nature-based solutions are gaining increasing attention in urban design practices, as they offer significant benefits for human health and the ecosystem by harmoniously integrating vegetation into urban spaces to improve quality of life and promote environmental sustainability.

The authors of most studies agree that prospective and/or mechanistic studies will help elucidate unsolved associations and draw quantitative conclusions. Future research should also move beyond the focus on green space presence or proximity, and integrate a deeper analysis of more specific aspects of individual agency that may influence use patterns and perceived psychological and well-being benefits.

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Riassunto

Come il verde esterno ed interno all'abitazione hanno effetto sulla salute umana: una revisione della letteratura

Introduzione. L'analisi delle complesse interazioni tra verde outdoor and indoor e la salute di individui ed ecosistemi è un argomento di attuale e crescente interesse.

Disegno dello studio. Questa revisione della letteratura ha lo scopo di esaminare e riassumere i risultati degli studi condotti per valutare gli effetti dell'esposizione al verde su vari aspetti della salute umana e dell'ambiente naturale.

Metodi. A tal fine, abbiamo condotto una ricerca bibliografica (aprile 2024) utilizzando PubMed, Web of Science, Scopus, Google Scholar e libri specializzati.

Risultati. Le evidenze raccolte dimostrano una correlazione tra l'esposizione al verde outdoor e indoor e il miglioramento della salute mentale, compresa la riduzione dello stress, dell'ansia e della depressione. Il contatto con il verde è anche associato a miglioramenti nella salute fisica, come la riduzione della pressione sanguigna, della frequenza cardiaca e delll'infiammazione, e nelle capacità cognitive, concentrazione e recupero complessivo.

Questi benefici sono riconoscibili sia negli spazi esterni, come parchi urbani, oasi e giardini pubblici, sia in spazi interni, attraverso l'introduzione di piante e elementi che evocano la natura negli ambienti di vita e di lavoro. La presenza di vegetazione in ambienti interni, come uffici, scuole, strutture sanitarie, carceri, ecc. può contribuire a migliorare la qualità degli spazi sociali, promuovere la comunicazione e la collaborazione, e attenuare l'aggressività e le disuguaglianze, aumentando così la soddisfazione dei dipendenti e l'efficienza del lavoro. La combinazione di verde outdoor e indoor e il benessere dell'ambiente abitabile comprende l'esposizione a

una maggiore biodiversità, la mitigazione degli eventi meteorologici estremi, l'assorbimento di inquinanti atmosferici, l'attenuazione del rumore di fondo urbano e l'aumento della privacy. La presenza di vegetazione nelle aree urbane ha un impatto positivo sulla coesione sociale, promuovendo l'interazione interpersonale e – tramite facilitazione dello sviluppo di comunità più coese e inclusive - sostenendo così un senso di appartenenza e identità collettiva.

Conclusioni. In conclusione, questi risultati sottolineano l'importanza di considerare il contatto con il verde come elemento fondamentale per promuovere la salute psicofisica e il benessere degli individui e degli ecosistemi, suggerendo l'adozione di terapie basate sulla natura e interventi nelle politiche di salute pubblica e nelle pratiche di pianificazione urbana.

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The impact of Mindfulness-based stress reduction on Covid-19 survivors. A randomized controlled trial

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Key words: Mindfulness-Based Stress Reduction; Intensive Care Unit; Long-COVID
Parole chiave: Riduzione dello stress basata sulla consapevolezza; Terapia Intensiva Long-Covid

Abstract

Introduction. *Long-COVID represents a clinical condition characterized by the inability of the patient who survived COVID-19 to regain the same state of health prior to the acute infection. Mindfulness-based stress reduction focuses on increasing awareness and acceptance of moment-to-moment experiences including difficult emotions and physical discomfort.*
Objective. To examine the effects of a Mindfulness-based stress reduction intervention on the functional and psychosocial outcomes of Long-COVID patients
Design. *A two-arm randomized controlled trial with repeated-measures design.*
Setting. *Department of Anesthesia and critical care.*
Participants. COVID-19 survivors (105 patients).
Methods. *The patients were randomly allocated to either psychoeducation (intervention group) or usual care (control group) (53 vs 52 patients per group). A Mindfulnes program was implemented in the intervention group included an 8-week Mindfulnes-program (2 hours per week) in a group format. Study outcomes included Chronic pain (pain intensity and pain interference) assessed with Brief Pain Inventory (primary outcomes), Anxiety and Depression assessed with Hospital anxiety and depression scale, Insomnia assessed with the Insomnia Severity Index. Data were collected at 6 month and 12 months after Mindfulness-program.*
Results. *A reduction in pain intensity and pain interference on some activities of daily living were observed 6 and 12 months after intervention. A statistically significant difference emerged in the mean score of symptoms of anxiety in favor of the intervention group (11.28 vs 13.15, t= -3.636, p< .001) at 6 month and at 12 months (10.88 vs 13.41, t= -5.167, p< .001) and in the mean score of the symptoms of depression in favor of the intervention group (9.95 vs 11.23, t= -2.823, p= .007) at 6 month and at 12 months (9.67 vs 10.69, t= -2.458, p= .018). Symptoms of insomnia were statistically reduced 6 months after the Mindfulness-program (score: 53.2 vs 30.4, x= 4.944, p= .026).*
Conclusions. *In light of what emerged from our study, we suggest a Mindfulness program in addition to drug therapy to be carried out once a year on patients with consequences of COVID-19. Studies with larger sample sizes that attempt to test a Mindfulness-program twice a year are needed.*

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Introduction

The SARS-CoV-2 pandemic has affected and continues to affect a very large number of individuals, with an enormous burden of disease and mortality (1). Although the clinical manifestations of the acute phase symptoms of the infection are relatively well defined, we observed the emergence, in an increasingly clear way, that the infection, after the end of the acute phase, can determine a heterogeneous complex of acute and chronic clinical manifestations that preclude a full return to the previous state of health (1).

The symptoms attributed to this condition are numerous and heterogeneous, they can concern subjects of any age, and with varying severity of the acute phase of the disease. The lack of a precise definition of this condition and the breadth of the symptoms' spectrum make epidemiological evaluation difficult (2). In fact, to define the epidemiology of the condition there is a need for a common definition to establish incidence, prevalence and risk factors and sociodemographic and clinical data to identify favorable factors and exclude confounding ones (3). However, it appears clear that, due to the unusual spread of the pandemic and the enormous number of people suffering from the acute infection, the persistence of significant symptoms, even if they affect only one part of the subjects suffering COVID-19, acquires great public health relevance in terms of number of patients and their care.

This need for assistance and treatment has been addressed in various ways, both from the point of view of clinical and instrumental diagnosis and from a management point of view, with the prompt creation in various locations of "post-COVID" clinics and clinics directly linked to varying degrees with general medicine and the hospital (4). The variety of symptoms and the age range of the affected population have clearly indicated the need for an integrated and multidisciplinary approach.

Long-COVID represents a clinical condition characterized by the failure of the patient to return to the same state of health enjoied prior to the acute infection (1). The mechanisms by which the infection determines Long-COVID have not yet been fully understood and defined. There is growing evidence that supports the hypothesis of a genesis caused by direct organ damage by the virus, but an innate immune response with release of cytokines could also involve inflammatory conditions or the development of a pro-coagulative state. The reasons why only some patients develop Long-COVID are currently unknown, although age advanced, female sex and hospitalization appear to be favorable factors (5). Even children, though rarely, may present sequelae of COVID-19 disease (6). Although there is no single symptom or test to diagnose Long-COVID, many patients complain profound asthenia, and a range of clinical symptoms that highlight the possible involvement of the majority of the body systems. For working people, Long-COVID can make it difficult to return to work, with obvious economic consequences and loss of working days (1). For older people the Long-COVID can have a significant impact on functional status and reduce their independence in carrying out daily activities (7).

The management of people with Long-COVID must be multidisciplinary to respond to the different clinical, functional, cognitive, psychological and nutritional manifestations. This approach must be personalized, modulated and adapted taking into account the variety of conditions that arise in the single patient. It is important to define timely and personalized follow-ups based on the characteristics and needs of each patient in order to re-evaluate the general conditions and plan new interventions, if necessary.

Non-pharmacological treatments for these symptoms are poorly understood.

Mindfulness Based Stress Reduction (MBSR) program is a Non-pharmacological treatment developed by Dr. Jon Kabat-Zinn in 1979 with some updates in recent years (8). Indeed, although initially developed for stress management, it has evolved to encompass the treatment of a variety of health related disorders such as anxiety, depression, skin diseases, pain, hypertension, diabetes and immune disorders (9). It employs mindfulness meditation to alleviate suffering associated with psychosomatic, psychiatric and physical disorders. Several specialized centers across the world offer MBSR as an alternative treatment option to patients. The MBSR programs include 2.5 hour/week, 8-weeks course with a 1-day retreat (8). Participants receive training in formal mindfulness meditation techniques involving simple stretches and postures.

An advantage of MBSR program is that these interventions have little risk and can increase the capability of patients to have control over their pain, mood swings and lives, as well as enhance quality of their life (9). Researches are warranted for investigation of the mechanism through which MBSR facilitates patients with chronic illnesses. This will lead to a better understanding of the applications of MBSR.

Aim

This Randomized Controlled Trial compared MBSR with usual care among patients who survived the acute phase of a SARS-COV-2 infection.

We hypothesized that adults with long-term consequence of COVID-19, randomized to receive MBSR, would show greater short- and long-term improvement in Long-Covid–related pain, anxiety, depression and insomnia - than those randomized to usual care.

Methods

Trial design

A two-arm randomized controlled trial, with repeated-measures design, was conducted from April 2023 to July 2024 (Figure 1). This study was prospectively registered at ClinicalTrials.gov (ClinicalTrials.gov ID: NCT05815693).

Participants

The study sample was recruited from one General Hospitals (Department of anesthesia) in Lecco, Italy from April 2023 to July 2024 (1 or 2 year after ICU discharged).

To identify eligible participants, the principal researcher examined the reasons for admission to the intensive care unit and approached potential patients for further assessment according to the study inclusion and exclusion criteria.

During the first interview the patients were asked: Do you remember suffering from problems such as anxiety, depression, chronic pain or insomnia before your admission to the Intensive Care Unit due to a SARS-COV-2 infection?

If patients being enrolled reported that they were suffering from pain, anxiety, depression and insomnia both before exposure to a SARS-COV-2 infection and after admission to the Intensive Care Unit they were not considered Long-COVID patients.

The inclusion criteria for Long-COVID patients was as follows: 1) patients with anxiety, depression, insomnia symptoms in drug therapy after ICU discharged; 2) patients with chronic pain on current drug therapy; 3) patients hospitalized in intensive care units in the years 2021-2022 for a Sars-CoV-2 infection; 4) patients older than 18 years; and 5) patients who, during enrollment, reported that they suffered from pain, anxiety, depression and insomnia only after SARS-COV-2 infection and after admission to the Intensive Care Unit.

Patients were excluded if 1) undergoing cognitive behavioral therapy before the COVID-19 event; 2) under 18 years of age; 3) affected with chronic

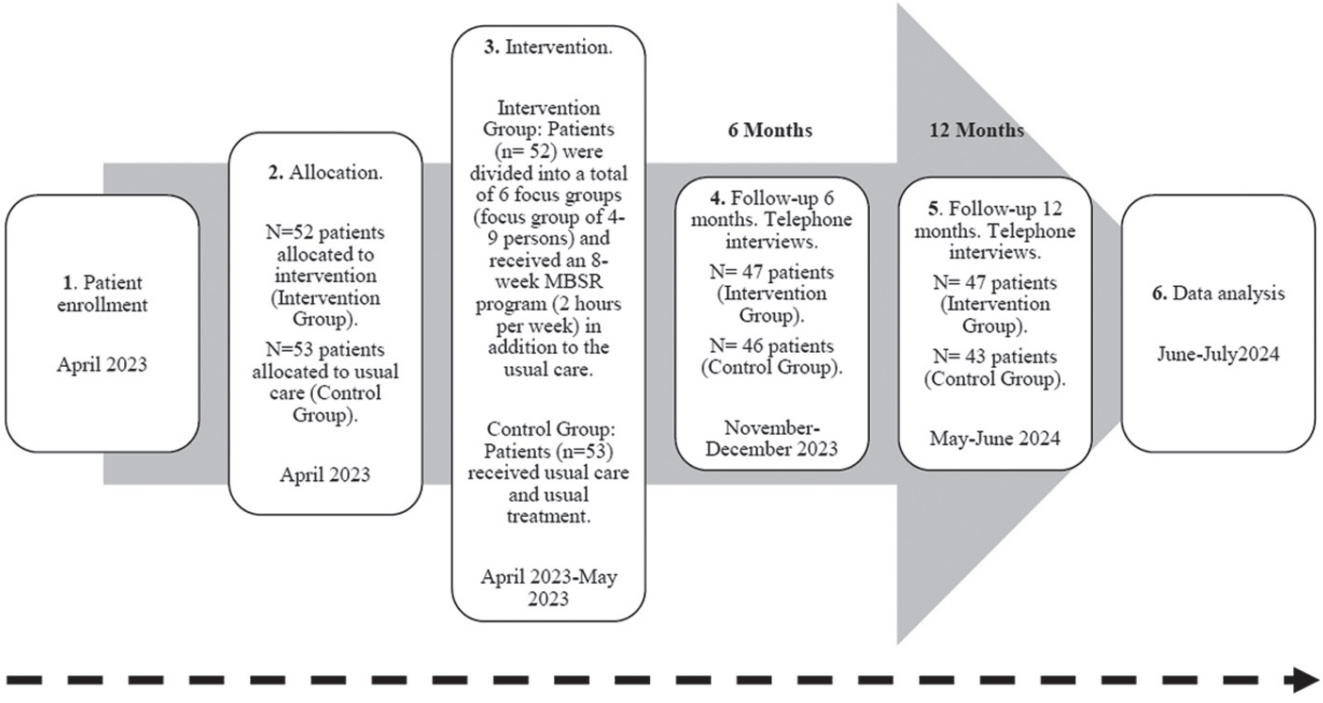

Figure 1 - Timeline for Study implementation and Mindfulness-Based Stress Reduction program.

cancer pain; 4) without current drug therapy; and 5) who reported during enrollment that they suffered from pain, anxiety, depression and insomnia prior to SARS-COV-2 infection and admission to the Intensive Care Unit.

Moreover, patients were required to demonstrate understanding of the study protocol and the ability to follow the instructions for the interventions and for filling questionnaires.

Experienced clinical nurses carefully referred those who met the criteria to the research staff and assessed patients. The participants who met the clinical criteria for this study were informed about the study and a written informed consent was obtained from each participant. Then the trained researchers presented participants with detailed information, and if the participant agreed to participate, an informed consent form was signed.

Sample Size

A priori estimation of sample size was based on the effect sizes calculated according to the similar clinical trials of MBSR approaches to patients (10).

In addition, we used our similar research to define the prevalence of symptoms in COVID-19 survivors after intensive care (11). One hundred and six (51.2%) patients between 6 and 12 months after ICU discharge reported at least one physical or cognitive impairment (7, 11).

We assumed a statistically difference by at least 5 % points in each issues (eg. reduction on the number of patients with anxiety, depression, insomnia) of BPI-pain intensity (four-items) between the MBSR and control groups at 12 months from enrollment.

Assuming to find 106 patients divided into 53 patients per arm, but assuming a hypothetical 18% dropout rate (n = 19), we aimed to recruit 125 participants (intervention group n = 63 vs control group n= 62). As the dropout rate was lower than expected, we stopped recruiting at 105.

Randomization

A randomisation sequence was generated, using an online programme (https://www.sealedenvelope.com/simple-randomiser/v1/lists), by a nurse who was not involved in the participant recruitment, intervention implementation, or outcome assessments of the present study. In each block, the two letters 'A' and 'B' indicated the intervention and control group, respectively.

The randomization was minimized, taking into account the imbalance between the groups over a number of prognostic clinical and demographic factors. With minimization, the treatment allocated to the next participant enrolled in the trial depends on the characteristics of those participants already enrolled.

Intervention

Introduction of the MBSR program among ICU patients was supported by ICU's staff after ICU's discharge.

The MBSR protocol is a structured and systematic program that uses mindfulness meditation as a central element to teach people to take better care of themselves and live a healthier and more adaptive life (8). The official MBSR protocol was developed by Jon Kabat-Zinn at the Center for Mindfulness at the University of Massachusetts and was created with the aim of facilitating stress reduction. Therefore, the specific objective of the MBSR course is to help participants reduce the level of subjective suffering and acquire and maintain greater well-being (8).

Detailed history-taking, including medical history, was provided to all participants, and written informed consent was obtained.

Participants included in the study received usual care with drug therapy, treatment, and evaluations during the study period.

In addition, patients received an 8-week MBSR program (2 hours per week) in a group format (focus groups of 4-9 persons each).

Patients were divided into a total of 6 focus groups (trying to respect the 12-month-period from discharge as much as possible). We managed to complete the 8 sessions in a total of two months (April-May 2023) (Figure 1).

In each of the 8 sessions carried out after ICU discharge, a different topic was addressed, in line with the MBSR program and our research protocol.

The themes of the individual sessions were:

1. Overview of mindfulness; 2. Facing difficulties; 3. Mindful breathing; 4. Staying present; 5. Allowing (letting it be); 6. Thoughts are not facts; 7. Taking care of yourself; 8. Dealing with future struggles.

The contents of each session concerned: psychoeducation, exercise and homework for each theme.

The original MBSR program was kept unchanged. However, we added a brief segment of psychoeducation to the first session to reflect on the distress of long consequences of ICU stay and of patients suffering from it, to show how Mindfulness-Based Interventions can be helpful for it. Finally, lectures and exercises on compassion were provided to the partecipants.

MBSR consisted of discussion and interaction among the participants in order to facilitate their learning, and of psychoeducation based on cognitive therapy and formal meditational exercises.

Homework was assigned to the participants at every session, which was supposed to take 20 - 45 minutes every day with a meditation-guide CD.

The therapists were clinical psychologists and nurses who had at least 5 years of Mindfulness experience and had undergone MBSR training provided by a Mindfulness Training Center, with an update course in the last three years.

The therapists followed the intervention protocol schedule at each session to ensure treatment integrity.

A research assistant directly observed the sessions and checked for treatment adherence.

There was no restriction on any co-interventions during the study period. However, patients were asked to refrain from participating in any type of Mindfulness-Based Interventions (MBIs) or from engaging in meditational exercises, yoga or other cognitive behavioral therapies during the study.

Measurements

General Characteristics

The study participants self-reported demographic characteristics (sex, age, education, marital status, caregiver, pain sites) using a structured instrument developed by the research team in a strictly individual interview, to protect each participant's privacy.

Outcomes and Instruments

We assessed pain with the Brief Pain Inventory-Short form (BPI-SF) (12). The BPI-SF is a brief, simple, self-administered questionnaire for evaluating pain, which addresses the relevant aspects of pain-history, intensity, timing, location and quality—and the pain's ability to interfere with the patient's activities. The short questionnaire we used is divided into two parts: Pain Intensity and Pain Interference. Pain intensity, with 4 domains, was rated on a NRS of 0 (no pain) to 10 (the worst pain imaginable) numeric rating scale (NRS). Pain interference with the 7 domains of functioning was rated on a NRS of 0 (does not interfere) to 10 (completely interferes).

In a previous validation study alpha coefficients for the pain severity and the pain interference scale were above 0.75 (12). The Italian version of the BPI-SF was carried out in 1996 (12).

We assessed anxiety and depression with the Hospital anxiety and depression scale (HADS). The HADS (13) is a 14-item scale designed to f1123assess anxiety and depression, with emphasis on reducing the impact of physical illness on the total score. The HADS includes seven items related to anxiety and seven related to depression, resulting in two scales, one for anxiety (HADS–A) and one for depression (HADS–D). The items concerning the concept of depression tend to focus on the anhedonic symptoms of depression. For each scale, the scores collected indicate: no problem score 0-7; mild problems score 8-10; moderate problems score 11-14; severe problems score 15-21. In a previous validation study the sensitivity and specificity for both HADS-A and HADS-D were approximately 0.80 (13).

The Italian version of the HADS was prepared in 2011 (14) and recently updated to 2020 (15).

We assessed the insomnia with the Insomnia Severity Index (ISI). The ISI (16) is a 7-item self-report questionnaire assessing the nature, severity, and impact of insomnia. The usual recall period is the "last month" and the dimensions evaluated are: severity of sleep onset, sleep maintenance, and early morning awakening problems, sleep dissatisfaction, interference of sleep difficulties with daytime functioning, noticeability of sleep problems by others, and distress caused by the sleep difficulties. A 5-point Likert scale is used to rate each item (e.g., 0 = no problem; 4 = very severe problem), yielding a total score ranging from 0 to 28. The total score is interpreted as follows: absence of insomnia (0–7); sub-threshold insomnia (8–14); moderate insomnia (15–21); and severe insomnia (22–28). In a previous validation study ISI internal consistency was excellent for both samples (Cronbach α of 0.90 and 0.91) and a cutoff score of 10 was optimal (86.1% sensitivity and 87.7% specificity) for detecting insomnia cases in the community sample (15). The ISI questionnaire maintains good psychometric properties in the Italian version, thus confirming that this instrument is reliable for detecting insomnia severity and identifying patients' symptoms (16).

We assessed the adherence to the intervention. The participants' adherence to the intervention was assessed using frequency of attendance at the MBI program. The patients who attended less than four (out of eight) sessions were considered dropouts, in line with the study protocol.

Quality control

Controls and quality standards were maintained throughout the study.

Researchers with unified training collected the relevant data, followed up, and stored the data in a dedicated electronic database. One researcher was assigned to check the data entries from each patient, and a third-party statistics agent rechecked all entries. In case of extreme or missing values, or in case of missing answers to the questionnaires the data were rechecked by the project coordinator.

Validity and Realibility

The research protocol was pilot tested prior to the beginning of the study among the research group.

Interventionists utilised a protocol manual to ensure intervention fidelity. Psychotherapeutic staff, physicians and nurses, were trained to ensure consistency. The participants of both groups did not participate in other studies during the intervention period and continued to participate in previously started activities.

None of the participants involved had carried out any previous mindfulness practices prior to our study.

Statistical analysis

Outcome data were analyzed and reported according to the CONSORT guidelines (17). We examined the differences at baseline (clinical-demographic data collected at enrollment), at 6 and 12 months between the intervention and control groups, and between participants who withdrew and those who remained in the study by means of chi-square and independent samples t tests.

Normally distributed measurement data were represented by means and standard deviations accordingly. Measurement data with non-normal distributions were represented by medians and interquartile ranges (IQR), and the number of cases or percentages represented the counting data.

All statistical analyses were performed using IBM SPSS software (version 25.0; IBM, Armonk, NY, USA), with the significance level set at 5% (two-tailed).

The independent t test or chi-square atests were applied to assess homogeneity between the intervention and control groups at 6 months and 12 months as appropriate.

Ethical approval and informed consent

The LONGCOVID trial was registred at ClinicalTrials.gov (ClinicalTrials.gov ID: NCT05815693) (ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt

Release Date: March 28, 2023; first patient enrolled 09/04/2023).

Ethical approval was obtained from the Institutional Ethics Committee (doc. 6534 of 16.03/23). The study questionnaires were introduced to each participant, and each participant was asked to answer the questions. The study protocol was in line with the Declaration of Helsinki, as revised in 2013, and the Oviedo Convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine (1996).

Written informed consent was obtained from all participants and they were informed (a) that all information would be handled strictly confidential, and (b) that it was possibility to withdraw the consent at any time.

Patient contributions

During the drafting of the research protocol, ten patients suffering from problems related to Long-COVID were involved to evaluate understanding of the project and understand whether the questionnaires to be used were simple or too long and complex (18). Positive feedback regarding the simplicity and understanding of the project came from 10 out of 10 patients.

At the end of the study, all included patients were involved to jointly evaluate the results of the article. The article was sent in the original language, via email, to each included patient. A total of 33 patients responded and all approved the work.

Results

Sample

One hundred and fourty-one patients were considered eligible (admitted to the Intensive Care Unit for COVID-related pneumonia and discharged after at least 48 hours of ICU-stay). After inclusion criteria assessments, a total of 105 patients (52 allocated to the intervention group and 53 allocated to the control group) were included in our trial (Figure 2). Of these, a total of 93 patients took part in the follow-up interviews and included in the analyses (47 in the intervention arm and 46 in the control arm). The average age of the study population was 60 years, and 65.6% were male (Table 1). The average stay in Intensive Care was 28 days and the hospital stay (post-ICU) was 19 days. No significant differences emerged between the characteristics of patients allocated to the intervention group or the control group (Table 1).

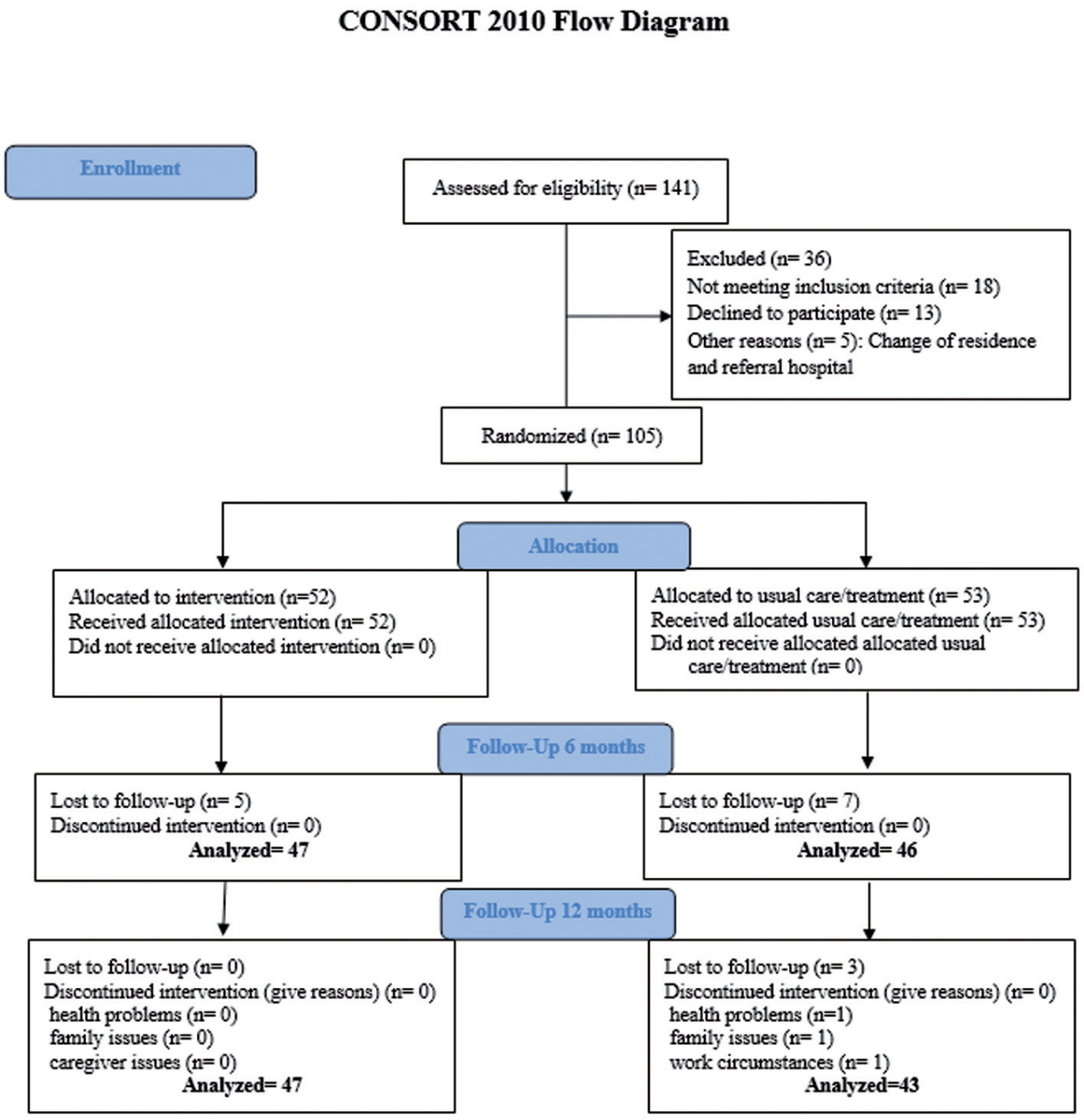

Figure 2 - Flowchart of four phases (recruitment, randomization, allocation, 6- and 12-month follow-up) modified from CONSORT (Consolidated Standards of Reporting Trials) 2010 Statement.

Intervention Adherence

No patients attended less than four sessions and were thus considered dropouts (dropout rate = 0%). However, five patients in the intervention group did not participate in the 6-month follow-up interviews. The average number of MBSR program sessions was 7.1/8.

Pain

The assessment of pain, pain intensity and interference of pain in people's lives was assessed using the BPI-SF questionnaire.

We observed lower intensity among patients in the experimental group for the domain: least pain

Table 1 - Demographic and clinic characteristics of studied population.

	All patients (n=93)	IG (n=47)	CG (n=46)	p.
Gender, n (%)				
Male	61 (65.6)	28 (59.6)	33 (71.7)	.217
Female	32 (34.4)	19 (40.4)	13 (28.3)	
Age in years, mean (sd)	60.02 (9.93)	58.95 (10.64)	61.1 (915)	.324
Marital status, n (%)				
married/engaged	65 (69.9)	34 (72.3)	31 (67.4)	.602
unmarried	19 (20.4)	8 (17.1)	11 (23.9)	
widower	9 (9.7)	5 (10.6)	4 (8.7)	
Anthropometric data, mean (sd)				
Weight in kg	79.45 (±8.26)	80.76 (±7.96)	78.10 (±8.43)	.097
BMI	27.71 (±2.35)	27.95 (±2.15)	27.47 (±2.55)	.399
ICU days, mean (sd)	28.67 (±9.63)	29.57 (±9.51)	28.8 (±10.4)	.941
Hospital ICU days, mean (sd)[1]	19.66 (±11.91)	21.17 (±10.27)	17.67 (±13.03)	.100
Anamnesis, n (%)				
diabetes	48 (51.6)	22 (46.8)	26 (56.5)	.348
hypertension	28 (30.1)	16 (34)	12 (26.1)	.403
kidney failure	23 (24.7)	9 (19.1)	14 (30.4)	.207
heart attack	12 (12.9)	5 (10.6)	7 (15.2)	.510
NYHA (I, II, III)	12 (12.9)	5 (10.6)	7 (15.2)	.510
oncological pathologies	8 (8.6)	3 (6.4)	5 (10.9)	.440
neurological pathologies	3 (3.22)	2 (4.3)	1 (2.2)	.570
Year of admission to ICU, n (%)				
2020	51 (54.8)	26 (55.3)	25 (54.3)	.925
2021	42 (45.2)	21 (44.7)	21 (45.7)	
Clinical characteristics				
p/f entrance, median (IQR)	141 (126-156)	145 (130-165)	139.5 (120-155.2)	.253
ETT, n (%)	78 (83.9)	39 (82.9)	39 (84.8)	.813
ETT in hours, median (IQR)	336 (0-480)	336 (0-480)	330 (0-486)	.739
tracheostomy, n (%)	12 (12.9)	7 (14.9)	5 (10.9)	.562
tracheostomy in hours, median (IQR)	0.0 (0-0)	0.0 (0-0)	0.0 (0-0)	.711
hemodialysis, n (%)	13 (14)	7 (14.9)	6 (13)	.797
hemodialysis in hours, median (IQR)	0.0 (0-0)	0.0 (0-0)	0.0 (0-0)	.811
PiCCO, n (%)	10 (10.8)	4 (8.5)	6 (13)	.480
PiCCO in hours, median (IQR)	0.0 (0-0)	0.0 (0-0)	0.0 (0-0)	.809
Swan-Ganz, n (%)	3 (3.2)	1 (2.1)	2 (4.3)	.557
Swan-Ganz in hours, median (IQR)	0.0 (0-0)	0.0 (0-0)	0.0 (0-0)	.809

Legend: BMI - body mass index; ICU - intensive care unit; p/f - partial pressur of oxygen/fraction of inspired oxygen; ETT - endo-tracheal tube; IQR= interquartile range 25-75; PiCCO - pulse contour cardiac output; NYHA -New York Heart Association; [1]Hospital Stay after ICU. Statistically significant difference (P<0.05).

in the last 24 h (0.91 vs 1.43, p= .035) six months after the intervention and the statistical significance remained stable even at 12 months (2.20 vs 2.83, p= .012) (Table 2).

An improvement in pain interference was observed in the experimental group, relating to the domains: interference with general activity (1.52 vs 2.21, p= .004), interference with mood (2.60 vs 4.13, p= .002), interference with sleep (3.06 vs 3.73, p= .015) and interference with enjoyment of life (2.67 vs 3.69, p= .007) six months after the intervention. An improvement in pain interference was observed

Table 2 - Results between **experimental** and control groups at 6 and 12 months from program MBSR.

	Scores at 6 months			Scores at 12 months		
	IG (n= 47)	CG (n= 46)	p.	IG (n= 47)	CG (n= 43)	p.
Pain						
Chronic Pain- case, n (%)	26 (55.3)	25 (54.3)	.925	26 (55.3)	24 (55.8)	.962
Worst pain in the last 24 h, M (SD)	4.93 (0.67)	4.89 (0.84)	.622	5.27 (1.48)	5.41 (0.85)	.587
Least pain in the last 24 h, M (SD)	0.91 (0.66)	1.43 (1.06)	**.035**	2.20 (0.70)	2.83 (1.23)	**.012**
Pain on average, M (SD)	1.87 (0.67)	2.02 (1.76)	.569	2.55 (0.90)	3.04 (1.29)	.051
Pain right now, M (SD)	0.91 (1.22)	1.15 (1.02)	.288	1.65 (1.36)	1.67 (1.04)	.919
Pain Interference with general activity, M (SD)	1.52 (1.06)	2.21 (1.28)	**.004**	1.81 (1.07)	2.04 (1.74)	.507
Pain Interference with mood, M (SD)	2.60 (1.84)	4.13 (2.62)	**.002**	2.48 (1.29)	3.32 (1.99)	**.031**
Pain Interference with general work, M (SD)	2.08 (1.60)	1.58 (2.24)	.127	1.97 (1.92)	1.69 (1.61)	.501
Pain Interference with walking ability, M (SD)	1.41 (1.96)	1.10 (1.80)	.479	2.46 (1.16)	2.04 (1.84)	.178
Pain Interference with relationship with other people, M (SD)	1.82 (1.08)	1.56 (1.69)	.452	2.41 (0.95)	2.48 (1.65)	.804
Pain Interference with sleep, M (SD)	3.06 (1.71)	3.73 (1,74)	**.015**	3.0 (1.66)	3.74 (1.80)	**.017**
Pain Interference with enjoyment of life, M (SD)	2.67 (2.25)	3.69 (1.28)	**.007**	3.23 (1.50)	3.76 (1.23)	.077
Anxiety						
Absence of anxiety 0-7, n (%)	9 (19.1)	8 (17.4)	.826	9 (19.1)	8 (18.6)	.947
Mild anxiety 8-10, n (%)	11 (23.4)	8 (17.4)	.472	9 (19.1)	9 (20.9)	.832
Moderate anxiety 11-14, n (%)	12 (25.5)	9 (19.6)	.491	11 (23.4)	7 (16.3)	.398
Severe anxiety 15-21, n (%)	15 (31.9)	21 (45.6)	.173	18 (38.3)	19 (44.2)	.570
Depression						
Absence of depression 0-7, n (%)	8 (17.4)	5 (10.6)	.392	10 (21.3)	7 (16.3)	.545
Mild depression 8-10, n (%)	18 (38.3)	17 (36.9)	.893	13 (27.6)	14 (32.6)	.612
Moderate depression 11-14, n (%)	13 (27.7)	12 (26.1)	.864	15 (31.9)	14 (32.6)	.877
Severe depression 15-21, n (%)	8 (17)	12 (25.5)	.287	9 (19.1)	8 (18.6)	.947
Insomnia						
Absence of insomnia- 0-7, n (%)	25 (53.2)	14 (30.4)	**.026**	21 (44.7)	18 (41.9)	.787
Sub-threshold insomnia- 8-14, n (%)	8 (17)	12 (26.1)	.287	13 (27.7)	11 (25.6)	.823
Moderate insomnia- 15-21, n (%)	6 (12.8)	9 (19.6)	.372	5 (10.6)	6 (13.9)	.631
Severe insomnia- 22-28, n (%)	8 (17)	11 (23.9)	.409	8 (17)	8 (18.6)	.844

Legend: *BPI-SF*-Brief Pain Inventory-Short Form; *HADS* - hospital anxiety and depression scale; *ISI* -Insomnia Severity Index. Statistically significant difference (P<0.05).

in the experimental group, relating to the domains: interference with mood (2.48 vs 3.32, p= .031) and interference with sleep (3.0 vs 3.74, p= .017) 12 months after the intervention (Table 2).

No gender differences emerged from statistical sub-analysis of data (male vs female participants) in the benefits of MBSR for pain intensity or pain interference.

No other significant findings emerged.

Anxiety and Depression

For the evaluation of cases of anxiety, no difference emerged in the reduction in the prevalence of non-cases, mild cases, moderate or severe cases between the intervention group and the control group. However, a statistically significant difference emerged in the mean score of the HADS-Anxiety scale in favor of the intervention group (11.28 vs 13.15, t= -3.636, p< .001) at 6 month and at 12 months (10.88 vs 13.41, t= -5.167, p< .001) (Figure 3).

For the evaluation of cases of depression, no difference emerged in the reduction in the prevalence of non-cases, mild cases, moderate or severe cases between the intervention group and the control group (Table 2). However a statistically significant difference emerged in the mean score of the HADS-Depression scale in favor of the intervention group (9.95 vs 11.23, t= -2.823, p= .007) at 6 month and at 12 months (9.67 vs 10.69, t= -2.458, p= .018) (Figure 3).

No gender differences emerged from statistical

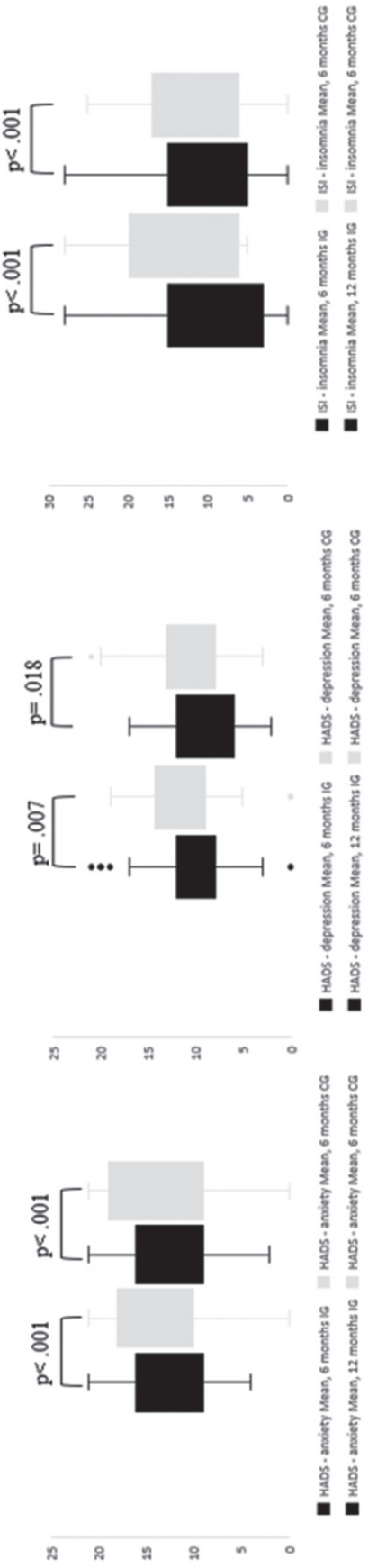

Figure 3 - Comparison between the intervention and control groups on the average anxiety and depression scores (assessed with the HADS scale) and average insomnia scores (assessed with the ISI scale) at 6 months and 12 months.

sub-analysis of data (male vs female participants) in the benefits of MBSR for anxiety or depression.

No other significant findings emerged.

Insomnia

No difference emerged in the reduction in the prevalence of non-cases, sub-threshold insomnia, moderate or severe between the intervention group and the control group at 12 months.

However a statistically significant difference emerged in the mean score of the Insomnia Severity Index in favor of the intervention group (9 vs 13.6, t= -8.801, p< .001) at 6 month and at 12 months (9.1 vs 11.1, t= -3.569, p< .001) (Figure 3).

No gender differences emerged from statistical sub-analysis of data (male vs female participants) in the benefits of MBSR for insomnia.

No other significant findings emerged.

Concurrent psychopathology

Table 3 show the concurrent caseness of chronic pain, anxiety, depression and insomnia in individual patients. The chi-square2 test was performed only if there was at least 1 prevalence associated with the comparison variable. No significant difference emerged between the prevalence of individual associations between the intervention group and the control group.

The four variables evaluated were simultaneously present in at least 12 (25.5%) patients at T0 and in 15 (31.9%) patients at T1 for the Intervention group, while they were simultaneously present in at least 16 (34.8%) patients at T0 and 14 (32.6%) patients at T1 for the control group (Figure 3).

No gender differences emerged from statistical sub-analysis of data (male vs female participants) in the benefits of MBSR for concurrent psychopathology.

No other significant findings emerged.

Discussion

The aim of this study was to evaluate the effectiveness of an MBSR program among patients suffering from anxiety, chronic pain, depression, insomnia who survived an intensive care unit admission for COVID-19. As per protocol, our evaluations were carried out 6 months and 12 months after the MBSR program which took place over a total of 2 months between April and May 2023. It is important to underline that of the 52 patients in the experimental group and therefore subjected to the

Table 3 - Concurrent caseness of chronic pain, anxiety, depression and insomnia in individual patients.

	Data at 6 months			Data at 12 months		
Caseness	IG (n=47)	CG (n=46)	p.	IG (n=47)	CG (n=43)	p.
Chronic Pain n, %	3 (6.4)	3 (6.5)	.978	5 (10.6)	3 (6.9)	.542
Chronic Pain and Anxiety n, %	0	0	-	1 (2.1)	0	-
Chronic Pain and Depression, n %	2 (4.2)	0	-	0	0	-
Chronic Pain, Anxiety and Depression, n %	9 (19.1)	6 (13)	.423	5 (10.6)	7 (16.3)	.431
Chronic Pain. Anxiety and Insomnia n, %	0	0	-	0	0	-
Chronic Pain, Depression and Insomnia n, %	0	0	-	0	0	-
Anxiety n, %	0	0	-	0	0	-
Anxiety and Depression n, %	7 (14.9)	0	-	6 (12.7)	3 (6.9)	.521
Anxiety and Insomnia, n, %	1 (2.1)	0	-	0	0	-
Anxiety, Depression and Insomnia n, %	9 (19.1)	16 (34.8)	.089	11 (23.4)	11 (25.6)	.810
Depression n, %	0	3 (6.5)	-	0	1 (2.3)	-
Depression and Insomnia n, %	0	0	-	0	0	-
Insomnia n, %	0	0	-	0	0	-
Chronic Pain, Anxiety, Depression and Insomnia n, %	12 (25.5)	16 (34.8)	.330	15 (31.9)	14 (32.6)	.948

The chi-square test was performed only if there was at least 1 prevalence associated with the comparison variable. Statistically significant difference (P<0.05).

MBSR program, 47 patients (90.4%) presented for follow-up evaluations at both 6 and 12 months. Our findings show a reduction in the perception of least pain in the last 24 hours, in the interference of pain with mood, general work, sleep and interference with enjoyment of life. At the same time, we observed lower scores on the scales for assessing anxiety, depression and insomnia. However, we would like to point out that, in our opinion, these reductions appear purely statistical and do not emerge as clinically relevant. However, it is important to underline that psychosocial factors play key roles in criticall illness and associated psychosocial and physical disability (19). Cognitive behavioral therapy (CBT), has demonstrated effectiveness for various chronic conditions and is widely recommended for patients with chronic illness (20,21).

A fact that makes us reflect is that in the intervention group, the four conditions analyzed (pain, anxiety, depression and insomnia) are less concomitant 6 months after the MBSR program (12 patients with all 4 conditions) and more concomitant at 1 year from the MBSR program (16 patients with all four conditions). This leads us to hypothesize that the MBSR program does not remain stable over time, at least not up to 1 year and further management of patients or a new treatment program is necessary (22,23). Rehabilitation involves the provision of nationally coordinated multidisciplinary programs to assess, test, diagnose and treat patients, including those who were not hospitalized during the acute phase of the infection; research requires coordinated and co-created multidisciplinary studies to understand the clinical consequences and develop treatment pathways for Long-COVID (1).

Although research generally points positive correlations between practice frequency and outcomes, the absence of correlations has also been reported (24), indicating that further investigation is needed regarding the influence of adherence to mindfulness practice on positive outcomes following interventions. The intervention group presented high levels of attendance to class. However, the type and amount of daily mindfulness practice are not always associated with relevant clinical outcomes. One possible explanation for this result is the use of self-report measures to assess both the health-related improvements and the adherence to practice. As self-report measures are subjective, it is possible that participant's expectation towards the practice played a role in their perception of improvements regardless of the amount of practice.

Mindfulness researchers have long advocated the potential of mindfulness for enhancing public health (8). And indeed, public health as pursued in many countries overlaps in promising ways with modernized "mindfulness" approaches, commonly traced to Kabat-Zinn's pioneering work in the early 1980s (8). Perhaps most prominently, modern approach to mindfulness

resonate with the public health field's emphasis on causally "upstream" approaches to foster salutary health behaviors and other protective factors that build resilience and prevent disease before it arises, helping engender communities that "can withstand known and novel threats that thrive every day" (8, 24). Moreover, reviews and meta-analyses suggest that in the USA and Europe, interventions oriented to mindfulness can foster well-being in general populations, and favorably affect conditions that include depression, anxiety, stress, insomnia, addiction, psychosis, pain, hypertension, bad weight control, and cancer-related symptoms (8, 25, 26). Reviews suggest that mindfulness approaches may be cost-effective and foster individual resilience (8, 24, 25). Emerging evidence suggests that mindfulness might also plausibly play a key role in building resilience at the level of populations and systems (25).

Limit

The main limitation of the study was that it did not reach the hypothesized sample size and that it lost 3 patients (6.5%) in the control group for the interviews carried out 12 months after the intervention. However, due to the unpredictable evolution of the COVID-19 pandemic, which saw various waves one after the other, this was a possibility that we had already considered. A further limitation of the study is its monocentric design influenced by the specificity of the case selection and the use of self-administered tools for the assessment of outcomes.

Implication for nursing practice

This short randomized trial provides evidence that physical, psychological, and cognitive symptom clusters exist among post-COVID-19 in ICU survivors. Our results indicate that the symptom clusters identified at baseline were sustained for 12 months, with an immediate benefit after the MBSR program. The patient's self-assessment constitutes the most reliable information on the experience of psychological and/or social disorders. It is currently known that post-COVID symptomatology is highly heterogeneous and more complex than expected, which may explain why a consensus on the definition of Long-COVID is not yet available. Several Authors have discussed aspects such as whether or not a previous positive diagnosis of COVID-19 is necessary. Patients with Long-COVID may not experience associated physiological changes and behaviors. Dealing with pain, anxiety, depression, or sleep-rest disorder can reduce the patient's energy for other activities and cause irritability, which in turn leads to worsening symptoms of insomnia and fatigue, causing greater irritability, depression and pain. Promoting the use of psychoeducation can have significant benefits in symptom management and acceptance. The main objective is to provide participants with the opportunity to develop self-care skills and improve their overall quality of life. The nurse may coach the patient, suggest self-directed meditation, or provide a recorded audio guide to help elicit the relaxation response. By trying and applying various cognitive and behavioral self-management techniques, participants learn how to set realistic goals and manage or accept some specific conditions in their life. In addition to improving outcomes for managing symptoms of pain, anxiety, depression, or insomnia, psychoeducation can also promote better communication between patient and healthcare provider and help reduce healthcare costs. Furthermore, nurses can encourage and support the patient's use of new methods to modify and manage specific symptoms, unless they are specifically contraindicated. Strategies may include seeking calm and solitude, knowing one's condition, pursuing interesting activities as a form of distraction, reciting prayers, or socializing.

Conclusions

Mortality rate during intensive care was high during the COVID-19 outbreak, often also associated with co-infections (27), but also severe long-term functional, physical and psychological problems emerged among COVID-survivors.

Long-COVID is an important public health problem and one of the approaches to address this problem is through MBSR. Understanding symptom clusters in COVID-survivors may result in greater therapeutic benefits by integrating treatments for concurrent symptoms, thus improving quality of life.

Despite the limitations of our study that used a randomized controlled design, had a small sample size, and employed different outcome measures, MBSR is a promising modality for Long-COVID among healthy individuals. The main results of this RCT demonstrate that the MBSR program reduced some chronic symptoms, improving the patients' insomnia and psychological disorders within one year.

In the light of what emerged from our study, we suggest a MBSR program in addition to pharmacological therapy to be carried out once a

year. Studies with larger sample sizes that attempt to test an MBSR program twice a year are needed.

Data availability: The datasets used during the study are avaible upon reasonable request from the corresponding Author.
Ethical Approval: The study was approved by the Institutional Ethical Committe and was registered on ClinicalTrials.gov Identifier: NCT05815693. All participants provided their informed written consent to participate during the enrollment. Consent was obtained by the nursing staff. The study protocol was in line with the Declaration of Helsinki, as revised in 2013, and the Oviedo Convention.
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Appendix:
BPI-SF = Brief Pain Inventory- Short form.
COVID-19 = COronaVIrus Disease 19.
SD = standard deviation.
HADS = Hospital anxiety and depression scale.
ICU = Intensive Care Unit.
ISI = Insomnia Severity Index.
MBSR = Mindfulness-based stress reduction.
N == number.
NRS §= Numerical Rating Scale.
RCT = randomized controlled trial.
vs = Versus.

Riassunto

L'impatto della "riduzione dello stress basata sulla consapevolezza" nei sopravvissuti al Covid-19. Uno studio randomizzato e controllato

Introduzione. Il Long-COVID rappresenta una condizione clinica caratterizzata dal mancato rientro del paziente affetto da COVID-19 nello stato di salute precedente all'infezione acuta. La riduzione dello stress basata sulla consapevolezza si concentra sull'aumento della consapevolezza e dell'accettazione delle esperienze momento per momento, comprese le emozioni difficili e il disagio fisico.

Obiettivo. Esaminare gli effetti di un intervento di riduzione dello stress basato sulla consapevolezza sugli esiti funzionali e psicosociali dei pazienti con Long-COVID.

Disegno. Studio randomizzato e controllato a due bracci con disegno a misure ripetute.

Metodi. I pazienti sono stati assegnati in modo casuale al percorso di psicoeducazione (gruppo di intervento) o alle cure abituali (gruppo di controllo) (53 vs 52 pazienti per gruppo). Nel gruppo di intervento è stato implementato un programma di Mindfulness di 8 settimane (2 ore settimanali) in formato di gruppo e il programma Mindfulness. I risultati dello studio includevano dolore cronico (intensità del dolore e interferenza del dolore) valutato con il Brief Pain Inventory (risultati primari), ansia e depressione valutate con la Hospital anxiety and depression scale ed insonnia valutata con l'Insomnia Severity Index. I dati sono stati raccolti a 6 mesi e 12 mesi dopo il programma Mindfulness.

Risultati. Una riduzione dell'intensità del dolore e dell'interferenza del dolore su alcune attività della vita quotidiana è stata osservata 6 e 12 mesi dopo l'intervento. Una differenza statisticamente significativa è emersa nel punteggio medio dei sintomi di ansia a favore del gruppo di intervento (11.28 vs 13.15, t= -3.636, p< .001) a 6 mesi e a 12 mesi (10.88 vs 13.41, t= -5.167, p< .001) e nel punteggio medio dei sintomi depressivi a favore del gruppo di intervento (9.95 vs 11.23, t= -2.823, p= .007) a 6 mesi e a 12 mesi (9.67 vs 10.69, t = -2.458, p= .018). I sintomi dell'insonnia sono stati statisticamente ridotti 6 mesi dopo il programma Mindfulness (punteggio: 53.2 vs 30.4, x= 4.944, p= .026).

Conclusioni. Alla luce di quanto emerso nel nostro studio, suggeriamo un programma di Mindfulness in aggiunta alla terapia farmacologica da effettuare una volta all'anno sui pazienti con consequenze di COVID-19. Sono necessari studi con campioni di dimensioni più ampie che tentano di testare un programma di consapevolezza due volte l'anno.

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Funding sources for public health research in Italy

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Keywords: Funding; public health; research; communicable diseases; non-communicable diseases; vaccines
Parole chiave: Fonti di finanziamento; Sanità Pubblica; ricerca; malattie infettive; malattie croniche; vaccini

Abstract

Background. *Funding sources play a critical role in shaping the landscape of scientific research, including the one in public health, as they often determine not only the feasibility of specific projects but also its broader directions.*
Study design. *We aimed at assessing current funding sources for public health research in Italy and related implications.*
Methods. *We conducted a systematic PubMed search from January 2023 to June 2024, focusing on publications by 208 Italian tenured professors in hygiene and public health. We included only original articles they authored as first or last authors, excluding editorials, comments, and letters. We categorized funding sources into public internal, public external, private external, and unmentioned.*
Results. *We retrieved 760 non-duplicate eligible publications. Research topics focused almost equally on communicable (48.2%) and non-communicable (51.8%) diseases. Public external funding were the most common overall (33.7%), followed by private external (14.3%) and public internal (7.5%). Notably, 58.7% of studies did not report any funding sources. Private external, regional and EU sources predominantly funded communicable disease research, while non-communicable disease research received more support from public external sources, especially governmental.*
Conclusions. *In a European country such as Italy the funding landscape in public health research appears to be complex, due to the wide range of topics and intertwined roles of funding actors. Public funding are more frequent than private funding also independently of research topics, though most research activities did not require specific financial support, implying that public health research frequently has limited financial needs. This likely enables more flexibility and independence to investigators in public health, with major implications in terms of feasibility and absence of conflicts of interest.*

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Introduction

Public health research is essential for advancing healthcare systems, informing policy decisions, and improving population health (1,2). The source of funding for research is critical as it can affect scope, topics and direction of the studies conducted, and have a possible influence on their outcomes. Indeed, the Equator Network highlighted the importance to assess source of funding in final publication, particularly in experimental trials but also in general, when reporting research findings for transparency purpose (3). Across all scientific fields, the largest contributors to research funding are usually government agencies, followed by independent organizations and industries, while Universities and hospitals have been shown to contribute in a marginal way in all G9 countries (4,5). Funding from government and international agencies are the highest competitive with low (<20%) success rate (5-7). Industry and profit organizations, often the second largest funding source, drive substantial progress and are pivotal in Research & Development. Though, their direct and indirect financial support to researchers can also influence research directions (8,9). More recently, COVID-19 pandemic has greatly affected both research and development funding (10), with also silver lining related to health and social benefits as well as shortened timing as seen in ethics committee legislation (11).

A few studies conducted at the national level have assessed funding sources in specific research fields and over time (12-15). However, little is known about this issue in the public health area. In the present study, we aimed at systematically evaluating the funding sources in public health research, in order to provide insights into the financial landscape supporting public health publications in Italy and their implications.

Methods

Data collection

We searched in the PubMed database the publications authored by the 208 Italian full and associate university professors in hygiene and public health from January 2023 to June 2024. Public Health professors were retrieved via the database "Cerca Università" (https://cercauniversita.mur.gov.it) of the Italian Ministry of University and Research - MUR (5), and further divided according to the geographical location of their institutions, i.e. Northern (n=60, 39%), Central (n=42, 27%) and Southern (n=53, 34%) Italy. Since almost all Italian universities with affiliated public health investigators are public, with only three exceptions (Vita-Salute San Raffaele University, Catholic University of the Sacred Hearth and Humanitas University) but still subject to MUR control and funding, in our analysis we considered all the Italian academic institutions as public.

We limited our search to publications where these professors were listed as either first or last authors. This approach allowed us to identify papers most likely primarily focusing on the field of hygiene, preventive medicine, and public health in general, though without excluding topics by imposing thematic restrictions. We selected two leading authorship positions (first and last) as inclusion criterion, to include publication where Italian researchers should be the principal investigators and for this reason, the main recipients of the funding source, if any. As a consequence, we excluded national and international multicenter studies where the role of the individual Italian researcher could not be clearly identified as leading one. We did not apply filters on the type of papers, but we excluded editorials, comments, and letters during screening phase of title and abstract. For each article, RM, MLT, and VEP reviewed the full-text and extracted the following information: author, university or institution of affiliation, title of the study, and detailed funding information. Titles and PMIDs were used to identify duplicates and count each article one time only.

Data classification

We used the funding acknowledgements section of the papers to identify financial sources of support, and we categorized them in four macro-categories (16-18): public internal, public external, private external, and unmentioned. By "public internal", we refer to funding sourced directly from the researcher's own institution (given the almost entirely public nature of Italian universities). Conversely, "public external" includes all funding from public institutions, entities, and agencies outside of the researcher's university. Details of the funding entities included in each macro-category used for data extraction and categorization are provided in Table 1.

The researcher's affiliation allowed for geographical stratification. We divided the papers into three macro areas according Italian Institute of Statistics classification (19): Northern Italy (Valle d'Aosta, Piedmont, Liguria, Lombardy, Emilia Romagna, Veneto, Friuli Venezia Giulia, Trento and Bolzano), Central Italy (Umbria, Marche, Tuscany and Lazio),

Table 1 - Subdivision of macro-categories of sources of funding.

Category	Source of funding
Public internal	• "University of..." • University funded-grants (e.g., FAR, Pia.ce.ri, etc.)
Public external	• European Union (NextGeneration EU, Horizon Europe, Life, etc.) • EU-agencies (EFSA, ESA, etc.) • Italian government (MS-Ministry of Health, MUR-Ministry of University and Research, etc.) • MUR-specific programs (Departments of Excellence, PRIN, CTN, etc.) • Italian regional governments and/or regional entities • Regional and local health authorities and hospitals (IRCCS included) • International, non-EU related (Germany, Czech Republic, etc.) government funding • Extra-EU (Switzerland, USA) government funding • International projects (COST, bilateral research, etc.) • National and international public bodies (ISS, AIFA, WHO, etc.)
Private external	• Not-For-Profit Organizations (NFP), including non-governmental organizations (NGOs), foundations (AIRC, Fondazione Veronesi, etc.), and national and international scientific societies (SItI, EUPHA, etc.) • For-Profit companies unrelated to biomedical and pharmacological research, production or distribution • Pharmaceutical companies (Sanofi, Pfizer, etc.)
Unmentioned	• "No external funding" was declared, or when the funding source was not specified.

Acronyms: AIFA = Agenzia Italiana del Farmaco (Italian Medicine Agency); AIRC = Associazione Italiana per la Ricerca sul Cancro (Italian Association for Cancer Research); COST = European Cooperation in Science and Technology; CTN = Cluster Tecnologici Nazionali (National Technological Clusters); EFSA = European Food Safety Authority; ESA = European Space Agency; EUPHA = European Public Health Association; FAR = Fondo Ateneo per la Ricerca (University Research Fund); IRCCS = Istituto di Ricovero e Cura a Carattere Scientifico (Scientific Institute for Research, Hospitalization, and Healthcare); ISS = Istituto Superiore di Sannità (National Health Institute); Pia.ce.ri = Piano di incentivi per la Ricerca di Ateneo (University Research Incentive Plan); PRIN = Progetti di Rilevante Interesse Nazionale (Projects of National Relevance); SItI = Società Italiana Igiene e Medicina Preventiva (Italian Society of Hygiene and Preventive Medicine); WHO = World Health Organization.

and Southern Italy and islands (Abruzzo, Molise, Campania, Apulia, Basilicata, Calabria, Sicily and Sardinia).

Based on the research focus, we eventually categorized publications into two main groups: communicable disease, including vaccination, COVID-19, infectious disease, and antibiotic resistance; and non-communicable diseases, covering publications on cancer, neurological, cardiovascular, obstetric and gynecological, pediatric diseases as main categories.

Data analysis and data presentation

We extracted data using an Excel spreadsheet and we computed absolute and relative frequencies for the categorical variables using 'tabulate', 'tabstat', and 'graph hbar' commands of Stata v18 (StataCorp LCC, College Station, TX, 2023). We also used the website SankeyMATIC.com for Sankey Plot generation. Such tool allows to visually map the flow of funding from its original source, through its classification, to its final application in specific research topics. The tool therefore allowed to depict the proportional distribution, flow and relations between different funding sources and research areas, offering an immediate understanding of complex funding pathways and highlighting key patterns in the allocation of research resources.

Since some articles have received funding from multiple entities (i.e. public internal and external and private external) within the same macro-category (communicable or non-communicable disease), and/or were funded by entities across different macro-categories, the overall number of funding sources exceeded the number of publications. As a result, when comparing the total number of funding to the total number of publications, the sum of the percentages could exceed 100%.

Results

Between January 2023 and June 2024, we identified 1012 publications, of which 252 were duplicates, with total 760 eligible research publications. Furthermore, out of the 208 tenured and full professors investigated,

Table 2 - Distribution of funding divided by source, topic and geographical area. The sum of the percentages in each column exceeds 100% due to funding overlap in categories. Values are percentages and absolute numbers in parenthesis.

	Communicable disease (n = 366)	Non-communicable diseases (n = 394)	Total (n = 760)
North	44.8% (164)	61.0% (240)	53.2% (404)
Public Internal	2.5% (9)	5.1% (20)	3.8% (29)
Public External	14.8% (54)	18.8% (74)	16.8% (128)
Private External	6.6% (24)	6.9% (27)	6.7% (51)
Unmentioned	21.0% (77)	30.2% (119)	25.8% (196)
Center	25.7% (94)	24.9% (98)	25.3% (192)
Public Internal	1.6% (6)	1.8% (7)	1.7% (13)
Public External	4.6% (17)	6.3% (25)	5.5% (42)
Private External	4.4% (16)	4.6% (18)	4.5% (34)
Unmentioned	15.0% (55)	12.2% (48)	13.6% (103)
South	40.2% (147)	31.7% (125)	35.8% (272)
Public Internal	1.4% (5)	2.5% (10)	2.0% (15)
Public External	14.2% (52)	8.6% (34)	11.3% (86)
Private External	4.1% (15)	2.3% (9)	3.2% (24)
Unmentioned	20.5% (75)	18.3% (72)	19.3% (147)
Italy	110.8% (405)	117.5% (463)	114.2% (868)
Public Internal	5.5% (20)	9.4% (37)	7.5% (57)
Public External	33.6% (123)	33.8% (133)	33.7% (256)
Private External	15.0% (55)	13.7% (54)	14.3% (109)
Unmentioned	56.7% (207)	60.7% (239)	58.7% (446)

53 did not have any publications during the period under review, leaving 155 (males/females: 76/79) professors.

Table 2 presents distribution of funding based on source (public/private external/internal), topic (communicable/non communicable disease), and geographical area (North, Center, South).

As regards source of funding, public external funding were the most common source (33.7%), followed by private external (14.3%) and public internal (7.5%). A higher proportion of studies (58.7%) did not declare any funding source. The 760 eligible research publications almost equally focused into communicable (48.2%) and non-communicable diseases (51.8%). Northern Italy authors focused more on non-communicable diseases (58.5%), while communicable diseases were the main focus for most of the publications from Southern Italy researchers (57.0%). Details on the geographical distributions of the topics of retrieved articles are listed in Supplementary Table S1.

Regarding geographical distribution, some minor regional disparities according to source of funding can be acknowledged. In the North, public external funding were the main source (61.5%), followed by private external (24.5%), and public internal (13.9%). The South also remarkably highlighted public external funding (68.8%), while reporting less private external (19.2%) and public internal (12.0%) funding compared to the North. The Center shows a more balanced but smaller-scale funding distribution, with 47.2% from public external sources, 38.2% from private external funding, whereas 14.1% from public internal funding. However, it must be noted that more than half of publications (58.7%) did not report funding information.

Figure 1 visualizes through a Sankey-plot the distribution of funding sources for publications on communicable and non-communicable diseases, while Figure 2 shows how funding sources are allocated between communicable and non-communicable diseases. The distribution is generally in favor of non-communicable diseases in the case of public internal funding, Ministry of Health and University,

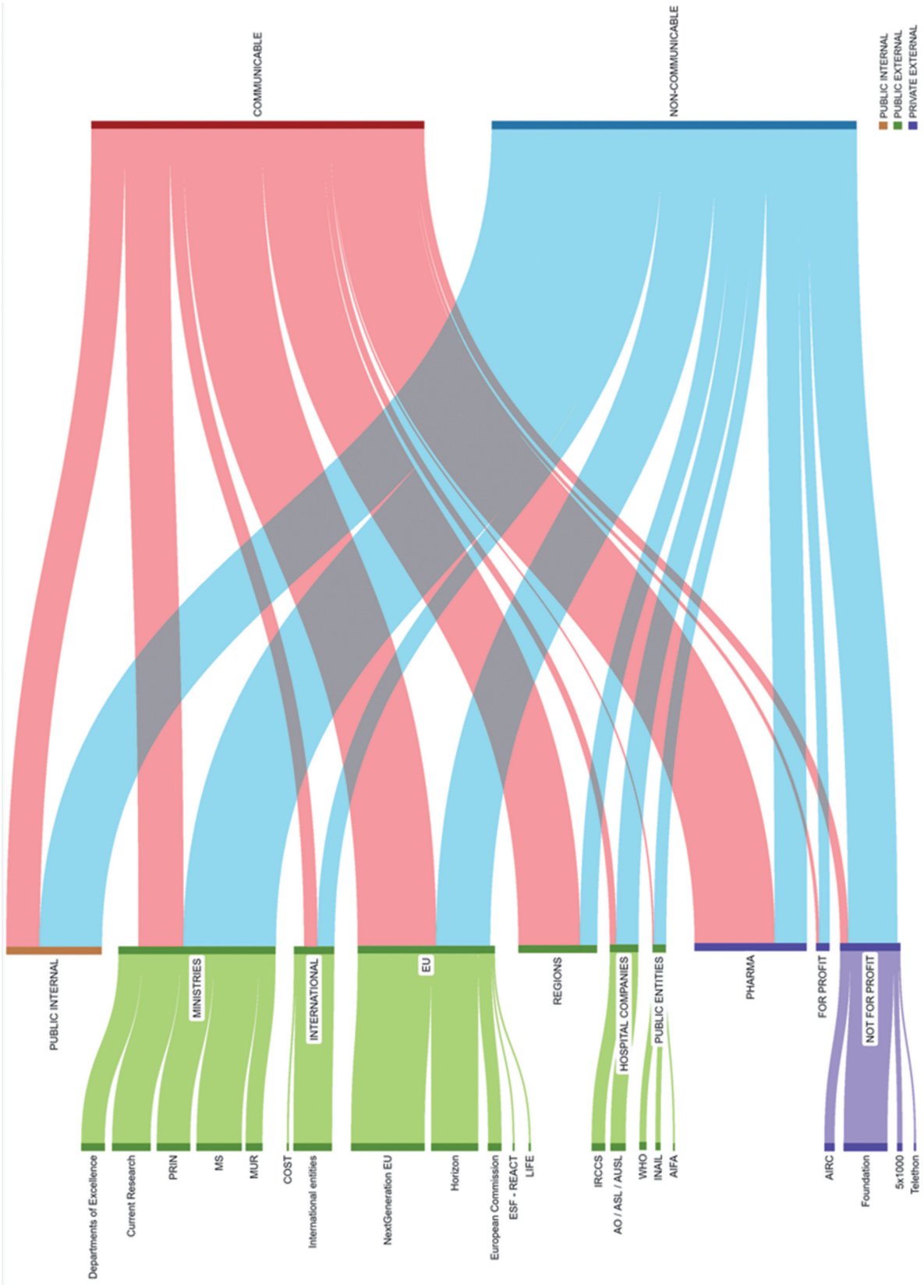

Figure 1 - Sankey-plot graph on funding allocation from source of funding to article topic (width of lines are proportional to the number of publication in each flow). Acronyms: AIFA = Agenzia Italiana del Farmaco (Italian Medicine Agency); AIRC = Associazione Italiana per la Ricerca sul Cancro (Italian Association for Cancer Research); COST = European Cooperation in Science and Technology; CTN = Cluster Tecnologici Nazionali (National Technological Clusters); EFSA = European Food Safety Authority; ESA = European Space Agency; EUPHA = European Public Health Association; FAR = Fondo Ateneo per la Ricerca (University Research Fund); IRCCS = Istituto di Ricovero e Cura a Carattere Scientifico (Scientific Institute for Research, Hospitalization, and Healthcare); ISS = Istituto Superiore di Sanità (National Health Institute); MUR = Ministero dell'Università e della Ricerca (Ministry of University and Research); MS = Ministero della Sanità (Ministry of Health); Pia.ce.ri = Piano di incentivi per la Ricerca di Ateneo (University Research Incentive Plan); PRIN = Progetti di Rilevante Interesse Nazionale (Projects of National Relevance); SItI = Società Italiana Igiene e Medicina Preventiva (Italian Society of Hygiene and Preventive Medicine); WHO = World Health Organization.

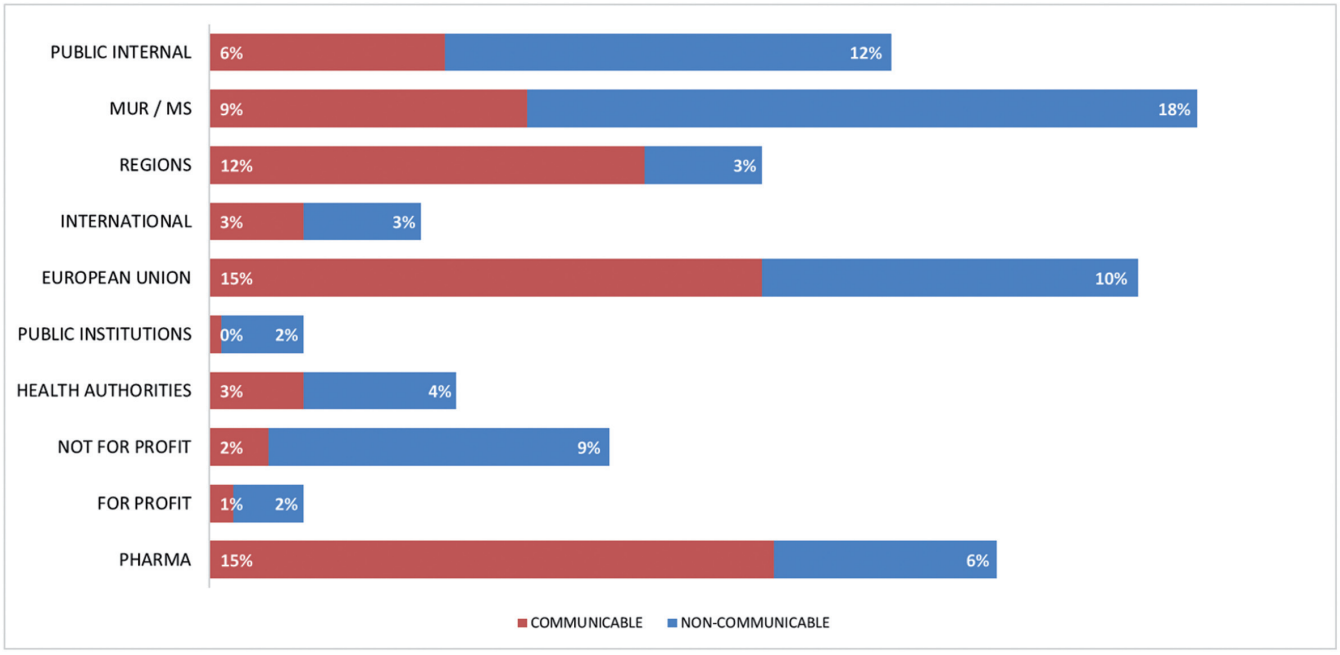

Figure 2 - Sources of funding by type of publication, excluding articles with unmentioned funding, total articles included (N=314). The sum of the percentages in each column exceeds 100% due to funding overlap in categories.
Acronyms: MUR = Ministero dell'Università e della Ricerca (Ministry of University and Research); MS = Ministero della Sanità (Ministry of Health).

and for not-for-profit organizations. On the converse, regional and EU funding were more common in the studies on communicable diseases, as compared to studies on non-communicable disease. Pharmaceutical companies more commonly funded research about communicable diseases (15%) compared to that on non-communicable diseases (6%).

Supplementary Figure S1 provides a detailed picture of the sources of funding by topic of publication.

Supplementary Table S2 shows the distribution of multiple sources of funding, also divided by geographical area. The majority of publications received funding from a single source, either public internal (7.5%), public external (7.5%), and private external (21.3%). A minority of the studies (6.5%) received multiple funding, generally public funds.

Discussion

Our investigation of funding sources currently supporting public health research in Italy showed a multidimensional landscape of financial opportunities and sources for Italian researchers, indicating the presence of a heterogeneous and dynamic research output in accordance with previous investigations conducted globally (18).

The distinction between funding for communicable and non-communicable diseases revealed targeted funding strategies, with the Ministry of Universities and Research, the Ministry of Health, and their funding calls and projects (e.g., Departments of Excellence, PRIN, etc.) showing a substantial focus on non-communicable diseases, possibly reflecting the public health burden of these diseases and the related financial implications in term of health care costs. Chronic conditions, such as cardiovascular disease and cancer, place in fact a considerable burden on healthcare systems (20). Furthermore, non-communicable diseases are the leading cause of mortality and morbidity in countries like Italy (21), which could explain why governmental agencies have decided to allocate relevant resources to research projects in the field of disease prevention and public health. In fact, in this research area the government-funded research showed a leading role, likely reflecting the awareness of the health burden associated with the high chronic disease prevalence in the population, and

the need to address related long-term health challenges (22,23). Addressing and supporting chronic disease prevention fully align with national health policies aimed at improving quality of life and at reducing the strain on the healthcare system, particularly as population ages (24).

Conversely, pharmaceutical companies exhibited a stronger investment in research on communicable diseases, a funding pattern that could align with the industry's interest in vaccine development and other treatments for infectious diseases, a priority likely more pronounced in the wake of the COVID-19 pandemic (25-27). This trend may be explained by market forces, i.e. the commercial potential of vaccine development and infectious disease treatment, particularly given the global demand for these products during and after public health emergencies such as the COVID-19 pandemic (28). Moreover, global health priorities, shaped by international organizations like the World Health Organization and national governments, increasingly emphasize the need to counteract the threat represented by both 'old' and emerging infectious diseases, especially for vulnerable groups like infants and the elderly. This may further incentivize pharmaceutical companies to allocate research resources to these areas (29).

This pattern contrasts with the approach by private non-profit and non-pharmaceutical for-profit entities, showing a more balanced picture and even a slight preference for supporting non-communicable diseases. These entities may choose to prioritize non-communicable diseases because these conditions align with their philanthropic goals, aimed at improving long-term societal well-being. This is particularly true for public health research in the fields of cancer, cardiovascular diseases, and mental health, which could arguably be seen as underfunded (30). For-profit organizations, such as insurance companies, may be more inclined to fund non-communicable disease research also to address the rising costs for management of chronic diseases, thus aligning their financial interests with the long-term sustainability of healthcare.

Funds like NextGeneration EU and Horizon exhibited a substantially even contribution to both disease categories, supporting an effective role of European funding in maintaining research diversity (31-33). Additionally, the relatively high prevalence of European Union and International funds in public health research within Italy suggests that Italian researchers are adequately integrated into the broader European and extra-EU research network. This allowed access to shared funding resources but also liked fostered cross-border collaboration and innovation. Unexpectedly, international entities like World Health Organization were a quite limited source of funding, with a slight emphasis on non-communicable diseases, possibly reflecting global health priorities of these sources (34,35). The limited international funding in Italy can also be explained by the global mandate of such agencies to allocate more resources to regions with fewer research capacities than Italy, specifically low-to-middle income countries where the scientific research networks and the healthcare systems may struggle to cope with chronic diseases (36).

As regards geographical area, it is important to acknowledge that the observed disparities in research focus and output between regions are likely influenced by the uneven geographical distribution of research institutions and personnel. Areas with a denser network of research facilities and academic institutions, such as Northern Italy, unavoidably reported higher number of publications. Researchers from Northern Italy focused on non-communicable disease, representing the 58.5% of the topics their publications. In contrast, the South gave emphasis to communicable diseases, comprising 57.0% of its research. However, this regional difference may also be attributed to varying public health needs, with Southern Italy facing more challenges in infectious diseases and Northern Italy needing to address chronic diseases more, which are more prevalent in aging and older populations, and in heavily polluted areas as frequently found in the industrialized areas characterizing Northern regions (37-41).

Public internal funding was not a major source of support across all regions and disease topics, representing only 3.8% of the total funding, highlighting the limited role of internal sources of specific financial support in public health research.

A high proportion of studies (58.7%) did not include funding sources, suggesting that public health research frequently relies on freely accessible research data or on already available resources (salaries, academic equipment, etc.). Therefore, in many instances specific 'additional' financial support, in addition to the basic one provided by Italian generally public academic institutions (tenure, and operational costs) and as such not formally acknowledged, was not needed to carry out scientific research in preventive medicine. While these are likely the most probable reasons underlying the absence of specific funding acknowledged by the investigators in the public health field, such an unexpectedly high rate of non-disclosure

warrants further examination, since also alternative reasons may at least in part explain it. Some journals could not explicitly require mandatory disclosure of funding sources (42), though this is unlikely to be a widespread approach, and they could also differ in their acknowledgment practices (43-45). Such a possible inconsistency in journal policies could contribute to underreporting, as researchers may not feel obligated to disclose all sources of funding, especially when the journal's guidelines are unclear or lenient, and could distort our understanding of the full spectrum of financial support behind public health research. However, transparency in research funding is necessary for maintaining the integrity of research (46-49): without detailed funding disclosures, it can be difficult for public, policymakers and practitioners to assess whether the research may be influenced by funders' interests. In some cases, researchers might unintentionally omit funding information due to oversight and permissive journal policies, but such omissions can anyhow lead to concerns about potential conflicts of interest, particularly if the funding source has a stake in the research outcomes. Given the potential impact of public health research on policy decisions and health interventions, clear reporting of funding sources is crucial for ensuring trust in the findings, and journal guidelines should make this as mandatory for manuscript authors. Finally, the absence of funding disclosures could reflect a broader issue of insufficient recognition for the role that funding plays in shaping research priorities and outputs. In fact, if funding is not systematically acknowledged, it becomes challenging to trace the influence of different financial sources on the research, which could limit the assessment of publication reliability, and limit stakeholders' ability to make informed decisions about where to allocate resources or how to address gaps in research underfunded fields. However, we consider it unlikely that Italian authors in the public health field may have substantially underreported their sources of funding, given the general requirement of the funders to acknowledge their support, the clear interest of authors to highlight it, and the major ethical and professional (if not even legal) consequences of hiding a funding sources. Overall, therefore, it seems clear that a substantial part of public health research in Italy is performed without a specific research support, and therefore without the need to acknowledge it. This could also make the Italian investigators swifter and more effective in addressing new and rapidly emerging public health issues, given the ability to start research activity even in the absence of specific financial support for it, or before receiving it.

Our assessment may have been hampered by the lack of exhaustive details about the specific grants (such as their codes and numbers) in the acknowledgement section, with consequent risk of indexing errors (especially for publications in languages other than English). Over- or under-representation of funding sources could also vary according to the research topic and its relevance, thus possibly introducing some differential bias.

Other limitations may affect our analysis. We based the evaluation on published papers, not taking into account other kind of publications, e.g. pre-prints, conference papers or grey literature (12). Secondarily, funding acknowledgment does not provide insight on the contributions nor combination or co-usage of researchers' funding, meaning that, when multiple funding sources were used, we could not understand how much a specific fund impacted that publication, also compared with the other sources (50). In addition, the exclusion of papers related to multicenter national and international studies where Italian researchers cannot be clearly identify as having a leading role likely prevented in our study a comprehensive reporting of funding sources for research carried out by Italian investigators, especially in the context of collaborations with EU-entities and International institutions, despite their 'non -primary' responsibility in such research activities. As a consequence, the assessment performed in this study must be considered as applicable only to scientific research in which Italian public health investigators had a clear leading role, either in a national or an international perspective.

We have not contacted researchers, opting instead to scan publications directly. Such approach should not suffer from reporting biases, as could occur by interviewing directly researchers about their current funding, and allow a clear, complete, and standardized approach in funding source mapping (51).

Conclusions

Through this initial screening, we hope to lay the groundwork for more in-depth investigations and discussions about sources, allocation, sustainability and equity of public health research funding in Italy. A better understanding of how funds are distributed across regions and disease categories can help to address disparities and to promote equitable access to research resources, especially in underfunded regions

and institutions and in underserved populations (52). Knowing which institutions or areas of research attract more funding could promote collaboration among regions or institutions with complementary expertise and infrastructure, providing capacity-building support, such as training, infrastructure, or research grants, eventually leading to more sustainable public health systems and more effective public health interventions. In addition, fostering a culture of declaring funding and monitoring the connection between funding and publication output can improve accountability among researchers, promote transparency in research, and ensure the distribution of resources to where they will have the greatest long-term impact under a public health perspective (53). Ultimately, we believe this type of analysis will help in identifying potential biases and funding gaps, and offer opportunities for the improvement of funding strategies, in order to ensure robust and transparent public health research in an EU country such as Italy.

Conflict of interest statement: The authors declare no conflict of interest.

Riassunto

Fonti di finanziamento alla ricerca in Sanità Pubblica in Italia

Introduzione. Le fonti di finanziamento possono avere un impatto cruciale nel definire il panorama della ricerca scientifica in generale, inclusa la Sanità Pubblica, poiché possono influenzare non solo la realizzazione di progetti, ma anche il loro contenuto.

Disegno dello studio. Questo studio ha l'obiettivo di analizzare le attuali fonti di finanziamento per la ricerca in Sanità Pubblica in Italia e le relative implicazioni.

Metodi. Abbiamo condotto una ricerca sistematica su PubMed, coprendo il periodo da gennaio 2023 a giugno 2024. Ci siamo concentrati sulle pubblicazioni dei 208 professori ordinari ed associati in Igiene Generale ed Applicata in servizio presso tutti gli Atenei italiani, includendo solo articoli in cui questi ricercatori fossero primi o ultimi autori, escludendo editoriali, commenti e lettere. Le fonti di finanziamento sono state classificate in: "pubbliche interne", "pubbliche esterne", "private esterne" e "non menzionate".

Risultati. Abbiamo identificato 760 articoli, una volta eliminati i duplicati. I temi di ricerca di tali pubblicazioni sono risultati equamente distribuiti tra malattie trasmissibili (48,2%) e non trasmissibili (51,8%). I finanziamenti pubblici esterni sono risultati i più comuni (33,7%), seguiti da quelli privati esterni (14,3%) e pubblici interni (7,5%), mentre il 58,7% degli studi non ha riportato fonti di finanziamento. La ricerca sulle malattie trasmissibili è stata principalmente sostenuta da fonti private esterne, regionali e dell'Unione Europea, mentre la ricerca sulle malattie non trasmissibili ha ricevuto maggiori finanziamenti da fonti pubbliche esterne, in particolare governative.

Conclusioni. In Italia, il panorama dei finanziamenti per la ricerca in Sanità Pubblica appare complesso, per via del vasto numero di temi trattati e dal frequente intreccio di finanziamenti provenienti da diversi enti. A prescindere dal tema di ricerca, i finanziamenti pubblici risultano più frequenti di quelli privati. Gran parte della ricerca in Sanità Pubblica non sembra tuttavia necessitare di supporti finanziari specifici, suggerendo come le esigenze finanziarie siano spesso contenute. Questo probabilmente offre ai ricercatori di tale disciplina maggiore flessibilità e indipendenza, con importanti implicazioni per la fattibilità degli studi e la riduzione dei conflitti di interesse.

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SUPPLEMENTARY MATERIAL

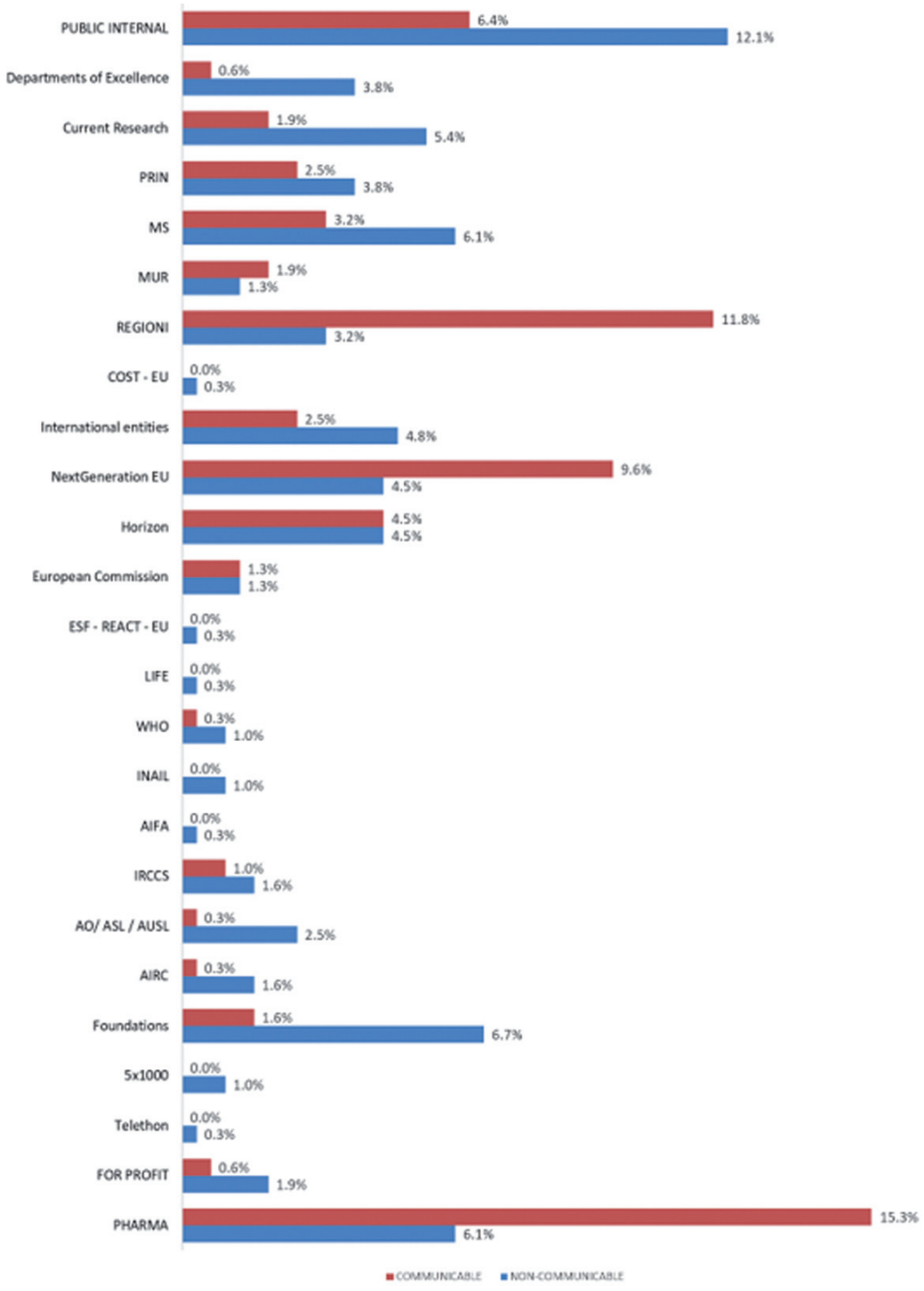
Supplementary Table S1. Main topics of the publications divided into communicable and non-communicable diseases and by geographical area.

	North (n = 342)	Center (n = 176)	South (n = 242)	Total (n = 760)
Communicable diseases	142 (41.5%)	86 (48.9%)	138 (57.0%)	366 (48.2%)
COVID-19	67 (19.6%)	41 (23.3%)	39 (16.1%)	147 (19.3%)
Infectious Disease	40 (11.7%)	21 (11.9%)	53 (21.9%)	114 (15.0%)
Vaccination	28 (8.2%)	21 (11.9%)	32 (13.2%)	81 (10.7%)
HPV	4 (1.2%)	2 (1.1%)	5 (2.1%)	11 (1.4%)
Antibiotic Resistance	3 (0.9%)	1 (0.6%)	9 (3.7%)	13 (1.7%)
Non-communicable diseases	200 (58.5%)	90 (51.1%)	104 (43.0%)	394 (51.8%)
Cancer	36 (10.5%)	7 (4.0%)	14 (5.8%)	57 (7.5%)
CVD	11 (3.2%)	3 (1.7%)	4 (1.7%)	18 (2.4%)
Neurology	11 (3.2%)	10 (5.7%)	2 (0.8%)	23 (3.0%)
Pediatric	15 (4.4%)	3 (1.7%)	4 (1.7%)	22 (2.9%)
Ob&Gyn	3 (0.9%)	1 (0.6%)	3 (1.2%)	7 (0.9%)
Other	124 (36.3%)	66 (37.5%)	77 (31.8%)	267 (35.1%)

Supplementary Table S2. Number of single and multiple sources of funding divided by geographical areas.

	One source of funding	Two sources of funding	Three sources of funding	Four sources of funding
Public Internal	57	-	-	-
North	29	-	-	-
Center	13	-	-	-
South	15	-	-	-
Public External	162	39	4	1
North	75	23	1	1
Center	28	4	2	-
South	59	12	1	-
Private External	105	2	-	-
North	49	1	-	-
Center	34	-	-	-
South	22	1	-	-
Unmentioned	**446**	-	-	-
North	196	-	-	-
Center	103	-	-	-
South	147	-	-	-

Supplementary Figure S1. Detailed sources of funding by type of topic. Values are percentages.



Acronyms: AIFA = Agenzia Italiana del Farmaco (Italian Medicine Agency); AIRC = Associazione Italiana per la Ricerca sul Cancro (Italian Association for Cancer Research); COST = European Cooperation in Science and Technology; CTN = Cluster Tecnologici Nazionali (National Technological Clusters); EFSA = European Food Safety Authority; ESA = European Space Agency; EUPHA = European Public Health Association; FAR = Fondo Ateneo per la Ricerca (University Research Fund); IRCCS = Istituto di Ricovero e Cura a Carattere Scientifico (Scientific Institute for Research, Hospitalization, and Healthcare); ISS = Istituto Superiore di Sannità (National Health Institute); MUR = Ministero dell'Università e della Ricerca (Ministry of University and Research); MS = Ministero della Sanità (Ministry of Health); Pia.ce.ri = Piano di incentivi per la Ricerca di Ateneo (University Research Incentive Plan); PRIN = Progetti di Rilevante Interesse Nazionale (Projects of National Relevance); SItI = Società Italiana Igiene e Medicina Preventiva (Italian Society of Hygiene and Preventive Medicine); WHO = World Health Organization

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SHORT PAPER

Impact of Mandatory Measles Vaccination on Coverage in Italy and the European Union: an observational study

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Keywords: Vaccination; Measles; Coverage; Mandatory
Parole chiave: Vaccinazione; Morbillo; Copertura vaccinale; Obbligatorietà

Abstract

Introduction. *Measles is a highly contagious disease, but it is preventable through vaccination. Despite the availability of measles vaccines, outbreaks continue to occur, due to factors such as vaccine hesitancy. In Italy, measles vaccination has been mandatory since 2017.*
Methods. *This study analyses vaccination coverage trends to assess the impact of this mandatory vaccination policy at regionjqal, national, and European Union levels.*
Results. *Results show a significant increase in measles vaccination coverage within Italy following implementation of the mandate, both at the national (+5,2%) and regional levels. However, the comparison of European countries with and without mandatory vaccination policies did not reveal statistically significant differences in coverage.*
Conclusion. *This suggests that while mandatory vaccination can improve coverage within a nation, additional strategies may be needed to address vaccine hesitancy and achieve herd immunity across broader geographical areas.*

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Introduction

Measles is a highly contagious viral respiratory disease caused by the Morbillivirus and preventable with vaccination (1). In Italy the measles vaccine was introduced in 1976 with different formulations, recommended in 1979, and mandatory since 2017 (2); despite this, there have been various measles outbreaks over the years (3). High levels of vaccination coverage are necessary to achieve herd immunity, reduce the incidence of this disease and prevent new outbreaks[1].

One of the main problems encountered in the last decade is the phenomenon of "vaccine hesitancy", often correlated with fake news or incorrect use of web information (4).

The World Health Organization (WHO) has set the goal of measles elimination, recommending a vaccination coverage of at least 95% with two doses (1).

In Italy, Law no. 119/2017 expanded the number of mandatory childhood vaccinations to ten, specifically including measles. This legislation mandates that proof of vaccination be provided for all children under the age of 16 seeking enrollment in state-operated educational institutions[2].

The National Vaccination Prevention Plan (PNPV) 2023-2025, in line with the indications of the previous plan (PNPV 17-19), recommends a two-dose measles vaccination schedule (12th month of age and 5th year) (5).

Evaluating trends in first-dose vaccine coverage levels during the five years preceding and following the implementation of mandatory vaccination is crucial to elucidate the law's impact on measles vaccination coverage.Additionally, this study seeks to assess the impact of mandatory vaccination policies on immunization coverage trends within the European Union by differentiating between countries with and without such mandates (6).

Materials and methods

Materials

Vaccination coverage rates at national level and for each European State were obtained through the ATLAS data collection tool, made available by the European Centre for Disease Prevention and Control (ECDC). This tool is based on data provided by the different member states through the European Surveillance System (TESSy) for infectious diseases Data updated to 2022.

Data on vaccination coverage for the different Italian regions were extracted from the reports available on the website of the Ministry of Health, calculated on the summaries sent by the Regions and PA.AA (7). Data updated to 2021.

Methods

Data on the mean measles vaccination coverage at 24 months in Italy were evaluated between 2013-2022. The coverage rates in 2013-17 were compared to 2018-22.

The mean regional vaccination coverage at 24 months was analysed between 2013 and 2021. To evaluate the impact of the mandatory vaccination law without the influence of the pandemic, 2015/16 was compared to 2018/19.

Ultimately, the mean coverages at 24 months in 2022 were compared between mandatory vaccination EU states and no mandatory vaccination countries.

Statistical analysis

The means of the groups defined above were calculated and compared using the Welch-corrected t-test for samples with unequal variance. Analyses with a p-value less than 0.05 were considered statistically significant.

The statistical analyses were conducted using the GraphPrism 5 software.

Results

Analyzing the Italian population in the period before the introduction of mandatory measles vaccination (2013-2017), the minimum vaccination coverage for the first dose was 85% in 2015, the maximum value 92% in 2017 with an average of 88.2% (SD 2.8). In the period after the introduction of mandatory measles vaccination (2018-2022), the minimum vaccination coverage was 92% in 2020, the maximum value 94% in 2022 with an average of 93.4% (SD 0.9).

Between the two analyzed groups, there was an increase on average of 5.2%, with statistical significance. ($p = 0{,}0163$; $df = 4$) (Fig. 1A).

This paper examines the impact of mandatory vaccination policies on regional vaccination coverage in Italy. Data from both before and after the introduction of the vaccination obligation (Law 119/2017) are analyzed to assess its effectiveness.

Prior to the implementation of the vaccination

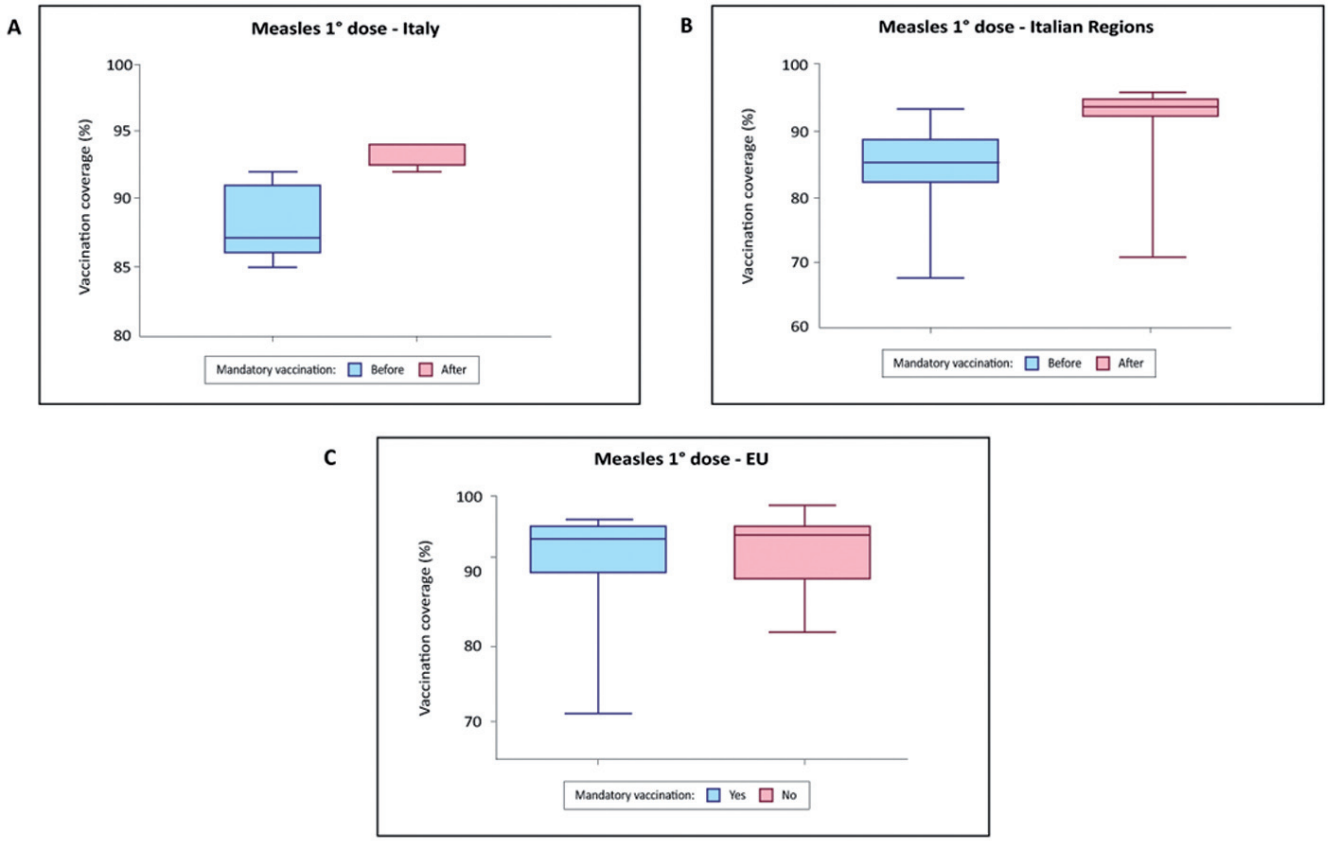

Figure 1 A - **Italian Vaccination Coverage Before and After Mandatory Law (2013-2022)**. This graph compares mean vaccination rates in Italy before (2013-2017) and after (2018-2022) the implementation of mandatory vaccination law (119/2017). B. **Regional Variation in Italian Vaccination Coverage** (2015-2016 vs. 2018-2019). This graph shows how mean vaccination rates differ across Italian regions before (2015-2016) and after (2018-2019) the introduction of mandatory vaccination law. C. **Measles Vaccination Rates: Mandatory vs. Non-Mandatory in Europe**. This graph compares mean measles vaccination coverage within European countries with and without mandatory vaccination policies.

obligation, regional disparities in vaccination coverage were evident. Lombardy registered the highest coverage rate at 24 months (93.4% in 2016), while the Autonomous Province of Bolzano had the lowest value (67.5% in 2016). Following the obligation's introduction (2018-2021), Lazio achieved the highest coverage (97.6% in 2021), while Abruzzo registered the lowest (62.1%). Molise exhibited the most significant increase in coverage in comparison to the 2013-2017 period (+11.6%). Conversely, Abruzzo experienced a decrease of 0.9%. In 2021, six regions and autonomous provinces attained coverage rates exceeding 95% (Fig. 2).

Comparing the coverage percentages at 24 months of all regions (Autonomous Provinces of Trento and Bolzano included) in 2015-2016 with those in 2018-2019, a statistically significant difference was obtained (mean 84.7% ± 0.97 vs 92.8% ± 0.7; $p < 0.0001$; df = 79). The median value in the period 2015-2016 was 85.2 with an interquartile range of 6.4 (82.2 - 88.5). In the period 2018-2019 the median was 93.5% with an interquartile range of 2.0 (92.3 - 94.3) (Fig. 1B).

The vaccination coverage for the first dose of measles in 2022 was analyzed by comparing 10 EU countries with mandatory vaccination (Bulgaria, Croatia, Czech Republic, France, Germany, Italy, Latvia, Poland, Slovakia, Slovenia) with 19 EU countries without mandatory vaccination (Austria, Belgium, Cyprus, Denmark, Estonia, Finland, Greece, Hungary, Iceland, Ireland, Lithuania, Luxembourg, Malta, Romania, Netherlands, Norway, Portugal, Spain, Sweden) (Fig. 3).

Regarding the group with mandatory vaccination, the minimum coverage value was 71% (Poland) and the maximum value obtained was 97% (Germany, Czech Republic) with an average of 91.9%.

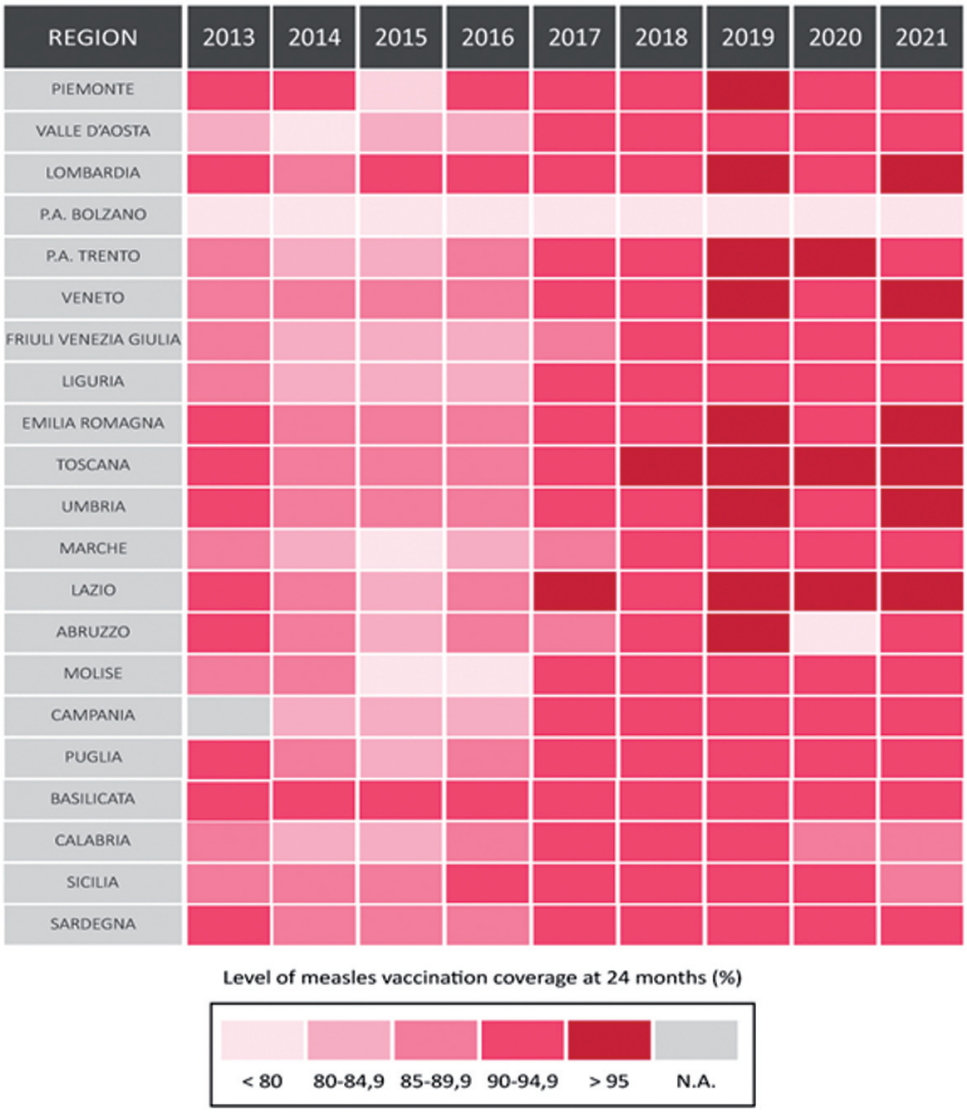

Figure 2 - Trends in coverage for first dose of measles vaccine (2013–2021) by Region/PP.AA.

The second group analyzed, without mandatory vaccination, showed a minimum value of 82% (Estonia) and a maximum value of 99% (Hungary) with an average of 92.7%.

The tests conducted did not show any statistical significance in the differences between the two groups. (p value = 0,7803; df = 13) (Fig. 1C).

Discussion and conclusions

The observed decline in immunization coverage and subsequent measles outbreaks within Italy during the 2015-2017 triennium (8) served as the impetus for the expansion of mandatory vaccination policies enacted through Law 119/2017.

The results show an improvement in the national average (+5.2%) during the five-year period 2018-2022 following the approval of the aforementioned law.

In 2020, in conjunction with the Covid-19 pandemic, there was a drop in vaccination coverage, with a subsequent realignment to pre-pandemic values in the period 2021-22.

In conclusion, this analysis offers further validation of the findings by Sindoni et al. regarding measles vaccination coverage between 2013 and 2019 (9).

The comparison at the regional level in the two years before (2015-2016) and after (2018-2019) the

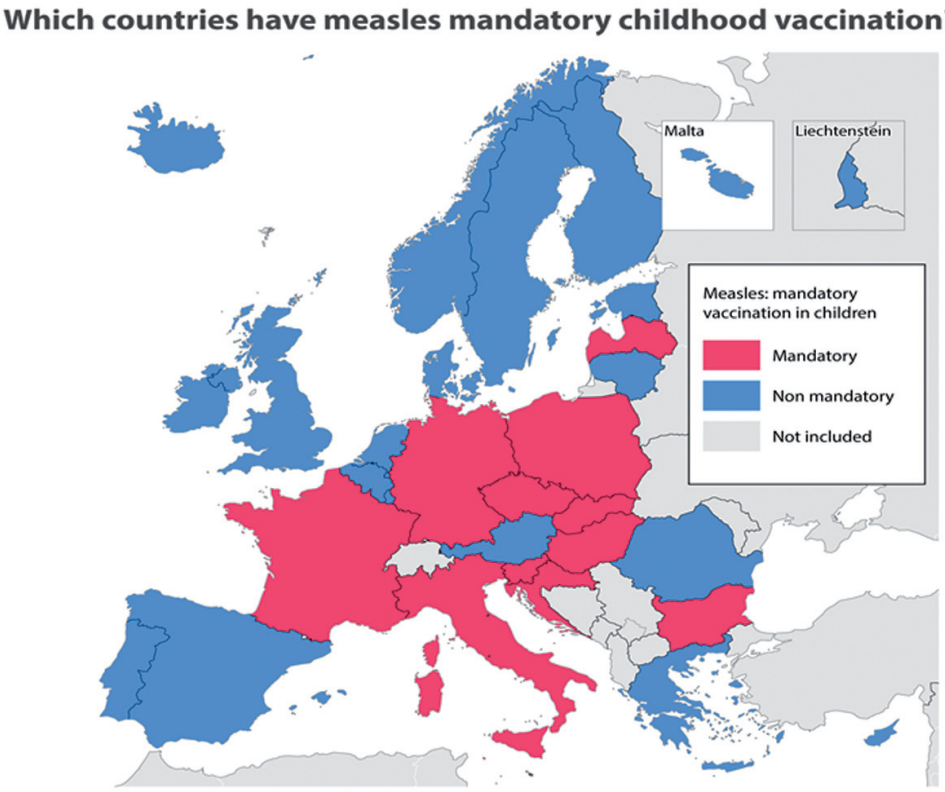

Fig. 3

introduction of Law 119/2017 showed a significant improvement in coverage at 24 months in most regions (+6% between 2016 and 2018), with 20 Regions/PA.AA. exceeding 90% coverage for the first dose. The average coverage increased from 84.6% to 92.8%, between the two periods. A reduction in the interquartile range was also observed in the period after the introduction of the obligation, suggesting that the law has allowed for the standardization of vaccination campaigns at the national level. In 2020, likely due to the pandemic, the average coverage decreased and only 3 regions maintained a coverage above 95%. In 2021 the situation improved, approaching the results of 2019.

In conclusion, the introduction of mandatory vaccination also had a positive impact on regional measles vaccination coverage and, despite some fluctuations, the general trend shows an improvement in coverage.

In 2022, the comparison between EU countries with mandatory measles vaccination and those without showed subtle differences in vaccination coverage. The group with mandatory vaccination had an average of 91.9%. The second group analyzed, without mandatory vaccination, had an average of 92.7%. The lack of statistical evidence between the means of the two groups could be influenced by several factors, such as data variability: although the means of the two groups seem similar, there could be a great deal of variability within each group.

Ultimately, from a statistical point of view, we cannot state that mandatory vaccination has a significant impact on first-dose measles vaccination coverage in European Union countries.

The European countries that express the greatest doubts about the safety of vaccines are those in Eastern and Southern Europe; those that are less skeptical are the countries of Northern and Western Europe, with the important exception of France and Italy, which show more negative feelings about the safety, efficacy and importance of vaccines among the population (10).

Country-level heterogeneities suggest that, while mandatory vaccination could be beneficial to improve coverage within an individual nation, additional strategies may be needed to address vaccine

hesitancy and achieve herd immunity across broader geographical areas.

Limitations of the study

This study possesses several strengths, notably its comprehensive analysis of mandatory vaccination policy impacts in Italy. However, certain limitations were encountered. Firstly, the inability to utilize second-dose data due to discrepancies created by the law's implementation skewed the analysis. Those receiving the second dose under mandate were not directly comparable to those with prior optional compliance. Additionally, the pandemic period presents a potential confounding factor, as it may have independently influenced vaccination coverage outcomes.

An additional limitation arises from the inability to analyze a full five-year period before and after the mandatory vaccination policy for all regions. Consequently, the analysis focused solely on data from the two years preceding and following the implementation of Law 119/2017.

At the European level, however, only 2022 was evaluated as it was not easy to evaluate the start date of the obligation for all European states.

Riassunto

L'impatto della vaccinazione obbligatoria contro il morbillo sulla copertura in Italia e nell'Unione Europea: uno studio osservazionale

Introduzione. Il morbillo è una malattia altamente contagiosa, ma è prevenibile attraverso la vaccinazione. Nonostante la disponibilità dei vaccini contro il morbillo, continuano a verificarsi epidemie a causa di fattori come l'esitazione vaccinale. In Italia, la vaccinazione contro il morbillo è obbligatoria dal 2017.

Metodi. Questo studio analizza le tendenze della copertura vaccinale per valutare l'impatto di questa politica di vaccinazione obbligatoria a livello nazionale, regionale e dell'Unione Europea.

Risultati. I risultati mostrano un significativo aumento della copertura vaccinale contro il morbillo in Italia a seguito dell'attuazione dell'obbligo, sia a livello nazionale (+5,2%) che regionale. Tuttavia, il confronto tra i Paesi europei con e senza politiche di vaccinazione obbligatoria non ha evidenziato differenze statisticamente significative nella copertura.

Conclusione. Ciò suggerisce che, sebbene la vaccinazione obbligatoria possa migliorare la copertura all'interno di una nazione, potrebbero essere necessarie ulteriori strategie per affrontare l'esitazione vaccinale e raggiungere l'immunità di gregge su aree geografiche più ampie.

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Vaccine hesitancy among nurses in the Marche Region

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Keywords: COVID-19 vaccination; nurse; vaccine hesitancy
Parole chiave: Vaccinazione anti COVID 19; personale infermieristico; esitazione vaccinale

Abstract

Background. *Vaccine hesitancy is considered one of the top ten threats to global health by the World Health Organization due to the potential public health consequences. Since April 1, 2021, the Italian Government has made COVID-19 vaccination mandatory for healthcare workers. Those who refused to undergo vaccination were suspended from activities involving patient care. This study aims to describe vaccine hesitancy among nurses in the Marche Region one year after the start of the COVID-19 vaccination campaign.*
Study design*. Observational study.*
Methods. *All nurses belongijg to the National Federation of Nursing Professions Orders of the Marche Region were included in the study. Data from December 27, 2021, to January 1, 2022, were provided by the FNOPI Presidents of provincial FNOPI for Pesaro-Urbino, Ancona, Macerata and Fermo.*
Results. *Among the 9,611 registered nurses, 1.34% were suspended because they refused to be vaccinated. The majority of suspended nurses were women (73.6%), 35.7% aged 50-59 years, and 29.4% aged 40-49 years, 21.7% aged 30-39 years, 10.1% aged ≥60 years and 3.8% aged <30 years. Vaccination hesitancy exhibited a north-south gradient: in particular, there was a prevalence of 1.73% suspended workers in Pesaro-Urbino, 1.46% in Ancona, 1.05% in Macerata and 0.71% in Fermo province.*
Conclusions. *Our study confirms the existence of vaccine hesitancy among nurses. The mandate imposed by the Government favored a higher adherence compared to the general population in the Marche Region, although it failed to reach full coverage by the entire nursing staff.*

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Introduction

Vaccine hesitancy refers to delay in acceptance or refusal of vaccination despite availability of vaccination services. It is a relevant issue in public health policies and a major concern worldwide, notwithstanding the large evidence on vaccine safety and effectiveness in preventing communicable diseases (1-4). Vaccine hesitancy is influenced by several factors, such as trust in importance, personal beliefs about safety and effectiveness of vaccines and perceived need for vaccination along with compatibility of vaccination with religious beliefs (1,2). Vaccine hesitancy is a problem in particular for the achievement of COVID-19 vaccination campaigns and policies in facing the pandemic, indeed, COVID-19 vaccination is considered the most effective measure to prevent the novel coronavirus spread and to reduce the hospital admission rates and deaths (5).

After the approval by the European Medicines Agency (EMA) of the first SARS-Cov-2 vaccines, the vaccination campaign started in Italy and in Europe in December 27, 2020 (6). The vaccines were offered free of charge to the entire population, with a priority according to the risk of developing severe symptoms, as well as the risk of exposure due to occupation, comorbidities and age. Following these guidelines, healthcare workers (HCWs) were among the first to benefit from the vaccine.

HCW are at higher risk of infection and their adherence to vaccination is a critical topic since they care for vulnerable people and play a key role in promoting health behaviors that encourage trust and adherence to vaccination among population (7). In our country, as vaccination coverage advanced, vaccine hesitancy grew among the general population and HCWs, mainly due to lack of trust or fear towards vaccines (8-12). Because of these critical issues and the ongoing spread of the virus, the Italian Government introduced mandatory COVID vaccination for all healthcare workers starting on April 1, 2021 (Decree Law 44/2021) which was later replaced by the Law n. 76 on May 28, 2021 (G.U. 31/05/2021, n. 128).

Italy was the first European country to make this decision, followed by France and Greece. According to this decree, the HCWs who chose not to get vaccinated were subject to job reassignment or unpaid suspension. The aim of our study was to describe the vaccination hesitancy of registered nurses in the Marche Region (Central Italy) one year after the start of the vaccination campaign.

Methods

Study design

This was an observational descriptive study carried out among the registered nurses members of the National Federation of Nursing Professions Orders (FNOPI) of the Marche Region. Data were provided by the FNOPI Presidents of Pesaro e Urbino, Ancona, Macerata and Fermo. For our purpose, we considered data from 27 December 2021 to January 1, 2022. Information on gender, age, province of membership and suspension status were recorded anonimously.

Statistical analysis

Categorical variables were presented as frequency and percentage and comparison was made using Chi square test. To assess a possible association of age and vaccination hesitancy, nurses were divided into two groups (over and under 40 years old, the median age of the sample) and a bivariate analysis was performed; statistical significance was set at 0.05. The analyses were conducted using STATA version 18 (Stata Corp. College Station, Texas, USA)

Results

Of the total 9,611 registered nurses, 129 (1.34%) were suspended for choosing not to be vaccinated. Examining the individual Provinces, a decreasing north-south gradient was observed: in the Order of Pesaro e Urbino (the northernmost province), the prevalence of suspended nurses was 1.73% (41 out of 2,368 registered nurses). This rate decreased to 1.46% (56 out of 3,832) in Ancona, 1.05% (24 out of 2,242) in Macerata, and down to 0.781% (8 out of 1,122) in the Province of Fermo (the southernmost province) (Figure 1). Fermo had a significantly lower percentage of suspended nurses compared to Pesaro-Urbino (0.71% vs 1.73%, $p<0.05$). The differences for the other Provinces were not statistically significant.

The ratio females/males and the age distribution of suspended nurses were similar in each Province. The majority of suspended nurses were females (95/129 or 73.6%) in the total sample, 30/41 (73.2%) in Pesaro-Urbino, 42/56 (75%) in Ancona, 18/24 (75%) in Macerata, 5/8 (62.5%) in Fermo Province. As concerning the age group, median age of the sample was 40 years, most suspended nurses were 50-59 years old, followed by those 40-49-year-old (Table 1).

The bivariate analysis showed that the differences between suspended nurses over 40 years of age and

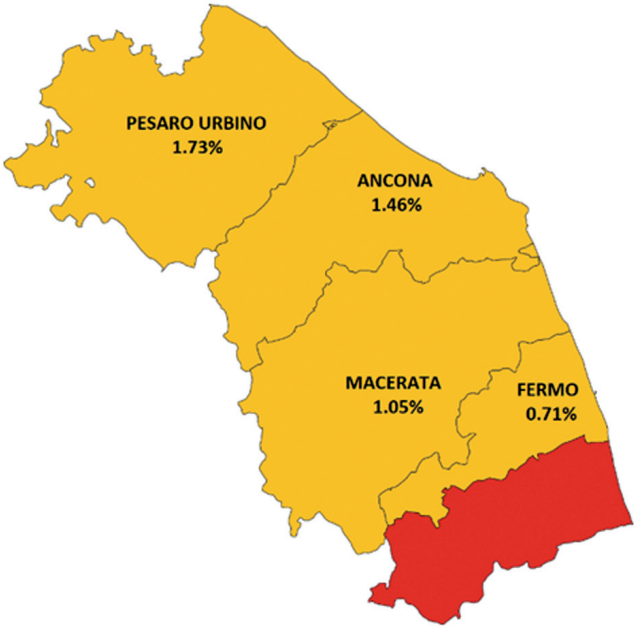

Figure 1 - Prevalence of suspended nurses by provincial orders. (In red: the province of Ascoli Piceno that did not provide data for the study and was therefore not included)

Table 2 - Bivariate analysis by age groups

	Suspended nurses		Registered nurses	p
Pesaro e Urbino				
<40 years (%)	11	(1.42%)	773	>0.05
≥ 40 years (%)	30	(1.88%)	1595	
Ancona				
<40 years (%)	12	(0.86%)	1400	<0.05
≥ 40 years (%)	44	(1.81%)	2432	
Macerata				
<40 years (%)	8	(0.93%)	857	>0.05
≥ 40 years (%)	16	(1.16%)	1385	
Fermo				
<40 years (%)	1	(0.21%)	479	>0.05
≥ 40 years (%)	7	(1.09%)	643	
Total sample				
<40 years (%)	32	(0.91%)	3509	<0.05
≥ 40 years (%)	97	(1.60%)	6055	

*total registered nurses/province

those under 40 were statistically significant only in Ancona Province and in the total sample (Table 2).

Discussion

Among the general population in the Marche Region, 11% refused vaccination for SARS-Cov-2, which corresponds to 136,595 out of 1,246,208 as of January 1, 2022 (13). This study showed that 1.34% of nurses in the Marche Region were suspended for choosing not to be vaccinated. This was in agreement with previous Italian studies reporting 1.1%-1.82% COVID-19 vaccine hesitancy (11,12).

Consistent with other studies, female gender and older population exhibited a higher degree of vaccination hesitancy. This could be attributed to greater confidence a/o stronger sense of responsibility among younger age groups, as well as differences in educational backgrounds (11, 14-17).

When examining the individual provinces, a decreasing north-south gradient was observed: Fermo (South of Marche) had a significant lower percentage of suspended nurses than Pesaro-Urbino in the

Table 1 - Characteristics of the suspended nurses

	Marche Provinces			
	Pesaro Urbino (N=41)	Ancona (N=56)	Macerata (N=24)	Fermo (N=8)
Gender				
Male (%)	11 (26.8%)	14 (25.0%)	6 (25.0%)	3 (37.5%)
Female (%)	30 (73.2%)	42 (75.0%)	18 (75.0%)	5 (62.5%)
Age Groups				
<30 (%)	2 (4.9%)	0 (0%)	3 (12.5%)	0 (0%)
30-39 (%)	9 (22.0%)	12 (21.4%)	5 (20.8%)	1 (12.5%)
40-49 (%)	11 (26.8%)	16 (28.6%)	8 (33.3%)	3 (37.5%)
50-59 (%)	13 (31.7%)	24 (42.9%)	5 (20.8%)	4 (50.0%)
≥60 (%)	6 (14.6%)	4 (7.1%)	3 (12.5%)	0 (0%)

north (0.71% vs 1.73%, p=0.03). Differences across Provinces might suggest different strategies to promote vaccination, and further studies may help clarify this point.

Among the determinants of vaccine hesitancy, communication and media environment may have played a key role, both at the individual and community level (18). Educational and communication interventions were the most commonly used strategies to increase COVID-19 vaccine uptake or decrease vaccine hesitancy across different Countries (19). Ledda et al (20) carried out interviews to HCWs who refused to get vaccinated, including physician (15.4 %), physiotherapist (11.5 %), nurse (40.4%), midwife (1.9 %), dentist (1.9 %), radiology technician (5.8 %), laboratory technician (7.7 %) and social health operator (15.4%). They found that these workers had a good knowledge of the Italian Vaccination Plan on COVID-19 (98%). Despite this, they developed a strong anti-vaccination belief, indeed only 6% of them were in favour of mandatory COVID-19 vaccination.

The obligation imposed by the Italian decree influenced the adherence to the vaccination program, although it failed in bringing coverage to the entire nursing staff. Previous Italian data showed a decrease in the vaccine refuse after the introduction of the compulsory vaccination (12). However, there is an open debate about the effectiveness of mandatory vaccinations.

In order to address the issues related to vaccine hesitancy, the identification of determinants of COVID-19 vaccine uptake is essential for developing effective strategies for promoting vaccination, including the Vaccine Literacy (VL) that has been proposed to allow vaccination to be understood as a social practice by the entire community (21-23).

Limitations

Our study has several limitations. Marche region is quite small (1,5 million persons) and the local findings give a small picture of the Italian Situation. Moreover, one Province decided not to provide their data, influencing the assessment at the regional level. Another limitation was that data were recorded anonymously and did not include the actual workplace, for this reason it was not possible to identify a possible correlation of vaccine exitancy to a type of hospital ward. Other investigations should be conducted to further analyze the phenomenon of vaccine hesitancy.

Conclusion

This study confirmed that vaccine hesitancy among nurses exists also in Marche Region. Socio-demographic factors (gender, age, Province) seem to be associated with the decision to not get vaccinated.

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Riassunto

Esitazione vaccinale tra gli infermieri della Regione Marche

Introduzione. L'esitazione vaccinale è considerata una delle dieci principali minacce alla salute globale dall'Organizzazione Mondiale della Sanità a causa delle potenziali conseguenze sulla salute pubblica. Dal 1° aprile 2021 il Governo Italiano ha reso obbligatoria la vaccinazione anti-COVID per gli operatori sanitari. Gli operatori sanitari che hanno rifiutato di sottoporsi alla vaccinazione sono stati sospesi dal lavoro di assistenza ai pazienti. Lo studio si propone di descrivere l'esitazione vaccinale tra gli infermieri della Regione Marche ad un anno dall'inizio della campagna vaccinale.

Disegno dello studio. Studio osservazionale.

Metodi. È stato incluso nello studio tutto il personale infermieristico iscritto alla Federazione nazionale degli ordini delle professioni infermieristiche della Regione Marche. I dati dal 27 dicembre 2021 al 1° gennaio 2022 sono stati forniti dai Presidenti dell'Ordine di Pesaro-Urbino, Ancona, Macerata e Fermo.

Risultati. Tra 9.611 infermieri registrati, l'1,34% è stato sospeso perché ha rifiutato di farsi vaccinare. La maggioranza erano donne (73,6%), il 35,7% aveva un'età compresa tra 50 e 59 anni e il 29,4% tra 40 e 49 anni, 21.7% aveva 30-39 anni, 10.1% aveva ≥60 anni e 3.8% aveva <30 anni. L'esitazione vaccinale ha un gradiente nord-sud, in particolare si registra una prevalenza dell'1,73% dei lavoratori sospesi nella provincia di Pesaro-Urbino, dell'1,46% a Ancona, dell'1,05% a Macerata e dello 0,71% a Fermo.

Conclusioni. Il nostro studio conferma l'esistenza di un'esitazione vaccinale tra gli infermieri. L'obbligo imposto dal Governo ha influito sulla maggiore adesione rispetto alla popolazione generale nella Regione Marche, pur non essendo riuscito a portare la copertura a tutto il personale infermieristico.

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Vaccination hesitancy: agreement between WHO and ChatGPT-4.0 or Gemini Advanced

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Keywords: ChatGPT; Gemini; AI; WHO; Vaccine; Vaccine Hesitancy
Parole chiave: ChatGPT; Gemini; IA; OMS; Vaccini; Esitazione Vaccinale

Abstract

Background. *An increasing number of individuals use online Artificial Intelligence (AI) - based chatbots to retrieve information on health-related topics. This study aims to evaluate the accuracy in answering vaccine-related answers of the currently most commonly used, advanced chatbots - ChatGPT-4.0 and Google Gemini Advanced.*
Methods. *We compared the answers provided by the World Health Organization (WHO) to 38 open questions on vaccination myths and misconception, with the answers created by ChatGPT-4.0 and Gemini Advanced. Responses were considered as "appropriate", if the information provided was coherent and not in contrast to current WHO recommendations or to drug regulatory indications.*
Results and Conclusions. *The rate of agreement between WHO answers and Chat-GPT-4.0 or Gemini Advanced was very high, as both provided 36 (94.7%) appropriate responses. The few discrepancies between WHO and AI-chatbots answers could not be considered "harmful", and both chatbots often invited the user to check reliable sources, such as CDC or the WHO websites, or to contact a local healthcare professional. In their current versions, both AI-chatbots may already be powerful instrument to support the traditional communication tools in primary prevention, with the potential to improve health literacy, medication adherence, and vaccine hesitancy and concerns. Given the rapid evolution of AI-based systems, further studies are strongly needed to monitor their accuracy and reliability over time.*

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Introduction

In the last decades, an increasing number of individuals have been using internet to retrieve information on health-related topics, with relevant implications on citizen's decisions and, in turn, public health (1,2). Search engines or social media were primarily used to access health-related contents, with serious concerns on the quality of online health information (3,4).

In the last few years, Artificial Intelligence (AI), and in particular AI Large Language Models (LLMs), has generated interest in the medical and academic communities, as they may become one of the main sources of health information seeking (5-7), and provide several Digital Health potential applications (8-10). Considering the gaining popularity of this technology, which can reproduce human language processing skills, generating realistic and coherent texts, several studies are evaluating their reliability and coherence with the best evidence available (11-15).

A few studies compared the reliability of different LLMs on vaccination-related topics (11,12,15): AI responses were not always fully accurate (15), and might even exacerbate vaccine hesitancy by spreading incorrect or misleading information (12).

This study aims to evaluate the accuracy of the currently most commonly used, advanced chatbots developed by OpenAI (ChatGPT-4.0) and Google (Gemini Advanced), comparing AI and World Health Organization (WHO) answers to the frequently asked questions (FAQs) about vaccines from WHO website (16-18). Given the substantial impact of these sources on the decision making of millions of individuals, it is crucial to verify that patients are informed according to the best available evidence.

Methods

Currently, two different versions of both ChatGPT and Gemini are publicly available: an open version (ChatGPT-3.5 and Gemini), and a more advanced version, which requires a monthly payment for access (ChatGPT-4.0 and Gemini Advanced) (19,20). This study collected the answers provided by ChatGPT-4.0 and Gemini Advanced to 38 open questions (Table 1), selected from the FAQs sections of WHO website (17-19). In particular, 13 questions pertain to the general topic of "Vaccines and immunization" (16); 11 questions focus on "Myths and misconceptions'' related to vaccines, originally written by the U.S. Centers for Disease Control and Prevention (CDC) to support practitioners involved in vaccinations for children (17); and 14 questions regards "COVID-19: Vaccines and vaccine safety" (18). These questions were posed by a single user to ChatGPT-4.0 and Gemini Advanced on February 13, 2024. Chatbots' answers were then independently and blindly evaluated by two authors (MF and AB), who compared AI answers with those answers provided by the WHO. AI responses were considered as "appropriate", if the information provided was:

(a) coherent with the information provided by the WHO;

(b) not related to a geographical area or other specific contexts only;

(c) not in contrast to current WHO recommendations on vaccination;

(d) not in contrast to drug regulatory agency indications about vaccines (21).

If an answer did not comply with the above-mentioned criteria, it was considered "inappropriate". Any discrepancy in the categorization was discussed by the pair, in order to achieve a consensus. If consensus was not achieved, the disagreement was reviewed and solved by a third author (LM). A precise description of the decision process was provided each time an answer was labeled as "inappropriate". Moreover, it was recorded when the chatbot invited the user to contact a healthcare professional or check reliable sources of information to have personalized and updated answers.

Data was managed with Google Sheets (Alphabet, San Francisco, CA, USA, 2024), and the overall accuracy rate of both chatbots was summarized using descriptive statistics. The transcription of all the 38 pairs of answers provided by the chatbots are available in the Supplementary Material, which can be requested to the corresponding author.

To ensure transparency, the screenshots of the entire chats with ChatGPT-4.0 and Gemini Advanced, and the html text of the WHO web pages' versions checked for this study (17-19) are available by request to the corresponding author.

Results

Overall, the rate of agreement between WHO answers and Chat-GPT-4.0 or Gemini Advanced was very high, as both provided 36 (94.7%) appropriate responses (Table 2).

Both chatbots reported a partially inappropriate

Table 1 - WHO's list of questions concerning (A) "Vaccines and immunization: What is vaccination?"; (B) "Vaccines and immunization: Myths and misconceptions"; (C) "Coronavirus disease (COVID-19): Vaccines and vaccine safety".

(A)
What is vaccination?
How does a vaccine work?
When should I get vaccinated (or vaccinate my child)?
Why should I get vaccinated?
What diseases do vaccines prevent?
Who can get vaccinated?
What is in a vaccine?
Are vaccines safe?
Are there side effects from vaccines?
Can a child be given more than one vaccine at a time?
Is there a link between vaccines and autism?
Should my daughter get vaccinated against human papillomavirus (HPV)?
I still have questions about vaccination. What should I do?
(B)
Weren't diseases already disappearing before vaccines were introduced because of better hygiene and sanitation?
Which disease show the impact of vaccines the best?
What about hepatitis B? Does that mean the vaccine didn't work?
What happens if countries don't immunize against diseases?
Can vaccines cause the disease? I've heard that the majority of people who get disease have been vaccinated.
Will vaccines cause harmful side effects, illnesses or even death? Could there be long term effects we don't know about yet?
Is it true that there is a link between the diphtheria-tetanus-pertussis (DTP) vaccine and sudden infant death syndrome (SIDS)?
Isn't even a small risk too much to justify vaccination?
Vaccine-preventable diseases have been virtually eliminated from my country. Why should I still vaccinate my child?
Is it true that giving a child multiple vaccinations for different diseases at the same time increases the risk of harmful side effects and can overload the immune system?
Why are some vaccines grouped together, such as those for measles, mumps and rubella?
(C)
What vaccines protect against COVID-19?
Who should get vaccinated against COVID-19?
Who should not be vaccinated against COVID-19?
Do I need to be revaccinated with the COVID-19 vaccine?
Can children and adolescents get vaccinated against COVID-19?
Do all COVID-19 vaccines protect against virus variants?
Should I be vaccinated if I have had COVID-19?
Can I be revaccinated with a vaccine different from my previous dose?
Can I still get COVID-19 after I have been vaccinated?
How do we know that COVID-19 vaccines are safe and effective?
What are the side effects of COVID-19 vaccines?
Can I get vaccinated against COVID-19 if I am pregnant?
Should I get vaccinated against COVID-19 if I am breastfeeding?
Should I get vaccinated if I want to have a baby in the future?

answer to the question "Can children and adolescents get vaccinated against COVID-19?", as they reported that COVID-19 vaccination is recommended for all children, while the WHO reported the following answer: "Healthy children and adolescents aged 6 months to 17 years belong to the low priority group for COVID-19 vaccination. Vaccinating them at this stage of the pandemic has limited public health impact […]. Children and adolescents at higher risk of severe COVID-19 (those who are immunocompromised, with severe obesity or with comorbidities) and never received COVID-19 vaccination, should get one dose" (22). Chat-GPT-4.0 also reported a partially incorrect answer to the question "When should I get vaccinated (or vaccinate my child)?", as it stated that the hepatitis B vaccine is commonly administered within 24 hours after birth. However, this is not a routine practice in many geographical contexts (*e.g.*, some European countries) (23). Finally, Gemini Advanced wrongly answered the question "What vaccines protect against COVID-19?", as it reported that the Moderna COVID-19 vaccine is authorized for adults only. However, according to the Food and Drug Administration, this vaccine may be administered to all individuals aged 6 months or older (24).

As regards the FAQs sections, both chatbots correctly answered to all the questions listed in the section "Vaccines and immunization: Myths and misconceptions". Finally, ChatGPT-4.0 and Gemini Advanced suggested to check reliable sources of information, or to contact a physician or a healthcare professional in 25 (65.8%) and 31 (81.5%) of the answers, respectively (Table 2).

Table 2 - Assessment of the answers of ChatGPT-4.0 and Gemini Advanced to WHO' FAQs.

Vaccines and immunization: What is vaccination?	ChatGPT-4.0	Gemini Advanced
What is vaccination?	1	1†
How does a vaccine work?	1	1
When should I get vaccinated (or vaccinate my child)?	0†a	1†
Why should I get vaccinated?	1	1†
What diseases do vaccines prevent?	1†	1†
Who can get vaccinated?	1†	1†
What is in a vaccine?	1†	1†
Are vaccines safe?	1†	1†
Are there side effects from vaccines?	1†	1†
Can a child be given more than one vaccine at a time?	1†	1†
Is there a link between vaccines and autism?	1†	1†
Should my daughter get vaccinated against human papillomavirus (HPV)?	1†	1†
I still have questions about vaccination. What should I do?	1†	1†
Agreement rate to WHO' FAQs	12/13 (92.3%)	13/13 (100%)
Vaccines and immunization: Myths and misconceptions.		
Weren't diseases already disappearing before vaccines were introduced because of better hygiene and sanitation?	1	1
Which disease show the impact of vaccines the best?	1	1
What about hepatitis B? Does that mean the vaccine didn't work?	1	1
What happens if countries don't immunize against diseases?	1	1
Can vaccines cause the disease? I've heard that the majority of people who get disease have been vaccinated.	1	1
Will vaccines cause harmful side effects, illnesses or even death? Could there be long term effects we don't know about yet?	1	1†
Is it true that there is a link between the diphtheria-tetanus-pertussis (DTP) vaccine and sudden infant death syndrome (SIDS)?	1†	1†
Isn't even a small risk too much to justify vaccination?	1†	1†
Vaccine-preventable diseases have been virtually eliminated from my country. Why should I still vaccinate my child?	1	1†
Is it true that giving a child multiple vaccinations for different diseases at the same time increases the risk of harmful side effects and can overload the immune system?	1†	1†
Why are some vaccines grouped together, such as those for measles, mumps and rubella?	1	1
Agreement rate to WHO' FAQs	11/11 (100%)	11/11 (100%)
Coronavirus disease (COVID-19): Vaccines and vaccine safety.		
What vaccines protect against COVID-19?	1†	0†b
Who should get vaccinated against COVID-19?	1†	1†
Who should not be vaccinated against COVID-19?	1†	1†
Do I need to be revaccinated with the COVID-19 vaccine?	1†	1†
Can children and adolescents get vaccinated against COVID-19?	0†c	0†c
Do all COVID-19 vaccines protect against virus variants?	1†	1†
Should I be vaccinated if I have had COVID-19?	1†	1†
Can I be revaccinated with a vaccine different from my previous dose?	1†	1†
Can I still get COVID-19 after I have been vaccinated?	1	1†
How do we know that COVID-19 vaccines are safe and effective?	1	1†
What are the side effects of COVID-19 vaccines?	1†	1†
Can I get vaccinated against COVID-19 if I am pregnant?	1†	1†
Should I get vaccinated against COVID-19 if I am breastfeeding?	1†	1†
Should I get vaccinated if I want to have a baby in the future?	1†	1†
Agreement rate to WHO' FAQs	13/14 (92.9%)	12/14 (85.7%)
Overall agreement rate to WHO' FAQs	36/38 (94.7%)	36/38 (94.7%)

1: Appropriate; 0: Inappropriate; †: the chatbot, in the answer, invited the user to check reliable sources of information to contact a healthcare professionals;
a: the answer provided by ChatGPT-4.0 stated that the hepatitis B vaccine is commonly administered within 24 hours after birth; however, this is not a routine practice in many geographical contexts (*e.g.*, some European countries) [23];
b: the answer provided by Gemini Advanced stated that the Moderna COVID-19 vaccine is authorized for adults only; however, this vaccine may be administered to all individuals aged 6 months or older according to the Food and Drug Administration [24];
c: the answer provided by both chatbots suggested that COVID-19 vaccination is recommended for all children; on the other hand, the WHO answer described children and adolescents as low priority categories and vaccination recommendations may vary by different geographical contexts, and specified that is recommended particularly for children with comorbidities that may expose them to higher COVID-19 related risks [22].

Discussion

In this study, focused on the list of FAQs about vaccines reported by the WHO, we observed a very high level of agreement between the answers provided by the same WHO and both ChatGPT-4.0 and Gemini Advanced. To date, no study explored the performance of Gemini Advance on vaccines-related topics to date, and only two studies previously evaluated the clarity, correctness and exhaustiveness of ChatGPT-3.5 and -4.0 in responding to vaccination misconceptions (13) or vaccine concerns and hesitancy (12). Our findings are in agreement with those from both of the above studies: Deiana et al. showed an accuracy higher than 85% for both versions of ChatGPT, with the more advanced 4.0 performing slightly better (13); and Torun et al. observed that ChatGPT-3.5 was a valuable source of information for guiding patients with vaccine hesitancy, boosting patient confidence in primary prevention (12). When other health-related topics are considered, the results have been similarly positive: as an example, according to Johnson et al. (25), ChatGPT-3.5 was capable of providing 96.9% correct answers to FAQs about cancer myths and misconceptions.

Given that digital resources should not replace the doctor-patient relationship, and even though a negative AI performance has been reported in some fields, such as parasitology (26), the available body of literature suggest that these AI-chatbots may already be powerful instrument to support the traditional communication tools in primary prevention, with the potential to improve vaccine literacy (27), medication adherence, and vaccine hesitancy and concerns (28), especially in developing countries (29). Clearly, it will be essential that the accuracy and reliability of AI-chatbots will be maintained over time, otherwise these technologies could facilitate the spread of misinformation that may be dangerously detrimental for patients (30,31). Importantly, however, in the present study the few discrepancies between WHO and AI-chatbots answers could not be considered "harmful", are simple to revise, and both chatbots often invited the user to check reliable sources, *e.g.,* the CDC or the WHO websites, or to contact a healthcare professional to seek out updated and additional information, finally to consult the Local Health Authorities for geographically-specific information. In any case, further studies should keep analyzing these and other AI-chatbots performances, compare them in different settings, and assess potential errors and biases (32,33).

This study has some limitations that must be considered in interpreting the results. First, although we adopted a strongly validated reference to identify the correct answers (WHO), and two investigators independently assessed every question, a certain level of subjectivity in evaluating the agreement of the responses could not be avoided. Also, the answers presented by ChatGPT-4.0 and Gemini Advanced were appropriate for the proposed questions, but in a real-case scenario, it cannot be excluded that an incoherently-written question about vaccines may lead to a misleading or incorrect answer. Third, ChatGPT-4.0 and Gemini Advanced are available for paying users only, which poses the problem of digital inequity, representing a recognized aspect of health disparity (34). Fourth, although we included a relatively long list of relevant questions, it cannot be considered a comprehensive list of the doubts faced by patients about vaccination. Finally, all the chats were conducted in English, so the performance of the chatbots in other languages may be different, and should be properly assessed.

Conclusions

Both ChatGPT-4.0 and Gemini Advanced showed a very high level of agreement with 38 answers provided by the WHO on important vaccine-related topics, including vaccination effectiveness, safety, schedules, and others. The few, partial discrepancies could not be considered potentially harmful, and both AI-chatbots often advised the user to check other reliable sources and seek a doctor to obtain further information. These findings suggest that both AI-chatbots can already be powerful instrument to support the traditional communication tools in primary prevention, with the potential to improve vaccine hesitancy and concerns. As AI-chatbots are evolving rapidly, further studies are strongly needed to monitor their accuracy and reliability over time.

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Riassunto

Esitazione Vaccinale: concordanza tra OMS e ChatGPT-4.0 o Gemini Advanced

Background. Un numero crescente di pazienti consulta chatbot basati sull'Intelligenza Artificiale (IA) per ottenere informazioni relative alla salute. Data la loro rilevanza, diffusione e le possibili applicazioni nella Digital Health, è fondamentale verificare che i pazienti siano informati da questi strumenti alla luce delle migliori evidenze disponibili. Tuttavia, in letteratura sono emerse inaccuratezze da parte dei chatbot-IA quando consultati su argomenti relativi alla salute. Tali imprecisioni potrebbero aggravare l'esitazione vaccinale diffondendo informazioni errate o fuorvianti. Pertanto, lo studio si propone di valutare l'accuratezza delle risposte fornite a domande sulla esitazione vaccinale da due dei chatbot più avanzati e comunemente utilizzati: ChatGPT-4.0 e Google Gemini Advanced.

Metodi. Le risposte fornite dall'Organizzazione Mondiale della Sanità (OMS) nel suo sito web a 38 domande frequenti (FAQs) su convinzioni errate riguardanti i vaccini sono state confrontate con quelle formulate da ChatGPT-4.0 e Gemini Advanced. Le risposte sono state considerate "appropriate" se le informazioni risultavano coerenti e non in contrasto con le attuali raccomandazioni dell'OMS o di altre autorità regolatorie internazionali. Inoltre, è stato registrato quando il chatbot invitava l'utente a consultare un professionista sanitario o fonti di informazione ufficiali per ottenere risposte personalizzate e aggiornate.

Risultati e Conclusioni. Il livello di concordanza tra le risposte dell'OMS e quelle di ChatGPT-4.0 o Gemini Advanced è risultato molto alto, con entrambi i chatbot-AI che hanno fornito 36 (94,7%) risposte appropriate. Le poche discrepanze tra le risposte dell'OMS e quelle dei chatbot-IA non sono state considerate pregiudizievoli per la salute pubblica. Entrambi i chatbot hanno consigliato spesso all'utente di verificare le fonti affidabili, come i siti web del CDC (Centro per la prevenzione e il controllo delle malattie) o dell'OMS, o di consultare un professionista sanitario. Pertanto, entrambe le versioni avanzate dei chatbot-IA, possono essere considerati alleati utili nelle strategie preventive, con la potenzialità di migliorare l'alfabetizzazione sanitaria riguardante i vaccini. Dato il rapido sviluppo della tecnologia IA, sono necessari ulteriori studi per monitorare costantemente l'accuratezza e l'affidabilità di questi strumenti.

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LETTER TO THE EDITOR

Comment on "Vaccination hesitancy: agreement between WHO and ChatGPT-4.0 or Gemini Advanced"

Dear Editor,

we would like to comment on "Vaccination hesitancy: agreement between WHO and ChatGPT-4.0 or Gemini Advanced (1)". The study's core premises for evaluating vaccine-related information from sophisticated chatbots such as ChatGPT-4.0 and Google Gemini sophisticated are intrinsically relevant, especially given the significance of misinformation in vaccine reluctance. However, such methods raise concerns about the validity of the comparison between chatbot responses and WHO guidelines. For example, the study did not explain how the open-ended questions were developed or whether they were based on current public disputes over vaccination myths. The selection criteria for the 38 questions are critical to comprehending the study's findings. Do these questions reflect the most common misconceptions regarding vaccines, or were they chosen at random?

Furthermore, the concept of a "appropriate" reaction appears to be highly subjective. Criteria for consistency and conformity to WHO criteria should be specified in order to develop a more transparent framework for evaluating replies. To improve the repeatability and validity of scientific findings, data assessment procedures must be carefully evaluated. Are any statistical methods utilized to calculate consistency rates, or is the data just qualitative observations? These shortcomings have the potential to damage the trustworthiness of the study's findings.

Looking ahead, there is an obvious need to enhance ways for evaluating the impact of AI chatbots in areas such as vaccine misinformation. Future research should include longitudinal studies that examine the changing accuracy of AI replies as they learn and adapt over time. Researchers should also investigate the usage of user demographics, as the effectiveness and appropriateness of answers can differ between populations. Furthermore, investigating how these chatbots respond to sensitive or critical thinking questions may reveal insights on chatbot limitations in real-world scenarios.

The novelty of this study is its approach to integrating AI technologies into public health communications, particularly in combating misinformation. However, it would be useful for the authors to delve deeper into the implications of their findings for vaccine promotion strategies, and what specific contexts might chatbot interactions have a meaningful impact on vaccine adoption. Furthermore, it is important to examine the potential risks associated with overreliance on AI in public health communications, as these technologies are increasingly integrated into health education campaigns. Understanding their limitations is essential to maximize their benefits while minimizing unintended consequences.

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HP 50% ideas, writing, analyzing, approval
VW 50% ideas, supervision, approval
HP 50% ideas, writing, analyzing, approval

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LETTER TO THE EDITOR

Reply to the Comment on "Vaccination hesitancy: agreement between WHO and ChatGPT-4.0 or Gemini Advanced" by Hinpetch Daungsupawong and Viroj Wiwanitkit

Dear Editor,

we would like to thank Dr. Daungsupawong and Wiwanitkit for their interesting comment (1) to our paper on the level of agreement between WHO and ChatGPT-4.0 or Gemini Advanced (2). With regard to the selection of the 38 questions, there was no selection, as we just used all the 38 frequently asked questions on vaccines and vaccine hesitancy listed by the WHO. We agree that any other choice would have been debatable.

Concerning the criteria adopted to evaluate the consistency and conformity between chatbots and WHO answers, we entirely agree that a level of subjectivity cannot be excluded. However, we specified the four criteria that were used and, in the absence of pre-established criteria in the literature, we believed, and still believe, that the judgment of two physicians with a long training in public health is the best and most reliable method to assess the level of agreement between complex, multifaceted answers to complex questions.

Finally, we entirely agree that longitudinal studies that examine the changing accuracy of AI replies as they learn and adapt over time, as well as how the answers can differ according to user demographics, will be extremely useful to better define chatbot strengths and limitations in real-world scenarios. We are currently expanding the investigation on the use of AI for vaccine hesitancy and hope to be able to address soon some of the above issues.

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LETTER TO THE EDITOR

Nutritional Project in School Setting: Analysis of Food Choices following Actions performed by Healthcare Workers

Progetto di educazione nutrizionale nel contesto scolastico: analisi delle scelte alimentari a seguito di interventi attuati dagli operatori sanitari

Keywords: Primary school; children; nutrition; snack; health promotion; healthcare workers.

Abstract

Schools continue to represent one of the main settings that guarantee health promotion interventions, as it has been widely demonstrated in numerous fields that diet and eating habits are shaped in the early stages of life and maintained into adulthood. Through the food education promotion project, "Healthy Snack", implemented by the Prevention Department of the Local Health Authority ULSS 1 Dolomiti, the interventions carried out by healthcare workers have been evaluated over time to measure their effectiveness in terms of changes in eating habits considered incorrect, with a particular focus on snacks eaten at school.

Dear Editor:

unhealthy dietary patterns, characterized by the presence of highly processed and high-calorie foods, low consumption of fruit and vegetables and a sedentary lifestyle, lead to an increase in body weight, which is an important risk factor for the development of non-communicable diseases. Currently, overweight and obesity are a public health concern and are already present in the early stages of children's lives (1). Several European studies on the dietary patterns adopted by children and adolescents confirm a decline in the quality of their diets in recent decades due to the increase in consumption of refined foods, sweets and fast food, in addition to a decrease in consumption of foods such as legumes, fruit, vegetables and fish. Furthermore, it is widely known that obese school-age children tend to become obese adults (2). Recent studies continue to highlight the association between obesity and bad eating habits, especially regarding the consumption of junk food, with a particular focus on breakfast and the mid-morning snack; other studies highlight further problem related to the choice of snacks due to the high consumption of processed foods and the minimal intake of fresh foods such as fruit (3,4).

School itself, given the time spent there, represents an effective setting for the implementation of childhood obesity prevention programs. Furthermore, prevention programs can have a more beneficial effect on body mass index if implemented from an early age, in particular from 6 to 12 years; such programs should involve both the child and the parents, in addition to teachers as educators (5-7).

The Italian Ministry of Health promoted the development of the OKkio alla SALUTE surveillance system, which involves children aged 8 to 9 who attend the third class of primary school. From the results of the most recent survey, conducted in 2023, the status report of Italy highlights that overweight children represent 19% and obese children

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represent 9.8% of the population, including children with severe obesity, who represent 2.6%. In particular, among those with unhealthy eating habits, 66.9% of children have a large mid-morning snack, a figure that has worsened compared to the previous survey (55.3%) (8). In the Veneto region, the data collected with OKkio alla SALUTE appear to be better than the national data: the values for excess weight are lower than the national average, with slightly lower values for overweight and obesity (17.3% overweight, 6.9% obesity) (9).

In the 2022-2023 school year, "Healthy Snack" project was conducted involving the primary schools located in the Province of Belluno, evaluating the changes in the choice of mid-morning snacks made at school, following the food education interventions implemented by the healthcare workers (HCWs) of the Health Promotion Service of the Prevention Department of ULSS 1 Dolomiti. During the investigation, a significant improvement in the children's choice of healthy snacks was observed (p-value equal to 0.0001) (10).

Through a follow-up investigation conducted in the same territory, the eating habits adopted by children attending primary school in the 2023-2024 school year have been assessed: 34 classes joined the training program, making a total of 482 students. In the current survey, no overall improvement was observed in terms of healthy snacks, but it is worth highlighting that between February 2024 and April 2024 (intermediate project time frame), a nutritional laboratory was conducted in the classes by the HCWs, which appears to be correlated with an improvement in the choice of snacks brought to school by children.

The school environment may play an important role in health promotion with regard to nutrition (11-13). Therefore, if developed with the aim of ensuring lifelong health, nutritional interventions in schools could play a decisive role and contribute to the reversal of the alarming prevalence of overweight and obesity in children and consequently reduce the development of possible future cardiometabolic diseases. Furthermore, these interventions represent a valuable public health tool that can improve the psychosocial factors associated with children's knowledge and attitudes to food and nutrition, particularly in mountainous regions that present sometimes challenging demographic and territorial extension characteristics. The effectiveness of such interventions should be monitored over time, as they are influenced by numerous variables, including the specific context, the target population and the many professionals involved.

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LETTER TO THE EDITOR

Comment on "Best practices for disinfection in dental settings: insights from Italian and European regulations"

Keywords: Disinfection; antiseptics; sterilisation; dental settings; dentistry; medical device, Italian laws, guidelines

Dear Editor,

We would like to comment on "Best practices for disinfection in dental settings: insights from Italian and European regulations (l)". The authors say that they report the key components of effective disinfection based on evidence-based protocols developed by international organizations such as the WHO and the US Centers for Disease Control and Prevention (CDC), as well as European and Italian regulatory standards. The ultimate aim is to highlight the need for better research and dissemination of best practice to improve infection control in dental care environments.

We have fully shared this approach and the objective of infection control and prevention (ICP) for years, but unfortunately the Italian laws, regulations and recommendations are more complex than described (2-5). Nowadays, the different authorisations in the Italian regional legislation (e.g. in terms of steam autoclave requirement, number of dynamic handpieces required depending on the workload, local space for the reprocessing of dental items separated from the operating areas, etc.) must be evaluated in the light of the indications of the Region State Conference Acts (RSCA) n°2016/104 (6).

With the main focus on patient safety in dentistry, we would like to highlight some issues that need to be clarified and hope to open a fruitful discussion among dental healthcare workers (DHCW).

Regarding the implementation of strict disinfection and sterilisation protocols (page 1, column 1, lines 7-17), these should be derived from standards, recommendations or "gold standard" updated guidelines. It's unclear because Triggiano et al. don't mention more recent international guidelines and more specific Italian ones (7-11). The more recent CDC document is based on the 2003 Dental Guidelines, but is innovative (8). It aims to help DHCW by clearly and concisely outlining all the standard precautions and, in particular, on page 16, the specific standard precautions for the prevention and control of environmental contamination in dentistry. It also provides two checklists: the first for planning and organisation (Annex A, section 1.11, page 27) and the second for assessing compliance with the recommendations (Annex A, section 2, page 36).

It should be noted that the HTM-01-05, UNI-TR11408 and INAIL guidelines (9-11) are based on EU Directives. The UNI/TR-11408 standard is particularly relevant to the reprocessing of items, as it is produced by UNI, the Italian national standardisation body (10). The obligation to always use sterile dental instruments (including dental handpieces), as provided for by RSCA n°2016/104 is clear (6). Then, the 2008 CDC recommendation must not be forgotten, as it contains the recommendation for the reconditioning (internal cleaning, cleaning, steam sterilisation) of dynamic devices (high-speed and contra-angle dental handpieces, etc.) (7), and internal contamination is relevant without proper reconditioning (12). Nowadays, steam sterilisation is recommended both when an instrument is critical and when it is semi-critical but has cavities or poorly accessible points (see Figure 1 in the UNI/TR 11408 recommendation) (10) and an EN 13060 class B autoclave is essential.

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In particular, there are other confounding factors:

• The authors don't report any information on the importance of cleaning (type of detergent, manual or automatic cleaning (EN ISO 15883), use of ultrasonic bath or thermal disinfector, etc.) before disinfection and sterilisation (2,8-11) and how this might be specific to some dental items (3-5).

• It appears that the table 1 is primarily intended for the instruction of dental students. But today's commercial disinfectant products contain many active ingredients, detergents, colourings, stabilisers, anti-adhesives and anti-corrosives substances. These are mixed together to do different jobs (for example, to decontaminate, to disinfect clinical contact surfaces or metal instruments, to decontaminate dental unit water lines or suction circuits, and analogical impressions). They are normally made up of water, but sometimes use gels or dry vapours. The instructions and safety data sheets (IFU and SDS) tell you exactly what the product is and what it can be used for.

• For heat-sensitive materials, the authors indicate the old approach as low-temperature sterilisation methods, including gas plasma or ethylene oxide autoclaves, or cold sterilisation using high-level disinfectants with extended contact times (up to 10 hours). However, gas plasma or ethylene oxide are only used in hospital settings, and cold sterilisation (using aldehyde, hydrogen peroxide, peracetic acid-based mixtures) used in private dental practices should be discouraged because of occupational hazards, corrosion of items, residues on optical fibres, difficulties with quality control, waste disposal and cost. The information in the table for both aldehydes (at the same concentration and exposure time) is misleading. It is known that a 2% solution of glutaraldehyde, activated with sodium bicarbonate, disinfects within 10 minutes and sterilises within 10 hours. In general, hazard statements for glutaraldehyde solution (2%) include: skin irritation, serious eye irritation, suspect of causing genetic defects, may cause an allergic skin reaction, suspected of damaging fertility of the unborn child, may cause damage to organs through prolonged or repeated exposure. Due to its respiratory sensitising properties, glutaraldehyde is included in the REACH Candidate List of Substances of Very High Concern as of July 2021. This leads to certain obligations for users at concentrations above 0.1% w/w. Finally, initial evidence suggests that the extent of volatile organic compounds (VOC) air contamination in the sterilisation room is relevant (13), then toxic and irritant products should be avoided, and recently 10 ACH has been recommended in the sterilisation room (14). In addition, many plastic instruments are now autoclavable, so the cost of the cold sterilisation procedure for few heat-sensitive materials should be carefully considered. We have previously discussed the specific problems of reconditioning some MD (e.g. laser safety eyewear, scanner tips) (3,5).

• The key actions to be taken on clinical contact surfaces (CCS) between patients are outlined in the CDC guidelines, in particular "clean, disinfect and cover" with certified products and the use of a certified low level (against HIV and HBV) or moderate level (against TBC) disinfectant if the surface is visibly contaminated with blood or other potentially infectious materials (7-9). We and other experts recommend using special wipes with a medium level of disinfectant (3-5) because there is a lot of microbial and blood contamination (around 50% of visible and invisible blood stains (15,16)) and emerging pathogens are resistant to disinfectants (4,17). Unfortunately, cleaning and disinfecting of CCS is a tedious manual activity that is too often overlooked in dental settings. DHCWs should carefully consider the consequences of carelessness and the significant benefits of improved interventions in reducing healthcare-associated infections (18,19). Recently, Oremade et al. evaluated the effect of a colour additive for disinfectant wipes on room cleanliness and turnaround time (20). The use of real-time visual feedback can improve the thoroughness of disinfectant cleaning while maintaining operational efficiency.

• As regards bacterial resistance to disinfectant activity, we believe that it is very important both to carefully evaluate the products used, including the specific biocidal activity (i.e. spectrum and duration of action) at least of the main microbes of dental interest, and to avoid gray products on the market (i.e., not approved according to European Community (EC) product guidelines and/or FDA requirements, defective, or expired) (4,21,22). In Italy, the Ministry of Health's Medical Device Safety Notices include some safety information letters that manufacturers send to users in the event of a market recall or other actions called field corrective actions (23). To the best of our knowledge, these are rare and relate only to defective dental instruments or contaminated disinfectants, but none alcohol-based hand rubs, despite EU Member States report illegal and ineffective products (22). The FDA advises consumers not to use certain hand sanitisers, due to the presence of methanol.

• Regarding manufacturer information and safety protocols, as underlined by APIC (24), DHCWs need better unambiguous IFUs and more transparency from manufacturers, certainly in line with the requirements of the Regulation EU n°2017/745. Also, someone should check the documents before marketing dental DM, especially for new technology. The specific ICP (3,5) should be checked, and the products on the market should be checked for the quality of the disinfectant. Some dental products marketed in Italy (i.e. endodontic solutions, dental adhesives, dental composites and products for the dissolution of alginate from impression trays) do not have yet an SDS in compliance with Regulation EU n°2020/878.

• The heterogeneity of recommendations for ICP is well known (25,26); only 40% of recommendations for sterilisation

are of level 2 (high quality evidence) and level 3 (moderate quality evidence) (25). Nevertheless, the lack of awareness of standards is demonstrated by the absence of Italian guidelines or best practices or international guidelines for ICP in dentistry in the Guideline National System (GNS, abbreviated in Italian as SNLG) (27). An Italian guideline on ICP is missing from the ECDC website (28).

It can be dangerous. In the new regulatory context indicated by Law no. 24/2017 (29), the GNS represents the institutional access point to the guidelines for clinical practice, clinical-care good practices or public health decisions developed for the National Health Service and for decision-makers, professionals and patients (27). We have highlighted the poor presence of guidelines and best practices on the GSN for dental settings, perhaps also due to the limited interest of institutions and professionals in their production (2,27). Nevertheless, the lack of guidelines for dentistry in the GSN makes it difficult, if not impossible, to achieve patient safety in dentistry, the primary objective of the Law n° 24/2017 (art. 1, paragraph 1) (29) and of recent WHO and CDC strategic documents (8,30-32).

To date (04.1.2025), in the GNS there are only two completed guidelines (not of interest to ICP) for the dental field out of 123 guidelines for healthcare (33,34). Among the other completed guidelines, four are of possible or limited interest for ICP in dental settings (35-37). In the infectious disease section, there is an old international guideline for the prevention of healthcare-associated infections (38) .

There is 1 guideline out of 3 under appraisal that gives therapeutic recommendations for non-tuberculous mycobacterial lung disease in adults; it may be of interest to dental patients (i.e. treatment of water-diffused infections caused by contaminated water pipes in dental units) (8,39).

In the GNS, there are no international guidelines (n°21) in the COVID-19 section, specific to dental settings (40). In addition, there are no best practices or international guidelines for ICP in dentistry or the dental section (41,42). A new methodology for the preparation and validation of best practices has been presented as of June 2024, but there are none yet included in the GNS.

• The standard mentioned by Triggiano et al. for the decontamination of the water supplied to the dental unit is not included in the GNS as a best practice (43). However, it is unclear whether the heterotrophic bacterial contamination of water used for dental care should be the one set for drinking water (100 CFU/mL at 22°C), according to European Directive 2020/2184, or lower than 300 CFU/mL, as indicated in the guideline of the CDC and some European countries (8).

In the absence of GNS guidelines for ICP, the judgment of the Cass. of 3.3.2023, n. 6386, indicates some standard precautions to limit infections related to healthcare (44). This must be taken into account in view of the medico-legal implications (2). There are three questions relating to the responsibilities established by Law n° 24/2017 and Cass. 3.3.2023, n° 6386 (29,44):

- Is it sufficient to refer only to the Directives and EU Regulation 745/2017, and the manufacturer's instructions for use in protocols and procedures?
- Alternatively, is it essential to refer to guidelines in GNS?
- In the absence of a guideline for ICP, could international or European guidelines be used even if they are not included in GNS?

We would like to express our gratitude to Triggiano et al. for their contribution to the field of ICP in dental settings. In our opinion, the most effective course of action would be the rapid implementation of a European regulation on ICP in dental settings, in line with the alarming outlook for the infectious risk and antimicrobial resistance in the European population (45) and with the need to prevent infective endocarditis in at-risk patients (46,47).

Conflict of interest: none

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The text has been checked by a common word processor and DeepL Write for "spelling" and "grammar".

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