Vol. 36 N. 5 - SEPTEMBER-OCTOBER 2024

# ANNALI DI IGIENE

## Medicina Preventiva e di Comunità

Bimonthly scientific publication founded by A. Celli in 1889 as
ANNALI DELL'ISTITUTO DI IGIENE SPERIMENTALE DELLA UNIVERSITÀ DI ROMA

*Editor-in-chief: Prof. G.M. Fara*

dal 1889

SOCIETÀ EDITRICE UNIVERSO
Via G.B. Morgagni 1 - 00161 Roma

ISSN 1120-9135 CONTIENE I.P.

Tariffa Roc: Poste Italiane S.p.A. Spedizione in Abbonamento Postale - D.L. 353/2003 (conv. in L. 27/02/2004 n. 46) art. 1 comma 1 - DCB - Roma

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**Publisher**
Società Editrice Universo srl
Via G.B. Morgagni, 1 - 00161 Roma
Tel 0644231171 - 064402053/4 Fax 064402033
E-mail: annali@seu-roma.it

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Ann Ig. 2024 Sept-Oct; 36(5): 499-512 doi: 10.7416/ai.2024.2626. Epub 2024 Apr 3.

# Smartphones' impact on nursing performances: a cross-sectional multicenter study

Emanuele Di Simone[1], Sara Dionisi[2], Noemi Giannetta[3], Nicolò Panattoni[4], Aurora De Leo[5,6], Sofia Di Mario[4], Antonella Surace[1], Jessica Urban[1], Gloria Liquori[6], Christian Napoli[7], Marzietta Montesano[8], Marco Di Muzio[1], Giovanni Battista Orsi[4]

*Keywords: Personal communication devices; smartphone; nursing performance; electronic distraction; nurses; work interruption; medical staff and/or hospitals; cellular phone*

*Parole chiave: Strumenti di comunicazione personale; smartphone; performance infermieristica; distrazione elettronica; infermieri; interruzione*

**Abstract**

***Background.*** *In recent years, the technology world has significantly shaped society. This study aims to survey the views of registered nurses with hospital working experience regarding the personal communication devices use impact in hospital units. The secondary outcome of this study was to identify differences in mobile device use based on demographic and organizational factors.*

***Study design.*** *Cross-sectional study by survey.*

***Methods.*** *The questionnaire comprises 22 items divided into four sections. Overall 778 questionnaires were included in the study, 329 questionnaires were collected on pen-and-paper, whereas 449 by an online survey.*

***Results.*** *Findings showed that smartphones have a different impact on performance, utilization and impact scale according to gender, age and educational attainment. Generally males using more frequently personal communication devices for non-work-related activities affected negatively their working performance by respect to females. Moreover, younger nurses report being more distracted by using smartphones for non-work-related activities than older nurses. At the same time, younger nurses believe that smartphones may lead to an improvement in patient care skills. Nurses with fewer years of service (1 month - 10 years) report being more distracted by non-work-related activities on their smartphones than nurses with more years of service (>20 years).*

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Annali di Igiene : Medicina Preventiva e di Comunità (Ann Ig)
ISSN 1120-9135 https://www.annali-igiene.it

***Conclusions.*** *The smartphone is a potential distraction source. The most exposed groups are the younger nurses' and those with little work experience, and both groups (young age, less experience) can be considered factors for potential distraction.*

## Introduction

In the last few years, the technology world has significantly re-shaped the society. Regardless of social conditions and age, most people own an electronic device, a smartphone, tablet or personal computer. It is the easiest and fastest mode of communication that allows the transmission of news instantly, using the Internet, messaging services or e-mail. These means of communication are also used in the health sector to support professionals in research, clinical activity and health education (1, 2).

A recent literature review has shown the smartphone use benefits in clinical practice: enhanced interprofessional communication; easy and quick access to clinical information; improved time management, and reduced work stress. At the same time, smartphone use is associated with many disadvantages: distraction from work and the appearance of unprofessionalism (3).

One study conducted by Schmenner et al. (4) demonstrated how age could affect mobile devices use: younger nurses seem more likely to use them, while older age professionals tend to be reluctant. An investigation conducted in Germany by Whitlow et al. (5), highlighted that 63% of the nurses who answered the questionnaire say they use the smartphone for purely personal purposes and that it can also improve communications between the multidisciplinary team, thus replacing the use of the pager (6). The smartphone is used by nurses in order to communicate with each other, to seek information and to document anything (7-10). Technologies provided by hospitals to healthcare workers should be used only for work purposes. However, many of these were deemed "unreliable and inferior compared to the personal smartphones that nurses have". Consequently, nurses frequently use their personal smartphones for work purposes (11). Different studies indicate that nurses use their smartphones for work purposes to enhance productivity (9, 10, 12).

Despite this, using the smartphone during nursing activities could cause distraction and possible errors with negative consequences on patient safety (13-15). Moreover, smartphones use could lead to several concerns about security and personal use (16). Distractions could lead nurses to make errors, such as medication errors, which are considered a serious public health problem (17-23). In 2015 McBride (13, 14) conducted a conceptual analysis to define the concept of distraction from smartphones and other mobile devices in hospitals (24, 25). McBride defines distraction as "*an interruption of a clinical care activity caused by internal or external stimuli to the individual. The source of distraction could come externally from another person, such as another doctor or patient, through a mechanical stimulus, such as a telephone ring or a call light, or an alarm triggered by a machine, such as that of the infusion pump*" (13,14). She characterises distractions due to "internal causes" as interruptions of the thought process or intrusive thoughts unrelated to the main task (26).

Leroy et al. (27) have shown that "*completing tasks without interruptions has become a luxury*" for today's employees. Interruptions in care provision are associated with procedural failures and errors (28,29).

Therefore not all studies agree about smartphone use during nurses' shift work. Undoubtedly is considered an important instrument supporting nurses' activities, but also the use could affect caring and patient safety (30-32). Therefore the heterogeneity of the experiences found in clinical practice and research suggests the need for further studies to highlight the impact of smartphone use in nursing care.

This study aimed to explore nurses' opinions and the impact of the use of the smartphone during the work shift and how this can affect caring activities.

Based on the Unified Theory of Acceptance and Use of Technology (UTAUT) (33), the secondary outcome of this study was to identify the differences in the mobile use devices between groups based on demographic and organizational factors.

## Methods

*1. Study design*

This study used a cross-sectional survey design. The study reporting was made and supported under the STROBE guidelines' and checklist (34) (TAB S1).

*2. Study procedures*

The questionnaire was administered both online, using the Google Form platform, and on paper. A dual mode of administration was chosen in order to reach the largest number of respondents. Data collection took place from January to May 2019. A convenience sample was recruited. All nurses who received the invitation to participate in the study were practicing in hospitals. Participation in the study was voluntary and anonymous. In the event of missing data from paper questionnaires, it was not included in the sample. On the contrary, all items were set up as mandatory for the web surveys.

*3. Study population*

A convenience sample was recruited. Nurses had to meet the following inclusion criteria: working in hospital settings providing care for the patient; having at least one year's work experience in clinical ward; willingness to participate in the study; knowledge and understanding of the Italian language. Exclusion criteria were students or other healthcare professionals or manager or head nurses.

*4. Instruments*

In 2013, McBride et al. (24) developed and validated a questionnaire to detect nurses' opinions regarding the impact of personal communication devices on patient care in a hospital setting: the Nurses' Use of Personal Communication Devices Questionnaire.

In 2014 (25), the questionnaire was further reduced to 32 items: 14 on the use for personal purposes during working hours, 9 on how the smartphone use can affect care performance, 6 related to smartphone use for communication between the members of the hospital team, and the last 3 items investigate nurses and patients opinion on smartphone use during treatment activities. The structuring of the responses uses three different forms of a 4-option Likert scale. 74% of the answers given in both questionnaires were the same, and the concordance analysis between the two versions, carried out through Cohen's K statistical test, generated values between .67 - .57, demonstrating internal reliability of the tool. Reliability of each of the four sections was also assessed, excluding the one relating to personal data, by calculating Cronbach's Alpha.

Di Muzio et al. adapted this questionnaire to the Italian context (35). Of the original 32 items, 16 were retained, and a further 6 on the socio-demographic data were added, for a total of 22 items. The final questionnaire is divided into 4 sections: demographic data, performance, use and impact.

The demographic section, made by 6 items collecting data relating to age, gender, professional qualifications achieved, post-basic qualifications, years of working experience and the care setting of reference.

The second and third sections (performance and use), made by 12 items, investigating smartphone use during the work shift and caring activities may be affected; the answers are structured with a 4-point Likert scale (never, once per shift, from 2 to 5 times per shift, more than five times per shift).

The last section (impact) consists of 4 items evaluating the opinion on smartphone use with a 4-point Likert scale (totally disagree, disagree, agree, totally agree). Italian version of the instrument reported a high internal consistency (from 0.749 to 0.799), however slightly lower than that of the original version (from 0.84 to 0.96) (24). The value of the KMO test was 0.784, and the Bartlett sphericity test was significant ($\chi 2 = 1042.782$, df = 120, $p < 0.001$), indicating that the analysis of the data factors is appropriate (31).

The instrument was submitted for exploratory factor analysis (31). In the results four factors emerged: demographics, performance, use, and impact of smartphones. In Di Muzio et al's study, KMO test was 0.821, and the Bartlett sphericity test was significant ($\chi 2 = 3299,632$, df = 120, $p < 0.001$). The instrument's reliability, measured through Cronbach's Alpha, was 0.78.

*5. Ethics*

Ethics Committee approval for the study and questionnaire administration was achieved before data collection (Prot. N. 1188/17). All participated voluntarily, were informed about the study aims and procedures, and about their right to participate or withdraw at any time. All participants signed informed consent. Those who filled the paper informed consent submitted it in a single closed envelope to the research center. For those who participated in online survey, participation to the study was considered as an expression of consensus. Also a unique identification

code for each participant was provided in order to guarantee data protection and anonymity.

*6. Statistical analysis*

Data obtained from the questionnaire administration was displayed on an Excel worksheet and associated with alphanumeric variables to identify questions and responses. Subsequently, the statistical analysis of the variables was carried out by *IBM SPSS Statistics version 25*. The descriptive analysis of all examined variables was performed using absolute frequencies and percentages. The analysis of variance (ANOVA) was subsequently carried out by inferential statistics technique, allowing hypotheses verification relating to differences between two or more populations means. Therefore, it allows the study of two or more data groups by comparing internal variability and between the groups. The variance homogeneity was verified through the Levene test, which represented the substrate for reading the results. The test verifies the null hypothesis that the error variance of dependent variables is equal between the groups; if Levene's statistic is significant at the 0.05 level, the null hypothesis that the groups have the same variance is rejected.

## Results

*1. Professional and socio-demographic characteristics of the sample*

778 Italian registered nurses working in Italian hospitals completed a self-administered questionnaire. *Table 1* shows nursing sample demographic and professional characteristics; 26.5% (n = 206) male, and 73.5% (n = 572) female; 38.6% (n = 300) were ≥41 years of age, 23.1% (n = 180) between 31-40, the mean being 36 years old, 5% (n = 284) were aged between 20-30; 14 (1.8%) did not declare their age.

The majority, 70.1% (n = 545), obtained a university degree (Degree or university diploma), while the remaining 29.8% (n = 232) obtained a non-university degree. Concerning post-basic qualifications, 26.6% (n = 207) stated having graduated with a Master's degree, and 36.1% (n = 281) had attended "Other". 49.2% (n = 383) reported having length of service between 1 month and 10 years, 24.2% (n = 188) between 10 and 20 years and 26.5 % (n = 206) over 20 years. About work setting, 22.1% (n = 172) work in Medicine, 24.4% (n = 190) in Surgery, 25.3% (n = 197) in a Critical / Emergency Area, 5.9% (n = 46) in a Pediatric Area and 21.6% (n = 168) in "Other – outpatient department".

Table 1 - Demographic and personal characteristics of the responding nurses

| Variables | N (%) |
|---|---|
| Age, years | |
| < 30 | 284 (36.5) |
| 31 – 40 | 180 (23.1) |
| 41 – 50 | 300 (38.6) |
| Missing values | 14 (1.8) |
| Gender | |
| Male | 206 (26.5) |
| Female | 572 (73.5) |
| Educational qualification | |
| University degree in nursing | 545 (70.1) |
| Non-university qualification | 232 (29.8) |
| Postgraduate training courses | |
| Courses not specified | 135 (17.4) |
| Master's degree | 104 (13.4) |
| Master courses | 207 (26.6) |
| Other (Ph.D.) | 281 (36.1) |
| Years of work | |
| 1 – 10 | 383 (49.2) |
| 11 – 20 | 188 (24.2) |
| >21 | 206 (26.5) |
| Workplace setting | |
| Medical Ward | 172 (22.1) |
| Surgical Ward | 190 (24.4) |
| Intensive Care Unit | 197 (25.3) |
| Pediatric Ward | 46 (5.9) |
| Other (outpatient department). | 168 (21.6) |

*2. Descriptive statistics on the performance scale*

The sample's responses allow us to deduce the smartphones impact on work performance. Most of the sample (n = 394, 50.6%) answered that using the smartphone for non-work related activities never distracted them from their clinical care activity, and 78.9% (n = 614) answered that it has never negatively affected their work performance. Despite this, 65.8% (n = 508) agreed that using the smartphone for unrelated activities has never helped the individual to be more concentrated during the assistance activities. 41.9% (n = 326) believe its use improved clinical-care activity once per shift. Only 269 respondents (34.9%) claimed to have seen another colleague using the smartphone 2-5 times per shift.

*3. Descriptive statistics on the utilization scale*

The sample's responses allow us to evaluate the use and related reasons for smartphone use during the work shift. Most respondents say they used the smartphone for business purposes:

- to access the Health App (n = 530, 68.3%) only once per shift;
- to consult procedures, protocols or guidelines (n = 362, 46.6%) only once per shift using the smartphone;
- to obtain information on drugs (n = 344, 44.2%) only once per shift;
- as a calculator (calculations / dosages) (n = 305, 39.3%) only once per shift. Only 37.8% (n = 292) say they have never used a smartphone to communicate with other care team members.

Regarding the use for non-working purposes, most responders (n = 348, 44.8%) claim to have used the smartphone only once per shift to send / check personal messages via e-mail and / or social networks (Facebook, WhatsApp, Twitter), and 40.2% (n = 312) to surf the Internet.

*4. Descriptive statistics on the impact scale*

The sample's responses allow the individual opinions evaluation on smartphone use during daily practice. Most responders (n = 393, 50.5%) agree that smartphone use encourages communication between team care members in order to improve the quality of care. 44.7% (n = 348) disagree that smartphone use improves patient safety, and 43.2% (n = 336) disagree about smartphone potential to reduce stress related to work and be an incentive for patient care. Most respondents (n = 365, 47%) agree that smartphone use increases the probability of making a mistake.

*5. Differences in performance, utilization and impact scale according to sex*

Table 2 shows the performance, utilization and impact scale differences according to sex. The t-test results showed that males, more than females, using personal communication devices for non-work-related activities, say it has negatively affected their work performance ($t$=3,358; p<0,001). At the same time, using personal communication devices at work for non-work-related activities improves their ability to focus on their work ($t$=3,077; p<0,001).

According to the utilization scale, females use personal communication devices to access work drug references more frequently than males ($t$=-,766; p<0,001), while males use personal communication devices to call or send messages to family or friends ($t$=2,218; p<0,001) or to post on social networking sites ($t$=4,108; p<0,05) more frequently than females.

*6. Differences in performance, utilization and impact scale according to age*

It was assessed whether smartphone use has a different impact on individual performance within the three age groups (20- 30 years; 31-40 years; 41 years onwards). The ANOVA analysis revealed significance in several variables. The post-hoc analysis, therefore, allowed the following deductions to be drawn (Table 3).

Younger nurses report being more distracted from using the smartphone for non-work-related activities than older nurses (F(2,759)=4.902, p<0,001). At the same time, they believe that smartphones use promotes their care skills improvement (F(2,760)=12.702, p<0,01).

Older nurses use smartphone less than younger nurses, both for work, such as obtaining information on drugs (F(2,761)=14.93, p<0,01) and as a calculator for calculations / dosages (F(2,759)=14.60, p<0,01), and for non-work activities during the shift, such as checking / sending personal messages via e-mail and / or social networks (F(2,760)=32,40, p<0,01) and for surfing the Internet (F(2,759)= 23,117, p<0,01).

In addition, older nurses believe less in using the smartphone to improve patient safety (F(2,758)= 7,790, p<0,01). Nurses in the middle age group (31-40 years) use the smartphone more during working hours to communicate with other members of the care team than the very young (20-30 years) (F(2,758)= 10,65, p<0,01). They also believe that the use of the smartphone during work does not increase the probability of making mistakes compared to the very young (20-30 years) and the elderly (41 years onwards) (F(2,759)= 3,889, p<0,05).

*7. Differences in performance, utilization and impact scale according to Educational Attainment*

Educational attainment refers to education qualifications (non-university or university degrees). The t-test results (Table 4) showed that responders with a non-university degree using personal communication devices for non-working related activities perceived a negative impact on working performance compared to responders with a bachelor's degree in nursing ($t$=1,028; p<0,05).

Moreover, the $t$-test results showed that those with bachelor's degrees in nursing find advantages in personal communication devices use in terms of

Table 2 - Differences according to Sex (T Test Results)

| Variables | Code[a] | N (% total) | n (% in sex) | | T test Results [mean (SD)] | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Male | Female | Male | Female | t | p |
| Performance 3 | 0 | 614 (79.2) | 147 (71.4) | 467 (82.1) | .36 (.638) | .21 (.495) | 3.358 | .001 |
| | 1 | 133 (17.2) | 47 (22.8) | 86 (15.1) | | | | |
| | 2 | 22 (2.8) | 9 (4.4) | 13 (2.3) | | | | |
| | 3 | 6 (0.8) | 3 (1.5) | 3 (0.5) | | | | |
| Performance 4 | 0 | 508 (65.8) | 121 (58.7) | 387 (68.4) | .59 (.814) | .41 (.677) | 3.077 | .001 |
| | 1 | 192 (24.9) | 56 (27.2) | 136 (24.0) | | | | |
| | 2 | 56 (7.3) | 22 (10.7) | 34 (6.0) | | | | |
| | 3 | 16 (2.1) | 7 (3.4) | 9 (1.6) | | | | |
| Utilization 1 | 0 | 82 (10.5) | 32 (15.5) | 50 (8.7) | 1.40 (.898) | 1.45 (.755) | -.766 | .001 |
| | 1 | 344 (44.2) | 86 (41.7) | 258 (45.1) | | | | |
| | 2 | 284 (36.5) | 62 (30.1) | 222 (38.8) | | | | |
| | 3 | 68 (8.7) | 26 (12.6) | 42 (7.3) | | | | |
| Utilization 3 | 0 | 257 (33.1) | 84 (40.8) | 173 (30.3) | .84 (.864) | .94 (.785) | -1.435 | .006 |
| | 1 | 362 (46.6) | 81 (39.3) | 281 (49.2) | | | | |
| | 2 | 126 (16.2) | 30 (14.6) | 96 (16.8) | | | | |
| | 3 | 32 (4.1) | 11 (5.3) | 21 (3.7) | | | | |
| Utilization 6 | 0 | 205 (26.4) | 54 (26.2) | 151 (26.4) | 1.20 (.946) | 1.05 (.826) | 2.218 | .000 |
| | 1 | 348 (44.8) | 271 (47.5) | 77 (37.4) | | | | |
| | 2 | 173 (22.3) | 54 (26.2) | 119 (20.8) | | | | |
| | 3 | 51 (6.6) | 21 (10.2) | 30 (5.3) | | | | |
| Utilization 7 | 0 | 284 (36.6) | 63 (30.6) | 221 (38.8) | 1.13 (.966) | .84 (.818) | 4.108 | .002 |
| | 1 | 312 (40.2) | 74 (35.9) | 238 (41.8) | | | | |
| | 2 | 138 (17.8) | 48 (23.3) | 90 (15.8) | | | | |
| | 3 | 42 (5.4) | 21 (10.2) | 21 (10.2) | | | | |
| Impact 4 | 0 | 41 (5.3) | 18 (8.7) | 23 (4.0) | 1.77 (.907) | 1.80 (.763) | -.505 | .000 |
| | 1 | 225 (29) | 60 (29.1) | 165 (28.9) | | | | |
| | 2 | 365 (47) | 80 (38.8) | 285 (50) | | | | |
| | 3 | 145 (18.7) | 48 (23.3) | 97 (17.0) | | | | |

[a] code = 0: never, 1 once per shift; 2: 2-5 times per shift; 3: > 5 times per shift

Performance 1: The use of my personal communication device for non-work related activities has distracted me while working
Performance 2: The use of my personal communication device improve my performance while working
Performance 3: The use of my personal communication device for non-work related activities has negatively effected my performance while working
Performance 4: Personal communication device use at work for non-work related activities improves my ability to focus on my work
Performance 5: I have witnessed another nurse whose personal communication device use was negatively effecting his/her performance while working

Utilization 1: I access work drug references
Utilization 2: I use the device as a calculator for nursing/medical formulas
Utilization 3: I access work-related protocols/guide lines
Utilization 4: I access work-related Health Apps that assist my patient care
Utilization 5: I call or check/send work related text messages or emails to other members of the healthcare team
Utilization 6: I call or check/send text messages or emails to family or friends (Facebook, Whatsapp, Twitter, etc.)
Utilization 7: I check/post on social networking sites

Impact 1: Does the use of personal communication device promote communication between the members of the care team?
Impact 2: Does Personal communication device use improve patient safety?
Impact 3: Does Personal communication device use reduce work-related stress?
Impact 4: Does Personal communication device use increase medical errors while working?

Table 3 - Differences according to Age (ANOVA Results)

| Variables | Age: mean (SD) | | | F | p |
|---|---|---|---|---|---|
| | < 30 years (n=284) | 31 – 40 (n=180) | 41 – 50 (n=300) | | |
| Performance Scale | | | | | |
| Performance 1 | .74 (.794) | .78 (.829) | .57 (.810) | 4.902 | .008 |
| Performance 2 | 1.24 (.785) | 1.22 (.841) | .86 (.840) | 18.89 | .000 |
| Performance 4 | .45 (.685) | .62 (.806) | .36 (.689) | 7.484 | .001 |
| Performance 5 | 1.98 (.908) | 2.12 (.899) | 1.86 (1.006) | 4.110 | .017 |
| Utilization Scale | | | | | |
| Utilization 1 | 1.67 (0.706) | 1.45 (0.734) | 1.21 (0.843) | 25.247 | .000 |
| Utilization 2 | 1.45 (0.866) | 1.41 (0.895) | 1.03 (0.906) | 18.491 | .000 |
| Utilization 3 | 1.04 (0.744) | 0.92 (0.855) | 0.8 (0.822) | 6.311 | .002 |
| Utilization 5 | 0.84 (0.832) | 1.08 (0.878) | 0.91 (0.894) | 4.385 | .013 |
| Utilization 6 | 1.26 (0.866) | 1.33 (0.839) | 0.8 (0.783) | 32.408 | .000 |
| Utilization 7 | 1.14 (0.893) | 1.01 (0.825) | 0.67 (0.803) | 23.117 | .000 |
| Impact Scale | | | | | |
| Impact 1 | 1.59 (0.786) | 1.64 (0.829) | 1.33 (0.855) | 10.652 | .000 |
| Impact 2 | 1.28 (0.701) | 1.34 (0.735) | 1.09 (0.764) | 7.790 | .000 |
| Impact 3 | 1.37 (0.793) | 1.43 (0.762) | 1.07 (0.759) | 16.308 | .000 |
| Impact 4 | 1.83 (0.769) | 1.65 (0.773) | 1.85 (0.847) | 3.889 | .021 |

Performance 1: The use of my personal communication device for non-work related activities has distracted me while working
Performance 2: The use of my personal communication device improve my performance while working
Performance 3: The use of my personal communication device for non-work related activities has negatively effected my performance while working
Performance 4: Personal communication device use at work for non-work related activities improves my ability to focus on my work
Performance 5: I have witnessed another nurse whose personal communication device use was negatively effecting his/her performance while working

Utilization 1: I access work drug references
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Impact 1: Does the use of personal communication device promote communication between the members of the care team?
Impact 2: Does Personal communication device use improve patient safety?
Impact 3: Does Personal communication device use reduce work-related stress?
Impact 4: Does Personal communication device use increase medical errors while working?

"ability to focus on work" ($t$=2,174; p<0,001) and stress prevention ($t$=4,404; p<0,001). Accordingly, responders with a bachelor's degree in nursing use personal communication devices more frequently to access work-related Health Apps than non-university ($t$=1,345; p<0,05).

*8. Differences in performance, utilization and impact scale according to working experience*

It was assessed whether smartphone use has a different impact between the three service seniority groups (1 month-10 years, 10 years-20 years, over 20 years).

ANOVA analysis revealed significance in several variables. Therefore post-hoc analysis allowed the following deductions to be drawn (Table 5).

Nurses with fewer service years (1 month-10 years) report being more distracted by using smartphone for non-work-related activities than nurses with greater experience (> 20 years) (F(2,773)=3.878, p<0,05). Also, they believe that smartphone use favours their care skills improvement (F(2,771)=26.461, p <0.01) compared to the other two categories (10-20 years and> 20 years).

Nurses with fewer years of service (1 month-10 years) report they use their smartphone to

obtain information on drugs ($F(2,774)=32.97$, $p<0.01$), as a calculator for calculations / dosages ($F(2,773)=23.179$, $p<0.01$), and to consult procedures and guidelines ($F(2,773)=23.179$, $p<0.01$). They also believe in improving security through technology ($F(2,771)=11.056$, $p<0.01$). Nurses with more years of service use the smartphone less to check / send personal messages via e-mail and / or social networks (Facebook, WhatsApp, Twitter...) compared to other categories (1 month-10 years and 10-20 years) ($p<0.01$).

## Discussion and conclusions

This study aimed to investigate the smartphone use during care practice, quantifing how different groups used smartphones according to demographic characteristics. This research findings may add to the current knowledge on smartphone use. Concerning the smartphone use for work-related activities, it was highlighted that the most common use is access to the Health App (applications aimed at the care and assistance of patients) followed by procedures, protocols or guidelines consultation. Most nurses believe that smartphone use limited to once per shift favours care skills improvement and agrees that smartphones use encourages communication between care team members, improving the quality of care. These findings are most common in younger registered nurses. Also, Bautista (7) showed that the most common smartphones use is related to healthcare team communication. Indeed, smartphone communication between team members is one of the favourable aspects of this device. Even if smartphones had several advantages (36,37), some studies focus on the risk that PCDs may be used to transmit pathogens: a recent literature review viewed smartphones as a bacterial reservoir in healthcare settings (38, 39).

Table 4 - Differences according to Education Attainment (T Test Results)

| Variables | Education qualification: mean (SD) | | | |
|---|---|---|---|---|
| | Non-university degree | University degree | t | p |
| Performance Scale | | | | |
| Performance 3 | .28 (599) | .24 (.500) | 1.028 | .032 |
| Performance 4 | .37 (.653) | .49 (.736) | -2.174 | .001 |
| Performance 5 | 1.81 (.995) | 2.02 (.925) | -2.797 | .049 |
| Utilization Scale | | | | |
| Utilization 3 | .76 (.791) | .98 (.805) | -3.465 | .037 |
| Utilization 4 | .36 (.624) | .44 (.705) | -1.345 | .006 |
| Impact Scale | | | | |
| Impact 3 | 1.07 (.753) | 1.34 (.790) | -4.404 | .000 |

Performance 1: The use of my personal communication device for non-work related activities has distracted me while working
Performance 2: The use of my personal communication device improve my performance while working
Performance 3: The use of my personal communication device for non-work related activities has negatively effected my performance while working
Performance 4: Personal communication device use at work for non-work related activities improves my ability to focus on my work
Performance 5: I have witnessed another nurse whose personal communication device use was negatively effecting his/her performance while working

Utilization 1: I access work drug references
Utilization 2: I use the device as a calculator for nursing/medical formulas
Utilization 3: I access work-related protocols/guide lines
Utilization 4: I access work-related Health Apps that assist my patient care
Utilization 5: I call or check/send work related text messages or emails to other members of the healthcare team
Utilization 6: I call or check/send text messages or emails to family or friends (Facebook, Whatsapp, Twitter, etc.)
Utilization 7: I check/post on social networking sites

Impact 1: Does the use of personal communication device promote communication between the members of the care team?
Impact 2: Does Personal communication device use improve patient safety?
Impact 3: Does Personal communication device use reduce work-related stress?
Impact 4: Does Personal communication device use increase medical errors while working?

Table 5 - Differences according to Working experience (ANOVA Results)

| Variables | Working experience (years) | | | F | p |
|---|---|---|---|---|---|
| | 1 to 10 years | 11 to 20 years | more than 21 | | |
| Performance Scale | | | | | |
| Performance 1 | .74 (.809) | .70 (.793) | .70 (.793) | 3.878 | .021 |
| Performance 2 | 1.29 (.794) | .97 (.827) | .80 (.827) | 26.461 | .000 |
| Performance 4 | .51 (.735) | .48 (.777) | .33 (.616) | 4.688 | .009 |
| Utilization Scale | | | | | |
| Utilization 1 | 1.66 (.701) | 1.23 (.793) | 1.20 (.846) | 32.977 | .000 |
| Utilization 2 | 1.49 (.865) | 1.18 (.925) | .99 (.883) | 23.179 | .000 |
| Utilization 3 | 1.07 (.794) | .75 (.757) | .77 (.821) | 14.792 | .000 |
| Utilization 6 | 1.24 (.860) | 1.13 (.898) | .77 (.740) | 21.323 | .000 |
| Utilization 7 | 1.09 (.861) | .86 (.897) | .66 (.786) | 17.659 | .000 |
| Impact Scale | | | | | |
| Impact 1 | 1.63 (.796) | 1.41 (.839) | 1.32 (.851) | 11.056 | .000 |
| Impact 2 | 1.33 (.710) | 1.12 (.758) | 1.11 (.759) | 8.314 | .000 |
| Impact 3 | 1.40 (.795) | 1.26 (.759) | 1.02 (.746) | 15.427 | .000 |

Performance 1: The use of my personal communication device for non-work related activities has distracted me while working
Performance 2: The use of my personal communication device improve my performance while working
Performance 3: The use of my personal communication device for non-work related activities has negatively effected my performance while working
Performance 4: Personal communication device use at work for non-work related activities improves my ability to focus on my work
Performance 5: I have witnessed another nurse whose personal communication device use was negatively effecting his/her performance while working

Utilization 1: I access work drug references
Utilization 2: I use the device as a calculator for nursing/medical formulas
Utilization 3: I access work-related protocols/guide lines
Utilization 4: I access work-related Health Apps that assist my patient care
Utilization 5: I call or check/send work related text messages or emails to other members of the healthcare team
Utilization 6: I call or check/send text messages or emails to family or friends (Facebook, Whatsapp, Twitter, etc.)
Utilization 7: I check/post on social networking sites

Impact 1: Does the use of personal communication device promote communication between the members of the care team?
Impact 2: Does Personal communication device use improve patient safety?
Impact 3: Does Personal communication device use reduce work-related stress?
Impact 4: Does Personal communication device use increase medical errors while working?

Regarding the use not related to work, the most frequent activity is sending/checking personal messages via e-mail and / or social networks (Facebook, WhatsApp, Twitter), allowing nurses to remain in contact with the outside environment during working hours, in accordance with the study of Bautista et al. (11). Differences according to sex were shown evident, with males accessing social media more frequently than females. These results must be interpreted cautiously and not generalised, as the male responders sample was smaller than females one. However, this aspect could be inquired by future research. Indeed, to the authors' knowledge, no specific studies about gender influence on nurses' smartphones use were conducted. Conversely, many studies addressed this phenomenon among young people, highlighting gender differences in smartphone use (40-42).

Other studies showed that nurses use smartphones primarily to send and receive messages (8,9,13,43). Our results show that nurses frequently use their smartphones to send voice or text messages, as supported by Bautista et al. (7). The majority of respondents disagreed that nurses could use the smartphone as a tool to improve patient safety and reduce stress related to work.

On the contrary, some studies argue that mobile devices can positively influence concentration and work performance as they reduce work-related stress (43). Although most nurses reported that smartphone use does not adversely affect performance or cause distraction, respondents also believe that using the smartphone could increase the probability of making mistakes. Distraction is a significant risk that can adversely affect patient safety (44,45); distraction is the cause of "inappropriate registration" (56.2%) or "inappropriate measurement of vital signs".(33.7%), as reported by Pucciarelli et al. (43).

This study has some limitations. First, participants come primarily from central Italy (more than 70%), which is partially representative of the Italian nursing population. Also gender subgroups show large difference in terms of sample size. Regarding the participants age, authors could not collect informed consent from any nurses over the age of 50. Therefore it would be interesting to continue this study by including a larger population with respect to age and different subgroups. Only professional nurses were involved in this investigation, excluding health professionals such as physiotherapists, midwives, doctors, pharmacists, etc. As many different health professionals perform patient care, future research involving different health professionals will allow a global view on wether smartphones act as a distraction, and how musc this affects patient care.

Furthermore, no specific analysis to define the sample size was conducted, imposing caution and prudence in using and generalizing the results. The questionnaire was administered using a dual-modality, both on paper and online, using a Google Form®, which reaches, as noted above, a wider reference population but does not allow access to data on non-response and adherence to the study. As it is a self-report scale, it is necessary to weigh the reliability of the answers.

Undoubtly the results show that respondents believe that smartphone use can lead to distractions. The most exposed categories were younger nurses and those with little working experience. Also this study provides ideas for further investigations on smartphone distraction in hospitals and territorial contexts. Although this research adds to current knowledge by providing the results of a survey of a large sample of nurses about their perceptions of smartphone use, using smartphones during acute care remains controversial. The results of this research add to the current state of science with a more objective approach that can still argue that smartphone use could be perceived as a source of distraction.

**Acknowledgments:** The authors wish to thank Dr. Deborah L McBride and Samuel Merritt University, San Mateo, CA, United States for their support.

**Author contributions:** Conceptualization, NG, EDS, SD, GBO, and MDM; methodology, EDS, CN, GBO, and MDM; investigation, SDM, GL, AS and JU; writing - original draft preparation: NG, EDS, SD, NP, and ADL; writing - review and editing, NG, SD, GBO, and MDM; supervision, NG, EDS, SD, GBO, and MDM. All the authors have read and agreed to the published version of the manuscript.

**Conflict of interest:** The authors declare that they have no conflict of interest and that the article has not been published previously and has not been forwarded to another journal.

**Financing sources:** The authors declare that no funding has been provided for the drafting of this study, and they have no financial interest in the subject matter, or the results obtained.

## Riassunto

***Impiego degli smartphones e Performance degli infermieri: uno studio multicentrico***

**Background.** Negli anni recenti, il mondo della tecnologia ha significativamente rimodellato la società. Questo studio desidera monitorare le opinioni degli infermieri che lavorano in ospedale riguardo l'impatto dei mezzi di comunicazione individuali nelle unità ospedaliere. Secondariamente l'identificazione delle differenze nell'uso dei telefonini basato sui fattori demografici ed organizzativi.

**Disegno dello studio.** Studio trasversale.

**Metodi.** Il questionario comprende 22 elementi divisi in quattro sezioni. Mediante un sondaggio sono stati raccolti 329 questionari cartacei e 449 on-line, per un totale di 778 questionari.

**Risultati.** I dati hanno evidenziato come gli smartphones abbiano un differente impatto sulla performance, rispetto al genere, l'età ed il titolo scolastico. Gli uomini che utilizzano i telefonini per attività non correlate al lavoro hanno influenzato negativamente la loro performance sul lavoro rispetto alle donne. Inoltre, gli infermieri più giovani riportano essere più distratti dall'utilizzo dei telefonini per attività non correlate al lavoro rispetto ai colleghi più anziani. Al tempo stesso, gli infermieri più giovani ritengono che i telefonini possano consentire un miglioramento nelle competenze per l'assistenza dei pazienti. Gli infermieri con minore esperienza lavorativa (≤10 anni) riferiscono di essere più distratti dalle attività non correlate al lavoro sui loro telefonini rispetto ai colleghi più anziani (>20 anni).

**Conclusioni.** Il telefonino costituisce una potenziale fonte di distrazione. Il gruppo più esposto è rappresentato dagli infermeri più giovani e quelli con minore esperienza lavorativa, ed entrambi i gruppi (giovane età, minore esperienza) possono essere considerati potenziali fattori di distrazione.

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## Supplemental Materials

Tab S1. STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

| | Item No | Recommendation | Page No |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 1 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 1 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 2-3 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 3 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 4-6 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 4-6 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants | 4-6 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 4-6 |
| Data sources/measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 4-6 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 4-5-6 |
| Study size | 10 | Explain how the study size was arrived at | 4-5-6 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 4-5-6 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 6 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 6 |
| | | (*c*) Explain how missing data were addressed | 6 |
| | | (*d*) If applicable, describe analytical methods taking account of sampling strategy | - |
| | | (*e*) Describe any sensitivity analyses | n.a. |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 6-11 |
| | | (b) Give reasons for non-participation at each stage | 6-11 |
| | | (c) Consider use of a flow diagram | n.a |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 6-11 |
| | | (b) Indicate number of participants with missing data for each variable of interest | 6-11 |
| Outcome data | 15* | Report numbers of outcome events or summary measures | 6-11 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 6-11 |
| | | (*b*) Report category boundaries when continuous variables were categorized | n.a. |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | n.a |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | n.a |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 11-13 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 11-13 |

| | | | |
|---|---|---|---|
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 11-13 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 11-13 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | Title page |

*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Ann Ig. 2024 Sep-Oct; 36(5): 513-524 doi: 10.7416/ai.2024.2631. Epub 2024 Apr 18.

# Enhancing Primary Health Care through Interprofessional education: Insights from a Training Workshop

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*Keywords: Education in healthcare; comprehensive Primary Health Care; c-PHC; medical education; interprofessional education; workshop*
*Parole chiave: Cure primarie; formazione interprofessionale; formazione medica*

**Abstract**

***Introduction***. *Strengthening primary care services with a focus on comprehensive Primary Health Care principles necessitates collaborative work practices within interprofessional teams. In Italy, the Local Health District of Florence embodies a comprehensive Primary Health Care -inspired model of primary care, prominently featuring the House of Community concept. This work presents findings and insights from a multidisciplinary, interprofessional education activity tailored for healthcare professionals, researchers, and students actively participating in the primary care reorganization.*

***Methods.*** *The activity was structured using a four-phase learning model (imaginative, analytical, common sense, and dynamic), aligning with four distinct activities (brainstorming, lecture, case study, and group project).*

***Results.*** *Key themes that emerged encompassed the significance of nurturing relationships among team members, the aspiration for an inclusive work environment, the vital role of community engagement and collaboration across various services, disciplines, and sectors beyond healthcare.*

***Discussion.*** *These themes highlight the essential attributes of successful primary care practices built on the principles of comprehensive comprehensive Primary Health Care. Throughout the innovation process of primary care services, interprofessional*

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Annali di Igiene : Medicina Preventiva e di Comunità (Ann Ig)
ISSN 1120-9135 https://www.annali-igiene.it

*education training events emerged as indispensable components for bolstering implementation and ensuring sustainability. This study underscores the crucial role of interprofessional education in bridging the gap between theoretical constructs and practical application, emphasizing that comprehensive Primary Healthcare principles find tangible manifestation in real-world scenarios.*

## Introduction

Primary Health Care (PHC) represents a holistic approach to health that aspires to maximize the overall well-being and health of individuals by prioritizing their health needs to reduce health inequalities towards equity in health, even during the COVID pandemic (1-3). This approach spans the entire spectrum of health-related activities, encompassing health promotion, disease prevention, treatment, rehabilitation, and palliative care. Its comprehensive meaning (comprehensive-PHC = c-PHC) integrates health services, professionals, and disciplines, combining primary care (PC) with public health functions and other sectors than health. In fact, it involves the implementation of cross-sectoral policies and initiatives aimed to address the broader determinants of health. Furthermore, it seeks to empower individuals, families, and communities, promoting social engagement, self-care, and self-reliance in health (4, 5). An essential aspect of fortifying PC systems, based on c-PHC principles, revolves around the constitution of multidisciplinary (MD) and interprofessional (IP) teams, which implies the sharing of values and actions (6). This is recognized as a pivotal strategy for enhancing the effectiveness and the quality of healthcare services, given the limitations faced by individual PC physicians because of time constraints, competencies, and, mostly, the increasingly diverse and complex health needs encountered in PC settings. Organized IP teams have demonstrated their positive impact on care quality, access, cost, perceived health status and satisfaction among healthcare professionals (HPs) (7-11). It is widely acknowledged that the inclusion of HPs from various disciplines in PC teams, such as medicine, nursing, pharmacy, social work, and psychology, can contribute to improved healthcare quality. Each profession brings unique skills, knowledge, and perspectives to the table, complementing the work of their colleagues within the team. This collaborative approach to care aims at ensuring that patients receive comprehensive and coordinated healthcare that addresses their physical, psychological, and social needs (12, 13). Interprofessional education (IPE) and interprofessional collaborative practice (IPCP) hold the potential to make a substantial impact on the challenges confronting healthcare systems worldwide (14, 15). The World Health Organization (WHO) defines IPE as the process through which HPs learn from each other to improve health outcomes. In contrast, IPCP involves HPs from diverse backgrounds collaborating with patients, families, caregivers, and communities to deliver comprehensive care and achieve the highest possible service quality (16), even in the post-COVID-19 pandemic era (17). Previous studies reported the positive impacts of IPE on HPs, students, and future HPs. Specifically, IPE enhances the ability of HPs to manage chronic and complex health conditions, improve team functionality and climate (18-20). For students and future HPs, IPE fosters collaborative learning practices by developing skills such as IP communication and role comprehension (16, 21). It also contributes to reducing stereotypes, enhancing mutual attitudes toward medical and nursing professions, and fostering mutual appreciation by promoting role understanding and patient safety (22). IPE serves as a valuable tool for enhancing and reinforcing collaborative work practices when three essential elements coexist: the pedagogical approach, the theoretical framework, and practical scenarios with an impact on population health needs (23). This framework revolves around the central concept of ongoing healthcare education, bridging the gap between healthcare services and academic institutions, with a focus on addressing specific population needs (23).

In the context of the present day, marked by ever-evolving healthcare challenges and the aftermath of the COVID-19 pandemic, there exists a pressing imperative to fortify PC services, guided by the principles of c-PHC (4, 5). These principles, while

universal in their aspiration, must be applied contextually, recognizing that different situation — shaped by policies, history, society, culture, and local health needs — call for tailored approaches.

In response to the current healthcare needs, the Italian government has introduced a novel approach to PC organization, establishing what is referred to as the House of Community (HoC – 'Casa della Comunità') within a public Local Health District (LHD). The primary goal of the HoC is to serve as accessible hubs for the community, facilitating health promotion, preventive measures, assistance, and the seamless provision of continuous care (24). Within the LHD of Florence we find a pioneering example of a c-PHC model that places the HoC concept at its core. Moreover, to our knowledge, no prior studies have been conducted in Italy that explore the implementation and impact of c-PHC principles within the House of Community (HoC) model, particularly within a public LHD.

Thus, the aim of this study is to share the findings and insights garnered from an exploration within the context of the implementation of this comprehensive PC model within the LHD of Florence. In particular, this study has a dual focus:

- to comprehensively describe the organization, design, and implementation of a training event aimed at fostering innovative models in primary care services.

- to identify and emphasize key themes and factors contributing to innovation within primary care services.

## Methods

*Workshop Developmemnt*

This IPE activity for HPs was created by a team (from now on "research team") of 5 young general practitioners and public health physicians (M.DR., C.M., G.N., G.O., I.P.) with previous experiences in medical education with the International Federation of Medical Students' Associations (IFMSA), the Italian Secretariat of Medical Students (SISM), and the Italian Society of Medical Pedagogy (SIPeM). The trainers also lead the IPE activity. All materials and written documents, presentations, and activities were created by the authors during the year before the realization of the workshop (March 2022 – March 2023). The workshop was endorsed by different institutions, involved in the reorganization analysis of PC service in the LHD of Florence: the Department of Health Sciences of the University of Florence, the LHD of Florence, the Florence M unicipality, the Health Society of Florence (a consortium between the LHD of Florence and the Florence Municipality) and the Regional Health Agency of Tuscany.

*The participants*

The decision was made to require a minimum of 15 participants for the IPE activation. Additionally, a maximum of 36 participants was set as an a priori target to ensure manageable group sizes during activities, such as creating six groups of six people, and to facilitate interactions among participants. To promote diverse perspectives and facilitate rich interactions among participants, the LHD identified potential participants from various backgrounds, specifically those actively engaged in PC services or pursuing educational and research experiences within the same context. The organizing group and the LHD mutually agreed that representing a wide range of disciplines and services in the workshop was essential. Consequently, the ideal pool of professionals was identified, with requested ideal participant numbers specified in parentheses based on their availability within the PC services: 10 General Practitioners, 5 Public Health Physicians, 5 Nurses, Physiotherapists, Healthcare Assistants, Obstetricians, and students in healthcare fields. Participation was extended to University Departments collaborating with the LHD. Prior to the workshop, the identified participants were emailed a preworkshop reading packet with instructions on location, tools to be known and used during the workshop, educational documents on c-PHC.

*The agenda and the activities*

The methodology used to design the training workshop and its activities was adapted from McCarthy's 4MAT model (25-27), a learning cycle that is designed to address the different learning styles and preferences of learners. It consists of four distinct phases, each corresponding to a different type of learner:

- the "imaginative phase" focuses on creativity and imagination. Learners engage in brainstorming, mind mapping, visual aids, and group discussion;

- the "analytical phase" focuses on logic and analysis. Learners focus on understanding and organizing information through activities such as lectures, readings, note-taking, and analysis of data;

- the "common-sense phase" focuses on practical application and real-world examples. Learners apply

what they have learned to real-world situations through activities such as case studies, simulations, role-playing, and problem-solving;

- the "dynamic phase" focuses on exploration and experimentation. Learners apply what they have learned to new situations and contexts through activities such as hands-on experiments, field trips, and group projects.

***Interprofessional Education***

The agenda was built over two days and included all the four phases, represented by four activities (Figure 1). In particular, after deciding and sharing the ground rules of the workshop (e.g. respect others' interventions, no interruptions during others' intervention, etc.) and collecting the participants' expectations on the event, the first activity consisted in a brainstorming and discussion on the participants' understanding of PHC meaning, and the aspects of their routine activities they deem the most relevant.

Afterwards, the second activity consisted in a lecture focused on PC services, the concept of c-PHC and its principles, and its applications in the local context. In the third activity, conducted as a group exercise, participants were tasked with addressing a real-world case scenario. They initially identified and discussed the primary health determinants that significantly influenced the circumstances presented in the case. Subsequently, they engaged in a discussion regarding the available resources that could be effectively activated to address the situation. Lastly, in the fourth activity, the participants were asked to reflect on factors contributing to positive working environment, and, in groups, to sketch or draw the best PC environment to work in and address population needs (Table 1).

The text of the case-study, as given to the participants, is reported in Supplementary file S1. The workshop ended with a brief evaluation where participants were asked to respond to two questions: 1) 'What did you like the most about this workshop?' and 2) 'What would you like to see changed if you were to participate in a future edition of the same workshop?'.

*Data collection and analysis*

For each activity, participants' responses were collected either individually or in groups using Mentimeter, a web-based Audience Response System commonly employed to enhance active learning in large classrooms (28). Additionally, notes were taken on a shared document by one of the trainers. In particular, Mentimeter was used to collect and summarize ideas during the first activity (e.g. brainstorming on the meaning of c-PHC), and for the final group discussion and evaluation.

The analysis was then conducted in two phases: the first phase involved a descriptive analysis, aimed at detailing the workshop activities and summarizing the outcomes based on materials produced by the participants. In the second phase, a qualitative analysis was carried out. This involved a thorough examination of the workshop-generated materials to identify pertinent themes emerging from participant

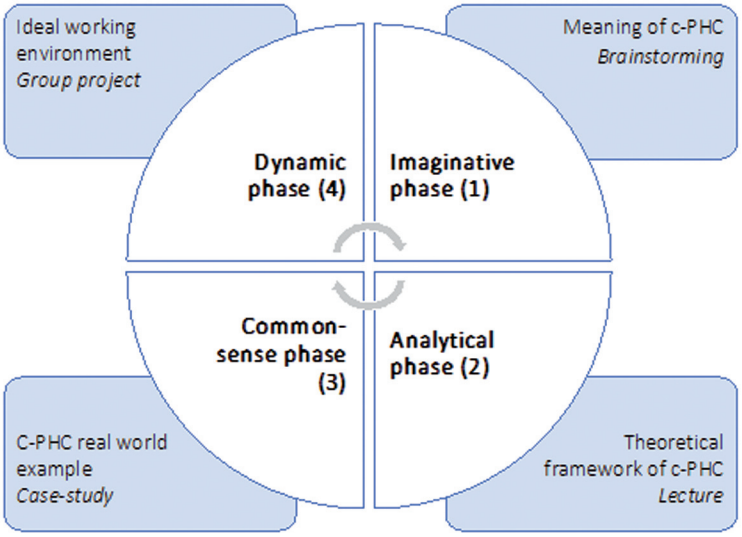


Figure 1 - Graphical representation of the four activities. Adapted from McCarthy's 4MAT model.

Table 1 - Description of the activities of the Workshop.

| 4MAT phase | Activity | Type of activity | Effective duration |
|---|---|---|---|
| 1 – Imaginative | Brainstorming on PC meanings | Individual activity | 45 min (of which 30 mins for review and discussion) |
| 2 – Analytical | Lecture on c-PHC (topics: principles of c-PHC; health inequalities and changing health needs in COVID-19 times; strengthening c-PHC in the present context; meaning and principles of the House of Community in the Italian context) | Led activity | 75 min (including question time) |
| 3 – Common sense | Case-study | Group activity | 180 min (of which 50 % review and discussion) |
| 4 – Dynamic | Design of ideal workspace | Group activity | 180 min (of which 50 % review and discussion) |

perspectives; these themes were considered essential for informing the planning and enhancement of primary care services.

Specifically, responses were initially transcribed and subsequently reviewed multiple times by two researchers from the research team to ensure a thorough comprehension of the content. These two researchers also developed initial codes, which were used to categorize similar responses based on their shared meaning. This process of coding and categorization was conducted iteratively, with categories refined and revised as necessary until a clear and comprehensive set of categories emerged (29). The initial analysis was then shared with the research team for validation, facilitating a comprehensive understanding of the participants' perspectives on the investigated topic.

## Results

The workshop took place in Florence on 14th (afternoon from 15:00 to 18:00 including a short break) and 15th (all day, including two breaks and one lunch break) April 2023. Twenty-two individuals participated in the workshop, and specifically 5 between GPs and trainees in family medicine, 6 public health physicians and public health residents, 5 nurses, 1 physiotherapist, 1 healthcare assistant, 2 architects, 2 medical students. The results of each activity are summarized in the following paragraphs.

*Ground rules and expectations*

During the ground rules discussion, a consensus emerged among the participants regarding the paramount importance of open and respectful communication. They emphasized the need for a collaborative and inclusive environment, fostering active engagement and knowledge sharing.

While discussing their expectations, most participants expressed a keen interest in developing IPCP. Additionally, the participants expressed a strong desire to establish connections with professionals working in the same field, who are dedicated to enhancing PC strategies for tangible, actionable outcomes.

*First activity – group brainstorming on what c-PHC means*

In the brainstorming session, participants shared insights and perspectives, forming a mosaic of words and phrases that collectively embodied their understanding of PHC. Among the diverse range of words and concepts, this collaborative exercise unveiled four predominant themes that encapsulated the essence of PHC for the participants, each chosen for its significance:

Comprehensiveness: participants emphasized the holistic nature of PHC, highlighting its role in addressing complex health needs that extend beyond the purview of single professions. Teamwork strongly emerged as a leading factor in innovating strategies for comprehensive care;

Care coordination, IPCP and Intersectoral Collaboration: beyond the mere act of working together, participants stressed the importance of coordination and the need for specific coordination roles. The concept of building a collective identity within the group ("learn how to build a 'we', instead of an 'I'") was prominent. The IP and MD group was seen as a fertile ground for the development and

improvement of practices, particularly in the context of complex problem-solving.

Equitable Resource, Allocation, and Responsibility Management: participants recognized that achieving health equity through PHC necessitates a profound understanding of a community's needs and the allocation of resources accordingly. The concept of fair resource distribution and management was underlined as integral to PHC's mission.

Accessibility to the Healthcare System: accessibility to healthcare services was identified as a multifaceted challenge influenced by a multiplicity of factors. Participants emphasized the futility of improving services or clinical pathways if they remained unknown or inaccessible to the intended beneficiaries. Furthermore, tailored services to address specific needs, such as mediation services, were highlighted as essential to reducing access barriers.

*Second activity – lecture on the theoretical framework of c-PHC and what primary care organization in Florence*

The words shared in the brainstorming and the 4 PHC principles identified were the starting point for theoretical alignment. The second activity was indeed designed to further develop the plausible insights generated during the initial brainstorming session and the identification of some PHC principles with practical examples. Here, the themes addressed in the lecture are listed: theoretical principles of c-PHC and its historical evolution; health inequalities and the changing health needs emerged during the COVID-19 pandemic; the need of strengthening c-PHC in the present historical and political context; the mission of the HoC - a newly proposed organizational model of local health and community center - which in Italian context can embrace c-PHC principles within a publicly funded LHD.

*Third Activity – Case Study Analysis*

The analysis of the case study by the four groups aimed to practically apply the theoretical content conveyed during the plenary session and resulted in the completion of a grid that delved into the health determinants and processes influencing the management of these needs. Moreover, it highlighted the activatable resources within the individual and the community levels (Table 2).

*Fourth Activity – Ideation and design of an ideal workspace*

The analysis of the drawings created and displayed by the groups yielded the identification of c-PHC related principles. These principles encompassed PHC-related challenges, the presence of a public healthcare service as a reference point, the importance of competencies, the significance of welcoming environments, nurturing relationships, and fostering empathy. Additionally, principles included community involvement, participatory health promotion, comprehensiveness in addressing individuals' health needs, as well as attention to the well-being of HPs. Furthermore, the integration of services and collaboration among various HPs and disciplines were

Table 2 - Health Determinants and Activatable resources and actions emerged from the Case study analysis (third activity).

| Health determinants | Activatable resources and actions to be taken |
|---|---|
| Individual determinants: level of education, personal health/ clinical conditions, vulnerability status, health literacy, etc. | (Deep understanding of the) family, social, and environmental context. |
| Familial factors: family environment, number of household members, caregiver presence and level of education. | Formal and informal resources within the community (volunteers, neighborhood networks, local social services). |
| Socio-economic and housing aspects: income, employment and housing conditions, built environment, neighborhood characteristics, presence of public transportation, local infrastructure, etc. | Interprofessional collaboration and integration among HPs in defining the care path. |
| Healthcare system organization: accessibility barriers, service reception capacity, facility visibility, integration and continuity between different levels and settings, interprofessional communication, proactive or reactive service approach. | Psychological services. |
| Level of education among PC professionals and social care providers. | Multidimensional assessment committees. |
| | Specialized services (geriatric specialists). |
| | Palliative care teams. |
| | Long-term care facilities. |
| | Involvement of the individual and caregiver in the development of the care plan to establish a foundation of trust. |
| | Continuing education and support for the family and the caregiver. |
| | Continuing education and training programs for primary care practitioners, involving students, interns/trainees, and researchers in joint initiatives. |

Table 3 - Symbols and themes drawn as representative of an ideal workspace (fourth activity).

| Symbols | Themes |
|---|---|
| Wind | Challenges in daily work - the variability of health, work, and social conditions (PHC-related challenges) |
| Boat in a stormy sea | National Health Service as the guarantor of the right to health currently facing difficulties |
| Rudder<br>Magnifying lens | Competencies that must be acquired by the professionals |
| Coffee pot<br>Coffee cup<br>Plants to care | Take care of relationships |
| Notebook with blank pages<br>Pencil | Participatory processes |
| Road<br>Circle | Communities |
| Lamppost | Comprehensiveness (global management of the person's health aspects)<br>Attention to the needs/well-being of the professional) |
| Hands holding the notebook with blank pages<br>Hands with different colors/sizes<br>Table | Collaboration and integration between professionals and disciplines |

emphasized. Symbols and themes displayed during the activity are summarized in Table 3.

*Final Evaluation*

The contents of evaluation by participants and final reflections revealed enthusiastic reactions, particularly regarding the following issues:

- Teaching Methodology: non-frontal, participatory methodology with activities in multi-professional groups allowed participants to experience collaboration and communication among participants and easier discussion among different professionals;

- Classroom atmosphere: positive energy, enthusiasm, creating environment favorable to exchange ideas;

- Training content/learning outcomes: usefulness of topics-MD collaboration, PHC through participants discussion.

- Two participants offered constructive feedback, suggesting that more time should have been allocated for the activities and discussions.

*Primary Themes from the Analysis*

Considering the themes described and emerged by the different activities, 3 main groups can be identified as the main relevant. The first refers to the importance of positive work relationships and welcoming environments. Another group is the community involvement and health promotion activities through community participation and comprehensiveness in addressing health needs. Lastly, the reinforcing of integration and collaboration between HPs and services is a common element to both the previous themes.

## Discussion

The present study describes our initial endeavor to design, implement, and report on a specialized IP training event that aligns with, and supports the ongoing reorganization of PC services in the LHD of Florence. This reorganization centers on the implementation of the HoC model, emphasizing the integration between different professionals and services and IPCP. The workshop took place in Florence and saw the presence of 22 participants among HPs, researchers, and students of different health-related fields. The first activity consisted in a group brainstorming where 4 principles were identified as main, necessary components of well-working PC services: comprehensiveness, IP collaboration, reflective learning spaces, and equitable resource distribution. The second activity, which consisted in a lecture on c-PHC, provided the group theoretical frame on this topic, and highlighted the presence of the four mentioned principles in the c-PHC framework (4, 5). The third activity – the analysis of a case study – was aimed at identifying all the factors that determined the health condition of hypothetical

subject depicted in the case study, and the resources that should be available and activated within the PC assistance. In their analysis, the groups included individual factors, family dynamics, socio-economic conditions, healthcare system organization, and the education level of PC professionals. Activatable resources, on the other hand, encompassed adapting responses to the family and social context, promoting IPCP, involving individuals and caregivers in care planning, and fostering HPs' well-being through education and training programs. As a secondary output of this activity, it should be highlighted that these themes mirror the topics emerged in the first activity: comprehensiveness (holistic management of health aspects); IPCP and intersectoral collaboration, which also necessitates dedicated educational and self-reflective spaces; equitable distribution of resources. Lastly, the fourth activity allowed the participants to draw their ideal working space within the PC services. Subsequent discussions highlighted a strong alignment between the symbolism in their drawings and the principles that had emerged in previous activities. Notably, welcoming environments and positive work relationships were cited as crucial for both HPs' well-being and the positive outcomes of their work. Additionally, community involvement, participatory health promotion, and comprehensiveness in addressing individuals' health needs, which had been previously discussed, resurfaced as key considerations in designing the ideal workspace.

The alignment between the themes emerging from practical activities and those deemed significant during the brainstorming phase carries significant implications. Specifically, the resonance between theoretical discussions and practical case analysis underscores the consistency and practical applicability of c-PHC concepts across various stages of the learning process. This observation highlights that these concepts extend beyond theoretical constructs and manifest tangibly in real-world scenarios. A pivotal theme revolves around the significance of nurturing supportive relationships among team members when implementing IPCP. This is closely linked to a shared desire for a welcoming work environment and the cultivation of positive working relationships. These aspects benefit from dedicated time frames for discussion and co-design, as well as team meetings for reflection and learning from daily practice (16, 21). IPE, in conjunction with an action-research process, facilitates the sustainability, observation, and monitoring of working practices. In this context, the inclusion of a training program designed to support reflection on practices and team dynamics becomes necessary (30-32). Moreover, the idea of creating an environment based on mutual respect and shared values, which include trust, honesty, and integrity, is a key aspect of the Core Competencies for Interprofessional Collaborative Practice outlined by IPEC in 2016 (33). Effective IP communication is indeed another important aspect and emphasizes the relevance of active listening, encouraging team members to share their ideas, giving constructive feedback in a timely manner, and respectfully responding to feedback from others. Furthermore, it involves recognizing that individual qualities, such as experience, expertise, cultural background, and role within the healthcare team, contribute to effective communication, resolving conflicts, and building positive relationships with other professionals (33).

The second important theme emerged refers to community engagement and collaboration across sectors. PC services aim to address community health issues and equity by working closely with community members and sectors beyond healthcare to ensure fair resource distribution (6). This involves understanding community health concerns and holding regular IP meetings with HPs, researchers, students, and community members to analyze health issues, set priorities, and plan activities (34, 35). IPE helps guide this process, encouraging reflection, impact assessment, and quality improvement. Students, trainees, and researchers participate in community-based education to analyze health problems, assess socio-economic factors, and build relationships with community stakeholders (4, 36). This experience enhances their skills and understanding of IPCP.

The reorganization analysis of Primary Care (PC) services within the Local Health District (LHD) – centered on the Houses of Care (HoCs) - aims to provide Comprehensive Primary Health Care by integrating health and social services and ensuring continuous care. This necessitates the inclusion of Interprofessional (IP) training experiences and active involvement of healthcare professionals (HPs) and management at various levels (24). The emphasis is on fostering Interprofessional Collaborative Practice (IPCP) and engaging professionals from diverse services and disciplines. These IP experiences provide valuable spaces for shared learning and reflection on practices, facilitating the adoption of c-PHC principles. Furthermore, they play a vital role in acquiring the foundational elements upon which IP teams are built, including shared values, a common language, trust,

and respect for defined roles. In this process, involving HPs, future HPs, and students helps in bridging the gap between PC services and universities. Students and trainees can also engage in practical research to support innovation. In this context, HoCs and similar new models in PC provide both physical and functional spaces where IPE training experiences can thrive; simultaneously, these experiences contribute to the implementation and sustainability of these new PC models.

Limitations of this study encompass several factors. First, the sample used for data collection was a convenience sample, which may limit the generalizability of our findings to a broader population. However, it's important to note that the learning methodology employed in the workshop is easily transferable, offering potential applicability in various healthcare contexts. Second, the study's focus on qualitative data predominantly restricts quantitative assessments of the workshop's impact. While this approach allowed for an in-depth analysis of participant insights, it may have missed quantitative nuances. Moreover, the single-location focus of our study ensures specificity and potential local applicability of our results. However, it poses challenges when attempting to extrapolate our findings to other healthcare settings or regions. Lastly, the long-term effects of the workshop on participants' knowledge and practice remain unexplored in this study. Nevertheless, our research group is actively considering follow-up studies with the same cohort. These potential follow-up studies could include longitudinal assessments to track sustained impacts and investigate the possibility of participants becoming peer educators who share workshop knowledge within their healthcare communities.

Despite these limitations, the study's strengths are evident. The workshop was meticulously designed and executed by a multidisciplinary research team, providing an engaging and informative educational experience. The diverse backgrounds of participants, including healthcare professionals, students, future professionals, and researchers from non-healthcare disciplines, enriched discussions and offered a holistic perspective.

## Conclusions

This study operates within the framework of IPE and c-PHC and it highlighted essential elements for designing, implementing multi(inter)professional training events that align with and support the reorganization of PC services.

The IPE experience described suggests the importance of associating an IPE training course with the reorganization of services and allowed to identify some priority themes in implementing such reorganization. In addition, this first experience showed the satisfaction of the participants, the consistency between the themes and principles to strive for, and some organizational elements to be acted upon.

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**Authors contributions:** Conceptualization: C.M., G.N., G.O., I.P., M.DR.; methodology: C.M., G.N., G.O., I.P., M.DR.; validation; L.B., M.N., C.L., L.T., G.B.; investigation and formal analysis; C.M., G.N., G.O., I.P., M.DR.; resources: L.B., M.N., C.L., L.T., G.B.; writing—original draft, C.M., G.N., G.O., I.P., M.DR.; writing—review and editing, L.B., M.N., C.L., L.T., G.B., members of the PHC-W working group. All authors have read and agreed to the published version of the manuscript**.**

**Institutional Review Board Statement:** The study was conducted according to the guidelines of the Declaration of Helsinki. Ethical approval was waived for this study, due to the deidentified nature of the data presented.

**Informed Consent Statement:** Not applicable.

**Conflicts of Interest:** All authors report no conflict of interest.

**Data Availability Statement:** Data supporting reported results are available upon request to the corresponding author. Data were collected and managed in aggregated form according to European Union Regulation 2016/679 of European Parliament and the Italian Legislative Decree 2018/101.

**Funding:** We acknowledge co-funding from Next Generation EU, in the context of the National Recovery and Re-silience Plan, Investment PE8 – Project Age-It: "Ageing Well in an Ageing Society". This resource was co-financed by the Next Generation EU [DM 1557 11.10.2022]. The views and opinions expressed are only those of the authors and do not necessarily reflect those of the European Union or the European Commission. Neither the European Union nor the European Commission can be held responsible for them.

**Riassunto**

***La formazione interprofessionale per il miglioramento delle Cure Primarie: riflessioni a partire dall'esperienza di un workshop***

**Introduzione.** Il rafforzamento dei servizi di cure primarie orientato ai principi della *comprehensive Primary Health Care* richiede di sviluppare pratiche collaborative in team interprofessionali. In Italia,

la zona Distretto di Firenze tende ad un modello di cure primarie di tipo *comprehensive Primary Health Care*, centrato sulle Case di comunità. Questo lavoro presenta i risultati e le riflessioni di un evento formativo multi e interprofessionale (*interprofessional education*), rivolto a professionisti sanitari, ricercatori e studenti coinvolti nella riorganizzazione dei servizi di cure primarie.

**Metodi.** L'attività è stata strutturata utilizzando un modello di apprendimento in quattro fasi (immaginativa, analitica, 'common-sense', dinamica), seguendo quattro attività distinte (brainstorming, lezione frontale, caso studio e progetto di gruppo).

**Risultati**. I temi salienti emersi hanno evidenziato l'importanza di coltivare relazioni tra i componenti del team, l'esigenza di un ambiente di lavoro inclusivo, il ruolo cruciale del coinvolgimento comunitario e della collaborazione tra diversi servizi e discipline e tra settori altri rispetto a quello socio-sanitario.

**Discussione.** Questi temi sottolineano gli aspetti essenziali delle pratiche di cure primarie orientate ai principi della comprehensive *Primary Health Care*. Gli spazi formativi di *Interprofessional Education* sono componenti indispensabili nel sostenere l'implementazione di processi di innovazione dei servizi di cure primarie e nel garantirne la sostenibilità. Questo studio sottolinea l'importante ruolo dell'*Interprofessional Education* nel colmare il distacco tra gli elementi teorici e la declinazione pratica, enfatizzando che i principi della *comprehensive Primary Health Care* si concretizzano in scenari del mondo reale.

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## Supplementary Material S1

Below is the full text of the case provided to the groups for work; it is divided into two parts, provided at different times to stimulate reflection.

Case Study – 1st Part

It's Monday morning, and Silvia, a primary care physician, is in a general practice clinic when she receives a call from the territorial nursing service. Mirko, a family nurse practitioner, informs her that he is in charge of one of his patients, 81-year-old Alberto. Mirko adds that Alberto was admitted to the emergency room (ER) over the weekend after a fall at home, resulting in a leg injury. The fall likely occurred during an episode of psychomotor agitation. Mirko also mentions that he plans to visit Alberto in the morning to continue hydration therapy. Finally, Mirko reports that he has already reached out to the contact person, his 72-year-old partner Anna, who mentioned that this is the second ER visit in the last month. Mirko asks Silvia if she has any additional useful information.

Silvia mentions that she hasn't seen Alberto and Anna at the outpatient clinic for about a year, but they've been consistently taking prescribed therapy. Alberto's therapy includes psychotropic, antihypertensive, anti-aggregant, and oral hypoglycemic medications. She also recalls a geriatric consultation from about a year ago, conducted privately, where cognitive impairment with initial behavioral disturbances was diagnosed. However, she cannot find a record of the scheduled re-evaluation. Additionally, Alberto has type II diabetes mellitus, arterial insufficiency, and had an ischemic stroke some time ago, resulting in motor limitations. Silvia notes that she hasn't received notifications of recent ER admissions and suggests that Mirko updates her for a possible joint evaluation.

Case Study – 2nd Part

Anna is the primary caregiver for Alberto. They met after both going through divorces. Alberto has a grandson who moved to London for work about a year ago, while Anna has a daughter who recently had a baby girl. For the past three months, they've hired someone to assist with Alberto's care for two hours a day, Monday through Friday. Anna faces challenges in getting around, especially with Alberto, and relies on her daughter or public transportation since she doesn't have a driver's license.

A few days later, Silvia decides to visit their home with Mirko. Alberto and Anna live on the third floor of an apartment building in the same neighborhood as the outpatient clinic. Anna explains that in recent months, managing the situation at home has become increasingly difficult. She's attentive to Alberto but visibly tired. Alberto has been experiencing frequent episodes of agitation, particularly at night, during which he becomes aggressive and refuses to take his medication. Due to this, Anna has had to contact the continuity of care service several times. During the latest episode of agitation, Anna called 112 due to Alberto's leg injury and the difficulty in calming him down.

Guiding questions - analysis grid

| | |
|---|---|
| What are the determinants of Albert's health, and how do they impact his ability to meet his needs? | What resources would you activate from the local area/community/living context? |

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Ann Ig. 2024 Sep-Oct; 36(5): 525-536 doi: 10.7416/ai.2024.2619. Epub 2024 Mar 7.

# Decade-long insights: tracking asbestos-related health impacts among formerly exposed workers in Palermo, Italy

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*Keywords: Asbestos-related diseases (ARDs); Mesothelioma; Occupational Health; lung cancer; smoking habits; asbestosis/pleural plaques*

*Parole Chiave: Patologie asbesto correlate; mesotelioma; medicina del lavoro; cancro polmonare; abitudine tabagica; asbestosi/placche pleuriche*

**Abstract**

***Background***. *Asbestos is a foremost occupational carcinogen globally. Despite the prohibition under Law 257/1992, Italy persists as one of the European nations most burdened by asbestos-related diseases (ARDs). This research assessed ARD cases in asbestos-exposed workers from the Province of Palermo, Italy, spanning 2010-2021.*

***Methods***. *Data acquisition utilized the epidemiological dataset from the 'Service of Prevention and Safety on Work Environment' under the Prevention Department of Palermo's Local Health Authority (LHA).*

***Results***. *Between 2010 and 2021, we identified 245 ARD instances, comprising 163 Asbestosis/Pleural plaques, 41 Lung Cancers, 38 Mesotheliomas, and 3 unspecified cases. Multivariate analysis indicated a notable decline in temporal exposure for mesothelioma (HR=0.933; 95% CI=0.902-0.965) and lung cancer (HR=0.93; 95% CI=0.90-0.978) relative to pleural plaques/asbestosis. Tobacco use displayed a pronounced correlation with lung cancer (smoker HR=64.520 95% CI=13,075-318.390; former smoker HR=20.917 95% CI=4,913-89.048). A significant link was observed between mesothelioma and pleural plaques/asbestosis in those employed in shipbuilding and repair (HR=0.371 95% CI=0.155-0.892).*

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Annali di Igiene : Medicina Preventiva e di Comunità (Ann Ig)
ISSN 1120-9135 https://www.annali-igiene.it

***Conclusions***. *ARDs persist in clinical observations, even following the 1992 cessation of asbestos-related activities, emphasizing an enduring public health challenge. Enhancing prevention strategies is paramount, focusing on amplifying anamnestic and occupational data collection, thereby facilitating superior early diagnosis strategies for these maladies in the occupationally exposed cohort.*

## Introduction

Asbestos is a group of naturally occurring mineral silicate fibres of the serpentine and amphibole series (1). According to the European legal references, six naturally occurring asbestos types have been identified, inclusing serpentine mineal chrysotile (also known as "white asbestos") and five amphiboles (i.e. actinolite, amosite, anthophyllite, crocidolite, and tremolite) (1, 2). Since 1973, all forms of asbestos have been considered as carcinogenic, being classified as a Group 1 carcinogen (known to cause cancer in humans) by the International Agency for Research on Cancer (IARC) (3), while the EC Regulation 1272/2008 of the European Community nowadays considers asbestos as a Carcinogen of Group 1A (i.e. known to have carcinogenic potential for humans, classification largely based on human evidence) (2). The mechanisms by which asbestos causes disease are not fully understood (4). Currently, the unique fibrous morphology of the asbestos fiber appears to be the main factor in its promoting its health risks (5): because of their surface charge, asbestos fibers can adsorb to cellular macrophages and induce changes in macromolecules, ultimately leading to interference with the mitotic spindle and causing chromosomal damages, while the failing of alveolar macrophages in digesting asbestos figure lead to the release of reactive oxygen species from macrophages to the alveolar spaces (4). Amphiboles, with their needle-like structure, are especially hazardous due to their resilience and ability to deeply penetrate lung tissues, whereas the spiral structure of serpentine-asbestos tends to lodge in the upper respiratory tract (6).

Throughout the 20th century, and until the 1990s, Italy was among the world leading producers, exporters, and consumers of asbestos, both as raw asbestos fibers and asbestos containing products (APC) (2): in 2014, INAIL has estimated a total output from World War II to 1992 of 3,800,000 t of raw asbestos from the Italian mines of Emarese, Balangero and Val Malenco, with further 1,900,000 t of imported asbestos (7). The extensive use of asbestos led to the present-day significant burden of asbestos-related diseases (ARDs): lung carcinoma, malignant mesothelioma of the lung pleura (MPM), of pericardium, of the tunica vaginalis testis, as well as non-malignant but severe conditions (asbestosis). Even though in 1992 Italy became one of the first countries to ban extraction, import, marketing and production of all products containing asbestos (8, 9), ARD still occur. Data from the National Institute for Insurance against Accidents at Work (INAIL) reveal a persisting trend: between 2018 and 2022, an annual average of 1,329 ARD cases have been compensated by INAIL, for a total of 7,377 diagnoses from 6,643 workers (10), mostly of male gender (96.1%). With a pooled occurrence of 2,455 diagnoses, around 33.3% of compensated disorders pertains to mesothelial tissue and soft tissues (11), with further 2,107 disorders associated with other pleural conditions (28.6%). New diagnoses exhibit a clear geographic trend, with the highest percentages in the North-Western regions (31%), followed by North-Eastern regions (25%), Southern (20%), and Central regions (14%) (12).

Since 2003, taking into account the rising number of cases of ARD due the intensive use of asbestos in the past, and the fact that some countries still continued to use chrysotile asbestos, international organizations, such as the International Labor Organization (ILO) and the World Health Organization (WHO), recommended that special attention should be paid at global level, advocating for comprehensive national strategies targeting to the eradicating of ARDs (13-15). Their emphasis also encompasses the mitigation of health risks arising from previous exposures as asbestos-related malignant diseases have very long latency period (up to 40 years). Moreover, appropriate policies should be implemented for the appropriate managing of existing structures and materials containing asbestos (16).

Abundant evidence associates the exposure to all types of asbestos with MM, but also with cancers of the respiratory tract (mostly lung and larynx), and ovaries. More limited evidence has otherwise linked asbestos with gastrointestinal malignancies, including cancers of the pharynx, stomach, and colorectal regions, hinting at the potential systemic migration

of asbestos fibers within the human body (17, 18). According to available estimates, 78% of occupational cancers recognized in EU member states can be related to previous asbestos exposure. Other recognized asbestos-induced conditions include pleural plaques, and interstitial disorders of the lung, ranging from aspecific fibrosis, and a pattern of interstitial fibrosis with characteristic asbestos bodies and ferruginous bodies also known as asbestosis (19).

MM is usually considered a rare malignancy in people not exposed to asbestos: with an estimated etiological fraction of 80% or more (20), it is usually acknowledged as a reliable indicator of previous asbestos exposure. Remarkably, even minimal asbestos exposure events, as seen in familial or residential contexts, can lead to MM, emphasizing the intricate role of genetic predisposition (21, 22). The prognosis for MM remains grim, averaging a life expectancy of merely ten months post-diagnosis (23). Concurrent tobacco and asbestos exposures amplify lung cancer risks, highlighting the synergy of these carcinogens. Notably, isolating lung cancers specific to either risk factor remains a challenge (24, 25).

As recently stressed by Catelan et al. (26), occupational settings remain the primary hub for asbestos exposure: in their study about a total of 6,226 MM cases (93.8% arising from lung pleura), 71.6% of males and 35.8% of females reported a work-related exposures to asbestos, with non-occupational, environmental exposures accounting for 2.1% of cases in males, and 4.9% in females, while 19.1% of male cases and 40.8% of female ones remained deprived of any documented exposure (16). No safe exposure limits can be acknowledged: not only, Italian Law n. 257 of March 27th, 1992, categorically prohibited any activities involving asbestos, encompassing mining, import, export, sale, and manufacturing (27), but consistently with the Directive 2009/148/EC of 30 November 2009 on the protection of workers from the risks related to exposure to asbestos at work, Italian Legislative Decree 81/2008 currently mandates an Occupational Exposure Limit (OEL) for airborne asbestos exposure, i.e. 0.1 fibers per cubic centimeter averaged over an 8-hour workday (28, 29). Following the recent evaluation of the OEL by European Chemicals Agency and the subsequent statement that there is no threshold below which there is no risk (30, 31), more stringent OEL have been recently approved by the European Parliament: in the plenary session of October 3rd, 2023, the OEL has been lowered from 0.1 to 0.01 fibres per cubic centimeter, without a transition period (32).

Despite the significance from a Public Health point of view, the actual burden of ARD has remained mostly uncertain, particularly in Italy. In order to improve registration and reporting of MM cases, a National Mesothelioma Registry (ReNaM) has been implemented since 2002 (33, 34), and diligently tracks incident cases of MM. According to the Seventh Report of ReNaM database, a total of 31,572 MM cases have been diagnosed between 1993 to 2018, and cataloged through extensive and systematic investigations of patients' occupational, residential, and familial histories (35, 36). Predominantly, MM manifests in the pleura (93.2%), with other sites like the peritoneum, pericardium, and tunica vaginalis of the testis being rarer. The average age of diagnosis hovers around 70 years, with males being affected more frequently, presenting a male to female ratio of 2.6 (37). Projections indicate that despite the 1992 asbestos ban, the MM epidemic in Italy might peak around 2024 for both genders (38).

Interestingly, Sicily (4,802,016 inhabitants according to 2023 census, i.e. 8.2% of total population) is among the most severely affected Italian regions (36). For instance, in 2022 alone 88 out of 939 diagnoses of ARD (9.4%) were associated with residents from this Region, including 16 out of 405 cases of malignant pleural mesothelioma (MM, 4.0%), and 60 out of 305 cases of respiratory tract neoplasia (19.7%) associated with exposure to asbestos fibers. In this study, we retrospectively analyze ARDs cases diagnosed in the province Palermo, the largest city of the region of Sicily, from 2010 to 2021. Additionally, we aim to discern the relationship between asbestos exposure and the onset of mesothelioma/lung cancer in workers across various asbestos-associated industries, with a specific focus on shipbuilding and the railway sector.

## Material and methods

*Study Area and Background*

Palermo, the fifth most populous city in Italy, boasts 630,733 inhabitants (39), while the encompassing Province of Palermo surpasses 1.2 million residents (39). The Palermo shipyard, established in 1984, stands as one of Italy's leading shipbuilding hubs and is among the most significant naval groups in Europe (40). The Palermo shipyard holds tripartite production missions: ship construction, repair, and conversion (41). The workforce count at Palermo's shipbuilding industry varies over the years, making it challenging

to provide an exact number. Historically, Palermo has been a hub for industries, like shipbuilding and railways, known for their significant asbestos usage, a fact underscored by its ranking as the top Sicilian province for malignant mesothelioma cases (42).

*Data collection*

Data on asbestos-related diseases (ARDs) were extracted from an epidemiological registry that logs all diagnosed cases within the Province of Palermo. This registry, maintained by the 'Service of Prevention and Safety on Work Environment' of the Local Health Authority of Palermo, houses socio-demographic, occupational, and health-related information. The dataset encompasses data between January 2010 and December 2021, collected during occupational visits. The association between ARDs and occupational settings was categorized as "possible," "probable," or "highly probable," in line with the prevailing legal guidelines (43). In the following report, only either "probable" or "highly probable" cases were eventually included.

Analysts noted the following variables: Gender; Year of birth; Asbestos-related pathology type and its year of diagnosis; Age at diagnosis; Occupational exposure timeline (start-end years); Age at initial asbestos exposure;

Exposure duration; Average latency of disease onset; Company and job role; Smoking habits

For analytical purposes, the 'average latency of onset of the disease' signified the interval between initial asbestos exposure and ARD diagnosis. The "duration of exposure" represents the cumulative period a worker was involved in asbestos-associated tasks, either from their employment commencement to retirement or from the instigation of law 257/92. In data analysis, workers with asbestosis and pleural plaques, given their analogous pathogenesis and better prognosis, were grouped (44, 45). Conversely, mesotheliomas and lung cancer were treated as distinct categories.

*Statistical Analysis*

Data processing employed STATA® software. For every qualitative variable, both absolute and relative frequencies were determined. Quantitative variables, on the other hand, were reported as mean values ± standard deviation. The ANOVA test evaluated quantitative variables, while the chi-square test assessed frequencies. A p-value below 0.05 in a multinomial logistic regression model, using asbestosis-pleural plaques as a reference, denoted statistical significance for variables associated with asbestos-linked diseases.

## Results

This research undertook a systematic evaluation of data spanning over a decade from the province of Palermo.

Upon scrutinizing the 245 documented cases of asbestos-related diseases in Palermo and its surrounding province from 2010 to 2021, certain pronounced patterns emerge. The affected subjects had an average age of 72.5 years, underlining the late manifestation of these diseases, with a significant latency period averaging 49.3 years from the initial exposure (Table 1). This prolonged latency accentuates the insidious nature of asbestos-induced ailments. Most subjects started their exposure at a relatively young age, around 20.3 years, and the average duration of exposure was 30.1 years.

A remarkable 92.2% of these cases were affiliated with the shipbuilding sector, pointing to a potent locus of asbestos exposure, while only a minor 7.8% were associated with railways and other sectors. Alarmingly, a vast majority, 67.1%, reported not using any form of Personal Protective Equipment (PPE) during their occupational tenure, highlighting potential shortcomings in protective measures adopted in the past (Table 1).

The influence of personal habits, particularly smoking, revealed a trifurcated distribution: 7.7% active smokers, 46.5% non-smokers, and a significant 45.8% being ex-smokers. Respiratory complications further evidenced by 53.6% of the subject's reporting bronchitis. As for the specific asbestos-related diagnoses, Asbestosis and Pleural plaques were predominant at 66.6%. Mesothelioma cases accounted for 15.5%, lung cancer constituted 16.7%, and a small fraction (1.2%) remained undefined (Table 1).

Analyzing the univariable associations between various diagnoses of asbestos-related diseases and their demographic and occupational characteristics within the period from 2010 to 2021 in Palermo and its province, the following patterns can be discerned:

When comparing the average ages across three major diagnoses, individuals with Asbestosis or Pleural plaques, as illustrated in Table 2, were, on average, 72.7 years old (with a standard deviation of 5.8). This is slightly older than those diagnosed with Lung Cancer, who averaged 71.4 years (with a broader variability, SD: 8.5), but marginally younger than those with Mesothelioma, who had an average

Table 1 - Socio-demographic and occupational characteristics of the 245 cases of asbestos-related disease observed in Palermo and Province between 2010 and 2021.

| | n (%) |
|---|---|
| Age, average in years ± sd | 72.5 ± 6.6 |
| Latency, mean in years ± sd | 49.3 ± 8.1 |
| Exposure duration, average in years ± sd | 30.1 ± 7.6 |
| Age at start of exposure, mean in years ± sd | 20.3 ± 5.1 |
| Sector and production, n (%) | |
| - Shipbuilding | 226 (92.2) |
| - Railway and other sectors | 19 (7.8) |
| PPE use, n (%) | |
| - Yes | 79 (32.9) |
| - No | 161 (67.1) |
| Smoking habit, n (%) | |
| - Yes | 19 (7.7) |
| - No | 114 (46.5) |
| - Former smokers | 112 (45.8) |
| Bronchitis, n (%) | |
| - Yes | 127 (53.6) |
| - No | 110 (46.4) |
| Diagnosis, n (%) | |
| - Asbestosis/Pleural plaques | 163 (66.6) |
| - Mesothelioma | 38 (15.5) |
| - Lung Cancer | 41 (16.7) |
| - Not defined | 3 (1.2) |

age of 73.2 years (SD: 7.2). Yet, these age differences were not statistically significant, as evidenced by a p-value of 0.41 (Table 2).

The latency period, or the interval from exposure to the manifestation of the disease, presented a more pronounced divergence among the diagnoses. Those with Asbestosis or Pleural plaques had an average latency of 52.4 years, contrasting with Lung Cancer patients (47.5 years) and Mesothelioma patients (51.6 years). The differences here were statistically significant, with a p-value less than 0.001 (Table 2).

A similar trend was noticed in exposure duration: individuals with Asbestosis or Pleural plaques were exposed for an average of 30.9 years, which was relatively longer than Lung Cancer patients (29.3 years) and notably longer than Mesothelioma patients (26.9 years). Again, these differences were statistically significant, having a p-value less than 0.01 (Table 2).

The age at which individuals began their exposure to asbestos demonstrated minor variation, with Asbestosis/Pleural plaques patients starting at approximately 19.8 years, Lung Cancer patients at 22.3 years, and Mesothelioma patients at 20.5 years. However, these differences were not statistically significant (p-value: 0.28) (Table 2).

Smoking habits showcased distinct patterns. Only 4.3% of Asbestosis/Pleural plaques patients were active smokers, in contrast to a considerable 24.4% of Lung Cancer patients and 5.2% of Mesothelioma patients. This association was notably significant with a p-value less than 0.001 (Table 2).

The majority of the diagnosed individuals across all disease categories predominantly belonged to the shipbuilding sector. However, the proportion was highest for Asbestosis/Pleural plaques (95.7%), followed by Mesothelioma (89.5%), and then Lung Cancer (80.5%). This difference was statistically significant with a p-value less than 0.01 (Table 2).

Lastly, the utilization of Personal Protective Equipment (PPE) was not extensively adopted across the groups. Nonetheless, its use was most prevalent among the Asbestosis/Pleural plaques patients (37.3%), compared to Lung Cancer (26.3%) and Mesothelioma patients (23.7%). Still, this difference wasn't deemed statistically significant, with a p-value of 0.17 (Table 2).

Table 3 delineates the multivariable analysis

Table 2 - Univariable analysis between different diagnoses of asbestos-related diseases with demographic and occupational characteristics observed in Palermo and Province between 2010 and 2021.

| | Asbestosis/ Pleural plaques | Lung Cancer | Mesothelioma | p-value |
|---|---|---|---|---|
| Age, average in years (SD) | 72.7 ± 5.8 | 71.4 ± 8.5 | 73.2 ± 7.2 | 0.41 |
| Latency, average in years (SD) | 52.4 ± 6.6 | 47.5 ± 9.6 | 51.6 ± 7.4 | <0.001 |
| Exposure duration, average in years (SD) | 30.9 ± 6.4 | 29.3 ± 7.2 | 26.9 ± 11.8 | <0.01 |
| Age at start of exposure, average in years (SD) | 19.8 ± 4.3 | 22.3 ± 5.7 | 20.5 ± 6.7 | 0.28 |
| Tobacco smoking habit, n (%) | | | | |
| - Smoker | 7 (4.3) | 10 (24.4) | 2 (5.2) | <0.001 |
| - Non-smoker | 94 (57.7) | 2 (4.9) | 18 (47.4) | |
| - Former smoker | 62 (38) | 29 (70.7) | 18 (47.4) | |
| Sector and production, n (%) | | | | |
| - Shipbuilding | 156 (95.7) | 33 (80.5) | 34 (89.5) | <0.01 |
| - Other | 7 (4.3) | 8 (19.5) | 4 (10.5) | |
| PPE use, n (%) | | | | |
| - Yes | 60 (37.3) | 10 (26.3) | 9 (23.7) | 0.17 |
| - No | 101 (62.7) | 28 (73.7) | 29 (76.3) | |

examining the associations between sociodemographic and occupational parameters with distinct diagnoses of asbestos-related diseases, using Asbestosis/Pleural plaques as the reference category.

The adjusted hazard ratio (HR) for Mesothelioma and Lung Cancer, in relation to exposure duration, indicates a decrement in relative risk for both diseases compared to Asbestosis/Pleural plaques with each successive year of exposure. Specifically, for Mesothelioma, the HR stands at 0.933 (95% CI: 0.902-0.965), while for Lung Cancer, it is 0.939 (95% CI: 0.902-0.978).

Regarding smoking habits, active smokers exhibit a significantly elevated risk for Lung Cancer, with an HR of 64.520 (95% CI: 13,075-318,390). Their Mesothelioma risk yields an HR of 2.078, albeit with a wider CI of 0.418 to 10,319. Former smokers present an increased risk for Lung Cancer (HR: 20.917, 95% CI: 4,913-89,048), and for Mesothelioma, the HR is 1.857 (95% CI: 0.920-3.751).

Sectoral analysis reveals that individuals engaged in shipbuilding and repair manifest a diminished risk for both Mesothelioma and Lung Cancer. The HR for Mesothelioma in this sector is 0.448 (95% CI: 0.143-1.406), and for Lung Cancer, it is 0.371 (95% CI: 0.155-0.892).

Concerning PPE utilization, Mesothelioma risk among users is depicted by an HR of 1.009 (95% CI: 0.446-2.287). For Lung Cancer, the non-use of PPE slightly amplifies the risk, showcasing an HR of 1.220 (95% CI: 0.571-2.605).

## Discussion

Summary of main findings. The current study offers a follow-up perspective from a previous investigation conducted a decade earlier, which included a more limited cohort (46). Our retrospective study, a total of 245 cases of work-related claims for ARD were reported between 2010 and 2021, mostly from naval industry (92.2%), including 38 cases of MM (15.5%), and 41 cases of lung cancer (16.7%) with documented occupational exposure to asbestos, while the large majority of claims were associated with non-malignant disorders, that is pleural plaques and asbestos. Our analysis revealed a notably shorter latency period for the development of lung cancer compared to other asbestos-related diseases in the dataset, while the observed incidence of MM compared to asbestosis or pleural plaques aligns with recent findings in international literature (47). In multivariable analysis, when non-malignant disorders were assumed as the reference group, diagnoses of respiratory neoplasia were more frequently associated with smoking habit (HR 64.520, 95%CI

Table 3 - Multivariable analysis of sociodemographic and occupational variables associated with different diagnoses of asbestos-related diseases (reference group: non-malignant diseases, asbestosis/pleural plaques) (note: HR = hazard ratio; 95%CI = 95% confidence interval).

| Asbestosis/pleural plaques | Mesothelioma | | | Lung Cancer | | |
|---|---|---|---|---|---|---|
| | HR | 95%CI | | HR | 95%CI | |
| Exposure duration, average in years | **0.933** | **0.902** | **0.965** | **0.939** | **0.902** | **0.978** |
| Smoking habits | | | | | | |
| - no smoker | | | | 1.000 | | - |
| - smoker | 2.078 | 0.418 | 10,319 | **64.520** | **13.075** | **318.390** |
| - former smoker | 1.857 | 0.920 | 3.751 | **20.917** | **4.913** | **89.048** |
| Sector and production | | | | | | |
| - other | 1.000 | - | - | 1.000 | - | - |
| - shipbuilding and repair | 0.448 | 0.143 | 1.406 | **0.371** | **0.155** | **0.892** |
| PPE use | | | | | | |
| - yes | 1.009 | 0.446 | 2.287 | 1.000 | - | - |
| - no | 1.000 | - | - | 1.220 | 0.571 | 2.605 |

13.075 to 318.390 for current smokers; HR 20.917, 95%CI 4.913 to 89.048 for former smokers), while no substantial differences were identified for MM. Interestingly, the occurrence of claims for MM and non-malignant ARD in shipbuilding sector was similar (HR 0.448, 95%CI 0.143 to 1.406), while having worked in shipbuilding sector was less frequently reported in cases of respiratory neoplasia than in cases non non-malignant diseases (HR 0.371, 95%CI 0.155 to 0.892).

Interpretation and Generalizability. According to our results, shipbuilding, a cornerstone industry in the region and particularly in the province of Palermo, emerges as a potent nexus of exposure, thereby underscoring its critical role in occupational health concerns. The use of asbestos in shipbuilding was quite common (48-49), particularly from early 1930s to late 1970s, when naval and commercial shipyards did use hundreds of tons asbestos, to build and repair naval vessels for guaranteeing appropriate thermal insulation where needed (i.e. boliers, steam, and hot water pipes), fire protection, sound absorption etc (50, 51).

The high occurrence of ARS among workers from shipyards was similarly well documented, particularly in Italy. In 1979 and 2001, Puntoni et al. (52, 53) specifically inquired the mortality in workers employed at the shipyard of Genoa (Italy) employed or retired between 1960 and 1981 (last follow up in 1995), and their study reported an increased mortality for MM, but also for respiratory neoplasia (lung, larynx), and bladder cancer. In a more recent follow up the aforementioned studies, Merlo et al., reported on the mortality of 3,984 shipyard workers from the Genoa shipyard, including a total of 3,331 deaths (83.6%), with excess mortality for all cancers (Standardized Mortality Ratio [SMR] 1.27, 95%CI 1.20-1.34), pleural MM (SMR 5.75, 95%CI 4.69 to 6.97), cancers of the larynx (SMR 1.83, 95%CI 1.34 to 2.44) and of the lung (SMR 1.54, 95%CI 1.39 to 1.70) (54). Notably, Authors did report an increased occurrence deaths associated with non-malignant respiratory disorders of the lungs (SMR 1.27, 95%CI 1.14 to 1.41), and particularly asbestosis (SMR 22.77, 95%CI 15.25 to 32.70).

A similar study from the shipyard workers of Monfalcone (55) on 1,403 workers hired in 1950-1959 identified 35 diagnoses of MM between 1978 and 2012, with the highest percentage of cases occurring in people aged 14 to 19 years et the employment.

More recently, in a pool of 43 Italian asbestos cohorts, a total of 5,120 shipyard workers (99.6% of male gender) were documented (56), with a SMR 1.08, 95%CI 1.00 to 1.16 for the whole of sampled workers on all malignant neoplasm, and SMR 8.42, 95%CI 6.07 to 11.38 for pleural MM, SMR 1.18, 95%CI 1.03 to 1.34 for lung cancer. An increased mortality ratio was also associated with MM occurring in workers having performed ship furniture (SMR 8.26, 95%CI 3.78 to 15.69) and worked in dockyards (SMR 10.52, 95%CI 6.67 to 15.79), the latter also reporting increased SMR for cancers of the lungs (SMR 1.61, 95%CI 1.36 to 1.89).

The reasons for high occurrence of ARD and similarly increased mortality of shipyard workers can be explained not only through the likelihood

of potential exposures to asbestos fibers due to the occupational tasks, but also to the specific settings of these exposures. Shipbuilding tasks require the workers to work in enclosed settings, where very high levels of asbestos exposure could be reached (57, 58). Moreover, as recently pointed out by Vimercati et al (59), only in recent years reliable substitute materials have been made available. Finally, vibration during sailing could release asbestos fibers from all asbestos containing materials, particularly from engine rooms, with resulting exposures of all workers involved in the maintenance of naval vessels even after the discontinuation of asbestos in naval industry.

While some of the aforementioned results were not unexpected, our results shed light on the occurrence of asbestos-related diseases in Palermo and its province over the studied period and the intricate interplay between socio-demographic characteristics, occupational settings, and individual habits. Most notably, our results underscores the inappropriate usage of PPE. Consistent use or neglect of personal protective equipment, might have substantial implications on the exposure levels and consequent health risks (60). Still, it should be stressed that the effectiveness of PPE in preventing ARD is affected by several factors that we were unable to properly track down because of the limited information retrieved by parent registry of the 'Service of Prevention and Safety on Work Environment' of the Local Health Authority of Palermo. First, PPE are effective only if properly worn, and workers have to be accurately and preventively trained (61). Assigned protection factors for the revised respiratory protection standard. www.osha.gov/sites/default/files/publications/3352-APF-respirators.pdf). Second, PPE have to be properly worn and removed in specifically designed rooms in order to avoid the potential contamination of workers' clothes. Third, PPE and/or their filters have to be changed regularly, and PPE repaired and replaced regularly or their efficacy is rapidly lost (62). Finally, as the potentially assessed timeframe ranged across 50 years or more, it is important to stress the very same industrial and legal requirements for PPE radically changed over time (63). As a consequence, while the low rate of workers reporting their accurate use cannot be underscored in any way, their potential preventive role should be carefully asseed.

Furthermore, personal habits, especially tobacco smoking, appeared to amplify the risk profile for respiratory cancers, suggesting that individual behavioral choices can act synergistically with occupational exposures to influence health outcomes. Again, these results were not unexpected (64). On the one hand, there is a vast body of research highlighting a strong correlation between lung cancer cases in the general populace and both occupational and environmental asbestos exposure (65). Our data on tobacco consumption further emphasizes the compounded health risks of smoking in combination with asbestos exposure. Previous studies have shown that smoking significantly augments lung cancer risks among those exposed to asbestos (46, 64), and some researchers suggest that the cellular damage caused by tobacco can be exacerbated by asbestos fibers, leading to a heightened risk of malignancy (64), particularly among individuals predisposed to asbestosis or pleural plaques (54). These results are reasonably due to the synergism between asbestos exposure and tobacco smoke in lung cancer causation at a biological level, resulting in the epidemiological evidence of a multiplicative model for the interaction effects of asbestos and smoking on the lung cancer risk, with no requirement for asbestosis. This observation was particularly pronounced for individuals employed within the shipbuilding and repair sector, who exhibited a heightened likelihood of developing asbestosis or pleural plaques over lung cancer, but again similar results previously documented and explained by the specific settings of naval yards (66).

In other words, as we delve deeper into the dynamics of these diseases, the patterns observed underscore the multifaceted nature of asbestos-related health risks and the imperativeness of a comprehensive approach to understanding and mitigation. This is particularly true when acknowledging gender disparities in the occurrence of ARD. As clearly documented by INAIL and ReNaM reports (19, 37), and recently pointed out by Mangone et al. (23) in their comprehensive review of MM cases documented by ReNaM of Emilia Romagna, ARD predominantly affect males, likely mirror patterns of occupational exposures, with the average age at diagnosis consistently exceeding 70 years (66). The influence of asbestos on male workers has been historically significant due to male-dominated occupations, especially in construction and shipbuilding (66).

Limits and strengths. Despite its potential interest and significance not only from an Occupational Health, but by a broader Public Health point of view, our study is affected by several shortcomings and substantial limits that should be accurately addressed. First of all, this observational study was designed to scrutinize the incidence and dynamics of asbestos-related diseases, which, despite advancements in clinical practice,

continue to pose a significant public health challenge (47). Having been developed by the 'Service of Prevention and Safety on Work Environment', the service of the competent Local Health Authority of Palermo, the parent registry includes data that medical professionals are compulsorily required to share with Judicial Police bodies for Occupational Health and Safety when diagnosing diseases of either documented or alleged occupational etiology (67, 68). As a consequence, the present registry likely contains a more extensive set of data than corresponding estimates from pathology registries such as ReNaM (that only contains data on MM), but results are possibly inflated by inaccurate diagnoses from sentinel professional. However, it should be stressed that all cases were accurately reviewed by trained and highly skilled personnel, and only "probable" or "highly probable" cases were eventually included. Second, the present study was designed and performed as a single-center study. Despite its valuable insights, a multi-centric approach involving multiple regions or countries might offer a more comprehensive perspective on the global dynamics of asbestos-related diseases, offering a broader understanding of variations in incidence and practice (60), overcoming another noteworthy limitation of this investigation, that is its restricted sample size and the lack of a control group of healthy workers with similar asbestos exposure. Such a comparison would've enriched our understanding of the relative risks. Third, our report is affected by some significant gaps in the gathered data, and most notably the lack of analyses on non-occupational exposures and risk factors, including genetic ones, that could predispose individuals to asbestos-related malignancies, independent of any defined exposure threshold (69). Fourth, as previously stressed, we only dichotomously assessed the usage of PPE (ever vs. never): similar studies on the awareness and training about asbestos hazards in the Italian construction sector (60) have stressed that some degree of "fatigue" may affect actual usage of PPE, even among individuals used to employ these devices properly and accurately, while recall bias may have substantially affected the eventual estimates.

## Conclusions

Our study underscores the enduring public health challenge posed by asbestos-related diseases in Italy, even after its prohibition in 1992. The persistent emergence of these diseases is attributed to the extensive latency between exposure and onset of asbestos-related diseases (ARDs). Notwithstanding the limitations inherent in this research, the findings have potential implications for the Italian estimation of ARD incidences. As advocated by international entities and governing bodies, the pivotal role of epidemiological surveillance in addressing ARDs cannot be overstated. Such surveillance stands as a beacon guiding concerted efforts aimed at the eventual eradication of these diseases. The overarching objective in public health should pivot towards refining prevention strategies, bolstering care provisions - encompassing psychological assistance, and augmenting the compilation of detailed anamnestic and occupational data. This would include specifics on job roles, average duration of exposure, adherence to personal protective equipment, and smoking tendencies. Such comprehensive data collection is imperative for accurately gauging the true prevalence of these diseases, particularly among those with occupational exposures.

**Supplementary Materials:** None
**Funding:** This research received no external funding
**Institutional Review Board Statement:** The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of University of Palermo in the 7 session of 2014 (22nd of October 2014)
**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study for data collection and analysis in anonymous form, by the Occupational Health Department of the Palermo Local Health Authority.
**Declaration of Interest:** The authors declare no conflict of interest with contents of the pre-sent work.

### Riassunto

***Valutazione dell'impatto di Salute delle patologie asbesto correlate in una coorte di lavoratori esposti professionalmente: un approfondimento decennale***

**Introduzione.** L'amianto è uno dei principali agenti cancerogeni professionali a livello globale. Nonostante il divieto previsto dalla legge 257/1992, l'Italia è una delle nazioni europee più gravate dal carico di malattie legate all'amianto (ARD). Il presente studio ha analizzato i casi di ARD nei lavoratori esposti all'amianto della provincia di Palermo, in Italia, nel periodo 2010-2021.

**Materiali e metodi.** L'acquisizione dei dati è stata effettuata durante l'attività di vigilanza del 'Servizio di Prevenzione e Sicurezza negli Ambienti di Lavoro' del Dipartimento di Prevenzione dell'Azienda Sanitaria Provinciale (ASP) di Palermo.

**Risultati.** Tra il 2010 e il 2021, abbiamo identificato 245 casi di ARD, comprendenti 163 casi di placche pleuriche, 41 tumori polmonari, 38 mesoteliomi e 3 casi di natura non specificata.

All'analisi multivariata il range temporale di insorgenza di mesotelioma (HR = 0,933; IC 95% = 0,902-0,965) e cancro polmonare (HR = 0,93; IC 95% = 0,90-0,978), rispetto alle placche pleuriche / asbestosi, è significativamente inferiore. L'abitudine tabagica è risultata significativamente associata con i casi d cancro al polmone (fumatore HR = 64.520 95% CI = 13.075-318.390; ex fumatore HR = 20.917 95% CI = 4.913-89.048). Infine si è osservata una correlazione statisticamente significativa tra i casi di mesotelioma e placche pleuriche/asbestosi nei soggetti impiegati nella cantieristica navale (HR = 0,371 IC 95% = 0,155-0,892).

**Conclusioni.** Nonostante la cessazione delle attività legate all'amianto nel 1992, le diagnosi di ARD persistono nelle osservazioni cliniche e della sorveglianza sanitaria degli ex lavoratori esposti, continuando a rappresentare una sfida per la Sanità Pubblica e la Medicina del Lavoro. L'attuazione di strategie di prevenzione e di diagnosi precoce nelle coorti professionalmente esposte, attraverso una adeguata raccolta di dati anamnestici e di esposizione, appare fondamentale per ancora diversi anni.

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Ann Ig. 2024 Sep-Oct; 36(5): 537-548 doi: 10.7416/ai.2024.2618. Epub 2024 Mar 7.

# Screening for colorectal cancer by full colonoscopy in first-degree relatives of colorectal cancer patients: a multicentric study by the Italian League for the Fight against Cancer

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*Keywords: Colorectal cancer; cancer screening; secondary prevention; colonoscopy; familial cancer*
*Parole chiave: Cancro del colon-retto; screening del cancro; prevenzione secondaria; colonscopia; cancro familiare*

**Abstract**

***Background.*** *Colorectal cancer currently presents the third-highest incidence of cancers worldwide, making secondary prevention through screening programs for colorectal cancer, usually by Fecal Occult Blood Testing, an essential preventive medicine intervention. First-degree relatives of colorectal cancer patients are a particularly at-risk group, with indications to consider direct screening by full colonoscopy. Colonoscopy is considered the gold standard for diagnosing colorectal cancer, as it has high sensitivity and specificity, and is both a diagnostic and therapeutic tool. However, it requires significant organizational and financial resources, and has a small but relatively higher risk of complications as opposed to fecal occult blood testing. The present study aimed to assess the appropriateness of a screening program without age restrictions of CRC by full colonoscopy in asymptomatic, first-degree adult relatives of patients with colorectal cancer, aiming both to actively increase screening coverage and to determine the detection rate of precancerous lesions and colorectal cancer in this population.*

***Study Design.*** *Uncontrolled interventional study – colorectal cancer screening by full colonoscopy for at-risk population.*

***Methods.*** *The Italian League for the Fight against Cancer started a colorectal cancer screening program by full colonoscopy for first-degree relatives of colorectal cancer patients in 1998 in the province of Latina, Lazio Region, Italy. The program was expanded to the provinces of Rieti, Lazio Region, and Sassari, Sardinia Region, in 2014 and 2016 respectively, and was concluded in 2018.*

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Annali di Igiene : Medicina Preventiva e di Comunità (Ann Ig)
ISSN 1120-9135 https://www.annali-igiene.it

*Subjects were actively and voluntarily recruited by the study's working group. Subjects that had already been subjected to a full colonoscopy in the preceding 5 years were excluded from this study. Identified neoplastic lesions were treated either directly or referred to the Day Hospital setting, and histologically diagnosed following World Health Organization guidelines.*

***Results.*** *In total, 2,288 subjects (age range 15-88, mean 52.3 yrs, M/F = 946/1,204) were screened by colonoscopy, of which 103 (4.5%) were incomplete and 2,173 (95.0%) complete, with data on colonoscopy performance missing for 12 participants. Out of 468 positive outcomes on colonoscopy, diagnosis for 422 (204M/173F), 19.4% of total subjects, was adenomatous polyps and 46 (20M/20F), 2.1% of total subjects, was colorectal cancer. Female sex was a protective factor against a positive test outcome, with a 35% reduction compared to male sex, with OR=0.64 95%CI (0.52-0.80). On the other hand, being over 50 years of age was found to be a risk factor, making a positive outcome more than twice as likely, with OR=2.3 95%CI (1.8-2.9). Subjects over 50 also had significantly more instances of multiple adenomas being found, however the size distribution of found adenomas was not significantly different between subjects under and over 50, despite size being a predictor of risk of neoplastic progression.*

***Conclusions.*** *Given the high detection rate of precancerous lesions and colorectal cancer in the studied population, it is our opinion that guidelines should continue to recommend earlier and more frequent screening in first-degree relatives of patients with colorectal cancer, and, barring the introduction of more cost-effective and/or lower risk procedures with a similar efficacy profile, maintain the use of colonoscopy as the main screening option.*

## Introduction

Colorectal cancer (CRC) currently presents the third-highest incidence (10% of diagnosed cases) and second highest mortality (9.4% of cancer deaths) of cancers worldwide, as evidenced by the WHO's GLOBOCAN 2020 estimates (1).

In 2020, it represented one of the top five most frequently diagnosed cancers in Italy, with 12% of all cancers diagnosed among men and 11.2% of all diagnosed among women (2).

The data from the Cancer Registry of the province of Latina (part of the Lazio Region in central Italy, with a population of 563 thousand residents in 2018) referring to 2018, follows the national trend: among men, colorectal cancer represents 13.9% of all diagnosed cancers, and among women 12.2% (3).

From 2008 to 2016, the incidence rate of many cancers decreased significantly in both sexes and all age groups. Colorectal cancer was one of these, decreasing 3.0% on average per year in men and women between 50 and 69 years of age (the age group subjected to population screening). The latest available Italian national data for colorectal cancer shows a slight decrease compared to 2015, but it nonetheless remains a cancer with high incidence in both sexes (4, 5). Despite being one of the main cancers diagnosed in the population, the incidence of CRC in Italy has thus been declining in recent years, a fact that can also be attributed to ongoing national efforts at secondary prevention (6).

Secondary prevention, or the early detection and treatment of precancerous lesions and early-stage cancer, has been shown to significantly reduce the incidence and mortality of colorectal cancer. The pioneering work in this field was published in the late 60s and 70s (7) showing remarkable results that were nonetheless hampered by significant limitations in study design and the use of sigmoidoscopy, a procedure that had a small but significant risk of complications. In 1967 however, Greegor introduced the first fecal occult blood test (FOBT) (8), based on a guaiac card test that could be self-administered at home. Promising results and the introduction of a practically risk-free testing device did not however eliminate the risk for biases in these studies, and it wasn't until 1996 that properly designed RCTs confirmed these promising preliminary outcomes (9-11). In this context, various public healthcare providers started their own screening programs by FOBTs at the regional and local level in Italy (12-14), confirming these results and paving the way for the introduction of a unified national cancer screening program in 2004 (15).

It should however be noted that, despite the well-established effectiveness of CRC screening and its importance in preventative healthcare, to the point that it is a core performance indicator of the regional public healthcare systems in Italy (16), significant gaps remain in reaching satisfactory levels of screened population. The Italian National Screening Observatory (ONS) reports that in 2019, out of the general population invited to FOBT screening (ages 50-69 in most regions, despite national guidelines aiming for ages 50-74), only 41.6% responded. Of these, only 45% of subjects with a positive outcome on FOBT underwent colonoscopy within 30 days from

the outcome, the Italian Colorectal Screening Group (GISCOR) acceptable standard being >90%. Even more worryingly, more than 20% of subjects with a positive outcome nonetheless refused to undergo colonoscopy entirely. The most recent ONS report, for 2020, paints an even more dire picture due to significant difficulties and reductions in screening volumes during the COVID-19 pandemic (17).

On a wider perspective, the latest OECD report showed that Italy maintained a higher than OECD average percentage of people aged 50-74 years who had fecal occult blood test at least once in their life by 2014, with 49.1% compared to the OECD's average 40.4%. While this is better than the OECD average, it should also be noted that Germany reached a percentage of 81.0% in the same survey (18).

While there has been a successful effort to improve and expand both screening programs and treatment options, the risk of developing CRC remains high in certain populations, including first-degree relatives of patients with CRC (19). These individuals have a two to four-fold increased risk of developing the disease compared to the general population, depending on both the number and age of affected relatives (20-22). A recent study also suggests that even first-degree relatives of patients with CRC precursor lesions (colorectal polyps) present an increased risk of CRC, evidencing both the importance of screening programs and the particular risk profile of this population (23). The Italian cancer screening program maintains a provision for the application of full colonoscopy as a direct form of secondary prevention and eventual treatment of at-risk populations, as full colonoscopy is a highly sensitive screening method for the detection of colorectal cancer and precancerous lesions. However, this provision remains limited by age restrictions. While CRC screening is currently the most effective means of reducing both the mortality and incidence of this malignancy, screening modes for first-degree relatives of patients with CRC are more nuanced than the simple application of the FOBT, and depend on a number of factors including age of the affected patient, age of the screened relative and possible genetic mutations (24). However, the cost and risk effectiveness of using full colonoscopy as a direct screening and secondary prevention strategy is still a matter of ongoing debate (25, 26).

Within this wider context, starting in 1998 the LILT ("Lega Italiana per la Lotta contro i Tumori", Italian League for the Fight against Cancer) started a colorectal cancer screening program by full colonoscopy for first-degree relatives of patients with colorectal cancer (CRC) in the province of Latina, Lazio Region, which ran successfully thanks to external funding and the work of LILT volunteers and was expanded to the provinces of Rieti, Lazio Region, and Sassari, Sardinia Region, in 2014 and 2016 respectively. The screening program had to be interrupted in 2018, due to a lack of sufficient further funding. Colonoscopy was chosen as the screening tool as it is considered the gold standard for diagnosing CRC, with high sensitivity and specificity, and is both a diagnostic and therapeutic tool. However, it requires significant organizational and financial resources, and has a small but relatively higher risk of complications as opposed to FOBTs, which, while it can be used as a direct screening tool (27-29), makes it preferable as a second line diagnosis and treatment approach following positive FOBT results in general population screening (30).

The present study aimed to assess the appropriateness of a screening program without age restrictions of CRC by full colonoscopy in asymptomatic, first-degree adult relatives of patients with colorectal cancer, with preliminary results published in 2008 (31). Specifically, we aimed both to actively increase the screening coverage and to determine the detection rate of precancerous lesions and colorectal cancer by full colonoscopy screening in this population, to contribute to the growing body of evidence to better determine the optimal approach to CRC prevention in this at-risk population.

## Materials and methods

The participating centers of this program were the Latina operational center with 2,078 subjects (91.3%), the Rieti center with 137 subjects (6%) and the Sassari center with 62 subjects (2.7%).

Approval for the study was granted by the LILT Latina ethics committee both in 1998 for the start of the study and, subsequently, in 2009 to expand the study to the Rieti and Sassari centers. The study actively recruited first-degree, adult relatives of patients affected by CRC who were directly contacted by members of the working team (oncologist, endoscopist, pathologist, nurses and volunteers). These relatives were informed about their increased risk profile and counselled on the possible steps they could undertake to mitigate it, including colonoscopy. Written informed consent forms to the procedure, and to the gathering of relevant patient data to study and evaluate the secondary prevention program,

were obtained after consulting with a working team physician. Subjects that had already been subjected to a full colonoscopy in the preceding 5 years were excluded from this study.

Endoscopy was always performed by two operators (endoscopist physician and specialized nurse) and in conscious sedation in the majority of cases, with some subjects requesting deep sedation. As it is standard, patients prepared for the procedure with a specific diet in the 3 days preceding it, followed by the ingestion of 4lt of a polyethylene glycol (PEG) solution in the preceding 24 hours. During the procedure, in the absence of contraindications to biopsy, endoscopic polypectomies were performed on any polyps not exceeding 1cm in size. For larger polyps, polypectomy was deferred to the *Day Hospital* setting, following additional controls for blood count and coagulation indexes (PT, PTT, INR). For voluminous lesions with a suspicion of malignancy, and/or frankly heteroplastic formations, no less than 5 biopsies were performed per lesion.

Biopsied material was fixed with 10% neutral buffered formalin solution, macroscopically described, sectioned where deemed necessary, included in paraffin and histologically diagnosed following WHO guidelines.

Quantitative data were summarized by descriptive statistics (mean, standard deviation, median, interquartilic range); categorical data were summarized by counts and percentages. To assess differences or associations between subgroups we perform chi square test (or Fisher exact test when appropriate) for categorical data; t-test was used to compare quantitative data. We performed a logistic regression, the dependent variable is the outcome (positive/negative), to determine the independent

Table 1 - Population Characteristics

**Population Characteristics (N = 2288)**

| Variables | Category | Frequency | Percent | Valid Percent | Cumulative Percent |
|---|---|---|---|---|---|
| Sex | Male | 946 | 41.3% | 44.0% | 44% |
| | Female | 1204 | 52.6% | 56.0% | 100% |
| | Missing | 138 | 6.0% | / | / |
| Age (years) | ≤49 | 984 | 43.0% | 43.1% | 43.1% |
| | ≥50 | 1297 | 56.7% | 56.9% | 100.0% |
| | Missing | 7 | 0.3% | / | / |
| Participating Center | Latina | 2089 | 91.3% | 91.3% | 91.3% |
| | Rieti | 137 | 6.0% | 6.0% | 97.3% |
| | Sassari | 62 | 2.7% | 2.7% | 100.0% |
| Colonoscopic Examination | Complete | 2173 | 95.0% | 95.5% | 95.5% |
| | Incomplete | 103 | 4.5% | 4.5% | 100.0% |
| | Missing | 12 | 0.5% | / | / |
| Diagnostic outcome | Negative | 1729 | 75.6% | 78.5% | 78.5% |
| | Adenomatous polyp | 428 | 18.7% | 19.4% | 97.9% |
| | CRC | 46 | 2.0% | 2.1% | 100.0% |
| | Missing | 85 | 3.7% | / | / |
| Distribution of adenomatous polyps by max. size (N = 428) | ≤5 mm | 192 | 44.9% | 52.0% | 52.0% |
| | 6-9 mm | 46 | 10.7% | 12.5% | 64.5% |
| | 10-19 mm | 50 | 11.7% | 13.6% | 78.0% |
| | 20-29 mm | 37 | 8.6% | 10.0% | 88.1% |
| | >30 mm | 44 | 10.3% | 11.9% | 100.0% |
| | Missing | 59 | 13.8% | / | / |
| Presence of multiple adenomatous polyps (N = 428) | No | 326 | 76.2% | 76.2% | 76.2% |
| | Yes | 102 | 23.8% | 23.8% | 100.0% |

predictors, we calcolate the Odds ratio with the 95% confidence interval.

Statistical significance was set at $p < 0.05$. Statistical analysis was performed using the Statistical Package for the Social Sciences (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp).

## Results

In total, 2,288 subjects were screened by colonoscopy, with the population characteristics summarized in table 1. A time distribution of subjects screened by year, is shown in Fig.1.

Performed colonoscopies were recorded as incomplete for 103 participants (4.5%) and complete (cecal intubation) for 2,173 (95.0%), with data on colonoscopy performance missing for 12 participants.

Looking at outcomes by sex (Tab. 2), we note that the screened participants for whom this variable was recorded (N = 2,150), included 946 males (44%) and 1,204 females (56%), with a mean age of 51.9±12.5 (median 51.9, IQR 43-61, range 19-88) and 52.4±12.4 (median 52, IQR 43-61, range 15-88) years, respectively. No significant statistical difference was found between age and sex.

However, a significant difference ($p<0.001$) was found in the bivariate analysis between sex and outcome: males shared a higher percent of the positive outcomes (53.3%) than femalesw (46.7%) on screening. No significant differences linked to sex were found between those who had complete or incomplete exams.

Going into an analysis of positive outcomes, separating them between the finding of polyps of variable degrees of dysplasia and the confirmed diagnosis of carcinoma, a more complete picture came in, evidencing how the difference in outcomes by sex is mostly driven by the higher percent of positive finding of polyps in males (54.1%) as opposed to females (45.9%) (Fig. 2). While the positive finding of carcinoma was evenly split by sex, it should still be noted that as a percentage of the screened population this represented a slightly higher percent incidence between the male (2.15%) and female (1.75%) population.

An analysis of the distribution of adenomatous polyps by maximum recorded size, and of the presence of single or multiple polyps, showed no significant statistical difference linked to sex.

It must be considered that individuals aged 50 to 69 in the general population are already covered by recommended screenings, while those aged 20 to 49 only have a generic recommendation to undergo checks (always within the context of familiarity). To

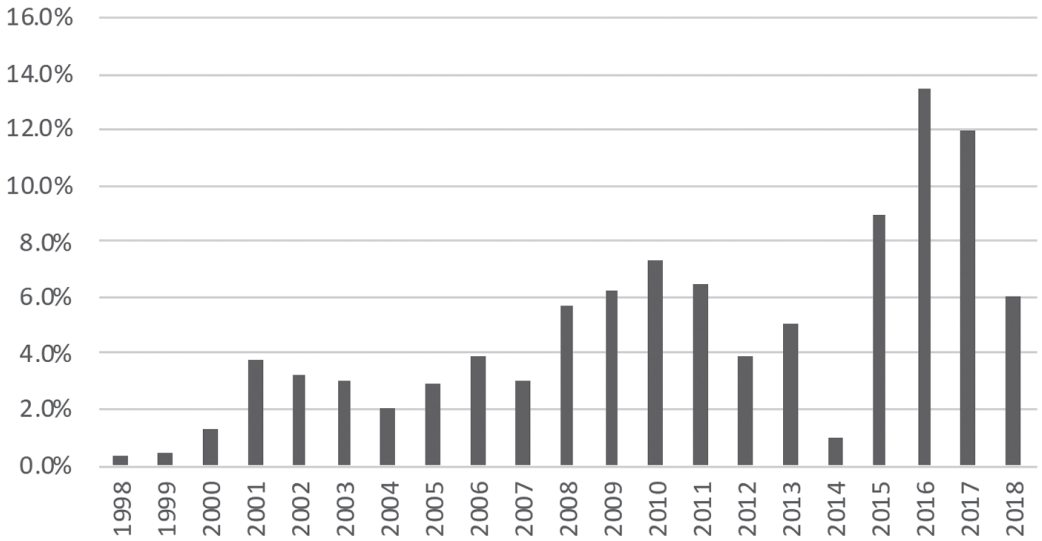


Figure 1 - Time distribution of subjects screened by colonoscopy, by percent of total

Table 2 – Age and outcomes by sex, p-values calculated by (a) t-test and (b) Pearson's chi-squared test

**Age and outcomes by sex (N = 2150)**

| Variables | | Male (N = 946) | | Female (N = 1204) | | p-value |
|---|---|---|---|---|---|---|
| Age expressed as mean ± SD, median, IQR, range) | | 51.93 ± 12.46, 51.92, 43-61, 19-85 | | 52.37 ± 12.38, 52.00, 43-61, 15-88 | | 0.413[a] |
| | **Category** | **Frequency** | **Valid Percent** | **Frequency** | **Valid Percent** | |
| Diagnostic outcome | Negative | 698 | 75.4% | 947 | 83.0% | <0.001[b] |
| | Adenomatous polyp | 208 | 22.5% | 174 | 15.2% | |
| | CRC | 20 | 2.2% | 20 | 1.8% | |
| | Missing | 20 | / | 63 | / | / |
| Distribution of adenomatous polyps by max. size (N = 382) | ≤5 mm | 94 | 48.5% | 72 | 49.0% | 0.591[b] |
| | 6-9 mm | 27 | 13.9% | 18 | 12.2% | |
| | 10-19 mm | 28 | 14.4% | 21 | 14.3% | |
| | 20-29 mm | 17 | 8.8% | 20 | 13.6% | |
| | >30 mm | 28 | 14.4% | 16 | 10.9% | |
| | Missing | 14 | / | 27 | / | / |
| Presence of multiple adenomatous polyps (N = 382) | No | 157 | 75.5% | 141 | 81.0% | 0.192[b] |
| | Yes | 51 | 24.5% | 33 | 19.0% | |

this end, the ages were divided according to two large classes, ≤49 years and ≥50 years (Tab. 3). As could be expected by the generally higher incidence of cancers and pre-cancerous lesions with increasing age, a statistically significant difference can be found with respect to the two age groups ($p<0.001$), with positive outcome values respectively equal to 14.3% and 27.5%. This is evidenced for all outcomes in Fig. 3. While we also see a statistically significant difference in the presence of multiple adenomatous lesions between the two groups ($p<0.001$), no significant difference in the distribution of the maximum recorded size of pre-cancerous lesions was found.

Further subdividing these age groups by sex reflects the above identified trends very clearly, giving us a more complete picture (Fig.4).

The results of the logistic regression, considering the outcome (positive/negative) as the dependent variable, showed that female sex was a protective factor against a positive test outcome, with a 35% reduction compared to male sex, with OR=0.64 95%CI (0.52-0.80). On the other hand, being over 50 years of age was found to be a risk factor, making a positive outcome more than twice as likely, with OR=2.30 95%CI (1.82-2.90).

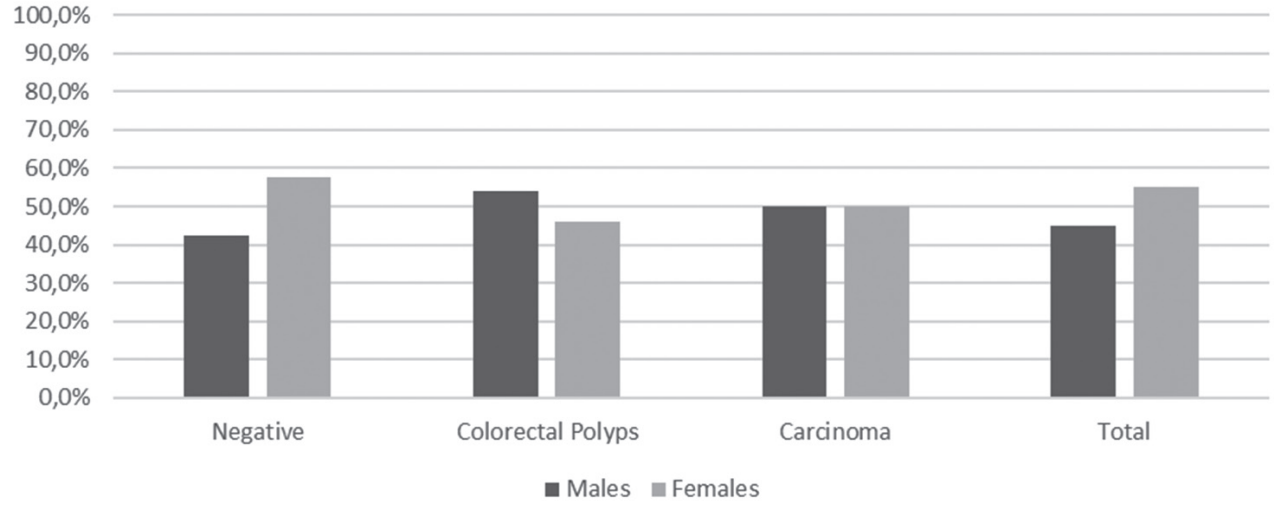


Figure 2 - Percent of outcomes by sex

Table 3 - Performed colonoscopies by age and outcome, p-values calculated by Pearson's chi-squared test

**Outcomes by age (N = 2281)**

| Variables | | Age (years) ≤ 49 (N = 984) | | Age (years) ≥ 50 (N = 1297) | | |
|---|---|---|---|---|---|---|
| | Category | Frequency | Valid Percent | Frequency | Valid Percent | p-value |
| Diagnostic outcome | Negative | 806 | 84.7% | 918 | 73.7% | <0.001 |
| | Adenomatous polyp | 134 | 14.1% | 293 | 23.5% | |
| | CRC | 12 | 1.3% | 34 | 2.7% | |
| | Missing | 32 | / | 52 | / | / |
| Distribution of adenomatous polyps by max. size (N = 427) | ≤5 mm | 68 | 59.1% | 124 | 49.0% | 0.290 |
| | 6-9 mm | 15 | 13.0% | 31 | 12.3% | |
| | 10-19 mm | 14 | 12.2% | 36 | 14.2% | |
| | 20-29 mm | 7 | 6.1% | 29 | 11.5% | |
| | >30 mm | 11 | 9.6% | 33 | 13.0% | |
| | Missing | 19 | / | 40 | / | / |
| Presence of multiple adenomatous polyps (N = 427) | No | 117 | 87.3% | 209 | 71.3% | <0.001 |
| | Yes | 17 | 12.7% | 84 | 28.7% | |

## Discussion and conclusions

Our cecal intubation rate (CIR) of 95,5% was in line with similar studies using conscious sedation (32, 33) and higher than a number of other studies that had made more limited use of sedation, which reached a CIR of 82-85% (34, 35). No serious adverse events (e.g. perforation, bleeding) were recorded, a testament to the expertise of the operators involved, as the procedure does still carry a small risk of complications, with 0.4 to 0.6 perforations and 0.2 to 6.8 bleeding events per 1000 colonoscopies registered in other studies (36-38).

In our study, 19.4% of first-degree relatives of CRC patients who underwent colonoscopy were positive for adenomatous polyps and 2.1% were positive for carcinoma. Of those over 50 years of age, 23.5% were positive for adenomatous polyps and 2.7% were positive for carcinoma, while our screened population below the age of 50 presented an incidence of adenomatous polyps of 14.1% and of CRC of 1.3%. These figures are similar to those in other studies (34, 39-43), though there is a range of results and classification approaches to adenomatous lesions may vary. It should be noted that our screened population below the age of 50 showed a significantly lower incidence of positive outcomes compared to the population over 50 in the same study. This was evident both in the number of positive diagnostic outcomes (adenomas and CRC) and multiple adenomas found. It should be noted, however, that the size distribution of found adenomas was not significantly different between subjects under and over 50, despite size being a predictor of risk of neoplastic progression. While the lower age may explain the lower incidence of lesions and CRC, among other factors simply due to a reduced time for precancerous lesions to develop into cancer, we wish to stress that it is well established that first-degree relatives have a higher risk than the general population of developing CRC, both in absolute terms over their lifetime and in those subjects under 50 (22, 43).

Our findings evidence the increased risk for males and for subjects above 50 in our studied population, a trend that is in line both with those seen in similar studies on first-degree relatives and in the general population (22, 24).

The study presents a number of limitations that should be taken into consideration. Unfortunately, we are not able to calculate the exact adhesion rate to the screening program of the population at risk, as we do not know the exact number of all first-degree relatives of each index-colon cancer patient. The study does not contain a control group, even if we had paired the at-risk population over 50 with general population controls in the same age group undergoing screening colonoscopies, it would not have been possible to do the same with our at risk population below the age of 50, a problem arising from the study being designed as a screening program without age restrictions for at-risk adults. Healthy controls with no indication for colonoscopy could not be included due to ethical reasons linked to the risk of complications associated with the procedure. While we did find that the size

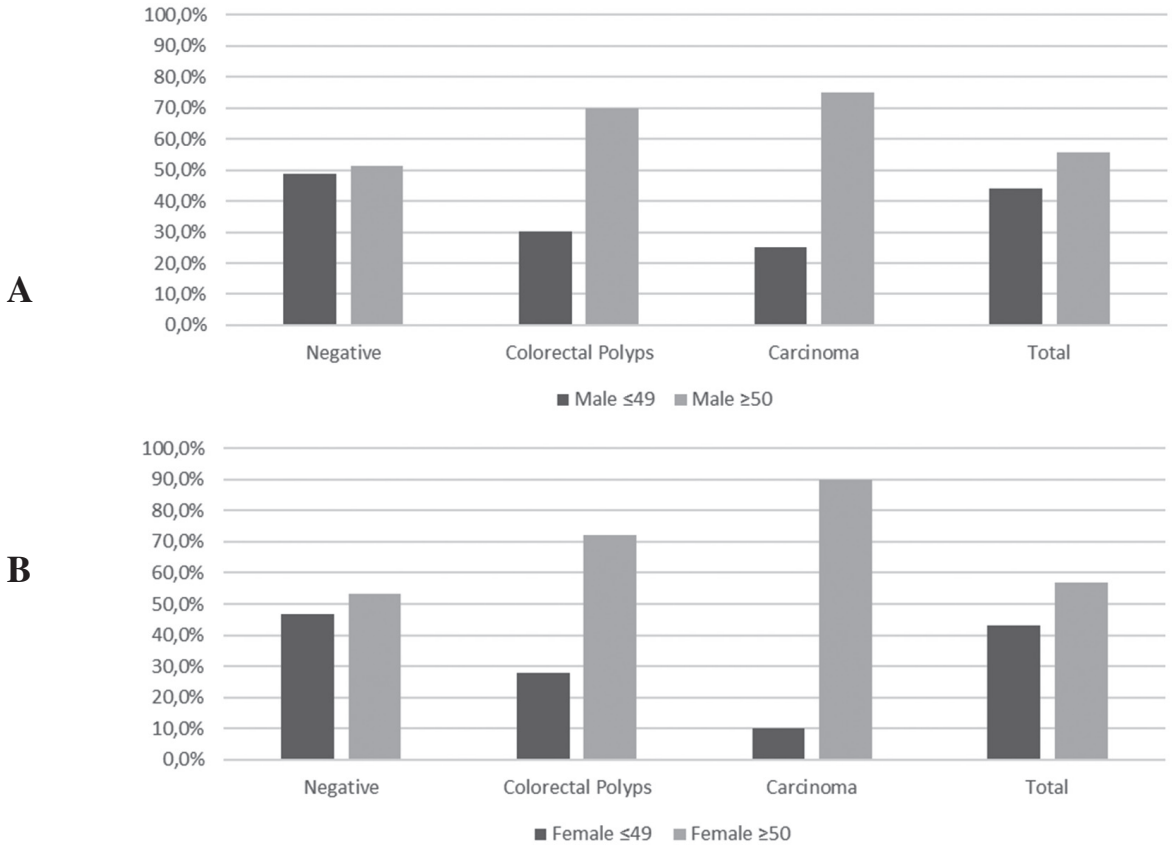


Figure 4 - Percent of outcomes by age and sex. A: male; B: Female

distribution of adenomas found in our population was not significantly different for both age and sex, we do not have comprehensive histological data at our disposal to further evaluate the risk profile of these adenomas beyond their size.

On the subject of the wider context of screening for CRC within which our study is situated, we note that the Italian National Screening Observatory (ONS) data for the 2014-2020 period, relating to the screening of the general Italian population, shows a similar percentage of adenomatous polyps and carcinomas (17.8% and 2.9% of total performed colonoscopies, respectively) identified in subjects over 50 who underwent colonoscopy, after having already resulted positive by FOBT (17). An italian study evaluating the prevalence of familial risk in subjects that resulted positive to FOBT screening in the general population, evidenced a prevalence of 12% of first-degree relatives of CRC patients, while confirming the increased risk for pathologically significant lesions in these subjects (44). This hints to an important issue of outreach in screening this

Table 4 - Logistic Regression Results

| Variables | Sign. | Exp(B) | 95% C.I. for EXP(B) | |
|---|---|---|---|---|
| | | | Inferior | Superior |
| Sex | 0.000 | 0.644 | 0.518 | 0.799 |
| Age (years, ≤ 49 or ≥ 50) | 0.000 | 2.296 | 1.820 | 2.896 |

at-risk population, as they should access screening sooner than the general population and there is no need to risk a possible false negative on FOBT testing when colonoscopy is an available and appropriate screening option. We note that our studied population presented a similar incidence of lesions found on direct colonoscopic screening to those found in the general population that had already resulted positive to FOBT. This is not meant as a direct comparison between these methodologies but aims to underline the importance of outreach and colonoscopic screening in first-degree relatives of CRC patients. A significant part of our screening program was represented by the active outreach to relatives of CRC patients and the work of LILT volunteers, who allowed us to provide a valuable service to our screened population but also inevitably meant the program had to eventually conclude in 2018.

Despite the clear scientific consensus on screening, significant work remains to be done to reach more widespread adoption and overcome barriers to screening access. This also underlines the importance of programs such as the one presented in this study, as active outreach to more at-risk populations becomes even more important in a context where general population screening is still not as widespread as one could expect (45). This matter has become even more pressing in the aftermath of the COVID-19 pandemic, as cancer screening programs have been significantly affected both internationally (46, 47) and in Italy (48, 49). Screening is a time-sensitive medical intervention, and delays and backlogs created by the pandemic could result in several late diagnosed cases, making it imperative that screening programs receive the resources to not only continue as before but also make up for what was lost. It will be particularly necessary to monitor even more closely the cases most at risk to develop a cancer, such as the at-risk population presented here.

Our findings provide further evidence for the appropriateness of full colonoscopy as a secondary prevention strategy in first-degree relatives of patients with colorectal cancer, and evidence the need for targeted and active management of this at-risk population. The high detection rate of precancerous lesions and colorectal cancer in this population underscores the importance of regular screening by full colonoscopy. Given the high risk of developing colorectal cancer in this population, it is our opinion that guidelines should continue to recommend earlier and more frequent screening in first-degree relatives of patients with colorectal cancer, and, barring the introduction of more cost-effective and/or lower risk procedures with a similar effectiveness profile, maintain the use of colonoscopy as the main screening option.

**Funding and Competing Interests**
This study was supported by the Rotary Club Latina, Rotary Club Rieti and Rotary
Club Sassari, with the patronage of District 2080 Rotary (LAZIO - SARDEGNA).
The authors declare no conflicts of interest.
**Acknowledgements**
We thank Dr. Lucrezia Mosillo and Dr. Marta Mosillo for their support and putting the LILT Latina operative spaces at our disposal. We also thank Dr. Marina Bellia for her work and oversight as President of the LILT Latina ethics committee.

## Riassunto

### *Screening colonscopico del cancro del colon-retto in parenti di primo grado di pazienti affetti da cancro del colon-retto: uno studio multicentrico della Lega Italiana per la Lotta contro i Tumori*

**Premesse.** Il cancro del colon-retto è attualmente il cancro con la terza più alta incidenza a livello mondiale, e i programmi di screening, solitamente effettuati tramite esame del sangue occulto nelle feci, rappresentano un intervento di medicina preventiva essenziale per contrastarlo. I parenti di primo grado di pazienti affetti da cancro del colon-retto sono un gruppo particolarmente a rischio, con indicazione di considerare direttamente lo screening in colonscopia. La colonscopia è considerata il gold standard per la diagnosi di cancro del colon-retto, ha alta sensibilità e specificità, ed è un mezzo sia diagnostico che terapeutico. Come mezzo di screening richiede però importanti risorse organizzative e finanziarie, ed ha un piccolo ma relativamente maggiore rischio di complicanze rispetto al test sangue occulto nelle feci. Il presente studio mirava a valutare l'appropriatezza di un programma di screening senza restrizioni di età per il cancro del colon-retto tramite colonscopia completa in adulti parenti di primo grado asintomatici di pazienti con cancro del colon-retto, con l'obiettivo sia di aumentare attivamente la copertura dello screening sia di determinare il tasso di individuazione di lesioni precancerose e di cancro del colon-retto in questa popolazione.

**Disegno dello studio.** Studio interventistico non controllato – screening colonscopico del cancro del colon-retto per popolazione a rischio.

**Metodi.** La Lega Italiana per la Lotta contro i Tumori ha avviato un programma di screening colonscopico del cancro del colon-retto per parenti di primo grado di pazienti affetti da cancro del colon-retto nel 1998, nella provincia di Latina, Lazio, Italia. Il programma è stato esteso alle province di Rieti, Lazio, e Sassari, Sardegna, rispettivamente nel 2014 e 2016, e si è concluso nel 2018. I soggetti partecipanti sono stati reclutati attivamente e volontariamente dal gruppo di lavoro dello studio. I soggetti già sottoposti a colonscopia nei 5 anni precedenti sono stati esclusi dallo studio. Le lesioni neoplastiche identificate sono state trattate direttamente oppure, ove appropriato,

riferite al setting di *Day Hospital*, con diagnosi istologica eseguita secondo linee guida dell'Organizzazione Mondiale della Sanità.

**Risultati.** Sono stati sottoposti a screening colonscopico 2,288 soggetti (età 15-88, età media 52, M/F = 946/1204), di cui 2,173 (95.0%) hanno completato l'esame. Di 468 soggetti positivi allo screening colonscopico, 422 (204M/173F), 19.4% del totale, sono stati diagnosticati come affetti da polipi adenomatosi e 46 (20M/20F), 2.1% del totale, da cancro del colon-retto. Il sesso femminile è risultato come un fattore protettivo contro l'outcome positivo, con una riduzione del 35% rispetto al sesso maschile, con OR = 0.64 95%CI (0.52-0.80). L'età maggiore di 50 anni invece risulta essere un fattore di rischio il quale più che raddoppia le possibilità di outcome positivo, con OR = 2.3 95%CI (1.8-2.9). I soggetti sopra ai 50 anni hanno presentato anche significativamente più casi di adenoma multipli diagnosticati, si nota però che la distribuzione delle dimensioni degli adenomi trovati tra soggetti sopra e sotto ai 50 anni di età non è risultata significativamente differente, malgrado questa sia un predittore di rischio di progressione neoplastica.

**Conclusioni.** Dato l'alto rischio di sviluppare il cancro del colon-retto in questa popolazione, siamo dell'opinione che le linee guida dovrebbero continuare a raccomandare screening precoci e più frequenti, colonscopici, nei parenti di primo grado di pazienti affetti da cancro del colon-retto, salvo l'introduzione di procedure con maggior profilo di costo-efficacia e minor rischio, che mantengano però un simile grado di accuratezza diagnostica.

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Ann Ig. 2024 Sep-Oct; 36(5): 549-568 doi: 10.7416/ai.2024.2610. Epub 2024 Mar 28.

# Infectious risk profile and strategies for prevention and control of outbreaks in refugee, asylum seekers and migrant populations in EU/EEA countries: a systematic narrative review of evidences

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*Keywords: Global health; migrant centers; shelters; vaccine-preventable diseases; immunization; screening; prevention*

*Parole chiave: Salute globale; centri per migranti; rifugi; malattie prevenibili da vaccino; immunizzazione; screening; prevenzione*

**Abstract**

***Introduction.*** *The recent surge in migration to and within the European Union and European Economic Area has brought the development of migration policy, including health policy, to the forefront of regional priorities. While migrants, in general, do not pose a health threat to the host population, specific subgroups of migrants, including refugees, asylum seekers, and irregular migrants, are particularly vulnerable to infectious diseases. To support public health policies in this area, the Emergency Preparedness and Management' working group of the Italian Society of Hygiene, Preventive Medicine and Public Health has conducted a systematic narrative review with the aim to comprehensively analyze the infectious disease risk within the refugee and asylum seeker populations in EU, EEA, and EU-applicant countries.*

***Methods.*** *Forty-two studies were systematically selected from scientific articles in the MEDLINE/PubMed database from January 1, 2008, to June 1, 2023. The infectious risk associated with each infectious disease among refugees and asylum seekers, as well as the strategies to prevent and control outbreaks, was collected from all available studies.*

***Results.*** *The congregate living conditions in refugee camps, transit centers, and temporary housing facilities make this population*

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Annali di Igiene : Medicina Preventiva e di Comunità (Ann Ig)
ISSN 1120-9135 https://www.annali-igiene.it

*particularly vulnerable to infectious diseases. As such, implementing stringent hygiene and preventive measures is critical to safeguarding the health of refugees and reducing the risk of outbreaks that may affect both the refugee population and the host communities.*

***Conclusion.*** *Effective vaccination and preventive strategies for migrants, refugees, and asylum seekers are vital for public health and the well-being of these populations. They should be delivered as part of universal health care. By addressing barriers and implementing tailored programs, we can ensure equitable access to vaccines and protect the health of these vulnerable individuals.*

## Introduction

The surge in migration to and within the European Union and European Economic Area (EU/EEA) has brought the development of migration policy, including health policy, to the forefront of regional priorities (1). By the end of 2022, the global population of forcibly displaced individuals increased by 21%, reaching an estimated 108.4 million (2). This accounts for 3.6% of the world's population and marks a threefold increase over the past five decades (3). Notably, middle- and high- income countries hosted 33% of the world's refugees and those in need of international protection (4).

EU countries serve as crucial transit hubs and corridors for migrants, particularly those from the Middle East, Asia, and Africa. Notably, these migration flows traverse the Mediterranean routes, with a notable increase in the number of migrants arriving in Europe, primarily through the Central Mediterranean route (from Africa to Italy) and the Eastern Mediterranean route (from the Middle East to Greece). This increase raises concerns that the usual epidemiological patterns of infectious diseases observed in Europe could be influenced (3, 5).

In this context, a migrant is defined as an individual who resides in a country, either temporarily or permanently, away from their usual residence for at least a year (1). While migrants do not usually pose a health threat to the host population, specific subgroups of migrants, including refugees, asylum seekers, and irregular migrants, could be particularly vulnerable to infectious diseases. Refugees, asylum seekers, and irregular migrants are distinct categories of individuals who are often associated with migration and displacement. Refugees are individuals who have fled their home countries due to a well-founded fear of persecution based on factors such as race, religion, nationality, political opinion, or membership in a particular social group. They seek refuge in another country and may be granted asylum, which provides legal protection and assistance. Asylum seekers are individuals who have applied for asylum in a foreign country but have not yet been granted refugee status. They are seeking international protection because they fear persecution in their home countries. During the asylum application process, they await a decision on whether they will be recognized as refugees and receive the associated legal protection. Irregular migrants, often referred to as undocumented or illegal migrants, are individuals who enter or stay in a country without the required legal authorization or in violation of immigration laws. Their migration status is irregular because it does not conform to the legal requirements of the destination country. This category includes individuals who may have overstayed visas, entered the country without proper documentation, or used unauthorized means to migrate. In several EU/EEA countries, these subgroups are disproportionately affected by infectious diseases such as tuberculosis, HIV, and hepatitis B and C (1).

Asylum seekers and refugees may carry an infectious risk influenced by various factors. Primarily, their living conditions, particularly in refugee camps or temporary shelters, often feature overcrowding and limited access to proper sanitation and healthcare facilities. These conditions create an environment conducive to the spread of infectious diseases, including respiratory infections and diarrheal diseases. Additionally, many asylum seekers and refugees originate from regions where specific infectious diseases are more prevalent or endemic. This includes countries burdened by tuberculosis, malaria, poliomyelitis, and other vaccine-preventable diseases.

Consequently, there is a potential for these diseases to be introduced into the host countries (6-8).

From a public health perspective, it is imperative to adequately manage the potential infectious risk among groups of migrants. These populations require access to healthcare services, including vaccinations and regular health check-ups, to prevent, detect, and treat infectious diseases. The public health infrastructure in host countries must be prepared to address the unique challenges posed by these populations, such as language barriers and cultural differences (9-11).

In Italy, this issue holds particular significance due to emergency concerns and political debate surrounding the topic. To support public health policies in this area, the "Emergency Preparedness and Management" working group of the Italian Society of Hygiene, Preventive Medicine and Public Health (S.It.I.) has conducted a systematic narrative review with the aim to comprehensively analyze the infectious disease risk within the refugee and asylum seeker populations in EU/EEA, and EU-applicant countries (12). Migration, driven by various complex factors, presents unique challenges in public health and epidemiology. One focal point of this research is to assess the prevalence and transmission patterns of infectious diseases within refugee and asylum seeker communities. Such an analysis is vital for recognizing potential infection hotspots and developing targeted interventions. In addition to identifying the health risks, this study will explore strategies and recommendations for disease prevention and outbreak control to propose practical, evidence-based strategies for safeguarding their health and preventing potential disease outbreaks. The objective is to establish a comprehensive framework encompassing immunization campaigns, routine healthcare access, sanitation and hygiene measures, and early detection systems. These strategies not only protect the health of the refugee and asylum seeker populations but also serve as a safeguard for the broader community. Furthermore, as the global landscape is witnessing increased forced migration due to conflicts and other crises, the importance of this study extends to predicting future trends. With ongoing wars in Ukraine, Middle East, and other regions, European countries are likely to witness a growing influx of migrants, further emphasizing the significance of understanding and addressing the health needs of these populations.

## Methods

The systematic review protocol followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (13). The population, intervention, comparison, and outcome (PICO) framework was used to formulate the review question. The question was "Infectious risks and prevention strategies for refugees and asylum seekers."

*Search strategy and selection criteria.* MEDLINE/PubMed was systematically searched. Research articles, brief reports, letters, and editorials published between January 1, 2008, and June 1, 2023, were included in our search. The chosen time span was intended to ensure a time interval that allows for a comprehensive view of the topic. The following terms were used for the search strategy: ("biological risk" OR "infectious disease*" OR "hepatitis B" OR "hepatitis C" OR "HIV" OR "tuberculosis" OR "measles" OR "mumps" OR "rubella" OR "influenza" OR "COVID-19" OR "pertussis" OR "coronavirus" OR "HCV" OR "HBV" OR "hepatitis A" OR "HAV" OR "SARS-CoV-2") AND ("migrant*" OR "refuge*" OR "displaced person*" OR "fugitive*" OR "asylum seeker*") AND ("prevention strateg*" OR "control strateg*" OR "outbreak control" OR "epidemic control" OR "outbreak*"). Studies in English with full text were included. Abstracts without full-text, reviews, meta-analyses, clinical trials, and all studies focusing on issues unrelated to the purpose of this review (e.g., psychiatric diseases, chronic conditions, etc.) were excluded (Table 1). When necessary, study authors were contacted to obtain additional information. The list of papers was screened by title and/or abstract independently by the members of the Working Group

Table 1 - Inclusion and exclusion criteria.

| Inclusion criteria | Exclusion criteria |
|---|---|
| English language | Abstracts without full text |
| Full text | Systematic reviews |
| Studies set in EU, EEA, and EU-applicant countries | Meta-analysis |
| | Clinical trials |
| | Out-of-scope papers |

who applied the predefined inclusion/exclusion criteria; discrepancies were recorded and resolved by consensus by two authors (FPB and ST).

*Data Extraction.* The members of the Working Group reviewed all relevant studies and extracted data, then organized them in a dataset with their respective characteristics to compile qualitative results. The extracted data included the publication year, origin and type of migrant population, host country, and the specific vaccination or infectious disease under analysis (Table 2). Any discrepancies were resolved through consensus by two authors (FPB and ST).

The infectious risk associated with each infectious disease among refugees and asylum seekers, as well as the strategies to prevent and control outbreaks, was collected from all available studies. The respective findings were then compared, with particular attention to the evidence presented in several of the included papers. Furthermore, a focus on vaccination strategies to reduce this risk was also addressed. These topics were elaborated based on information from the included studies and synthesized within the systematic review section.

## Results

*Identification of relevant studies.* The flowchart, constructed following the PRISMA guidance (13) (Figure 1), illustrates the article selection process. Based on the previously mentioned search strategy, we identified 703 articles in MEDLINE/PubMed, and an additional five records were located through citation searching. Consequently, we had 708 studies that met the initial screening. Following the application of inclusion criteria, 56 studies remained eligible. Among these, four were excluded due to an unclear definition of the study population, three because they were literature reviews, three because they were conducted outside of EU/EEA countries, two because they were not in English, and two because of unavailability of full-text. As a result, 42 studies were deemed eligible (14-55) (Table 2). In total, 666 studies did not meet the inclusion criteria and were subsequently excluded.

*Findings*

In this section, we synthesize the main quantitative evidence extracted from the included studies, describing the primary pathologies in alphabetical order.

*COVID-19*

The vulnerability of asylum seekers and migrants' reception centers to COVID-19 outbreaks has been previously stressed, and it is reasonably due to factors such as overcrowded living conditions, limited awareness of COVID-19 prevention measures,

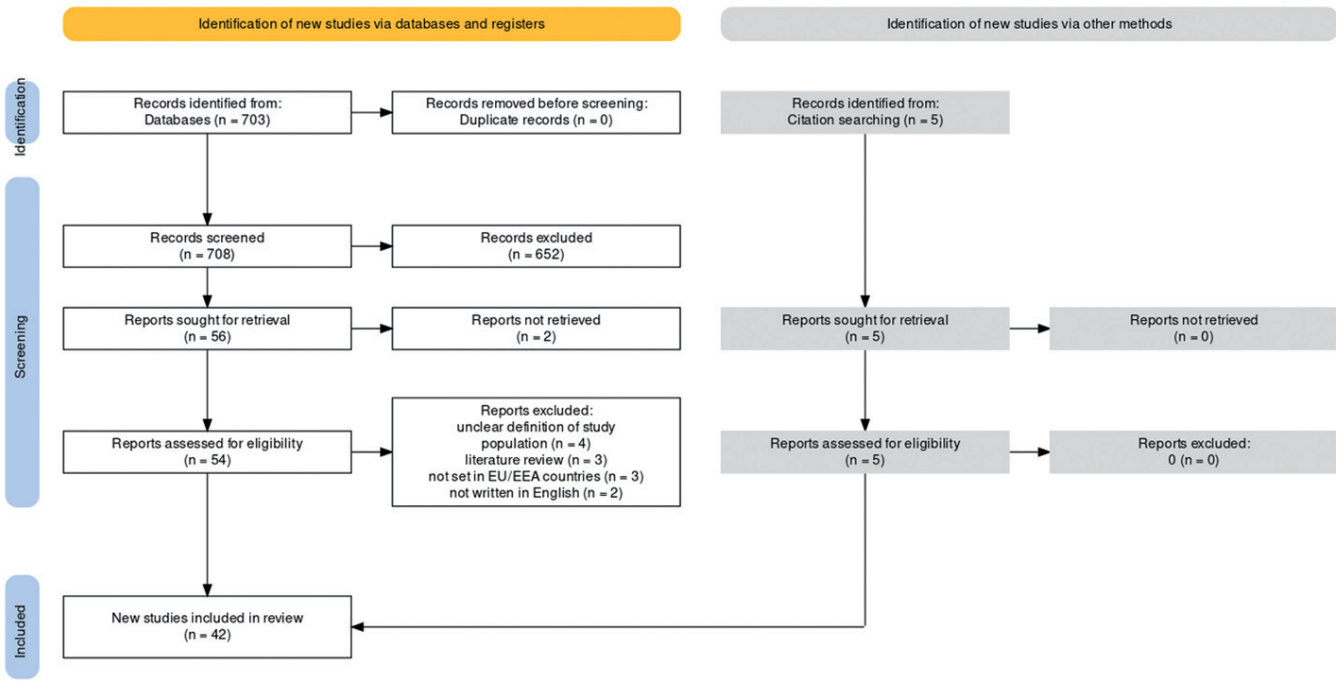


Figure 1 - Flowchart of the bibliographic research.

Table 2 - Characteristics of the selected studies included in the systematic review.

| Author | Year | Population | Country | Infectious disease(s) | Country of origin |
|---|---|---|---|---|---|
| Schultze T | 2023 | Refugees | Germany | Multidrug-resistant bacteria | Ukraine |
| Solomos Z | 2023 | Refugees | Greece | COVID-19 | Afghanistan, Syria, Iraq, and African countries |
| Badenschier F | 2022 | Asylum seekers and refugees | Germany | Diphtheria | Syria, Afghanistan, Tunisia, Yemen |
| Creutz I | 2022 | Asylum seekers and refugees | Germany | Multidrug-resistant bacteria | Middle East |
| Louka C | 2022 | Asylum seekers and refugees | Greece | Scabies | n.r. |
| Mellou K | 2022 | Vulnerable migrants | Greece | COVID-19 | sub-Saharan African countries |
| Troiano G | 2022 | Refugees | Italy | Vaccine-preventable diseases | Ukraine |
| Fabris S | 2021 | Asylum seekers and refugees | Italy | COVID-19 | North Africa, the Gulf of Guinea, the Horn of Africa, Syria, Pakistan, and Bangladesh |
| Kondilis E | 2021 | Asylum seekers and refugees | Greece | COVID-19 | n.r. |
| Le Bihan C | 2021 | Asylum seekers and refugees | France | COVID | n.r. |
| Norman FF | 2021 | Irregular migrants and refugees | Spain | MMRV, HAV, HBV, HCV, HIV | Africa, Latin America, and other |
| Sisti LG | 2021 | Asylum seekers and refugees | Italy | COVID-19 | Nigeria, Pakistan, Gambia, Bangladesh, Senegal |
| Turunen T | 2021 | Refugees | Finland | COVID-19 | n.r. |
| Bosetti P | 2020 | Refugees | Turkey | Measles | Syria |
| Donisi A | 2020 | Asylum seekers | Italy | Tuberculosis, HBV, HIV, HCV, syphilis | Africa, Asia |
| Gilman RT | 2020 | Refugees | Greece | COVID-19 | n.r. |
| Grecchi C | 2020 | Asylum seekers | Italy | Tuberculosis | Africa, South East Asia, Mediterranean area, and other |
| Padovese V | 2020 | Asylum seekers, refugees, subsidiary protection | Malta | Sexually transmitted diseases | Asia, Africa, South America |
| Pogka V | 2020 | Refugees | Greece | Measles | Afghanistan, Syria, Iran, Iraq, and other |
| El-Khatib Z | 2019 | Asylum seekers | Austria | syndromic surveillance | Afghanistan, Syria, Iraq, Iran, Pakistan, and other |
| Giambi C | 2019 | Irregular migrants, refugees, and asylum seekers | Croatia, Greece, Italy, Malta, Portugal, Slovenia | Vaccine-preventable diseases | n.r. |
| Ackermann N | 2018 | Asylum seekers | Germany | Tuberculosis, HIV, HBV, Helminthic infections | Africa, Asia, Est Europe |
| Alberer M | 2018 | Asylum seekers and refugees | Germany | Hepatitis B, hepatitis C, HIV, scabies, tuberculosis | Syria, Afghanistan, Eritrea, Nigeria, Sierra Leone, Somalia |
| Buonfrate D | 2018 | Asylum seekers | Italy | Tuberculosis, Helminthic infections, syphilis, HIV, HBV, HCV | Sub-Saharan Africa, Asia, North Africa |
| Ceccarelli G | 2018 | Asylum seekers | Italy | Measles | Eritrea, Nigeria, Gambia, Senegal, Mali, Pakistan, Bangladesh |
| Ciccozzi M | 2018 | Asylum seekers | Italy | Herpesviruses | Pakistan, Bangladesh, Nigeria, and other |
| Collin SM | 2018 | Undocumented migrants | EU/EEA countries | Tuberculosis | n.r. |

| | | | | | |
|---|---|---|---|---|---|
| Ehlkes L | 2018 | Asylum seekers | Germany | Enteric pathogens | Syria, Afghanistan, Iraq, Albania, Kosovo, other |
| Freidl GS | 2018 | Asylum seekers | Netherlands | MMRV, diphtheria, tetanus, polio, HAV, HBV | Syria, Afghanistan, Eritrea, Ethiopia, Iran, Iraq |
| Kloning T | 2018 | Refugees and undocumented migrants | Germany | HAV, HBV, HCV, HIV, syphilis, tuberculosis | Somalia, Eritrea, Afghanistan, Syria, other |
| Rojek AM | 2018 | Refugees and undocumented migrants | Greece | Syndromic surveillance | n.r. |
| Sarma N | 2018 | Asylum seekers, refugees, and irregular migrants | Germany | Syndromic surveillance | Syria, Afghanistan, Iraq, Albania, Kosovo, other |
| Walker TM | 2018 | Refugees | Germany | Tuberculosis | Horn of Africa |
| Mellou K | 2017 | Asylum seekers and refugees | Greece | Hepatitis A | Syria, other |
| Michaelis K | 2017 | Asylum seekers and refugees | Germany | Hepatitis A | n.r. |
| Vairo F | 2017 | Asylum seekers | Italy | Varicella zoster | Eritrea, Nigeria, Gambia, Senegal, Mali, Pakistan, Bangladesh, other |
| Coppola N | 2015 | Undocumented migrants and refugees | Italy | HBV, HCV, HIV | Africa, Asia, Eastern Europe |
| Germinario C | 2015 | Asylum seekers | Italy | Tuberculosis, HBV, HIV, HCV, poliomyelitis, vaccine-preventable diseases, syndromic surveillance | Africa, other |
| Pace-Asciak A | 2013 | Undocumented migrants | Malta | Tuberculosis | Sub-Saharan Africa, Northern Africa, Western Asia, Southern Asia |
| Takla A | 2012 | Asylum seeker | Germany | Measles | Afghanistan, Serbia, Macedonia, Iraq, Iran, Syria, Turkey, and other |
| Riccardo F | 2011 | Refugees | Italy | Syndromic surveillance | North Africa |
| Schmid D | 2008 | Refugees | Austria | Tuberculosis | Chechen Republic |

n.r.= not reported

language barriers, and social gatherings within these centers (19, 21, 22, 25). The risk of COVID-19 among refugees has been the subject of scrutiny by two studies. Sisti et al. (25) found that the incidence of COVID-19 within the reception system was similar to that in the resident Italian population during the same period. Migrants had lower comorbidity rates but a higher likelihood of requiring hospitalization, likely due to the precautionary measures taken by the facility staff and the potential unfamiliarity of health professionals with the migrants' complete medical histories. In contrast, Kondilis et al. (22) reported notably high COVID-19 transmission rates among asylum seekers and refugees residing in reception centers and refugee settlements in Greece compared to the general Greek population.

These studies have provided valuable insights into managing COVID-19 outbreaks in such settings. Mass screening has proven to be a valuable tool for creating a comprehensive overview of suspected outbreaks, including identifying asymptomatic or presymptomatic carriers of the virus (15, 21, 23, 26). To enhance adherence to COVID-19 public health guidelines and prevention measures, the living conditions within these facilities should be improved (22). Potential improvements include reducing overcrowding, dividing camps into sectors, enhancing sanitation services, and ensuring access to necessities like food and medical care (19, 29). Authors have advocated for the fair and equal application of quarantine and lockdown measures without discrimination while striving to avoid mass quarantine when feasible due to its associated health risks for vulnerable populations (15, 22, 26, 29). Individuals in quarantine should receive comprehensive support, including healthcare, social and psychosocial assistance, and access to fundamental requirements such as food and water.

Furthermore, authors have stressed the importance of providing consistent primary healthcare for marginalized migrants, which has been associated with reduced morbidity and mortality (15, 21, 23). Recommendations include the daily presence of

medical personnel, daily patient monitoring, early medical interventions, and selective transfers to tertiary centers (15). It is also advisable to strengthen epidemiological surveillance systems to more effectively record COVID-19 cases, hospitalizations, and fatalities among refugees, asylum seekers, and other migrants in host countries. Establishing a robust system for public data sharing with an emphasis on transparency and timeliness has been highlighted (21, 22). Moreover, ensuring equal access to COVID-19 vaccines for refugees and asylum seekers is a critical consideration (22, 25, 26).

These strategies necessitate social and political measures to reduce SARS-CoV-2 incidence and the risk of viral spread within this population (23). Cultural background and the heterogeneity of the sheltered population should be taken into account when designing and implementing prevention strategies. Using geospatial epidemiology to identify case clusters and investigate local risk factors is essential, given that specific ethnic groups are more susceptible to clustering, posing a significant risk for infection (21). Local governments should implement cross-disciplinary strategies that provide culturally sensitive medical and sanitary support for COVID-19 diagnosis and management, treating outbreaks among asylum seekers and refugees with the same urgency as any other population while considering the vulnerabilities of the elderly and other high-risk groups (26).

*Diphtheria*

Moderate to high levels of susceptibility among refugees and asylum seekers (19-35%) were observed, particularly among migrants from Afghanistan (42). Notably, Badenschier et al. (16) documented an outbreak of diphtheria cases among migrants from Syria, Afghanistan, Tunisia, and Yemen in Germany. This outbreak started in July 2022 and persisted until at least October 2022, primarily manifesting as cutaneous diphtheria, a less severe form of the disease affecting the skin. However, two secondary cases of respiratory diphtheria were also reported. The authors explored various factors that could have contributed to the outbreak, including (i) an increase in diphtheria incidence in the migrants' countries of origin, (ii) a rise in the number of migrants arriving in the host country, (iii) potential diagnostic biases stemming from heightened skin lesion evaluations following the monkeypox outbreak, and (iv) human-to-human transmission in reception centers in Germany. Several recommendations were outlined to prevent and manage these outbreaks, including (i) identifying the outbreak's source(s), (ii) conducting active case identification in the host country, other destination nations, and countries along the Balkan route, and (iii) implementing infection prevention and control measures, such as targeted and efficient vaccination campaigns (16, 42).

*Hepatitis A*

Three studies assessed the seroprevalence of hepatitis A virus (HAV) among migrants and refugees, revealing susceptibility rates ranging from 7 to 16% (24, 42, 43).

Two outbreaks of HAV among asylum seekers were reported in the literature (47, 48). These outbreaks posed significant challenges to control due to overcrowding and suboptimal sanitation conditions in the refugee camps, difficulties in identifying and tracing close contacts, and the high mobility of the refugee population. Michaelis et al. (48) noted that the impact of hepatitis A was disproportionately high among asylum-seeking children and adolescents. This discrepancy was attributed to the limited opportunity for young individuals from non-endemic regions to develop natural immunity to HAV, unlike adults from high-endemic areas. The outbreaks were effectively contained through an intensified surveillance system, prompt vaccination of contacts, and the implementation of enhanced hygiene standards within the camps. Enhanced housing conditions (including reducing overcrowding and enhancing sanitation and hygiene standards) were essential to mitigating the transmission of hepatitis A. The authors also proposed conducting information campaigns to raise awareness about the risks of HAV infection and preventive measures. The comprehensive adherence of the entire refugee child population, ranging from 1 to 14 years, to Greece's routine national childhood immunization program as a long-term goal was proposed by Mellou et al. (47).

*Measles, Mumps, Rubella, Varicella zoster (MMRV) virus*

Several authors (24, 42) found gaps in seroprevalence for rubella, measles, and mumps among refugees and asylum seekers, with over 6-12% of screened subjects potentially susceptible to these diseases. They also found that women of childbearing age constituted a high-risk group, with suboptimal seroprevalence rates for these viral infections. The authors recommended a focus not only on immunization programs for recently arrived undocumented migrants but also on involving

more established migrant populations in older age groups, who may have been previously unvaccinated or exhibited evidence of waning immunity (24, 42).

In this light, to prevent outbreaks in asylum seekers' centers, improved screening and vaccination strategies are necessary for migrants, especially those from specific geographical regions and women of childbearing age. Takla et al. (53) compared two containment strategies for addressing measles outbreaks in asylum shelters that hosted refugees from various countries. The two strategies under consideration were serological testing with selective vaccination and immediate mass vaccination. The researchers found that serological testing with selective vaccination was a more time-consuming and expensive approach when compared to immediate mass vaccination. On the other hand, mass vaccination appeared to be more effective in preventing secondary cases, especially in situations with limited personnel and infrastructure resources. This method was also deemed safe and efficient, even for individuals who had previously received measles vaccinations. Furthermore, the study suggested that implementing routine vaccination upon initial intake could be instrumental in averting future outbreaks in such settings. Similar conclusions have been reached by Vairo et al. (49), who described a Varicella zoster virus outbreak in an asylum seeker center in Italy. The authors highlighted that chickenpox history is not the optimal method to identify susceptible individuals, proposing a universal screening of all individuals, regardless of history status, and the vaccine for susceptible. Both studies highlighted the role of national and local surveillance systems for reception centers for migrants in early detection and response to communicable disease outbreaks and the value of a coordinated response integrating collective housing facilities, public health authorities, reference laboratories, and high-level specialist hospitals (49, 53).

Several studies evaluated the risk of introducing the measles wild virus from various countries into a highly-vaccinated nation. Pogka et al. (32) suggested multiple introductions of the measles virus from other European countries, contributing to establishing a reservoir within the Greek population. Bosetti et al. (27) proposed a mathematical model to investigate the impact of social integration on measles risk in Turkey. According to the researchers' estimates, because of suboptimal vaccination during the past civil war, Syrian refugees hosted in Turkey displayed a considerably large fraction of individuals who were susceptible to measles. They found that high levels of mixing between Syrian refugees and Turkish citizens had been highly beneficial in drastically reducing the potential spatial spread of measles and the incidence of measles in both the refugee and host populations. This was because the high immunization coverage among Turkish citizens helped shield Syrian refugees from infection.

These studies also noted that the proportion of patients not tested for Varicella zoster virus (VZV) immunity ranged from 4% to 28%, possibly due to excluding patients who reported a previous history of natural infection.

As a recommendation, the authors suggested that host countries should intensify their vaccination program to target more vulnerable populations and provide the measles, mumps, and rubella vaccine for children and adults, both for migrants and the hosting population (27, 32). Regardless of that, Ceccarelli et al. (38) suggested implementing a screening specifically for individuals arriving from countries with low second-dose vaccine coverage or in situations where data on the second dose administration are unavailable. Moreover, the authors provided evidence that social integration of refugees and maximizing their dispersal had been effective countermeasures in reducing the risk of measles epidemics in host countries (27, 32, 38).

*Multidrug-resistant bacteria*

Schultze et al. (14) investigated the prevalence of multidrug-resistant Gram-negative bacteria (including carbapenem-resistant bacteria) in Ukrainian patients admitted to a university hospital in Germany. The study found that the carriage prevalence of carbapenem-resistant bacteria in Ukrainian patients was high (9.7%), significantly higher than the prevalence in non-Ukrainian patients (0.79%). The prevalence of carbapenem-resistant bacteria in Ukrainian patients was likely attributable to various factors, including a high background prevalence of antimicrobial resistances, and the ongoing war in Ukraine, which disrupted public health services and led to an increased and empiric antibiotic usage, often based on drugs available on spot rather than on more appropriate ones. The study's authors concluded that additional measures were necessary to prevent the transmission of carbapenem-resistant bacteria from Ukrainian patients to others in hospitals. These measures should include screening Ukrainian patients for carbapenem-resistant bacteria upon admission, isolating those who test positive, and implementing rigorous infection

control protocols in hospitals. They recommended that hospitals implement infection control measures to prevent the spread of these bacteria, such as screening Ukrainian patients for carbapenem-resistant bacteria upon admission and isolating those who are positive.

Creutz et al. (17) screened 161 refugees residing in accommodations in Germany to assess nasal carriage of Staphylococcus aureus. The isolates underwent examination for resistance and virulence characteristics, phenotypically and through whole-genome data analysis. The results showed that 5.6% of the refugees were carriers of S. aureus, with 2.5% being carriers of methicillin-resistant S. aureus. The identification of strains originating from the Middle East supported the hypothesis that these strains traveled with the refugees and persisted despite changes in the living conditions of the host population.

*Poliomyelitis*

Germinario et al. (51) assessed the presence of wild poliovirus or Sabin-like poliovirus in stool samples periodically collected from refugees hosted in Italy. The examination of the 152 stool samples revealed no presence of enterovirus.

Seroprevalence for all three poliovirus types ranged from 88% to 99% for polio type 1, 90% to 99% for polio type 2, and 76% to 89% for polio type 3 (42, 51). Freidl et al. (42) reported lower seroprevalence for polio type 3 in Iraq (76%) and Eritrea (78%). When stratified by age group, only two subgroups fell below the threshold: 26-35-year-olds from Iraq (63% polio type 3) and Eritrea (71% polio type 3).

*Scabies and pediculosis*

Since the beginning of the migratory crisis in early 2010s, scabies and pediculosis emerged as one of the most frequently reported infectious diseases among refugees and asylum seekers living in reception camps (18, 36). This high prevalence was attributed to various factors, including (i) crowded living conditions in refugee camps and reception centers, (ii) the rapid turnover of populations within these facilities, increasing the risk of reinfestations and outbreaks, and (iii) seasonality of infectious diseases, with a higher incidence during the winter months due to close interpersonal contact in refugee camps (18). The authors underscored the necessity of improving living conditions and healthcare access for refugees and asylum seekers. They emphasized the importance of continuous and systematic data collection regarding infectious diseases among refugee and asylum populations. Louka et al. (18) recommended the consideration of mass drug administration (MDA) as a strategy to alleviate the burden of scabies among refugees and asylum seekers. MDA involves the administration of medication to an entire population group, regardless of their infection status, as individual case management may not always be effective.

Ackermann et al. (35) reported 40 cases of Louse-borne relapsing fever (LBRF), caused by Borrelia recurrentis and transmitted by the body louse Pediculus humanus humanus, among asylum seekers hosted in Germany. This pathogen is endemic in the Horn of Africa and is linked to extreme poverty, wars, and civil unrest. Risk factors, such as low socioeconomic status, overcrowding, and limited personal hygiene facilities, facilitate its transmission, particularly in refugee camps and shelters.

*Sexually transmitted diseases*

Six studies (24, 28, 35, 37, 50, 51) have assessed the seroprevalence of hepatits B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) among migrants and refugees. The seroprevalence of HBV surface antigen carriers ranged from 6% to 11% (24,28,35,37,50,51). Notably, around 50% to 80% of the tested migrants were found to be susceptible to HBV (24, 42, 43). This susceptibility likely reflects previous vaccination strategies that primarily targeted high-risk groups, in contrast to recent national programs that advocate universal vaccination from birth. The seroprevalence rate for HCV ranged from 0.9% to 2% (24, 28, 37, 50, 51). Calculated seroprevalence rates for HIV ranged from 0.3% to 6% overall, with higher rates among males (24, 28, 35, 37, 50, 51). Additionally, syphilis had a prevalence ranging from 1% to 4.5% (28, 37, 43).

Padovese et al. (31) examined migrants' access to sexual health services in Malta and assessed their susceptibility to sexually transmitted infections (STIs). The migrant cohort primarily consisted of young, unmarried men from Africa or South-East Asia. The study revealed that migrants were sexually active and engaged in high-risk behaviors related to STIs, with a significant lack of knowledge about these infections. Consequently, a substantial proportion of migrants, 73.3% among males and 71% among females were diagnosed with STIs. Various comprehensive prevention measures were suggested. These include screening, providing access to pre-exposure prophylaxis for migrants at a significant risk of HIV infection, and ensuring access to antiretroviral treatment regardless of

migrants' legal status (31). Assessing the HBV status and vaccinating susceptible individuals was also recommended (24, 42, 43). To raise awareness among migrants regarding STI risks and testing, community-based education interventions should be implemented. These interventions encompass the distribution of multilingual educational materials in reception centers and culturally sensitive information sessions targeting various migrant groups (24, 31, 42, 43). Furthermore, STI prevention strategies within migrant communities should be closely intertwined with interventions aimed at addressing issues such as human trafficking, Female Genital Mutilation (FGM), and other forms of sexual and gender-based violence (S/GBV) or exploitation (24, 31). The confluence of these concerns underscores the pivotal role of healthcare staff in the early identification of victims among migrant patients seeking sexual health services. To enhance this capability, specialized staff training, along with improved access to interpretation and intercultural mediation services, would be instrumental in preventing and combating S/GBV within the migrant population.

*Syndromic surveillance*

The syndromic surveillance system is described as a valuable tool for monitoring the health of asylum-seeking refugees and preventing the spread of infectious diseases. Its implementation is instrumental during large refugee influx, enabling the identification and response to potential public health threats (33, 44, 45, 51, 54). This system provides flexible and rapid surveillance within migrant accommodations integrated with medical services. It can detect over 400 statistical signals, primarily related to five syndromes: suspected acute upper respiratory tract infections, rash without fever, suspected acute lower respiratory tract infections, watery diarrhea, and skin, soft tissue, or bone abnormalities. The system triggers prompt public health actions, including investigations of alerts, exclusion of individuals suspected of being contagious from crowded activities, and referrals to specialized secondary healthcare for adequate treatment. The importance of communication among stakeholders and sharing best practices is emphasized (45).

Several studies evidenced that the results of syndromic surveillance showed that the migration flow was not associated with an increased risk of communicable disease transmission in hosting countries (51, 54). Nevertheless, in a study by Rojek et al. (44), the clinical characterization and documentation of medical syndromes among patients in refugee camps were evaluated. It was noted that incomplete clinical assessments presented challenges in identifying patients with syndromes under surveillance. Case records lacking comprehensive information could hinder outbreak teams' ability to investigate and verify cases. Communication difficulties and interruptions during consultations in busy clinics were identified as potential factors affecting comprehensive patient evaluation. The study suggests that improving the performance of syndromic surveillance in humanitarian settings can be achieved by enhancing the documentation of clinical information obtained during patient consultations and by improving clinicians' understanding and utilization of surveillance tools, such as case definitions for syndromes under surveillance.

As evidenced by El-Khatib et al. (33), systematic data collection on the health of asylum seekers is limited in the EU/EEA, necessitating enhancements in national health surveillance systems and innovative health surveillance methods for monitoring asylum seekers' health.

*Tuberculosis*

Several studies have drawn attention to the risk of tuberculosis (TB) among migrants and the host population. Pace-Asciak et al. (52) screened 4,570 undocumented migrants in Malta using chest X-rays (CXR), finding that around 3.5% of them had CXR results suggesting potential TB. Of these, approximately 12.5% were diagnosed with active TB cases. Through both active and passive surveillance, a total of 33 active TB cases were identified among these immigrants, resulting in a reported TB incidence of 390 cases per 100,000 individuals among immigrants, in stark contrast to the 2.1 cases per 100,000 incidence rate among those born in Malta. Studies focused on screening programs for latent tuberculosis infection (LTBI) revealed a TB prevalence ranging from 1% to 14.5% and an LTBI prevalence ranging from 4% to 44% (28, 30, 35, 37, 43, 51).

Moreover, two studies (46, 55) documented the risk of multidrug-resistant tuberculosis (MDR-TB) outbreaks among refugees, even among HIV-seronegative individuals. Schmid et al. (55) highlighted that the multidrug-resistant tuberculosis outbreak was facilitated by deficiencies in case management by Austrian health authorities, such as the index case not initially receiving directly observed therapy in an outpatient setting and being lost to follow-up for four months. Furthermore, this individual received an inappropriate anti-tuberculosis regimen for MDR-TB

for four weeks.

All authors stressed that these findings underscore the necessity of strengthening the TB control programs in host countries. In particular, 25% of the EU/EEA interviewees in the study conducted by Collin MS et al. reported that inadequate systems for TB control program monitoring and evaluation were identified as factors impeding TB control, emphasizing the importance of improving monitoring and evaluation processes (40). Implementing evidence-based national TB guidelines that regulate treatment monitoring, contact investigation procedures, and interprovincial communication is essential. Despite the benefits of entry screening and follow-up (30), immigrants face an elevated risk of developing TB for several years after their arrival (52). Unfortunately, the relative inaccessibility of services due to information gaps, language barriers, and cultural differences can lead to diagnostic delays. Other perceived obstacles include issues related to care recipients (e.g., lack of TB knowledge, treatment seeking/adherence), care providers (including the need for specialist training of nurses and doctors), and health system constraints (e.g., funding and communication between healthcare and social care systems) (40). To address these challenges, it is crucial to raise awareness about TB among migrants and general practitioners (52). Providing migrants with linguistically appropriate information on TB, community health centers, and culturally sensitive healthcare facilities, possibly through cultural mediators, is strongly recommended.

Additionally, to control multidrug-resistant tuberculosis outbreaks, national guidelines for the programmatic management of drug-resistant TB, HIV testing, tuberculin skin tests, and interferon-gamma release assay (IGRA) tests are essential components of the screening policy for immigrants (40, 55). Moreover, New technologies are crucial in controlling multi-drug resistant tuberculosis outbreaks. Specifically, the molecular epidemiological approach that synthesizes whole-genome sequencing data with epidemiological information has proven instrumental in more effectively identifying and managing MDR-TB outbreaks (46). Strengthening the laboratory network and improving surveillance were also highlighted (40, 55).

*Other infectious diseases*

Ciccozzi et al. (39) focus on an outbreak of acute febrile syndrome that affected 22 refugees residing at the Asylum Seekers Centre in Italy. The study identified a potential respiratory-transmitted cause for the outbreak and concurrent reactivation of multiple herpesviruses. The epidemiological investigation revealed that the rapid spread of the epidemic was facilitated by patients being housed in adjacent rooms or even sharing the same room. Based on the evidence, preventive measures for infection control were instituted, demonstrating a commendable approach to outbreak management. The authors underscored the significance of microbiological surveillance in enhancing public health standards and recommended its continued use.

Ehlkes et al. (41) recommend the ongoing screening of one stool sample from asymptomatic children, adolescents, asylum seekers, and refugees. These groups exhibit a higher prevalence of enteric pathogens and are less likely to adhere to hand hygiene and other infection prevention measures. Additionally, specific helminth infestations can have severe consequences in children, making targeted screening valuable. Continuous testing for enteric pathogens in a representative subsample of all newly arrived asylum seekers will be essential to adapt to changing migration patterns and associated risks (37, 41). These studies also indicated that the import of enteric bacteria by newly arrived asylum seekers has had a minimal impact on the public health of the host population (35, 37, 41). Specifically, from January 2015 to May 2016, Ehlkes et al. (41) tested 23,410 stool samples, revealing a prevalence of 0.2% for Salmonella spp., 2.4% for helminth infestation, 0.2% for E. vermicularis, 0.3% for Hymenolepis nana, with 47 cases of schistosomiasis, and none tested positive for Shigella spp.

Freidl et al. (42) reported a tetanus seroprevalence among refugees ranging from 96% to 100%, except for participants from Eritrea (86%). Among Eritreans, the lowest tetanus seroprevalence was observed in the age group of 36-45 years, which was 79%.

*Prevention of vaccine-preventable diseases*

Most authors widely recommend vaccination in refugees and asylum seekers for vaccine-preventable diseases. This is crucial to protect the health of refugees and prevent potential disease outbreaks in both refugee populations and host communities.

Troiano et al. (20) analyzed the characteristics of Ukrainian minor refugees accessing the Rozzano Vaccination Center (northern Italy). The authors observed high rejection rates for certain vaccines, with the HPV vaccine having a 100% rejection rate, followed by measles, mumps, rubella (63%), and meningococcus C (61%). Factors contributing

to vaccine hesitancy included concerns about side effects, lack of information, and doubts about vaccine efficacy. The authors' findings suggest that more needs to be done to address the factors that are preventing Ukrainian refugees from getting vaccinated. This could include providing culturally appropriate information about vaccines, addressing language barriers, and building trust in the Italian healthcare system. Additionally, the study's authors suggest that the Italian government should consider implementing mandatory vaccination for refugees against certain vaccine-preventable diseases, such as measles, mumps, and rubella. This would help to protect refugees from these diseases and reduce the risk of outbreaks in the Italian population.

Germinario et al. (51) described an immunization protocol applied to children refugees and asylum seekers hosted in a refugee center in Apulia (southern Italy). Following this protocol, healthcare workers, in collaboration with cultural mediators, reviewed the health records of the children and inquired about their prior vaccinations. The immunization schedule of the child's home country, obtained from the WHO guidelines, was also examined. Subsequently, an individualized vaccination plan was established for each child. If there were any uncertainties, serological tests for hepatitis B, measles, rubella, and varicella were conducted. One hundred twenty-nine migrants received appropriate vaccination, according to the Apulian immunization schedule.

Regarding vaccination policy among EU/EEA countries, Giambi et al. (34) evaluated the migrant vaccination strategies, comparing them between six European countries (Croatia, Greece, Italy, Malta, Slovenia, and Portugal). While they vary across the six surveyed EU countries, they generally align with WHO (56) and ECDC guidelines (1, 57, 58). Nevertheless, a detailed examination of these strategies has highlighted areas of concern. Several strategies were suggested by the authors, including (i) the establishment of protocols for tracking migrants' immunization records within and across countries to prevent vaccine shortages or duplications, (ii) the promotion of collaboration among public health authorities from different nations to establish shared procedures for data exchange, (iii) the development of migrant-friendly approaches to enhance and supervise vaccination accessibility at the community level, and (iv) the gathering data on vaccination coverage among migrant populations (34).

## Conclusions

The displacement of refugees and asylum seekers has intensified in recent years due to conflicts, natural disasters, and economic hardships. The congregate living conditions in refugee camps, transit centers, and temporary housing facilities make this population particularly vulnerable to infectious diseases. As such, the implementation of stringent hygiene and preventive measures is critical to safeguarding the health of refugees and reducing the risk of outbreaks that may affect both the refugee population and the host communities (59).

Maintaining adequate hygiene and sanitation in refugee camps is essential to prevent the outbreaks and spread of infectious diseases. Overcrowding, limited sanitation facilities, and inadequate access to clean water are common challenges refugees face. Hygiene measures must include regular handwashing with soap and clean water, providing safe food, proper waste disposal to prevent environmental contamination, ensuring access to clean drinking water sources, and sanitary facilities that are functional, private, and culturally appropriate (60). Moreover, it is essential to educate refugees on personal hygiene through health education programs, posters, and other materials (61). In the same area, it is crucial to vector control through insecticide spraying, the use of mosquito nets, and the removal of standing water; indeed, mosquitoes, flies, and other insects can transmit diseases such as malaria, dengue fever, Chikungunya, West Nile Virus, Zika, and yellow fever (62).

Timely and accurate surveillance of infectious diseases in refugee camps is essential for early detection and response. Surveillance should include prompt reporting of suspected cases, diagnostic testing and contact tracing, comprehensive data collection, rapid isolation of affected individuals, and data-driven public health policies and resource allocation. Surveillance systems should be sensitive and specific to identify even small outbreaks of infectious diseases. Data collected from surveillance systems should be analyzed regularly to identify patterns of spread of infectious diseases (63). As reported by the ECDC, completeness, and timeliness of reporting are essential aspects of the surveillance system. Completeness should be reviewed weekly, and if a reporting unit is not submitting data daily, healthcare providers in that unit should be contacted to request missing data promptly. Missing a day of reporting can disrupt baseline data for threshold calculations, necessitating a whole week's data to restore it, making 100%

completeness a recommended goal. Timeliness should also be evaluated weekly, considering predefined targets for the number of reports from each unit. In cases of repeated delays, the coordinating team should contact healthcare providers to ensure daily reporting as per the surveillance protocol. The specific timeliness targets, such as 48 hours, should be set by the implementing country, balancing field constraints with surveillance objectives (64). Public health authorities, such as the Health Prevention Departments in Italy, must develop expertise and adapt organizational models to ensure effective surveillance activities. The evolving nature of health threats requires a proactive approach to surveillance, necessitating continuous skill development and organizational flexibility to meet the demands of the ever-changing health landscape.

Mass screening and isolation appear to be proactive strategies for the prevention and control of infectious diseases within refugee and asylum seeker populations. Mass screening emerges as a crucial tool in identifying infections, especially in crowded and often resource-constrained refugee settings. It is critical in early detection, timely intervention, and safeguarding public health. As the global refugee crisis persists, it is imperative to prioritize mass screening as part of comprehensive public health strategies for this vulnerable group, thereby ensuring a healthier and more secure future for all (65). It offers several advantages, including (i) the identification of infections at an early stage in order to facilitate timely medical intervention, reducing the risk of complications and transmission, (ii) contact tracing, and (iii) implementation of preventive measures to contain outbreaks (66, 67), even if some authors report that it may infringe upon fundamental rights of those screened, thus creating an ethical dilemma (68). The ECDC reported that it is likely to be effective and cost-effective to screen child, adolescent, and adult migrants for active TB and LTBI, HIV, HCV, HBV, strongyloidiasis, and schistosomiasis, especially considering newly arrived migrants (1). In particular, screening for active TB and LTBI can be effective and cost-effective depending on the setting, target group, and screening approach, with the best potential results achieved if screening is restricted to high-risk groups and/or to migrants from high-burden countries (69).

Isolation is a critical measure to control the spread of infectious diseases within refugee camps. It helps prevent the spread of infectious diseases, safeguarding the affected individuals and the broader camp community and allowing the early identification of infected individuals. Moreover, Isolation allows for timely medical care and reduces severe outcomes (29). Well-structured isolation procedures should incorporate the following key components: (i) early Identification, (ii) dedicated facilities and isolated areas or units within the camp for individuals with suspected or confirmed infections, (iii) medical care, including access to healthcare providers, and (iv) resource allocation, ensuring an adequate supply of medical equipment and supplies for isolates. On this topic, specific guidelines have been published by the ECDC and WHO regarding the prevention and control of COVID-19 in migrant and refugee reception and detention centers. Both institutions reported that there is no evidence that quarantining whole camps effectively limits transmission of SARS-CoV-2 in settings of reception and detention or provides any additional protective effects for the general population outside those that could be achieved by conventional containment and protection measures (70, 71).

Central to this effort is the promotion of vaccinations for vaccine-preventable diseases, which plays a pivotal role in disease prevention and control. Vaccination is a cornerstone of preventive healthcare. Ensuring that refugees have access to vaccinations against vaccine-preventable diseases is crucial. These vaccinations not only protect the health of the refugees themselves but also contribute to herd immunity, reducing the risk of disease outbreaks in the host community (72). As reported by the literature, refugees and asylum seekers show moderate-high levels of serosusceptibility to several vaccine-preventable diseases, including measles, mumps, rubella, varicella zoster, hepatitis A and B (24). Moreover, several outbreaks of hepatitis A, measles, and diphtheria have been described (15, 16, 47, 48). Therefore, vaccination programs in refugee camps should be comprehensive and include all the recommended vaccines for the age group. Vaccines should be provided free of charge and should be accessible to all refugees. Tailoring vaccination programs to the specific needs of displaced populations is essential, consisting of a risk assessment, timely immunization, and catch-up vaccination. The risk assessment consists of identifying high-risk groups based on the migrants' origin and the prevalence of diseases in their home countries (1). Between 2012 and 2013, Ukraine had vaccination coverage of 76% (DPT3 - Diphtheria-tetanus-pertussis 3rd dose), dramatically dropping to 23% in 2014 due to the conflict in Donbass. This low vaccination coverage was further exacerbated by ongoing conflict and displacement in the East, leading

to the confirmation of vaccine-derived poliovirus and increased cases of infectious diseases like rubella, pertussis, and mumps (20). Vaccines should be administered promptly upon arrival, as many migrants may lack adequate immunization records. There is no need for serological screening as there are no risks associated with vaccinating individuals who have previously received vaccines. Access to catch-up vaccination should be ensured for individuals who have missed previous immunization schedules. Finally, it is recommended to provide migrants with documentation of the vaccination intervention.

The measures described above must be optimized for the difficulties related to the population under analysis. All these measures should be culturally sensitive and inclusive. Refugees and migrants may have different cultural beliefs about health and disease, and these beliefs should be considered when designing surveillance systems. They should be tailored to the specific needs of the refugee population (73). The types of infectious diseases that are a risk in a particular refugee population will vary depending on the country of origin of the refugees, their travel history, and the conditions in the refugee camp. To overcome these barriers, effective communication should be empowered, including the development of information materials in multiple languages and the encouragement of cooperation between host countries and organizations working with migrants (74, 75). In this context, public health authorities, particularly the Local Health Units, should avail themselves of cultural mediators and specific personnel with skills to effectively communicate with these at-risk populations. Moreover, healthcare providers should be culturally sensitive, understand potential cultural concerns, and preferably speak migrants' languages (76). Furthermore, to ensure equitable access, financial barriers should be removed (77, 78). One significant challenge in this context is vaccine hesitancy among refugees, influenced by various factors, including lack of available information in the native language of the immigrants' country of origin, vaccine safety concerns or lack of awareness, logistical difficulties, and fear of legal consequences (79-81). Addressing these concerns necessitates culturally sensitive communication tailored to the diverse backgrounds of the refugee population, as well as measures to overcome language barriers and enhance trust in the local healthcare system (20).

European governments have a responsibility to ensure the health of all people, including migrants. This encompasses taking steps to prevent the spread of infectious diseases. European governments can take many steps to help prevent the spread of infectious diseases in the migrant population, including providing access to vaccination, implementing surveillance programs, and providing access to quality healthcare (82). Significant policy disparities exist throughout Europe concerning vaccination strategies for both adult and child migrants. To enhance vaccine delivery and uptake in diverse migrant populations across the region, there should be an increased focus on disseminating migrant-specific guidance to frontline healthcare professionals (83). Moreover, governments and institutions should identify efficient ways of conveying recommendations to develop more effective health-related risk communication to vulnerable groups of migrants (84). The protection of health in the migrant population is essential for the health of the host population because infectious diseases can easily spread from one population to another. For example, public health institutions must remain vigilant for the potential reemergence of poliomyelitis virus 1 until it is completely eradicated. Reserves of OPV vaccine are readily available in case the wild virus is reintroduced within European territory (85). When migrants are healthy, they are less likely to spread infectious diseases to the host population. In addition, protecting the health of the migrant population is a matter of fairness and social justice. All people, regardless of their immigration status, have the right to be healthy (86).

In addition to the steps mentioned above, European governments should also interact with international organizations and Non-Governmental Organizations (NGOs) to ensure the protection and safeguarding of the health of migrants. International organizations, such as the World Health Organization (WHO) and the United Nations High Commissioner for Refugees (UNHCR), have developed guidelines and recommendations for the prevention and control of infectious diseases in migrant populations (87, 88). European governments should use these guidelines to develop their policies and programs. NGOs, such as Médecins Sans Frontières (MSF) and Doctors Without Borders (DWB), provide direct healthcare services to migrants. European governments should work with NGOs to ensure migrants access quality healthcare, including preventive care. By working with international organizations and NGOs, European governments can help to ensure that migrants have access to the healthcare they need to stay healthy.

The study has several limitations, such as a restricted analysis of existing literature and a lack of robust quantitative data sources, which prevented a

meta-analysis. One major limitation is the reliance on a single digital archive (MEDLINE/Pubmed). This choice was made due to the need for a rapid review, given the ongoing Russo-Ukrainian and Israeli-Palestinian conflicts, as well as the urgency to provide an updated perspective on the prevention and control of infectious diseases among refugees and asylum seekers. However, despite these limitations, this study is noteworthy for offering the most comprehensive overview of the topic to date and addressing various aspects of prevention. Furthermore, the selected studies encompass several EU/EEA countries, providing a nearly complete picture of the situation in Europe. Additionally, the study specifically examines the impact of the COVID-19 pandemic on the health of refugees, migrants, and asylum seekers.

In essence, protecting migrant health has far-reaching implications for public health. It is not only a matter of humanitarian responsibility but a strategic approach to ensuring the well-being and resilience of host communities and addressing global health concerns. Public health policies and actions that prioritize migrant health are essential for building healthier, more resilient, and inclusive societies. The health of populations is a significant focus of the UN Sustainable Development Goals. Goal 10 explicitly targets migration and calls for the medical and scientific community to understand the complex dynamics of migration. This requires a trans-disciplinary approach that combines humanitarian, economic, sociological, and public health perspectives. Accessing and improving basic rights, including healthcare, along transit routes is a definite priority (89).

The significance of this study is further highlighted in the context of the ongoing conflicts in Ukraine and Palestine. European countries are already witnessing the migration of individuals fleeing from these conflict zones, and it is expected that these flows will increase. From a public health perspective, understanding the factors influencing infectious disease risk and the role of vaccination and preventive measures is of paramount importance in addressing the health needs of these vulnerable populations and safeguarding the broader public health of the host nations (90).

Effective vaccination and preventive strategies for migrants, refugees, and asylum seekers are vital for public health and the well-being of these populations. They should be delivered as part of universal healthcare system (91). By reducing barriers and implementing tailored programs, we can ensure equitable access to vaccines and protect the health of these vulnerable individuals.

**Abbreviations**
ECDC: European Centre for Disease Prevention and Control
WHO: World Health Organization
UNHCR: United Nations High Commissioner for Refugees

**Conflict of interest:** The authors declare that they have no competing interests.
**Funding:** The study has been funded by Italian Society of Hygiene, Preventive Medicine and Public Health (S.It.I.).
**Acknowledgment:** On behalf of the Working Group on "Emergency Preparedness and Management" of the Italian Society of Hygiene, Preventive Medicine and Public Health (S.It.I.)

## Riassunto

***Profilo di rischio infettivo e strategie per la prevenzione e il controllo dei focolai epidemici tra rifugiati, richiedenti asilo e migranti nei Paesi dell'UE/EEA: una revisione sistematica delle evidenze***

**Introduzione.** L'incremento recente della migrazione verso e all'interno dell'Unione Europea e dell'Area Economica Europea ha portato le politiche migratorie, comprese quella sanitarie, al centro delle priorità dei singoli Paesi membri. Mentre i migranti, in generale, non costituiscono una minaccia per la salute della popolazione ospitante, specifici sottogruppi, tra cui i rifugiati, i richiedenti asilo e i migranti irregolari, possono essere particolarmente vulnerabili alle malattie infettive. Per sostenere le politiche di sanità pubblica in questo settore, il gruppo di lavoro "Prevenzione e gestione delle emergenze" della Società Italiana di Igiene, Medicina Preventiva e Sanità Pubblica ha condotto una revisione sistematica narrativa con l'obiettivo di definire il rischio di malattie infettive nelle popolazioni di rifugiati e richiedenti asilo nei Paesi dell'UE, EEA e candidati all'UE.

**Metodi.** Quarantadue studi sono stati selezionati sistematicamente da articoli scientifici estratti dal database MEDLINE/PubMed dal 1° gennaio 2008 al 1° giugno 2023. Il rischio infettivo associato a ciascuna malattia infettiva tra rifugiati e richiedenti asilo, nonché le strategie per prevenire e controllare i focolai epidemici, sono stati raccolti da tutti gli studi inclusi nella review.

**Risultati.** Le condizioni di vita congregata nei campi profughi, nei centri di transito e nelle strutture abitative temporanee rendono la popolazione in studio particolarmente vulnerabile alle malattie infettive. Pertanto, è fondamentale attuare misure igieniche e preventive rigorose per salvaguardare la salute dei rifugiati e ridurre il rischio di focolai che potrebbero interessare sia la popolazione rifugiata che le comunità ospitanti.

**Conclusioni.** Strategie di vaccinazione efficaci e misure preventive per migranti, rifugiati e richiedenti asilo sono vitali per la salute pubblica e il benessere di queste popolazioni. Esse dovrebbero essere fornite come parte dell'assistenza sanitaria universale. Definendo le barriere alle misure di prevenzione e attuando programmi mirati, possiamo garantire un accesso equo ai vaccini e alle cure e proteggere la salute di questa popolazione particolarmente vulnerabile.

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Ann Ig. 2024 Sep-Oct; 36(5): 569-579 doi: 10.7416/ai.2024.2625. Epub 2024 Mar 28.

# Vaccine hesitancy in South Tyrol: a narrative review of insights and strategies for public health improvement

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*Keywords: Vaccine Hesitancy; Public Health; Cultural Diversity; Health Communication; Trust in Healthcare*
*Parole chiave: Esitazione Vaccinale; Salute Pubblica; Diversità Culturale; Comunicazione Sanitaria; Fiducia nelle Istituzioni Sanitarie*

**Abstract**

***Introduction.*** *This review examines vaccine hesitancy in South Tyrol, Italy, a region characterized by cultural and linguistic diversity. The critical need for vaccination to control infectious diseases contrasts with the region's low vaccination rates, which pose a significant public health challenge.*
***Methods.*** *Based on literature, reports, and studies, we used PubMed, Embase, and Google Scholar to explore vaccine hesitancy in South Tyrol. It emphasizes the analysis of historical, cultural, and socioeconomic factors, and focuses on quantitative surveys and qualitative interviews to understand the roots of vaccine hesitancy.*
***Results.*** *In two studies with four reports, mistrust in health policies and institutions, misinformation, and cultural and linguistic barriers were identified as key factors contributing to vaccine hesitancy in South Tyrol. These factors are accentuated by the region's unique sociopolitical landscape, which influences public health policies and vaccination initiatives.*
***Conclusions.*** *These findings highlight the need for public health strategies specifically tailored to South Tyrol. Recommended actions include developing culturally sensitive and multilingual communication campaigns, increasing community involvement, and rebuilding trust in healthcare systems. These approaches are essential for addressing the specific challenges in South Tyrol, thereby improving vaccine uptake and overall public health outcomes.*

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Annali di Igiene : Medicina Preventiva e di Comunità (Ann Ig)
ISSN 1120-9135 https://www.annali-igiene.it

## Introduction

Vaccination, a major public health success, faces challenges owing to the rising anti-vaccine sentiment. The European Union area, as revealed by the Vaccine Confidence Project in 2016, exhibits lower confidence in vaccine safety (1), with Italy among the countries showing significant hesitancy (2). This skepticism contributed to a major measles outbreak in Italy in 2017, linked to persistently low vaccination rates since the introduction in 1976 (3). Despite initiatives such as the National Plan of Measles and Congenital Rubella Elimination, aimed at 95% coverage (4), sociopolitical factors and rising populism have fueled skepticism and hindered these goals. Efforts to counteract this trend include the "VaccinarSì" portal by the Italian Society of Hygiene that offers accessible scientific vaccination information (5). However challenges, such as declining user engagement with the portal persisted, highlighting the ongoing battle against vaccine hesitancy (6).

Administratively, the Italian Republic is divided into 19 regions and two autonomous provinces, Trentino and Alto Adige | South Tyrol (7), forming the Trentino-Alto Adige autonomous region. Each province has legislative power, yet vaccination has been subject to the national plan since 2017 (8). South Tyrol has a unique sociocultural landscape that significantly influences public health initiatives, including vaccination programs. A notable characteristic of the region is its linguistic diversity, with German speakers constituting approximately 70% of the population, Italian speakers constituting around 25%, and the Ladin community making up about 5%. This multilingual composition is a result of the region's complex history, marked by periods of conflict and cultural tension between German and Italian-speaking communities. The resolution of these conflicts in the early 1970s through the granting of special autonomy to South Tyrol was pivotal in the region's history, establishing a framework for peaceful coexistence and cultural preservation (9). This unique political and cultural arrangement has implications for public health policies, including vaccination strategies, because it necessitates culturally sensitive and linguistically diverse approaches to health communication and intervention. The intertwining of these linguistic groups, along with South Tyrol's distinct governance structure, provides a backdrop against which vaccine hesitancy and acceptance must be understood, underscoring the need for tailored public health strategies that respect and address the region's diverse cultural and linguistic needs.

Vaccine hesitancy is particularly pronounced in the South Tyrol. In 2003, the study of Kreidl and Morosetti (10), which focused on the autonomous Province of Bolzano, revealed that the MMR (Measles, Mumps, and Rubella) vaccine coverage was notably low, especially in rural areas with coverage rates as low as 40%, compared to 80% in urban areas. They also observed a linguistic dimension, where the communes with a higher percentage of Italian-speaking inhabitants had greater vaccine coverage than those that were predominantly German-speaking. These disparities contributed to measles epidemics in 1997 and 1999, predominantly affecting children aged five–nine years, and were particularly severe in communes, with vaccine coverage rates below 40% (10). Their findings underscored the urgency of addressing vaccine hesitancy in South Tyrol. In 2006, another cluster of measles cases was linked to low vaccination rates, particularly within the Roma/Sinti communities in South Tyrol (11).

In 2021, poliomyelitis vaccination coverage at two years of age in South Tyrol was markedly lower than that in other Italian regions, including the neighboring Trentino. With South Tyrol at 75.62% and Trento at 94.84%, the contrast is stark if compared to the Italian national average of 94.00% (12). This gap points to specific challenges in vaccine acceptance and uptake within South Tyrol. Moreover, a similar pattern emerges in influenza vaccination rates among the elderly in South Tyrol, which consistently lags behind those in Trentino and other regions (13). Despite ongoing public health initiatives to improve vaccination, these persistently lower rates across multiple vaccines and demographic groups in South Tyrol highlight broader issues of vaccine hesitancy. Such enduring trends highlight the critical need for specialized interventions to effectively address the roots of vaccine hesitancy in the region.

The COVID-19 pandemic provided an unprecedented opportunity to observe health behavior dynamics in real time, particularly in South Tyrol, where mass testing initiatives have revealed critical insights. The study by Stillman and Tonin (14) found that testing uptake was closely related to community characteristics, such as local prevalence of the virus, access to testing facilities, and public trust in health authorities. In a region like South Tyrol, marked by its cultural and linguistic diversity, the decision to participate in health measures, such as testing, was significantly influenced by these community factors. Furthermore, the study highlighted the role of social networks and the flow of information in shaping

individuals' responses to public health measures, indicating that vaccine acceptance and testing behaviors are the product of an interplay of social, economic, and cultural elements (15).

This narrative review aimed to systematically explore the complex phenomenon of vaccine hesitancy in the socio-politically unique region of South Tyrol. By bringing together the threads of historical context, linguistic diversity, and the impact of recent public health challenges, this study aimed to derive lessons from past and present vaccination efforts. The goal was to identify the underlying factors that contribute to vaccine hesitancy and to propose informed strategies that could improve vaccine uptake. This review seeks to contribute to the broader discourse on public health in diverse cultural settings and to support the development of effective, culturally congruent health policies that can serve as models for similar regions faced with vaccine hesitancy.

## Methods

*Searching Strategy*

To analyze vaccine hesitancy in South Tyrol, a systematic literature search was conducted across multiple databases guided by a set of specific search terms. PubMed searches were conducted using the terms "(vaccine OR vaccination) AND (((South Tyrol[Title/Abstract]) OR (Alto Adige[Title/Abstract]) OR (Bolzano[Title/Abstract])))". The search yielded a total of 23 records. On EBSCOhost's CINAHL database, the search terms used were "TX (Vaccine OR Vaccination) AND AB ("South Tyrol" OR "Alto Adige" OR "Bolzano") OR TI ("South Tyrol" OR "Alto Adige" OR "Bolzano")." The search returned 35 records. In Embase, the search strategy employed was "('vaccine'/exp OR vaccine OR 'vaccination'/exp OR vaccination) AND ('south tyrol':ab,ti OR 'bolzano':ab,ti)," resulting in 25 records.

From these searches, a total of 83 records were identified. After removing 21 duplicate records, 62 records were screened.

*Study Selection*

The primary criterion for study selection was the direct relevance of the article to vaccinations or vaccine-related issues. Articles that did not specifically address vaccination, vaccine hesitancy, vaccine uptake, or related topics were excluded at the initial stage. Given the specific focus on South Tyrol, articles that did not pertain to this geographical area were excluded. Animal and wildlife vaccination studies were excluded because they were not the target population. Peer-reviewed research articles and original study results were analyzed, excluding publications such as reviews, editorials, or commentaries. No restrictions on the language or date of publication were provided.

The results of the search are presented in Figure 1. Of the 62 records, four reports from two studies met all the inclusion criteria and were selected for this review.

## Results

The systematic literature search on vaccine hesitancy in South Tyrol yielded only two original studies, resulting in four publications (16-19), all of which were conducted by the affiliated institution of this narrative review, with no other independent study articles identified. One of the two studies was identified as a survey assessing vaccination attitudes quantitatively (16–18), while the other employed a qualitative methodology to explore in depth the underlying reasons for vaccine hesitancy (19). The survey used a cross-sectional design and captured vaccine-related attitudes of the population. This study involved a significant cohort of subjects, with over thousand participants surveyed in detail, ensuring that the sample was stratified to reflect the linguistic and demographic diversity of the region. Attitudes towards vaccines, vaccination intentions, and trust in vaccine information sources were assessed in more detail, along with a range of sociodemographic variables such as age, education, and language group (16). Complementing this, qualitative research has examined the psyche of the community through a series of structured interviews, exploring the layers of individual and collective influences on vaccine hesitancy (19). Together, these studies provide a methodologically comprehensive picture of the vaccine hesitancy landscape, contributing refined and actionable data to inform culturally congruent public health strategies.

*Prevalence and Correlates of Vaccine Hesitancy in South Tyrol*

In the initial phase of the COVID-19 vaccination campaign in South Tyrol, a quantitative study was conducted to understand the prevalence and factors associated with vaccine hesitancy (16). The COVID-19 findings are summarized in Table 1.

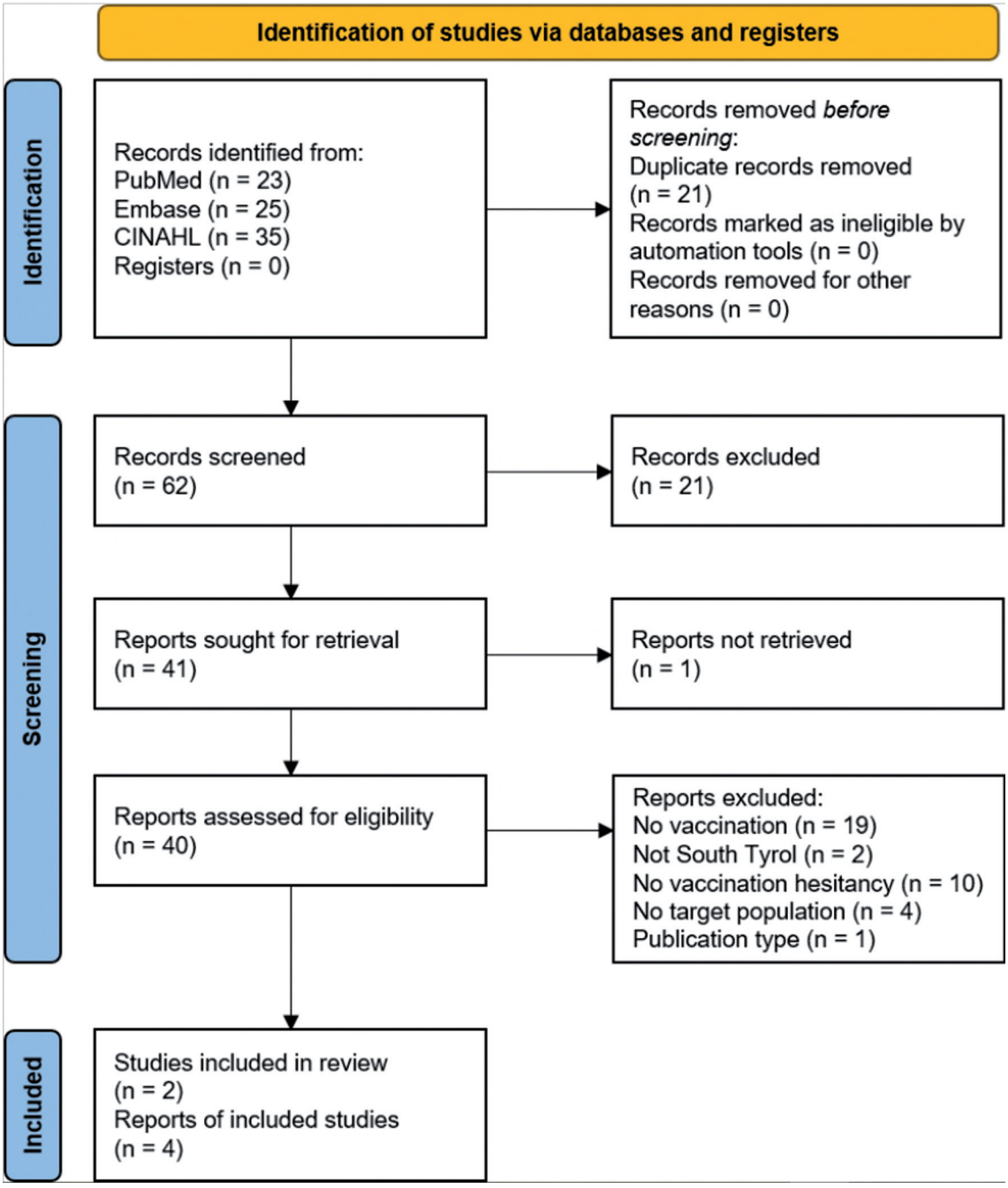


Figure 1 - PRISMA 2020 Flow Diagram for Reports on Vaccine Hesitancy in South Tyrol, Which Included Searches of Databases and Registers Only

Table 1 - Prevalence and Correlates of Vaccine Hesitancy for COVID-19 Vaccination at the Start of the Vaccination Campaign in South Tyrol

| Variable | Prevalence and Correlates of Hesitancy [1] |
|---|---|
| General Prevalence | 15.6% |
| Demographic Factors | |
| Age Group | Higher among younger participants |
| Educational Level | Higher among participants with lower education |
| Health-Related Factors | |
| Chronic Illness | Higher among participants without chronic illness |
| Socioeconomic and Cultural Factors | |
| Trust in Institutions | Lower among distrustful participants; associated with conspiratorial thinking |
| Economic Status | Higher in worse economic situations |
| Family Structure | Higher in families with children aged 0-6 years |
| Place of Residence [2] | Higher in rural areas; not an independent predictor in logistic regression analysis |
| Linguistic Group | Significantly varies; not an independent predictor in logistic regression analysis |

[1] Vaccine hesitancy in this study was assessed through a dichotomous question asking participants, 'Would you get vaccinated against COVID-19?' Responses to this question were used to categorize participants as hesitant or non-hesitant towards receiving the COVID-19 vaccine.
[2] South Tyrol is an alpine region with approximately 533.000 inhabitants and an area of 7.400 km$^2$. According to the official definition, eight towns (219,340 inhabitants) were categorized as *urban areas* and all other villages as *rural areas.*

The overall prevalence of vaccination hesitancy was 15.6%. Notably, younger participants showed a higher inclination towards hesitancy compared to older age groups. Additionally, hesitancy was more pronounced among individuals with lower educational levels, highlighting the role of educational attainment in shaping vaccine attitudes. Participants without chronic diseases were more likely to exhibit vaccine hesitancy, suggesting a perception of lower personal risks. There was a lower level of hesitancy among participants who trusted institutions, but a link to conspiracy thinking was observed in distrustful institutions. Economic distress due to the pandemic also played a role, with greater hesitancy observed in those in worse economic situations. Interestingly, families with children aged 0-6 years showed higher vaccine hesitancy, indicating specific concerns or considerations among parents of young children (16).

Geographical factors, such as residing in rural areas, showed higher hesitancy, although this was not an independent predictor in the logistic regression analysis (17). Similarly, linguistic group membership showed significant variance in vaccine hesitancy but was not an independent predictor (16). This study suggests that while linguistic group membership shows variance in hesitancy, it is not an independent predictor when considering other factors. In particular, higher education levels and trust in institutions, which vary across linguistic groups, may play key roles in explaining this. Italian-speaking participants had higher educational levels, potentially translating to better health literacy. Moreover, the levels of trust in institutions also appear to be closely related to linguistic group membership. Italian speakers, for instance, exhibit higher trust levels in national and regional institutions than German or Ladin speakers (16).

Differences in education, trust, and linguistic group membership are not only distinct between linguistic groups but also between rural and urban participants. In urban areas, 27.9% of participants had a university education compared to 14.5% in rural areas, suggesting a link between educational attainment and vaccine hesitancy (17). Trust in various health and government institutions differed significantly between urban and rural residents, with urban residents generally exhibiting higher levels of trust. The geographic characteristics of being rural or urban may not be independent predictors of vaccine hesitancy because of their level of education. A significant proportion of the German-speaking population, that accounted for 61.7% of the total participants in the study, predominantly resided in rural areas (80.0% of German speakers), compared to Italian speakers who were more concentrated in urban areas (52.7% of Italian speakers). German speakers in the study displayed more risk factors associated with vaccine hesitancy, such as lower education levels and

higher levels of mistrust in institutions. Given that rural areas have a higher concentration of German-speaking residents, this explains the higher prevalence of hesitancy in these areas (17).

Altruism influences attitudes towards COVID-19 vaccination and public health measures, especially in the sociocultural context of South Tyrol. In general, altruistic individuals are more likely to agree with and follow public health guidelines and less likely to believe in conspiracy theories or misinformation about COVID-19. The differences in altruism scores between vaccine-hesitant and non-hesitant individuals are small, suggesting that, while higher altruism is slightly more associated with lower vaccine hesitancy in the elderly, its overall influence remains modest (18). This highlights that, in South Tyrol, where different linguistic groups and rural-urban diversities with different levels of education and trust in institutions intersect, altruism is only one part of a complex set of factors influencing vaccine hesitancy. The unique demographic characteristics of the region suggest that understanding vaccine hesitancy requires consideration of a range of motivational and psychological factors beyond singular traits, such as altruism.

*Motivational and psychological factors of vaccine hesitancy in South Tyrol*

A qualitative study on vaccine hesitancy and refusal provides insights into the personal, relational, and structural factors influencing vaccine hesitancy in South Tyrol (19). Conducted through in-depth interviews with vaccine-skeptical parents, the study focuses on pediatric vaccination and describes individual experiences, social contexts, and perceptions of healthcare and state systems that shape vaccination decisions.

In understanding vaccine hesitancy, the concept of "self-relatedness" was apparent among parents, highlighting the role of individual experiences and perceptions in determining attitudes towards vaccination. This concept underscores the importance that participants place on their individual experiences and how these experiences shape their perceptions and attitudes towards vaccination. Participants often relied on information from personal social circles, which tended to consist of like-minded individuals, reinforcing their existing vaccination attitudes. This suggests a tendency to seek and accept information that aligns with pre-existing beliefs, creating a feedback loop that further reinforces vaccine skepticism.

The study also found that participants harbored distrust of healthcare professionals and state orders, perceiving them as one-sided and uncritical. The participants perceived themselves as tolerant and health-conscious, yet critical, questioning the mainstream narratives of health care (19).

This mistrust, rooted in negative experiences of the healthcare system, was exacerbated by the COVID-19 pandemic. In the quantitative study, the majority of participants (about three-quarters) did not change their attitudes towards mandatory vaccination for non-coronavirus diseases as a result of the pandemic, and about one-fifth of participants became more supportive of vaccination as a result of the pandemic. This shift was more pronounced among non-hesitant participants, with 23% showing increased support for mandatory childhood vaccinations. By contrast, among hesitant participants, a significant proportion (35%) became less supportive of such mandates (16). This divergence in attitudes can be linked to the concept of "self-relatedness", which implies that personal experiences and perceptions strongly influence individuals' attitudes towards health-related issues, including vaccination. As a global health crisis with a direct personal impact, the pandemic is likely to have reinforced people's pre-existing beliefs and attitudes towards vaccines and public health measures. Those who were already inclined to trust vaccination and public health guidelines may have increased their support because of heightened awareness of health risks and the importance of vaccines. Conversely, those who were hesitant or skeptical may have become more entrenched in their views, especially if their personal experiences during the pandemic reinforced their mistrust or skepticism.

Interestingly, the label "No-vax" was met with resistance by participants, who did not identify themselves with this media-created social phenomenon. They displayed high sensitivity to health issues and preferred informed decisions based on their understanding of health and illness. This highlights the importance of personal autonomy in health-related decision-making (19). The findings emphasize the need for appreciative, personal, and well-founded information exchanges with vaccine-hesitant individuals. This underscores the necessity for broad and comprehensible information dissemination, along with flexibility and freedom of choice, to enhance informed decision-msaking regarding vaccination.

## Discussion

A review of vaccine hesitancy in South Tyrol identified two key studies: a quantitative survey of

COVID-19 vaccination (16-18) and a qualitative analysis of parental attitudes towards childhood vaccination (19). The survey revealed a vaccine hesitancy rate of 16%, which was influenced by factors such as age, economic status, family structure, and pandemic burden. Education level and trust in institutions are particularly important in understanding the variance in vaccine hesitancy between linguistic and geographical groups. The qualitative study highlighted 'self-relatedness' as a key factor, emphasizing the influence of personal experiences and perceptions on vaccination attitudes. It revealed a complex set of individual, relational, and structural factors, including mistrust of healthcare and a preference for informed, autonomous decision-making.

Melot et al. (20) found that 18% of respondents in Trentino were vaccine-hesitant in 2019 before the pandemic, particularly among younger people and those with lower levels of information, highlighting the reliance on healthcare professionals and the Internet for vaccine-related information. Given this pre-pandemic hesitancy rate in Trentino, it is plausible that the 16% hesitancy rate observed in South Tyrol during the pandemic (12, 13) may be an underestimate, considering the lower vaccination rates in South Tyrol than in Trentino (12, 13) and the potential positive effects on vaccination acceptance of COVID-19 as an immediate health threat (21). Although vaccine hesitancy in South Tyrol (16%) and Trentino (18%) appears similar, the significant differences in vaccination rates suggest that additional factors, such as service accessibility and convenience, could also play a role, especially if the impact of the pandemic on the hesitancy rate in South Tyrol is considered minimal.

When analyzing studies conducted during the COVID-19 pandemic, the results, including the estimated 16% vaccine hesitancy rate in South Tyrol, may have been significantly influenced by the pandemic context. This is in line with the study by Giardiello et al. (22) on COVID-19 testing in the rural Val Venosta/Vinschgau district of South Tyrol, where testing behavior was influenced more by pandemic-related contextual factors than by individual characteristics. Key influencing factors included symptoms, exposure to infected individuals, and reporting times aligned with the severity of the pandemic and public health measures. This suggests that even in the case of vaccine hesitancy, external circumstances, in addition to sociodemographic factors, influence vaccination decisions.

In South Tyrol, different patterns of health information seeking, influenced by age, sex, education, and language, may contribute to these differences in vaccination rates. A 2014 survey showed that Italian speakers in South Tyrol predominantly used online platforms for health information, while German speakers showed a preference for interpersonal sources, including discussions with health professionals and advice from friends and family, which may influence the way vaccination messages are received and acted upon (23).

An additional factor influencing vaccine hesitancy among the German-speaking population in South Tyrol could be their preference for German language information sources. When German-speaking South Tyroleans search for health information online, such as 'Pflichtimpfungen Kinder' (mandatory vaccinations children), they often encounter content relevant to Germany and Austria where vaccination policies differ from those in Italy. This discrepancy in information can create a sense of arbitrariness and uncertainty as they are exposed to differing regulations and recommendations. By contrast, Italian-speaking citizens are more likely to access coherent and consistent information, as they predominantly seek and consume Italian language sources. This divergence in the initial informational landscape between German and Italian speakers might have contributed to differing perceptions and attitudes towards vaccinations. Understanding these language-based disparities in information access is crucial for developing effective communication strategies that address the specific needs and contexts of the diverse linguistic groups in South Tyrol.

A study of COVID-19 mass testing in South Tyrol by Stillman and Tonin (14) highlighted how community characteristics such as convenience, social capital, and attitudes towards public health interventions align with factors influencing vaccine hesitancy. Higher testing rates were associated with socioeconomic status, religiosity, and lower childhood vaccine refusal, suggesting a complex relationship between trust, community engagement, and health beliefs and shedding light on the dynamics of vaccine hesitancy in the region.

Additional findings on COVID-19 vaccine adherence in South Tyrol highlight the impact of geographical, cultural, and sociodemographic characteristics on vaccination rates, supporting the findings of the narrative review on vaccine hesitancy. The study was conducted in all districts of South Tyrol and analyzed variables such as altitude, population density, and linguistic affiliation. In early 2022, there

was notable variation in vaccine adherence, ranging from 57.1% to 74.8%, with lower rates in areas with higher altitudes, lower population densities, and a greater prevalence of German speakers or those with German cultural heritage (24). These results reflect the importance of geographic diversity and the influence of cultural and linguistic factors on health behavior.

*Recommendations and Future Directions for Research and Policy*

Strategies to address vaccine hesitancy in South Tyrol are summarized in Table 2, tailored to the specific needs of South Tyrol's diverse communities, with a particular focus on German-speaking (predominantly rural) and Italian-speaking (predominantly urban) populations.

Therefore, the health systems must be strengthened. The focus was on improving access to healthcare in rural areas. For German-speaking/rural communities, this could include improving the availability of vaccines at local health facilities. For Italian speaking/ urban populations, improving health infrastructure and access to services in urban centers is equally important.

Culturally congruent communication strategies require a more person-centered approach. This recommendation focuses on the use of culturally sensitive communication channels. In German-speaking/rural areas, this may involve more use of local media and interpersonal communication than in Italian-speaking/urban communities, where digital platforms are more likely to be used, and social media may be more effective.

Given the significant impact of education level and trust in healthcazre systems on vaccine hesitancy (25), as confirmed in the South Tyrol studies (16-19), two recommendations are critical. First, tailoring educational materials to different literacy levels and cultural contexts is essential for promoting vaccine literacy. For rural communities, this could include community workshops, whereas urban areas could benefit from multilingual online educational campaigns. Second, to build trust, initiatives should include transparent communication and ethical health care practices. In rural areas, this could mean more community engagement activities, whereas in urban areas, it could involve public forums and open dialogue with health professionals.

A better understanding of how socioeconomic factors and community engagement affect vaccine

Table 2 - Strategies to Address Vaccine Hesitancy in South Tyrol: Focused Recommendations for Diverse Communities

| Variable | | Recommentations [1] |
|---|---|---|
| Healthcare System Enhancements | German-Speaking / Rural | Enhanced healthcare and vaccination accessibility |
| | Italian-Speaking / Urban | Enhanced healthcare accessibility |
| Culturally Congruent Communication | German-Speaking / Rural | Interpersonal communication, local media outreach |
| | Italian-Speaking / Urban | Online platforms and social media use |
| Vaccine Literacy Promotion | German-Speaking / Rural | Tailored educational materials and campaigns |
| | Italian-Speaking / Urban | Multilingual and culturally sensitive education |
| Trust-Building Initiatives | General Recommendations | Transparent communication<br>Community engagement<br>Cultural sensitivity through open dialogue<br>Respectful interaction<br>Active listening |
| Research on Contextual Influences | German-Speaking / Rural | Socio-economic and community engagement impact |
| | Italian-Speaking / Urban: | Pandemic and external influence effects |
| Policy Interventions for Specific Subpopulations | German-Speaking / Rural | Policies tailored to rural and German-speaking needs |
| | Italian-Speaking / Urban | Urban-focused public health campaigns and strategies |
| Investment in Primary Care | German-Speaking / Rural | Strengthen family medicine and primary care |
| | Italian-Speaking / Urban | Invest in urban primary care facilities and resources |

[1] The recommendations provided in the table are organized to address the specific needs of diverse communities within South Tyrol, particularly focusing on the German-speaking people, predominantly residing in rural areas and Italian-speaking populations, who are primarily found in the region's urban areas. The "German-Speaking / Rural" lines contain strategies tailored to the cultural, linguistic, and geographical characteristics of the German-speaking population. In contrast, the "Italian-Speaking / Urban" lines present approaches more suited to the Italian-speaking residents, who are primarily found in the region's urban areas. These recommendations are designed to be flexible and adaptable, acknowledging the unique challenges and opportunities in each setting for effectively addressing vaccine hesitancy.

hesitancy is essential. In rural areas, this could include studying the impact of community ties, whereas in urban areas, research could focus on the influence of urban lifestyles and infrastructure on health behaviors.

It is essential to tailor public health policies to meet the specific needs of different groups. In rural areas, this could mean policies that address the unique challenges faced by these communities, whereas in urban areas, it could mean strategies that target urban population density and the multiple lifestyles.

Enhancing primary care is crucial for effective vaccine uptake, especially considering the pivotal role of general practitioners (25). In rural areas, this could mean bolstering family medicine practices by establishing Primary Care Units staffed with specially trained nursing personnel focused on targeted counseling and vaccine education. Similarly, in urban areas, the expansion of primary care resources should include similar units, equipped to handle higher patient demand. Addressing the increasing shortage of general practitioners is vital, making this recommendation increasingly pertinent (26). Additionally, offering comprehensive training programs for healthcare professionals on effective communication with vaccine sceptics is essential. These programs should provide strategies for engaging in constructive dialogues, addressing misconceptions, and building trust with patients who may be hesitant about vaccinations. By focusing on these areas, primary care can become more responsive and effective in addressing the unique challenges posed by vaccine hesitancy in both rural and urban settings.

*Limitations of the Included Studies*

However, it is important to acknowledge the inherent limitations of these studies. In quantitative surveys (16-18), the use of a non-probability sampling method may limit the generalizability of the results. The self-administered nature of the survey may have introduced information biases, and the study questionnaire did not extend to exploring the underlying reasons for vaccine hesitancy. The timing of data collection during the initial phase of the COVID-19 vaccination campaign may also have influenced the participants' responses, reflecting the current state of the pandemic and evolving information about the vaccine. In addition, psychological factors influencing vaccine hesitancy have not been extensively investigated. The typical limitations of qualitative research are likely to apply to the second study (19). These include potential limitations on the generalizability of the findings due to the small and specific sample size, the possibility of researcher bias in data interpretation, and a focus that prioritizes depth of understanding over breadth, which may miss broader trends or patterns.

The limitations of our study include the initial lack of specific data on vaccine literacy levels among different native language groups in South Tyrol. Recognizing this gap, the Institute of Statistics of Alto Adige|South Tyrol (ASTAT) is undertaking a survey using the European Health Literacy Survey (EU-HLS 16) questionnaire to assess health and vaccine literacy. This initiative will provide insights for tailoring health education interventions to the unique needs and challenges of each population group.

## Conclusion

This narrative review sheds light on the complex dynamics of vaccine hesitancy in South Tyrol, which is influenced by its distinctive cultural and linguistic diversity. Two studies analyzed in four reports highlighted that vaccine hesitancy is linked to the socio-cultural context of the region, ranging from individual to geographical factors. This review highlights the need for public health strategies specifically tailored to the region's more German-speaking rural population and more Italian-speaking urban population. The critical roles of family medicine, primary care, and community engagement in building trust and facilitating culturally appropriate communication are also evident. The COVID-19 pandemic has further complicated vaccine hesitancy, emphasizing the importance of adaptable and responsive public health strategies. Therefore, addressing vaccine hesitancy in South Tyrol requires a multidisciplinary approach that integrates cultural sensitivity with ongoing research to inform effective public health policies and interventions. This approach is essential for improving vaccine uptake and promoting the overall public health in this region.

**Funding:** This study did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

**CRediT authorship contribution statement:** ***Christian J. Wiedermann:*** Conceptualization, methodology, writing, and editing of the manuscript. ***Verena Barbieri*****:** Conceptualization, literature analysis, writing, and editing of the manuscript. ***Barbara Plagg*****:** Editing manuscript. ***Giuliano Piccoliori:*** Editing of the manuscript. ***Adolf Engl*****:** Editing of the manuscript and supervision

**Declaration of Competing Interest:** None.

## Riassunto

***Esitazione vaccinale in Alto Adige: una revisione narrativa su intuizioni e strategie per il miglioramento della salute pubblica***

**Introduzione**. Questa revisione esamina l'esitazione vaccinale in Alto Adige, Italia, una regione contraddistinta dalla sua diversità culturale e linguistica. La necessità cruciale della vaccinazione nel controllo delle malattie infettive contrasta con i bassi tassi di vaccinazione della regione, rappresentando una sfida significativa per la salute pubblica.

**Metodi**. Attingendo dalla letteratura, dai report e dagli studi, la revisione utilizza PubMed, Embase e Google Scholar per esplorare l'esitazione vaccinale in Alto Adige. Pone l'accento sull'analisi dei fattori storici, culturali e socio-economici, concentrando l'attenzione su metodi qualitativi, sondaggi e interviste per comprendere le radici dell'esitazione vaccinale.

**Risultati**. La revisione identifica la sfiducia nelle istituzioni sanitarie, la disinformazione e le barriere culturali e linguistiche come fattori chiave che contribuiscono all'esitazione vaccinale in Alto Adige. Questi fattori sono ulteriormente intensificati dal particolare contesto socio-politico della regione, influenzando le misure di salute pubblica e le iniziative di vaccinazione.

**Conclusione**. I risultati evidenziano l'importanza di strategie di salute pubblica pensate specificamente per l'Alto Adige. Le azioni raccomandate includono lo sviluppo di campagne di comunicazione culturalmente sensibili e multilingue, un maggiore coinvolgimento della comunità e il ristabilimento della fiducia nei sistemi sanitari. Questi approcci sono essenziali per affrontare le sfide specifiche dell'Alto Adige, migliorando così l'adozione del vaccino e i risultati complessivi in termini di salute pubblica.


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Ann Ig. 2024 Sep-Oct; 36(5): 581-587 doi: 10.7416/ai.2024.2627. Epub 2024 Apr 3.

# A snapshot of Physical Education in Italian primary schools: assessing the resources available for an instrument of health promotion

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*Keywords: Physical Activity; Children; Prevention; Teacher; Gym*
*Parole chiave: Attività Motoria; Bambini; Prevenzione; Insegnante; Palestra*

**Abstract**

***Background.*** *Regular physical activity is crucial in preventing chronic diseases. International health authorities recommend that children and adolescents engage in at least 60 minutes of moderate to vigorous physical activity per day to achieve health benefits. Offering regular exercise opportunities to young people can promote the development of healthy lifestyles. In 2021, a new regulation introduced up to two compulsory hours of Physical Education per week in Italy and established that Physical Education should be entrusted to adequately trained teachers. The present study aimed to assess, from the perspective of the new teachers, the resources available for Physical Education in Italian primary schools.*

***Methods.*** *A questionnaire-based cross-sectional study was conducted among primary school Physical Education teachers during the year 2022-2023. Their opinion about the school resources were analyzed in light of their demographic characteristics and work experience.*

***Results.*** *Out of the 118 participating teachers, 96 (81.3%) reported the presence of a gym in their school. Participants expressed satisfaction with the size and windows of the gym, particularly for the schools of the North, as well as the adequacy of outdoor*

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Annali di Igiene : Medicina Preventiva e di Comunità (Ann Ig)
ISSN 1120-9135 https://www.annali-igiene.it

*spaces. However, lower levels of satisfaction for locker rooms and gym small equipment emerged, especially among those teachers with less work experience.*
***Conclusions.*** *The introduction of the Physical Education teacher figure in Italian primary schools was an important step for health promotion in our country. However, some aspects related to the structural resources should be considered in future policies.*

## Introduction

Physical activity (PA) was recently defined as "people moving, acting and performing within culturally specific spaces and contexts, and influenced by a unique array of interests" (1).

According to scientific evidence, PA practiced in children and adolescents has multiple beneficial outcomes such as cardiorespiratory fitness, academic performance, cognitive functioning, and social and mental health (2-5).

The recent guidelines published by the World Health Organization (WHO) and several other European international health agencies guidelines suggested that children and adolescents from 5 to 17 years of age should perform at least an average of 60 minutes of moderate to vigorous physical activity (MVPA) per day to obtain healthy benefits (6-8). To promote movement experiences in different settings, the WHO member States are invited to identify effective multi-sectoral approaches, with the involvement of the health, sports, and education sectors, paying particular attention to the need of counteracting the rapid decline in PA levels and the consequent decline in motor skills during developmental age (9).

During childhood and youth, the practice of physical education (PE) at school offers excellent opportunity to learn and practice skills that can improve long-term fitness and health the course of life. All European countries recognize the importance of PE at school including PE classes as part of everyone curricula both primary and secondary schools. As stated by the "National indications for the curriculum of nursery school and the first cycle of education" by the Italian Ministry of School in 2012, PE in the first cycle of school (i.e., primary school) should promote knowledge of oneself and one's potential in the constant relationship with the environment, the others and the objects. It contributes to the formation of the students' personality through knowledge and awareness of their own bodily identity as well as the continuous need for movement as constant care of one's person and one's well-being (10).

However, the percentage of children attending primary school in Italy who met the recommended levels of PA is lower than 19.9% (11). The report on PE practice published by the European Commission in 2013 showed Italy in a low rank position, with no mandatory PE classes and trained teachers in primary schools. PE teaching was assigned to other teachers, sometimes supported by graduate assistants in PE on the basis of a project initiative (12).

With the introduction of the law no. 234/2021, up to two mandatory hours per week of PE were finally introduced in the fifth class of the Italian primary schools starting from the 2022/2023 school year and in the fourth class starting from the 2023/2024 school year (13). The new law in force established for the first time the assignment of PE teaching to properly trained teachers.

In a public health perspective, the new regulation can represent an important health promotion strategy. However, in order to ensure that the new teachers can fulfill their role and children can really benefit from this action by increasing their PA level and enhance their skills, it is fundamental that schools are able to provide even adequate facilities and equipment for PE teaching (14). Given this consideration, the present study was aimed to assess, from the point of view of the new teachers, the resources available for PE in the Italian primary schools.

## Methods

*Study design and procedures*

This cross-sectional study was performed by the Working Group "Movement Sciences for Health" of the Italian Society of Hygiene, Preventive Medicine and Public Health between May and July 2023 across the whole Italian territory. A web-based questionnaire was used to collect teachers' data and opinions. Teachers were invited to participate through the website of the Italian Confederation of the Associations of Physical Education Teachers (CAPDI & LSM) and social media. Before completing

the questionnaire, participants were asked to provide their informed consent to the collection and treatment of personal information. The study was approved by the Research Committee of the University of Rome "Foro Italico" (approval n. CAR 165/2023). All the procedures followed the principles of the Declaration of Helsinki.

*Participants*

Only teachers who were engaged in teaching PE in Italian primary school during the school year 2022-2023 were specifically invited to participate. Estimating a total population of 14,804 teachers (at least one for each Italian primary school) (15), a sample of at least 375 teachers would have been required assuming a 95% confidence level and a 50% response proportion.

*Questionnaire*

A link to an anonymous questionnaire structured in a Google form was provided to the teachers. The questionnaire included a brief description of the aim of the study and two subsequent sections. The first section was aimed at collecting socio-demographic information: gender, age, type of degree, region of the school they worked in during the school year 2023-24, number of previous years of PE teaching performed in primary, middle or high schools. The second section was aimed at exploring the presence of gyms, outdoor places dedicated to PE and swimming pools in the school they worked in. Furthermore, participants were asked to provide their opinion about suitability of available places, availability of great or small gym equipment, adequacy of locker rooms, toilets and fenestration, and to express an overall judgment about the teaching performed in the last school year. A Likert 5-point scale was used to collect their satisfaction, with 1 = "very dissatisfied" and 5 = "very satisfied".

*Statistical analyses*

A descriptive analysis was performed on the participants' sociodemographic characteristics and reported information about the available resources. Quantitative data were expressed as mean values ± Standard Deviation (SD) or median and Inter-Quartile Range (IQR) considering their distribution, while categorical variables were summarized as number and percentage of respondents for each category. Kendall's and Spearman's correlation analyses were performed to highlight possible associations between participants' characteristics and their judgments about school resources for PE and teaching performed. A value of p=0.05 was assumed as level of significance. Statistical analyses were performed using the Statistical Package for Social Science (SPSS) version 28.0 (IMB; Armonk, NY, USA).

## Results

A total of 118 teachers (62.7% females, mean age 39.2±10.2 years) participated in the survey. Table 1 shows the main characteristics of the sample.

Ninety-six (81.3%) of the teachers reported the presence of a gym in the school in which they worked in the last year. Only three of them declared that the gym was not feasible. In 85 cases (88.5%) the school gym was reported to be used by local associations after school time, and 53 (62.3%) of them had separated entrances. No swimming pools were present in the schools in which participants worked. Outdoor spaces for PE were reported by 41 (34.7%) respondents. Thirteen of these were reported for schools which did not have a gym available.

As for the judgments expressed towards the suitability of school structures and equipment for PE, the lower satisfaction was expressed for locker rooms and gym equipment, while the higher satisfaction was declared towards gym dimensions and fenestration, and outdoor spaces adequacy (Table 2).

In the correlation analyses, male gender was shown to be related with better judgment about gym equipment and toilets, while a negative correlation was found between school allocation in Center/Southern regions and opinion about gym fenestration (Table 3). Having previously worked in a primary school was positively related with the opinion about the availability of small equipment, locker rooms adequacy and gym fenestration.

The sample expressed a highly positive overall judgment regarding their own teaching experience (mean satisfaction value 3.97±0.99). In the correlation analysis, their satisfaction level did not correlate with any of the variables examined.

## Discussion

Lights and shadows regarding PE teaching in Italian primary schools emerged from this survey. First of all, more than 80% of the respondents reported the presence of a gym in the school, and this number is higher than the 40.8% reported in 2018 for all Italian schools (16). Furthermore, outdoor spaces for PE were

Table 1 - Main characteristics of participants.

| Variable | N (%) |
|---|---|
| Geographical area | |
| North | 60 (50.8) |
| Center | 25 (21.2) |
| South | 33 (28.0) |
| Previous teaching in primary schools | |
| no | 28 (23.7) |
| yes | 90 (76.3) |
| years (mean±SD) | 6.5±7.7 |
| Previous teaching in middle schools | |
| no | 64 (54.2) |
| yes | 54 (45.8) |
| years (mean±SD) | 2.8±3.0 |
| Previous teaching in high schools | |
| no | 62 (52.5) |
| yes | 56 (47.5) |
| years (mean±SD) | 2.4±3.6 |

reported for the majority of the schools where a gym was lacking. However, it should be noted that around 20% of participants reported no gym, no one reported swimming pools, and 65% reported no available outdoor spaces for PE, which represents a critical issue especially considering that in 2021 about 330 million euros were allocated by the Italian government in a school sports infrastructure plan aimed at improving the safety of existing spaces and building new gyms in the schools (17).

As for the judgments about the available resources, they were generally at an average rating. Participants expressed lower satisfaction for locker rooms and gym equipment and higher satisfaction towards gym dimensions and fenestration, and outdoor spaces adequacy. Gender and previous teaching experiences in the primary school were found to be related with these judgments. These findings could be related

Table 2 - Personal judgment about the adequacy of gym and outdoor spaces of the school for physical education.

| Variable | Opinion (mean±SD; median, IQR) |
|---|---|
| Suitability of gym dimensions | 3.69±0.97; 4, 3-4 |
| Suitability of great gym equipment | 2.62±1.16; 3, 2-3 |
| Availability of small equipment in the gym | 3.24±1.20; 3, 2-4 |
| Adequacy of locker rooms in the gym | 2.60±1.35; 3, 1-4 |
| Adequacy of gym toilets | 2.79±1.26; 3, 2-4 |
| Adequacy of gym fenestration | 3.30±1.23; 3, 2-4 |
| Suitability of outdoor spaces | 3.51±1.12; 3, 3-5 |

Table 3 - Results of the Kendall's or Spearman's correlation analyses performed between participants' characteristics and their judgments about school resources for physical education.

| Variable | Kendall's tau-b/Spearman's Rho<br>*p value* | | | | | | |
|---|---|---|---|---|---|---|---|
| | Age | Gender | Education | Geographical area | Primary school teaching | Middle school teaching | High school teaching |
| Suitability of gym dimensions | 0.044<br>*0.671* | -0.019<br>*0.868* | -0.005<br>*0.949* | -0.022<br>*0.811* | 0.076<br>*0.524* | 0.036<br>*0.813* | -0.200<br>*0.199* |
| Suitability of gym equipment | -0.074<br>*0.472* | **0.243**<br>***0.009*** | 0.065<br>*0.449* | -0.075<br>*0.398* | 0.044<br>*0.714* | 0.167<br>*0.268* | -0.008<br>*0.962* |
| Availability of little sport tools in the gym | 0.084<br>*0.417* | 0.042<br>*0.652* | -0.104<br>*0.220* | -0.068<br>*0.441* | **0.285**<br>***0.014*** | 0.168<br>*0.265* | -0.082<br>*0.603* |
| Adequacy of locker rooms in the gym | -0.052<br>*0.613* | 0.145<br>*0.116* | 0.127<br>*0.133* | -0.094<br>*0.285* | **0.257**<br>***0.028*** | 0.121<br>*0.422* | -0.078<br>*0.618* |
| Adequacy of gym toilets | 0.034<br>*0.740* | **0.209**<br>***0.024*** | 0.053<br>*0.533* | -0.107<br>*0.227* | 0.187<br>*0.113* | 0.135<br>*0.370* | -0.031<br>*0.844* |
| Adequacy of gym fenestration | 0.162<br>*0.116* | 0.048<br>*0.601* | -0.084<br>*0.320* | **-0.252**<br>***0.004*** | **0.338**<br>***0.003*** | 0.290<br>*0.051* | 0.204<br>*0.189* |
| Suitability of outdoor spaces | -0.019<br>*0.906* | -0.186<br>*0.200* | -0.028<br>*0.834* | -0.036<br>*0.791* | 0.032<br>*0.861* | 0.308<br>*0.213* | 0.172<br>*0.481* |

with a different individual perception of some environmental aspects. It should be noted also that the opinion regarding the adequacy of fenestration was inversely related to the geographical area of the school. Although an association was found only regarding this aspect, it should be considered that it could be related with the worst condition of school buildings which was previously reported for Central and Southern Italian regions (16). Further research should explore in depth these geographical differences.

The analyzed structural aspects should be considered in future policies regarding health promotion at school. In fact, altough facility provision alone may not be enough to support higher levels of physical activity among children, as this also depends on adequate supervision and instruction, the availability of facilities and equipment is associated with more physical activity opportunities, especially for disadvantaged groups (18-20). Therefore, an improvement in structural conditions and equipment of school gyms should proceed hand in hand with the application of the new legislation concerning PE. Our investigation did not explore how teachers faced the lack of facilities or equipment during their work. Therefore, we cannot speculate on how this aspect affected the renewed PE teaching. Future studies should analyze this possible relationship.

A general positive judgment was expressed by participants regarding their teaching experience. Interestingly, these judgments were independent of individual characteristics and geographical area. This is in line with the findings of a scoping literature aimed at identifying the predictors of PE teachers' satisfaction, which showed that workplace and interpersonal relationships, more than demographic variables, may influence how teachers experience their work (21).

This study has some limitation. First of all, the sample cannot be considered representative of the whole population of teachers involved in PE teaching in the Italian primary schools during the year examined. The number of participants was not sufficient to reach the needed statistical power and the proportion of respondents from northern Italy was slightly higher than the expected value of 43.9% (15). Second, the information related to the available resources should be interpreted with caution, since they were self-reported and not objectively assessed.

However, this study has the merit of having provided a snapshot of the introduction of the PE teachers in Italian primary schools, which represented an important step for health promotion in our country. Since PE hours contribute to the achievement of the recommended amount of daily MVPA (22), it is hoped that this strategy can have positive effects on PA levels and physical fitness of Italian children. Future research should be addressed at assessing these effects to verify the effectiveness of this strategy and its possible extension to the lower school years.

**Acknowledgements:** The authors would like to thank the Italian Confederation of the Associations of Physical Education Teachers (CAPDI & LSM) for having contributed to the enrollment of the participants, Dr. Michele Felisatti for his contribute to the organization of the survey and all the teachers who participated in the survey.

**Data availability:** The datasets used during the study are available upon reasonable request from the corresponding author.

**Ethical Approval:** Data were collected in completely anonymous form. However, nurses were asked to give informed consent prior to participating in the study and completing the questionnaires. The study protocol was in line with the Declaration of Helsinki.

**Conflict of Interest:** The authors declare that they have no conflicts of interest.

## Riassunto

***Un'istantanea dell'insegnamento di educazione fisica nelle scuole primarie italiane: valutazione delle risorse disponibili per uno strumento di promozione della salute***

**Premessa.** Un'attività fisica regolare svolge un ruolo importante nella prevenzione delle malattie croniche. Le autorità sanitarie internazionali raccomandano che i bambini e gli adolescenti svolgano almeno 60 minuti di attività fisica da moderata a vigorosa al giorno per ottenere benefici di salute. Offrire regolari opportunità ai giovani di fare movimento può facilitare lo sviluppo di stili di vita sani. Nel 2021 in Italia è stata emanata una nuova normativa che stabilisce l'introduzione di fino a due ore settimanali obbligatorie di educazione motoria e l'affidamento dell'insegnamento a docenti adeguatamente formati. Il presente studio è stato finalizzato a valutare, dal punto di vista dei nuovi insegnanti, le risorse disponibili per l'insegnamento di educazione motoria nelle scuole primarie italiane.

**Metodi.** Uno studio trasversale basato su un questionario è stato svolto tra gli insegnanti di educazione motoria nella scuola primaria italiana nell'anno scolastico 2022-2023.

**Risultati.** Novantasei (81,3%) dei 118 insegnanti partecipanti hanno segnalato la presenza di una palestra nella scuola in cui hanno lavorato nell'ultimo anno, con un buon livello di gradimento per le dimensioni e le finestrature, soprattutto per le scuole del Nord, e per l'adeguatezza degli spazi esterni, e un minore gradimento per gli spogliatoi e le attrezzature delle palestre, riportato soprattutto da docenti con minore esperienza di insegnamento.

**Conclusioni.** L'introduzione dell'insegnante di educazione fisica nelle scuole primarie italiane ha rappresentato un passo importante per la promozione della salute in Italia. Tuttavia, alcuni aspetti relativi alle strutture disponibili andrebbero considerati nelle future azioni.

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Ann Ig. 2024 Sep-Oct; 36(5): 588-596 doi: 10.7416/ai.2024.2628. Epub 2024 Apr 18.

# Knowledge and self-perceived competence about cardiopulmonary resuscitation among youths: a cross-sectional study in a sample of Italian undergraduates

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*Keywords: Cardiovascular disease; University students; Heart attack symptoms; Emergency; Cardiopulmonary Resuscitation*

*Parole chiave: Malattie cardiovascolari; Studenti universitari; Sintomi di attacco cardiaco; Emergenza; Rianimazione cardiopolmonare*

**Abstract**

***Introduction.*** *Cardiopulmonary resuscitation is fundamental to improve the outcomes of a life-threatening event. The correct knowledge of first aid actions to provide may guarantee the victim's survival. This study was aimed at evaluating the competence about cardiopulmonary resuscitation and its predictors in a sample of Italian undergraduate students.*

***Methods.*** *Information on socio-demographic characteristics, first aid training, knowledge of stroke and heart attack symptoms and perceived ability to provide first aid, were collected through a web-based questionnaire.*

***Results.*** *On a total of 744 respondents (mean age 23.9±5.4 years, 62.5% female), 71.4% identified correctly first aid actions, 59.9% and 60.8% showed a good knowledge of stroke and heart attack symptoms, respectively. However, only 39.0% of them declared their ability to intervene in case of emergency. Attending a healthcare degree course and having had first aid training were associated with knowledge of symptoms and perceived ability to provide first aid. Female gender was negatively related with perceived ability to intervene.*

***Conclusions.*** *In spite of the satisfactory level of knowledge, these findings highlight the need to enhance the competence about cardiopulmonary resuscitation in the lay population, especially among females.*

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Annali di Igiene : Medicina Preventiva e di Comunità (Ann Ig)
ISSN 1120-9135 https://www.annali-igiene.it

## Introduction

Cardiovascular diseases (CVDs) are the leading cause of death globally, sustaining 31% of all global deaths. Overall, 85% of cardiovascular deaths are due to heart attack and stroke (1, 2). In particular, the incidence rate of heart attack was calculated as 40.6 per 100,000 person-years in Europe, 47.3 in North America, 45.9 in Asia, and 51.1 in Australia (3-5). A quarter of patients affected by this disease have an initial ventricular fibrillation, which evolves into asystole before extra-hospital rescuers arrive (6). Thus, shortening the time before resuscitative manoeuvres is crucial to improve outcomes in cardiac arrest cases (7-11). Indeed, if the resuscitation actions are performed within the first minute, the chances of success are up to 98%, while from the fifth minute on, the chances drop to 25%, and survival rates drop to 1% if the resuscitation manoeuvres are performed after ten minutes (12). However, in most developed countries, it takes at least 8-12 minutes to emergency medical services to reach the location after a victim's collapse, making immediate relief impossible (13). In these situations, each spectator, also any lay rescuer, can play a key role, providing first aid (14, 15). The critical lifesaving steps are i) prevention, ii) immediate recognition of the clinical signs of cardiac arrest (loss of consciousness, abnormal breathing patterns and no pulse) and iii) activation of the emergency response system, iv) early high-quality cardiopulmonary resuscitation, and rapid defibrillation for shockable rhythms (16). Three of these actions can also be performed by lay people (17). Some factors, such as an available telephone guide, educational training, or the presence and use knowledge of an automated external defibrillator (AED) may be helpful in increasing survival, supporting the resuscitator (14-17). In support of the importance of these factors, especially the presence of an AED, Okabayashi et al. (18) found significant differences in the outcomes of an out-of-hospital cardiac arrest based on where it occurs. In particular, cardiac arrests occurring in public showed the best outcomes respect to those occurring in residential area or nursing facilities, probably due to the presence of other people who intervene for resuscitation and the increased availability of public-access automatic external defibrillators.

Governments and health authorities have developed laws and guidelines to improve training of lay people in cardiopulmonary resuscitation (19-21). However, the literature shows that the general population and even the medical students seem not to be sufficiently prepared to face such emergencies (22-25).

The objective of this study was to evaluate the competence about cardiopulmonary resuscitation among Italian undergraduate students attending healthcare and other degree courses. To this aim their knowledge of stroke and heart attack symptoms and their perceived ability to provide first aid were evaluated. Furthermore, possible predictors of these variables were also investigated.

## Materials and Methods

*Study design and participants*

The present cross-sectional study was nested in the "Study on undergraduates Preparation on cardiovascular Events and Risks" – SPERi – conducted among undergraduate students from three universities located in central and southern Italy by using a web-based questionnaire. Students from the Universities "Sapienza" and "Foro Italico" of Rome and "Parthenope" of Naples participated in the study and data were collected between January 2021 and December 2022. Participation was voluntary and anonymous. The survey was performed according to the principles of the Declaration of Helsinki. Ethical approval was obtained from the Research Committee of the University of Rome "Foro Italico" (approval n CAR 80/2021).

*Questionnaire*

A questionnaire was adapted for the purposes of this investigation from tools used in previous studies (26-29). The following topics were investigated: socio-demographic information (age, gender, university, degree course attended, educational level of parents), attendance of a first aid and basic life support/defibrillation training courses, ability to identify normal blood pressure values, correct order of first aid actions, symptoms of stroke/TIA (trouble speaking, sudden weakness or loss of vision, sudden and severe headache, sudden numbness, weakness or paralysis in the face, arm, or leg, especially in one side of the body, unexplained dizziness) and of heart attack (chest pain, fatigue, nausea, pain or discomfort in neck, arm, or shoulder, chest tightness, shortness of breath), and a self-evaluation about how competent they feel to act in an emergency situation or in the event of a cardiac arrest on a scale from 1 to 10, with 1 representing the lowest level and 10 representing the highest level. The questionnaire was preliminary validated by its administration to 20 participants

with similar age and education level of the study population to identify any critical issues (such as structure, clarity and comprehensibility of questions and answers). Subsequently, the questionnaire was modified according to the comments and suggestions of the respondents who participated in the validation. The validity of the tool was also assessing by using Cronbach's alpha statistical index. The questionnaire was administered through Google modules platform.

*Statistical analysis*

Statistical software STATA® (STATA 17.0, Stat-aCorp LLC, College Station, TX, USA) was used to conduct statistical analyses. First of all, a descriptive analysis was performed on collected data. The sample's age distribution had an appreciable skewness; therefore, we determined the median age (22 years) and dichotomized the age variable into two groups: those aged 19 to 22 and those older than 22. The number of correct answers regarding knowledge of stroke/TIA and heart attack symptoms was quantified, and the median of correct answers was calculated: 4 out of 5 for stroke/TIA and 5 out of 6 for heart attack. Participants were then classified as those who provided at least as many correct answers regarding both stroke/TIA and heart attack symptoms equal or higher than the median value and those who did not. A further dichotomic variable was created, indicating the participants' perceived ability to provide first aid, based on their self-evaluation score: not enough, with a score from 1 to 5, and enough, with a score from 6 to 10.

The Chi-squared test was used, in univariate analyses, to assess potential variations in participants' characteristics for each of these dichotomous variables.

Multiple logistic regression analyses were performed by considering knowledge of stroke symptoms, knowledge of heart attack symptoms, and ability to provide first aid as outcome, and considering variables that showed significant differences in the univariate analyses for each outcome as possible predictors. Odds Ratios and corresponding 95% Confidence Intervals (OR 95%CI) were reported. The significance level assumed was $p<0.05$.

## Results

A total of 744 complete questionnaires were obtained. Table 1 shows the socio-demographic characteristics of the sample.

Table 2 shows the proportions of participants with correct knowledge of normal blood pressure values and sequence of first aid actions, good or poor knowledge of symptoms associated with stroke and heart attack, and the perceived ability to provide first aid to a victim of one of these events. The majority of the sample showed good levels of knowledge about the items proposed. However, only the 39% of

Table 1 - Socio-demographic characteristics of the sample (n=744).

| Variable | Value |
|---|---|
| Age, mean±SD | 23.9±5.4 |
| median (IQR) | 22 (3) |
| Gender, n (%) | |
| female | 465 (62.5) |
| male | 279 (37.5) |
| Mother's educational level, n (%) | |
| mandatory | 149 (20) |
| high school | 351 (47.2) |
| degree | 244 (32.8) |
| Father's educational level, n (%) | |
| mandatory | 183 (24.6) |
| high school | 346 (46.5) |
| degree | 215 (28.9) |
| Educational area | |
| healthcare | 434 (58.3) |
| other | 310 (41.7) |
| First aid training | |
| no | 291 (39.1) |
| yes | 453 (60.9) |

Table 2 - Participants' knowledge of stroke and heart attack symptoms and perceived ability to provide first aid.

| Variable | Participants n (%) |
|---|---|
| Correct knowledge of normal blood pressure values | |
| no | 300 (40.3) |
| yes | 444 (59.7) |
| Correct knowledge of first aid actions | |
| no | 213 (28.6) |
| yes | 531 (71.4) |
| Knowledge of stroke symptoms | |
| poor | 298 (40.1) |
| good | 446 (59.9) |
| Knowledge of heart attack symptoms | |
| poor | 292 (39.2) |
| good | 452 (60.8) |
| Ability to provide first aid | |
| not enough | 454 (61.0) |
| enough | 290 (39.0) |

respondents perceived themselves as able to provide first aid, if needed. Table 3, 4 and 5 show the results of the comparison of socio-demographic characteristics performed through chi-squared test between subgroups defined by knowledge of stroke symptoms, knowledge of heart attack symptoms and perceived ability to provide first aid. Higher age was more represented among participants with better knowledge of heart attack symptoms and with a lower perceived ability to provide first aid. Female participants showed better symptoms knowledge but lower perceived ability to provide first aid. Parents' educational level did not differ between the subgroups, while those with better symptoms knowledge included higher proportions of students who attended healthcare degree courses. Those who received first aid training exhibited better symptoms knowledge and higher ability to provide first aid. A good knowledge of both stroke and heart attack symptoms is more common among those who reported higher confidence in their ability to provide first aid.

The results of the regression analyses are reported in Table 6. Good knowledge of stroke symptoms was found to be positively related with (a) female gender, (b) attending a healthcare degree course and (c) having had a first aid training, while good knowledge of heart attack symptoms was associated with higher age, better healthcare education and first aid training. Perceived ability to provide first aid was positively related with higher age, healthcare educational area, first aid training and good symptoms knowledge, and negatively related with female gender.

## Discussion

The first relevant finding of the present study is related to the percentage of the sample with correct knowledge about normal blood pressure values, first aid actions order, and symptoms associated with stroke and heart attack: most of the participants showed good levels of knowledge about the items proposed. This result is in line with those reported previously by other studies. For example, a cross-sectional study conducted among students of the National Polytechnic Institute of Côte d'Ivoire evidenced that, overall, the majority of the participants were aware of hypertension, its causes and consequences (30). Another study performed to evaluate the awareness of university students toward strokes demonstrated that the participants presented an adequate knowledge on the main risk factors and warning symptoms of this syndrome (31). Besides, a research carried out to assess university students' level of knowledge and awareness on some medical conditions including hypertension, stroke, and myocardial infarction, showed that more than 80% of the participants correctly identified symptoms and complications of

Table 3 - Differences in characteristics of participants grouped by level of stroke symptoms knowledge.

| | Knowledge of stroke symptoms | | *p* value |
|---|---|---|---|
| Variable | Poor n=298 | Good n=446 | |
| Age | | | |
| ≤22 years | 164 (42.0) | 226 (58.0) | 0.243 |
| >22 years | 134 (37.8) | 220 (62.2) | |
| Gender | | | |
| female | 168 (36.1) | 297 (63.9) | 0.005 |
| male | 130 (46.6) | 149 (53.4) | |
| Mother's educational level | | | |
| mandatory/high school | 210 (42.0) | 290 (58.0) | 0.121 |
| degree | 88 (36.0) | 156 (64.0) | |
| Father's educational level | | | |
| mandatory/high school | 224 (42.3) | 305 (57.7) | 0.046 |
| degree | 74 (34.4) | 141 (65.6) | |
| Educational area | | | |
| other than healthcare | 155 (50.0) | 155 (50.0) | <0.001 |
| healthcare | 143 (32.9) | 291 (67.1) | |
| First aid training | | | |
| no | 136 (46.7) | 155 (53.3) | 0.003 |
| yes | 162 (35.8) | 291 (64.2) | |

Table 4 - Differences in characteristics of participants grouped by level of heart attack symptoms knowledge.

| | Knowledge of heart attack symptoms | | p value |
|---|---|---|---|
| Variable | poor n=292 | good n=452 | |
| Age | | | |
| ≤22 years | 177 (45.4) | 213 (54.6) | <0.001 |
| >22 years | 115 (32.5) | 239 (67.5) | |
| Gender | | | |
| female | 167 (35.9) | 298 (64.1) | 0.016 |
| male | 125 (44.8) | 154 (55.2) | |
| Mother's educational level | | | |
| mandatory/high school | 198 (39.6) | 302 (60.4) | 0.778 |
| degree | 94 (38.5) | 150 (61.5) | |
| Father's educational level | | | |
| mandatory/high school | 208 (39.3) | 321 (60.7) | 0.950 |
| degree | 84 (39.1) | 131 (60.9) | |
| Educational area | | | |
| other than healthcare | 158 (54.1) | 152 (45.9) | <0.001 |
| healthcare | 134 (30.9) | 300 (69.1) | |
| First aid training | | | |
| no | 136 (46.6) | 155 (53.4) | 0.001 |
| yes | 156 (34.4) | 297 (65.6) | |

Table 5 - Differences in characteristics of participants grouped by level of perceived ability to provide first aid.

| | Perceived ability to provide first aid | | |
|---|---|---|---|
| Variable | not enough n=454 | enough n=290 | *p* value |
| Age | | | |
| ≤22 years | 266 (68.2) | 124 (31.8) | <0.001 |
| >22 years | 188 (53.1) | 166 (46.9) | |
| Gender | | | |
| female | 316 (67.9) | 149 (32.1) | <0.001 |
| male | 138 (49.5) | 141 (50.5) | |
| Mother's educational level | | | |
| mandatory/high school | 314 (62.8) | 186 (37.2) | 0.154 |
| degree | 140 (57.4) | 104 (42.6) | |
| Father's educational level | | | |
| mandatory/high school | 330 (62.4) | 199 (37.6) | 0.233 |
| degree | 124 (57.7) | 91 (42.3) | |
| Educational area | | | |
| other than healthcare | 194 (62.6) | 116 (37.4) | 0.461 |
| healthcare | 260 (59.9) | 174 (40.1) | |
| First aid training | | | |
| no | 230 (79.0) | 61 (21.0) | 0.001 |
| yes | 224 (49.4) | 229 (50.6) | |
| Knowledge of stroke symptoms | | | |
| poor | 202 (67.8) | 96 (32.2) | 0.002 |
| good | 252 (56.5) | 194 (43.5) | |
| Knowledge of heart attack symptoms | | | |
| poor | 202 (69.2) | 90 (30.8) | <0.001 |
| good | 252 (55.8) | 200 (44.2) | |

Table 6 - Results of the regression analyses performed on symptoms knowledge and perceived competence as outcomes.

| | Outcome<br>OR (CI95%)<br>p value | | |
|---|---|---|---|
| Variable | Stroke<br>symptoms knowledge | Heart attack<br>symptoms knowledge | Perceived ability<br>to provide first aid |
| Age<br>(>22 years) | 1.19 (0.87-1.62)<br>0.300 | 1.77 (1.29-2.43)<br><0.001 | 1.44 (1.04-1.99)<br>0.027 |
| Gender<br>(female) | 1.44 (1.05-1.98)<br>0.023 | 1.35 (0.98-1.87)<br>0.064 | 0.44 (0.32-0.61)<br><0.001 |
| Father's educational level<br>(degree) | 1.21 (0.86-1.72)<br>0.300 | n. s. | n. s. |
| Educational area<br>(healthcare) | 1.83 (1.34-2.51)<br><0.001 | 2.29 (1.67-3.13)<br><0.001 | n. s. |
| First aid training<br>(yes) | 1.53 (1.12-2.10)<br>0.007 | 1.51 (1.10-2.07)<br>0.011 | 3.30 (2.34-4.70)<br><0.001 |
| Knowledge of stroke symptoms<br>(good) | n. s. | n. s. | 1.44 (1.03-2.04)<br>0.036 |
| Knowledge of heart attack symptoms<br>(good) | n. s. | n. s. | 1.52 (1.07-2.15)<br>0.019 |

the investigated disorders (32). Probably, the great relevance of cardiovascular diseases has made them very popular and general population received much information from various sources, such as other persons and media. In this regard, a systematic review on knowledge of the symptoms of acute myocardial infarction evidenced a moderate - good knowledge of classic symptoms like pain or discomfort in arms or shoulders, chest pain or discomfort, shortness of breath. However, the results of the same review showed an insufficient knowledge of less obvious symptoms such as feeling of anxiety, headache, stomach or abdominal discomfort and nausea or vomiting (33), highlighting the need of disseminating information about lesser-known symptoms and signs of cardiovascular diseases and acute events.

Another relevant result of our study is related to the participants' perceived ability to provide first aid to a victim of acute cardiovascular events. Indeed, even if the overall knowledge of the appropriate sequence of first aid actions was "good" in the most part of the sample, only slightly more than a third of participants consider themselves sufficiently prepared to act adequately in the face of a subject with an acute life-threatening event. This result agrees with those found previously (34). A study investigating the level of first aid knowledge among university students revealed the inability of the majority of them to provide competent first aid in an emergency situation (35). Besides, another study in this field reported that about 20% of the students had met cases in which cardiopulmonary resuscitation was required and about 65% of them had not provided first aid due to the nervousness, lack of knowledge, and other issues (36).

As regard to the factors influencing the knowledge of stroke symptoms, of heart attack symptoms and the perceived ability to provide first aid, as expected, having had a first aid training were significant predictors in all cases. Moreover, attending a healthcare degree course was a significant predictor of the knowledge of stroke symptoms and of heart attack symptoms. Comparable results were found by Abdela et al. (37): students attending the college of medicine and health sciences were more knowledgeable about cardiovascular diseases respect to students from other colleges (37, 38). Similarly, other studies reported a significant higher knowledge of first-aid management in medical, respect to non-medical students (39).

Other significant predictors were age and gender. In particular, higher age was positively correlated with the knowledge of heart attack symptoms and the perceived ability to provide first aid.

Regarding to the gender difference, being female was positively correlated with the knowledge of stroke, but negatively associated to perceived ability to provide first aid. Overall, as demonstrated by a systematic review, female population seems to be more prepared in terms of knowledge in risk factor and in warning signs of stroke respect to male populatin (40). Despite of this evidence, we found a greater

perceived ability in males compared to females. The reasons behind these contrasting results should be further investigated. Indeed, in case of emergency, persons more knowledgeable could not intervene and, conversely, individuals less knowledgeable could intervene inappropriately.

This study presents some limitations. First of all, this is a cross-sectional study and the study population was selected by convenience. These two limitations reduce the generalizability of the results. However, the sample was composed with comparable proportions of participants of each gender and different educational areas, which allowed to highlight some differences between groups that need to be further explored.

## Conclusions

The findings of this study show a satisfactory level of knowledge about blood pressure and cardiovascular first aid in the majority of the sample examined. However, a low proportion declared a perceived ability to provide first aid in case of emergency, notwithstanding the training received. Given the importance to act immediately in front of an acute life-threatening event, it is essential to enhance the people's competence about cardiopulmonary resuscitation, especially among young individuals and those attending non-medical courses. Besides, females showed better knowledge but less confidence in their own ability to act in an emergency situation respect to males. This finding deserves to be investigated with further studies.

Funding: This study was partially funded by University of Rome "Foro Italico" Project [CUP H83C23000160001]
Conflict of interest: the authors declare no competing interests.
Informed consent: Informed consent was obtained from all individual participants included in the study.
Ethical approval: The research protocol was approved by the Research Committee of the University of Rome "Foro Italico" (approval n CAR 80/2021) and was in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments.

### Riassunto

***Conoscenze e competenze percepite dai giovani sulla rianimazione cardiopolmonare: uno studio trasversale su un campione di studenti universitari italiani***

**Premessa.** La rianimazione cardiopolmonare è fondamentale per migliorare gli esiti di un possibile evento avverso. La corretta conoscenza delle azioni di primo soccorso da fornire può garantire la sopravvivenza della vittima. Lo scopo di questo studio è stato quello di valutare la competenza sulla rianimazione cardiopolmonare e i suoi determinanti in un campione di studenti universitari italiani.

**Metodi.** Le caratteristiche socio-demografiche, la formazione sul primo soccorso, la conoscenza dei sintomi di ictus e infarto e la capacità percepita di fornire il primo soccorso sono informazioni che sono state raccolte attraverso un questionario online.

**Risultati.** Su un totale di 744 intervistati (età media 23,9±5,4 anni, 62,5% donne), il 71,4% ha identificato correttamente le azioni di primo soccorso, il 59,9% e il 60,8% hanno mostrato una buona conoscenza rispettivamente dei sintomi di ictus e infarto. Tuttavia, solo il 39,0% ha dichiarato di sentirsi competente ad intervenire in caso di emergenza. La frequenza di un corso di laurea in ambito sanitario e l'aver seguito una formazione di primo soccorso sono fattori che risultano associati alla conoscenza dei sintomi e alla capacità percepita di fornire il primo soccorso. Il genere femminile è stato correlato negativamente con la capacità di intervenire.

**Conclusioni.** Nonostante il livello soddisfacente di conoscenza, questi risultati evidenziano la necessità di migliorare le competenze sulla rianimazione cardiopolmonare nella popolazione laica, soprattutto tra le donne.

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Ann Ig. 2024 Sep-Oct; 36(5): 597-613 doi: 10.7416/ai.2024.2617. Epub 2024 Mar 1.

# Low-intensity rehabilitation in persistent post COVID-19 dyspnoea: the value of Spa health resort as appropriate setting

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*Keywords: Post COVID-19 syndrome; dyspnoea; fatigue; exercise intolerance; low-intensivity rehabilitation setting; Spa rehabilitation setting*

*Parole chiave: Sindrome post COVID-19; dispnea; affaticamento; intolleranza all'esercizio; contesto riabilitativo a bassa intensità; riabilitazione termale*

**Abstract**

***Background.*** *Post COVID-19 syndrome is a frequent disabling outcome, leading to a delay in social reintegration and return to working life.*

***Study design.*** *This was a prospective observational cohort study. The main objective was to explore the effectiveness of a Spa rehabilitation treatment on the improvement of post COVID-19 dyspnoea and fatigue, also analyzing the relationship between such symptoms. Additionally, it was assessed if different clinical characteristics could predispose patients in experiencing post COVID-19 symptoms or could influence the effectiveness of a Spa intervention.*

***Methods.*** *From July to November 2021, 187 post COVID-19 patients were enrolled in the study. All the patients complained persisting dyspnoea, whose impact on daily activities was assessed using the modified Medical Research Council dyspnoea scale. 144 patients (77.0%) reported also fatigue. The Spa treatment was started at least 3 months after COVID-19 acute phase. At the end of the treatment, patients were asked to rate the improvement in the dyspnoea and fatigue sensation. 118 patients also underwent the modified Borg Dyspnoea Scale for severity estimation of Exertion Dyspnoea and the Barthel index for severity estimation of Physical Limitation.*

***Results.*** *165 out of 187 patients (88.2%) reported an improvement in dyspnoea, while 116 out 144 patients (80.6%) reported an improvement in both dyspnoea and fatigue. On a total of 118 subjects, a clinically significant improvement in the modified Borg*

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Annali di Igiene : Medicina Preventiva e di Comunità (Ann Ig)
ISSN 1120-9135 https://www.annali-igiene.it

*Dyspnoea Scale (i.e. Delta Borg equal or more than -2.0 points) was reached by the 50.8% of patients, while a clinically significant improvement in the Barthel index (i.e. Delta Barthel equal or more than +10.0 points) was reached by the 51.7% of them. The 31.4% of patients reached a minimal clinically important improvement in both the modified Borg Dyspnoea Scale and the Barthel index. No risk factors were associated to a clinically impacting dyspnoea at entry, while a BMI>30 Kg/m$^2$ was the main risk factor for chronic fatigue. Presence of respiratory comorbidities, obesity and severe acute COVID-19 (phenotype 4) configured risk factors for the lack of improvement of dyspnoea after the treatment, while no risk factors were associated to a lack of improvement for fatigue. Older age, obesity and comorbidities seemed to make more difficult to reach a clinically meaningful improvement in the modified Borg Dyspnoea Scale and the Barthel index after treatment. Female gender may imply more physical limitation at entry, while male patients seem to show less improvement in the Barthel index after treatment.*

***Conclusions.*** *Dyspnoea and fatigue were confirmed to be important post COVID-19 symptoms even in younger subjects of working age and subjects with absent or modest pulmonary alterations at distance from acute COVID-19. A Spa health resort seems to be an effective "low-intensity" setting for a rehabilitation program of such patients. There is a strong relationship in terms of improvement between dyspnoea and fatigue, even if risk factors for their occurrence appear to be different. The improvement in exertion dyspnoea and physical limitation seemed to be less mutually related, probably due to a greater complexity in the assessment questionnaires. Some risk factors may predict a lack of improvement in symptoms after treatment.*

## Introduction

At the end of 2020 and in 2021, different authors coined the term of "post-acute COVID-19" to standardize that pattern of symptoms related to SARS-CoV-2 infection that some patients continue to complain even for months after the acute phase and negativization of the nasopharyngeal swab (1, 2). Currently, the World Health Organization (WHO) defines as "post COVID-19 syndrome" a condition characterized by persistent or new onset symptoms beyond 3 months from a probable or confirmed SARS-CoV-2 infection, after excluding other causes (3). The most common symptoms are fatigue and dyspnoea, but a variety of other persistent disturbances are reported, including cough, chest pain, myalgia, joint pain, cognitive impairment, sleep disorders, depression, anxiety, post-traumatic stress disorder, gastrointestinal upset, rashes, and palpitations (4, 5). The percentage frequency of such symptoms is highly variable depending on age, gender and the concomitant presence of other comorbidities. It ranges from 53 to 87% for fatigue and from 43 to 71% for dyspnoea (6-8).

Although the magnitude of the post COVID-19 syndrome is still unknown, its prevalence has been estimated to vary between 10 and 35% of infected individuals, whether treated in intensive or sub-intensive wards or at home (9, 10). Since million of individuals have been and still continue to be infected by SARS-CoV-2 worldwide, the societal impact of this new chronic health condition is likely to become economically relevant in terms of days off from work and utilisation of healthcare resources and treatment.

Post COVID-19 syndrome has been associated with reduced health-related quality of life and poor functional status. However, surprisingly, several studies have reported an apparent discrepancy between presence of symptoms limiting daily activities and lung function tests or chest CT. Indeed, in approximately 35% to 65% of patients exercise intolerance and dyspnoea were present despite normal pulmonary function tests and absence of abnormal chest CT findings (11-13). Based on these evidences, some authors have proposed the possibility of a distinct emerging long COVID-19 phenotype (14).

In order to reduce the possibility of long-term disabling outcomes, a coordinated American Thoracic Society (ATS)/European Respiratory Society (ERS) international task force recommended tailored rehabilitative interventions in all patients hospitalized with COVID-19, not only at the discharge from the hospital, but also after the resolution of the acute infection (15). The American Academy of Physical Medicine and Rehabilitation (AAPM&R) specifically recommended rehabilitation for patients with post

COVID-19 related fatigue and breathing discomfort to promote functional improvement and to facilitate a return to activities of daily living (16, 17). However, to date, evidence from high-quality trials on the effectiveness of rehabilitation programmes in post COVID-19 patients is scarce (18-20). In a systematic review and meta-analysis of the literature, Chen et al. (18) highlighted that effects of pulmonary rehabilitation on lung function and quality of life in post COVID-19 patients should be cautiously interpreted due to conflicting data across studies. Furthermore, data on younger patients (i.e. aged under 55 years), on non-hospitalized patients and on the effects of a rehabilitation treatment undertaken after a longer time (i.e. 6-9 months after the acute phase of COVID-19) are lacking (20). As a result, the same guidelines acknowledge the need for further research investigating the effectiveness of rehabilitation interventions and exercise for individuals with post COVID-19 syndrome (16, 17).

Unfortunately, there are no specific and adequate structures to receive the large number of post COVID-19 patients who need a rehabilitation treatment. To deal with this new health emergency, it is therefore necessary to identify alternative out of-hospital "low-intensity" rehabilitation settings allowing to reduce the pressure on hospital rehabilitation units, which are overworked by acute rehabilitation of COVID-19 patients.

From this perspective, some authors suggested a remotely monitored tele-rehabilitation programme that can be carried out at home (21-23). As another viable option, respiratory rehabilitation in Spa centers have been shown to improve respiratory functions, reduce mucus and chronic inflammation in the airways, ameliorate chest wall kinematics, and increase, not only physical health, but also mental wellbeing in patients with respiratory diseases (24). Already since 2021, almost 700 articles on the effectiveness of Spa treatments in chronic pulmonary diseases had been published and available on Pubmed (25-28). Starting from already existing rehabilitative plans prescribed for work-related respiratory diseases, some authors suggested a Spa-based rehabilitative program also in post-COVID-19 patients (29). Currently, a similar Spa rehabilitation program has been made available for post COVID-19 patients at the "Margherita di Savoia's Baths" (Italy).

On this background, the primary aim of this study was to explore through standardized clinical indices the effectiveness of a Spa respiratory rehabilitation treatment on the improvement of post COVID-19 dyspnoea and fatigue and to explore the relationship between such symptoms. Secondary aims were to assess if different clinical characteristics could predispose patients in experiencing post COVID-19 symptoms or could influence the achievement of the clinical outcomes of effectiveness after Spa intervention.

## Materials and methods

*Study setting and participants*

From July to November 2021, 340 patients who were referred for a Spa rehabilitation protocol of treatment to "Margherita di Savoia's Baths" (Italy) as a result of SARS-CoV2 infection during the first wave of pandemic in Italy were recruited in the study.

Inclusion criteria were: 1) adult patients (aged >18 years); 2) a previous diagnosis of SARS-CoV2 infection from positive result of real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay on nasal swabs; 3) a post-COVID-19 syndrome (regarded as persistence of dyspnoea with or without fatigue for at least more than 3 months after the past infection); 4) a written informed consent to participate in the study.

Exclusion criteria were: 1) acute respiratory diseases; 2) signs of cardiovascular instability; 3) cognitive impairment, 4) physical disability.

The study was conducted in accordance to the amended Declaration of Helsinki. The Apulia Region authorized the "Margherita di Savoia's Baths" to provide the day-service package "THERMAL TREATMENTS - REHABILITATION IN POST-COVID PATIENT" with Regional Council Resolution No. 963 of 16/06/2021 supplemented by the Executive Determination of the Department of Health - Health Promotion Department - Strategies and Supply Governance Service (Prot. AOO_183/PROT/10789 OF 06/30/2021).

*Patients' assessment*

Upon admission in the Baths, the following information were collected for each patient: 1) age; 2) sex; 3) Body Mass Index (BMI); 4) comorbidities; 5) data on the past COVID-19 course and management.

According to the COVID-19 related course and management, patients were classified into four phenotypes:

- Phenotype 1: characterised by patients with no need for oxygen therapy who recovered from COVID-

19 at home;

- Phenotype 2: characterised by patients with hypoxaemia which was possible to correct with oxygen therapy and no need for hospitalization;

- Phenotype 3: characterized by patients with hypoxemia who needed hospitalization and non-invasive mechanical ventilation;

- Phenotype 4: characterised by patients with severe hypoxaemia who required intubation or tracheotomy and hospitalization in intensive care unit (ICU).

Each patient underwent initial and final evaluations with validated questionnaires to determine the degree of patients' symptoms at entry and verify the effects of the rehabilitation treatment. According to the AAPM&R consensus guidance statement on breathing discomfort in in post-acute sequelae of SARS-CoV-2 infection (16) the clinical impact of dyspnoea was assessed using the modified Medical Research Council (mMRC) dyspnoea scale. It consists in a 5-point scale (ranging from 0 to 4) in which higher score correspond to increased dyspnoea. Patients who selected from grade 2 to grade 4 were regarded as affected by clinically important dyspnoea (30). According to the AAPM&R consensus guidance statement on fatigue in post-acute sequelae of SARS-CoV-2 infection (17), "fatigue" was defined as a physical, cognitive or emotional, mild to severe, intermittent to persistent, feeling of weariness, tiredness or lack of energy affecting a person's energy, motivation, and concentration. At the beginning of the Spa treatment, patients were asked whether or not they experienced fatigue. At the end of the treatment, patients were asked to rate the improvement of their dyspnoea and/or fatigue on a 4-point scale as follows: 0 ("unchanged"), 1 ("slight improvement"), 2 ("good improvement") and 3 ("resolution"). Minimal clinically meaningful improvement was considered to be 2 to 3 points. Each patient was also asked to relate the improvement of fatigue to that of dyspnoea as follows: improved more, improved less, improved the same, not improved (in contrast to dyspnoea), both not improved.

In some patient, we also valued the Borg Exertion Dyspnoea (BED) and the Barthel Physical Limitation (BPL). The modified Borg Dyspnoea Scale for exertion dyspnoea consists in a 10-point scale, ranging from 0 ("no exertion dyspnoea at all") to 9 ("maximal exertion dyspnoea"). The minimal clinically important difference (MCID) from the beginning ($T_1$) to completion ($T_2$) of the Spa rehabilitation treatment was considered to be -2.0 points (31). The Barthel Index for physical limitation ranges from 0 (maximum level of dependency) to 100 (complete autonomy). A score of 0-20 indicate "total" dependency, 21-60 indicate "severe" dependency, 61-90 indicate "moderate" dependency and 91-99 indicates "slight" dependency (32). The MCID in scores on the BI was considered to be 10 points (33).

At entry, all patients underwent a complete medical examination and functional evaluations. A spirometry, consisting in three reproducible measurements of maximally forced inspiratory and expiratory manoeuvres was used to obtain the forced expiratory volume in the first second ($FEV_1$) and the forced vital capacity (FVC). A 6 minutes walking test (6MWT) over an incline-free circuit was carried out to evaluate the eventual onset of exercise desaturation. Such functional data were used to plan the rehabilitation treatment but were not taken into consideration in the present preliminary study. Anyhow, we have observed in another study that there is no relationship between functional data and reported symptoms at entry (34).

Effectiveness data were examined one month after the conclusion of the rehabilitation program.

*Intervention*

The treatment offered to post COVID-19 patients at the "Margherita di Savoia's Baths" was borrowed from the existing ones offered to patients with work-related respiratory diseases (e.g. pulmonary fibrosis due to silicosis and asbestosis) and covered by the Italian public insurance agency called "Istituto nazionale Assicurazione Infortuni sul Lavoro" (INAIL) (35, 36). The post COVID-19 program included a total of 12 therapy sessions, each consisting in about 2-3 hours of daily therapy, disbursed for 12 consecutive days in two weeks (excluding Sundays). Each therapy session aimed at general and respiratory rehabilitation, with the possibility of diversifying treatments according to the comorbidities and symptoms complained by the patient in order to speed up the recovery. The Spa rehabilitation program was started at least 3 months after the COVID-19 acute phase.

Spa treatments provided consisted of:

- Inhalation therapy with mineral water;

- Respiratory physiochinesis of therapy;

- Meccanical pulmonary ventilation with mineral water for rehabilitative purpose;

- Hydrokinesitherapy.

Inhalation treatments consist in the inhalation of a mixture of water vapor and thermal water at a temperature reaching almost 40°C through a mouthpiece. The thermal water of the "Margherita di Savoia's Baths" is a sodium-chloride-bromide-iodide

water with high salinity, rich in chlorides, bromides, iodides and trace elements, such as sulphur. It is particularly effective in determine the reduction of inflammation and congestion of the respiratory system, the fluidification of the mucus and the improvement of the mucociliary clearance in the upper airways.

In patients with chronic bronchitis and bronchiectasis (with or without obstruction), inhalation treatments were associated with controlled pulmonary ventilation with personalized inspiratory and expiratory pressures. Pulmonary ventilations consist in the delivery of thermal aerosol with intermittent positive pressure. This treatment has the dual purpose of allowing the achievement of the beneficial effects of thermal water in the deepest parts of the lungs and of reducing the work of breathing and breathing discomfort, acting as a controlled respiratory gymnastic improving lung functionality and expandability.

Hydrokinesitherapy combines respiratory physiotherapy techniques for breath control (pursed lip breathing, diaphragmatic breathing and secretion mobilization) with the beneficial effects of thermal water in terms of vasodilatation, muscle toning and anti-inflammatory properties.

*Study Outcomes*

The primary outcome of the study was to assess at the beginning ($T_1$) and upon completion ($T_2$) of the Spa rehabilitation treatment the eventual improvement on dyspnoea and fatigue sensation and to explore the relationship between such symptoms.

Secondary outcomes were to assess if different clinical conditions could predispose patients in experiencing a clinically important dyspnoea (mMRC 2-4) and fatigue in the post COVID-19 period or could influence the achievement of the clinical outcomes of effectiveness after Spa intervention.

*Statistical analysis*

Continuous variables are presented as means and standard deviations, whereas categorical variables are expressed as counts and percentages. Skewness and Kurtosis tests were conducted to evaluate the normality of the continuous variables; in case of a non-normal distribution, a normalization model was established. Student's t-test for independent data (parametric) was used to compare continuous variables between groups. Differences between groups were assessed by $\chi$2-squared test for categorical variables. The strength of the association between patients' conditions and post COVID-19 dyspnoea and fatigue at the start (T1) and upon completion of the treatment (T2) was evaluated through univariate logistic regression analyses; the Odds Ratio (OR) values were indicated together with their 95% confidence intervals (95%CIs).

For all tests, a two-sided p-value<0.05 was considered to indicate statistical significance.

## Results

*Demographic characteristics of patients*

From July to November 2021, 340 patients were referred to the Margherita di Savoia's Baths due to persistent COVID-19 related symptoms. 130 patients were excluded from the study because they didn't meet inclusion criteria (the majority of them didn't complain persistent COVID-19 dyspnoea). Considering a population of 210 subjects with persistent COVID-19 related dyspnoea for the present study, 23 patients were finally excluded because they didn't complete the rehabilitation Spa protocol by undergoing all the 12 scheduled sessions of treatment. Among the remaining 187 participants enrolled, 118 patients also underwent the modified Borg Dyspnoea Scale and the Barthel Index for the assessment of the severity of the daily dyspnoea sensation and the physical limitation, respectively. The study flow chart is summarized in Figure 1.

Demographic descriptive data of the 187 participants who met the inclusion criteria and gave their informed consent to the enrolled in the study are displayed in Table 1.

124 of the 187 patients (66.3%) had at least one comorbidities, while 41 patients had more than one comorbidities. Specifically, a total of 85 patients (45.45%) had at least one cardiovascular disease, of which the most frequently reported was hypertension (38.0%). A total of 30 patients (16.0%) had a chronic respiratory disease; among them, 16 patients (8.6%) had COPD, 13 (7.0%) had asthma and 1 (0.5%) had pulmonary fibrosis. Other most represented comorbidities were type 2 diabetes (7.5%) and thyroid diseases (5.4%).

Among the 187 enrolled patients, 53 patients (28.3%) reported a mMRC grade 1, 82 patients (43.9%) reported a mMRC grade 2, 51 patients (27.3%) a mMRC grade 3 and only 1 patient (0.5%) reported a mMRC grade 4. Therefore, 134 out of 187 patients (71.7%) complained a clinically important dyspnoea according to the mMRC dyspnoea scale. 144 out of 187 patients (77.0%) reported fatigue. 105 out of 134 (55.6%) patients reported either a clinically important dyspnoea and fatigue.

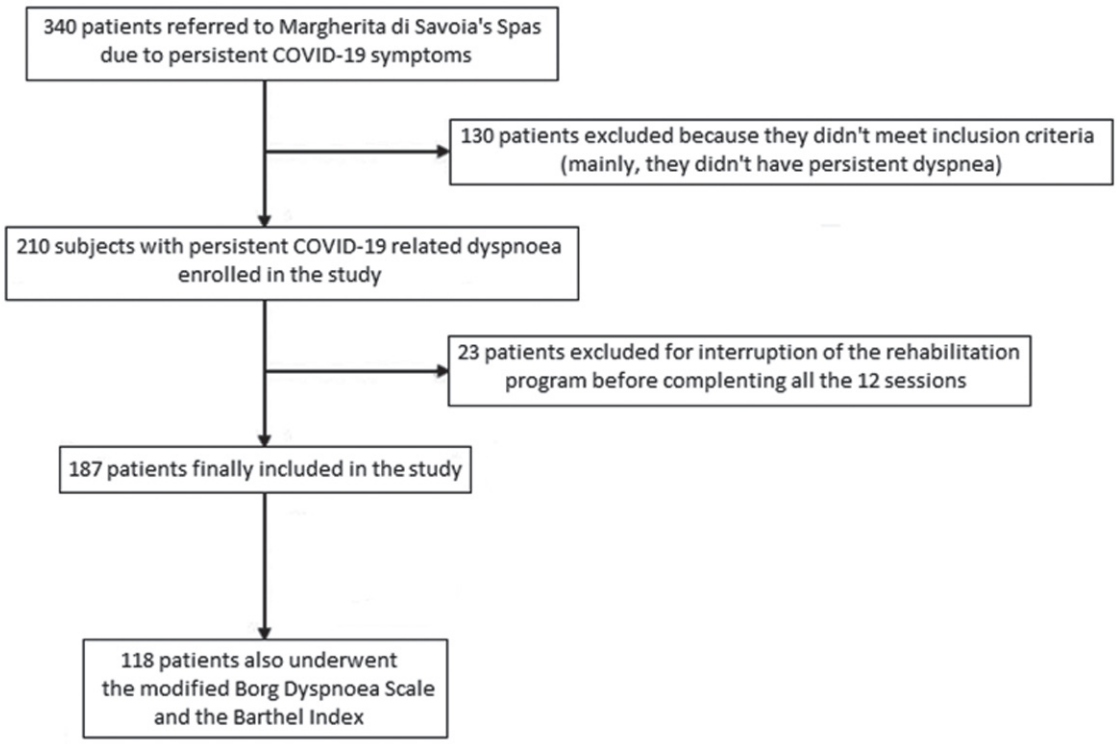


Figure 1 - Study flow chart

*Subjective evaluation of the improvement of dyspnoea and fatigue after the treatment*

Upon completion of the Spa rehabilitation treatment, 165 out of 187 patients (88.2%) reported an improvement in the dyspnoea sensation, while 116 out 144 patients (80.6%) reported an improvement in the fatigue sensation. The judgment of improvement for dyspnoea and fatigue reported by patients is detailed in Table 2.

Among the 144 patients complaining both the symptoms, 116 subjects (80.6%) reported an improvement in both dyspnoea and fatigue, for 11 subjects (7.6%) fatigue had not improved in contrast to dyspnoea and for 17 subjects (11.8%) both symptoms had not improved. The judgment on the improvement of fatigue compared to that of dyspnoea reported by patients is detailed in Table 3.

A subgroup of 118 patients further underwent the BED and BPL at the beginning ($T_1$) and the end ($T_2$) of the treatment. Results are displayed in Table 4.

The mean pre-treatment Borg was 3.60±1.30, while the mean post-treatment Borg was 1.41±0.67. The median Delta Borg was –2.0 points. 60 out of 118 patients (50.8%) reached a clinically significant improvement in BED (i.e. Delta Borg equal or more than -2.0 points).

The mean pre-treatment Barthel was 74.00±13.72, while the mean post-treatment Barthel was 86.55±8.81. The median Delta Barthel was +10 points. 61 out of 118 patients (51.7%) reached a clinically significant improvement in BPL (i.e. Delta Barthel equal or more than +10 points).

37 patients (31.4%) reached a minimal clinically important improvement in both the BED and the BPL, 23 patients (19.5%) reached a minimal clinically important improvement in the BED but no in the BPL, 24 patients (20.3%) reached a minimal clinically important improvement in BPL but no in the BED and 34 (28.9%) didn't reach a minimal clinically important improvement in both the BED and the BPL.

*Risk factors for clinically relevant dyspnoea or fatigue at entry and improvement of both symptoms after treatment*

No substantial risk factors for clinically relevant dyspnoea were found analyzing differences in clinical characteristics presented by patients who reported a mMRC grade 1 or a mMRC grade 2-4 at entry. However, we unexpectedly recorded a lower likelihood of experiencing important breathlessness in patients with chronic respiratory diseases (OR: 0.42; 95% CI: 0.20-0.87). On the other hand, BMI

Table 1 - Demographic characteristics of the 187 patients enrolled in the study.

| | |
|---|---|
| Demographic Characteristics | |
| Age; mean ± SD (range) | 58.10 ± 13.54 (18 - 85) |
| Sex; % male | 100 (53.5%) |
| Sex, % female | 87 (46.5%) |
| BMI; mean ± SD (range) | 28.28±3.57 |
| COVID-19 symptoms onset (months); mean ± SD (range) | 9.05 ± 3.38 (3 - 15) |
| COVID-19 phenotype: | |
| Phenotype 1, n % | 67 (35.8%) |
| Phenotype 2, n % | 55 (29.4%) |
| Phenotype 3, n % | 55 (29.4%) |
| Phenotype 4, n % | 10 (5.4%) |
| Post-COVID-19 symptoms: | |
| Dyspnoea and asthenia, n % | 144 (77.0%) |
| Dyspnoea mMRC 1, n % | 53 (28.3%) |
| Dyspnoea mMRC 2, n % | 82 (43.9%) |
| Dyspnoea mMRC 3, n % | 51 (27.3%) |
| Dyspnoea mMRC 4, n % | 1 (0.5%) |
| Comorbidities (at least one), n % | 124 (66.3%) |
| Multiple comorbidities (more than one), n % | 41 (21.9%) |
| Comorbidities: | |
| Hypertension | 71 (38.0%) |
| Left heart failure | 18 (4.8%) |
| COPD | 16 (8.6%) |
| Type 2 diabetes | 14 (7.5%) |
| Asthma | 13 (7.0%) |
| Thyroid disease | 10 (5.4%) |
| Chronic ischaemic heart disease | 3 (1.6%) |
| Arrhythmias | 2 (1.1%) |
| Pulmonary fibrosis | 1 (0.5%) |
| Fibromyalgia | 1 (0.5%) |
| Multiple sclerosis | 1 (0.5%) |
| Ulcerative colitis | 1 (0.5%) |
| Psoriasis | 1 (0.5%) |
| Neoplasm | 1 (0.5%) |

Table 2. Subjective evaluation of the improvement of dyspnoea and fatigue after the treatment.

| Subjective judgment | Dyspnoea (n=187) | Fatigue (n=144) |
|---|---|---|
| 0 = unchanged | 22 (11.8%) | 28 (19.4%) |
| 1 = slight improvement | 77 (41.2%) | 66 (45.8%) |
| 2 = good improvement | 70 (37.4%) | 36 (25.0%) |
| 3 = resolution | 18 (9.6%) | 14 (9.7%) |
| Total improvement | 165 (88.2%) | 116 (80.6%) |

Table 3 - Relationship between the improvement of fatigue compared to that of dyspnoea based on the subjective judgment of patients affected by both the symptoms.

| Subjective judgment | Patients (n=144) |
|---|---|
| "Improved more" | 8 (5.6%) |
| "Improved the same" | 90 (62.5%) |
| "Improved less" | 18 (12.5%) |
| "Not improved" (in contrast to dyspnoea) | 11 (7.6%) |
| "Both not improved" | 17 (11.8%) |

Table 4 - Pre-treatment ($T_1$) and post-treatment ($T_2$) evaluation of exertion dyspnoea and physical limitation.

| Exertion dyspnoea | | Physical limitation | |
|---|---|---|---|
| Pre-treatment Borg ($T_1$) | 3.60±1.30 | Pre-treatment Barthel ($T_1$) | 74.00±13.72 |
| Post-treatment Borg ($T_2$) | 1.41±0.67 | Post-treatment Barthel ($T_2$) | 86.55±8.81 |
| Median Delta Borg | -2.0 | Median Delta Barthel | +10 |
| Delta Borg >\|-2.0\| | 60 (50.8%) | Delta Barthel >\|+10\| | 61 (51.7%) |

Table 5 - Comparison of the frequencies of clinical characteristics between patients without and with clinical impacting dyspnoea at the entry ($T_1$) and between patients without and with clinical improvement of dyspnoea after treatment ($T_2$).

| Demographic characteristics | Impact of dyspnoea at entry ($T_1$) | | | Improvement of dyspnoea ($T_2$) | | |
|---|---|---|---|---|---|---|
| | Not relevant mMRC 1 (n=53) | Relevant mMRC 2-4 (n=134) | p-value | Unchanged or slight 0-1 point (n=99) | Good or resolution 2-3 points (n=88) | p-value |
| Age > 65 anni (n=60) | 16 (30.2%) | 44 (32.8%) | 0.12 | 29 (29.3%) | 31 (35.2%) | 0.39 |
| Male sex (n=100) | 32 (60.4%) | 68 (50.7%) | 0.23 | 55 (55.6%) | 45 (51.1%) | 0.55 |
| Female sex (n=87) | 21 (39.6%) | 66 (49.3%) | 0.23 | 44 (44.4%) | 43 (48.9%) | 0.55 |
| BMI > 30 (n=53) | 12 (22.6%) | 41 (30.6%) | 0.28 | 41 (41.4%) | 12 (13.6%) | <0.0001* |
| Phenotype 1 (n=67) | 19 (35.8%) | 48 (35.8%) | 1.00 | 34 (34.3%) | 33 (37.5%) | 0.65 |
| Phenotype 2 (n=55) | 13 (24.5%) | 42 (31.3%) | 0.36 | 26 (26.3%) | 29 (33.0%) | 0.32 |
| Phenotype 3 (n=55) | 16 (30.2%) | 39 (29.1%) | 0.88 | 30 (30.3%) | 25 (28.4%) | 0.78 |
| Phenotype 4 (n=10) | 5 (9.4%) | 5 (3.7%) | 0.12 | 9 (9.1%) | 1 (1.1%) | 0.02* |
| Comorbidities (n=124) | 41 (77.4%) | 83 (61.9%) | 0.04* | 68 (68.7%) | 56 (63.6%) | 0.95 |
| Multiple comorbidities (n=41) | 9 (17.0%) | 32 (23.9%) | 0.30 | 22 (22.2%) | 19 (21.6%) | 0.92 |
| Cardiovascular disease (n=85) | 17 (32.1%) | 58 (43.3%) | 0.16 | 43 (43.4%) | 42 (47.7%) | 0.56 |
| Respiratory disease (n=39) | 17 (32.1%) | 22 (16.4%) | 0.02* | 29 (29.3%) | 10 (11.4%) | 0.003* |

above 30 Kg/m$^2$ (OR: 0.22; 95% CI: 0.11-0.46), severe phenotype 4 acute COVID-19 (OR: 0.11; 95% CI: 0.01-0.93) and respiratory comorbidities (OR: 0.31, 95% CI: 0.14-0.68; p=0.003) configured risk factors for no significant improvement or lack of improvement in dyspnoea after treatment (Table 5).

Obesity (i.e. BMI above 30 Kg/m$^2$) configured a risk factor (OR: 3.80, 95% CI: 0.41-10.28) for chronic fatigue at entry, while a lower likelihood of experiencing fatigue was found for patients with chronic respiratory diseases (OR: 0.28, 95% CI: 0.13-0.68). Contrary to dyspnoea, no risk factors were found for no significant improvement or lack of improvement in fatigue after treatment (Table 6).

*Clinical characteristics associated to the lack of improvement of BED and BPL*

Patients aged over 65 years, obese patients and patients affected by comorbidies (i.e. one or more than one comorbidites) didn't reach a clinically significant median Delta Borg upon completion of the treatment (Table 7).

Female patients showed a significantly lower pre-treatment BI compared to male patients (70.33±14.40 *vs.* 77.41±12.82; p=0.006). Similarly, patients with a BMI over 30 Kg/m$^2$ had a significantly lower pre-treatment BI compared patients with a BMI under 30 Kg/m$^2$ (70.05±13.40 *vs.* 77.24±11.56; p=0.02) and patients with multiple comorbidities had a lower pre-treatment BI compared patients without or with only one comorbidity (65.46±12.97 *vs*. 75.86±11.47; p=0.0002). Patients aged over 65 years, males, obese patients and patients affected by multiple comorbidities didn't reach a clinically meaningful median Delta Barthel (Table 8).

Table 6 - Association between patients' clinical characteristics, presence of fatigue at the entry ($T_1$) and the improvement of fatigue after treatment ($T_2$).

| Fatigue at entry ($T_1$) | | | | Improvement of fatigue ($T_2$) | | | |
|---|---|---|---|---|---|---|---|
| Demographic characteristics | Present (n=144) | Not present (n=43) | p-value | Demographic characteristics | Unchanged or slight 0-1 point (n=94) | Good or resolution 2-3 points (n=50) | p-value |
| Age > 65 years (n=60) | 44 (30.6%) | 16 (37.2%) | 0.41 | Age > 65 years (n=44) | 31 (33.0%) | 13 (26.0%) | 0.39 |
| Male sex (n=100) | 77 (53.5%) | 23 (53.5%) | 1.00 | Male sex (n=77) | 53 (56.4%) | 24 (48.0%) | 0.34 |
| Female sex (n=87) | 67 (46.5%) | 20 (46.5%) | 1.00 | Female sex (n=67) | 41 (43.6%) | 26 (52.0%) | 0.34 |
| BMI > 30 (n=53) | 48 (33.3%) | 5 (11.6%) | 0.006* | BMI > 30 (n=48) | 33 (35.1%) | 15 (30.0%) | 0.54 |
| Phenotype 1 (n=67) | 50 (34.7%) | 17 (39.5%) | 0.56 | Phenotype 1 (n=50) | 28 (29.8%) | 22 (44.0%) | 0.09 |
| Phenotype 2 (n=55) | 42 (29.2%) | 13 (30.2%) | 0.89 | Phenotype 2 (n=42) | 26 (27.7%) | 16 (32.0%) | 0.59 |
| Phenotype 3 (n=55) | 44 (30.5%) | 11 (25.6%) | 0.53 | Phenotype 3 (n=44) | 30 (31.9%) | 14 (28.0%) | 0.63 |
| Phenotype 4 (n=10) | 8 (5.6%) | 2 (4.7%) | 0.82 | Phenotype 4 (n=8) | 7 (7.4%) | 1 (2.0%) | 0.17 |
| Comorbidities (n=124) | 96 (66.7%) | 26 (60.5%) | 0.45 | Comorbidities (n=96) | 60 (63.8%) | 36 (27.0%) | 0.32 |
| Multiple comorbidities (n=41) | 31 (21.5%) | 10 (23.3%) | 0.81 | Multiple comorbidities (n=31) | 20 (21.3%) | 11 (22.0%) | 0.92 |
| Cardiovascular disease (n=85) | 67 (46.5%) | 18 (41.9%) | 0.59 | Cardiovascular disease (n=67) | 39 (41.5%) | 28 (56.0%) | 0.10 |
| Respiratory disease (n=39) | 22 (15.3%) | 17 (39.5%) | 0.0006* | Respiratory disease (n=22) | 16 (17.0%) | 6 (12.0%) | 0.43 |

Table 7 - Evaluation of BED stratified according to patients' clinical characteristics

| | | | |
|---|---|---|---|
| Age: | > 65 years (n=48) | ≤ 65 years (n=70) | p-value |
| Pre-treatment Borg ($T_1$) | 3.49±1.36 | 3.67±1.25 | 0.59 |
| Delta Borg ($T_2$) | **-1.5** | -2.0 | |
| Sex: | Male (n=62) | Female (n=56) | p-value |
| Pre-treatment Borg ($T_1$) | 3.36±1.20 | 3.85±1.44 | 0.14 |
| Delta Borg ($T_2$) | -2.0 | -2.0 | |
| BMI: | >30 Kg/m$^2$ (n=24) | ≤30 Kg/m$^2$ (n=94) | p-value |
| Pre-treatment Borg ($T_1$) | 3.29±1.11 | 3.51±1.28 | 0.44 |
| Delta Borg ($T_2$) | **-1.5** | -2.0 | |
| Comorbidities: | Yes (n=61) | No (n=57) | p-value |
| Pre-treatment Borg ($T_1$) | 3.62±1.33 | 3.58±1.28 | 0.87 |
| Delta Borg ($T_2$) | **-1.75** | -2.0 | |
| Multiple comorbidities: | Yes (n=24) | No (n=94) | |
| Pre-treatment Borg ($T_1$) | 3.54±1.37 | 3.31±1.15 | 0.40 |
| Delta Borg ($T_2$) | -1.5 | -2.0 | |
| Respiratory Comorbidities: | Yes (n=13) | No (n=105) | |
| Pre-treatment Borg ($T_1$) | 3.00±0.77 | 3.67±1.38 | 0.09 |
| Delta Borg ($T_2$) | **-1.0** | -2.0 | |
| Cardiovascular Comorbidities: | Yes (n=40) | No (n=78) | |
| Pre-treatment Borg ($T_1$) | 3.64±1.38 | 3.58±1.26 | 0.81 |
| Delta Borg ($T_2$) | **-1.75** | -2.0 | |

## Discussion

To the best of our knowledge this is the first study evaluating whether Spa health resort is an appropriate "low-intensity" setting to undertake a rehabilitation treatment protocol in a cohort of post COVID-19 patients.

More specifically, our study focused on a respiratory rehabilitation and all the patients complained persistent post COVID-19 dyspnoea at entry. The dyspnoea symptom was reported as "clinically significant" (i.e. mMRC grade 2-4) by 71.7% of patients. The 77% of patients referred also fatigue.

At the end of the intervention, most of the subjects (88.2%) improved their dyspnoea. Such improvement was reported as "good" or "complete" by 47.0% of patients and as "slight" by 41.2% of them. Among patients complaining both the symptoms, the 80.55% reported an improvement in both dyspnoea and fatigue. The improvement in the fatigue sensation was reported as "good" or "complete" by 34.7% of patients and as "slight" by 45.8% of them. In a subgroup of subjects, we also assessed the BED and the BPL. A clinically significant improvement in BED (i.e. Delta Borg equal or more than -2.0 points) was reached by the 50.8% of patients, while a clinically significant improvement in BPL (i.e. Delta Barthel equal or more than +10.0 points) was reached by the 51.7% of them. The 31.4% of patients reached a minimal clinically important improvement in both the BED and the BPL.

Our overall results seem to support the effectiveness of a rehabilitation protocol of treatment in a "low-intensity" Spa setting for post COVID-19 patients. According to the former literature, the percentage frequency of post COVID-19 symptoms ranges from 53 to 87% for fatigue and from 43 to 71% for dyspnoea (6-8). As our study focused more on pulmonary rehabilitation, post COVID-19 symptoms rates reported by our patients are slightly higher than in other case series.

Table 8 - Pre-treatment ($T_1$) and post-treatment ($T_2$) evaluation of the physical limitation stratified according to patients' clinical characteristics.

| Age: | > 65 years (n=48) | ≤ 65 years (n=70) | p-value |
|---|---|---|---|
| Pre-treatment Barthel ($T_1$) | 75.06±13.14 | 72.44±14.76 | 0.32 |
| Delta Barthel ($T_2$) | 12.03±7.89 | 13.33±8.65 | 0.41 |
| Median Delta Barthel | **9.5** | 11 | |
| Sex: | Male (n=62) | Female (n=56) | p-value |
| Pre-treatment Barthel ($T_1$) | 77.41±12.82 | 70.33±14.40 | 0.006* |
| Delta Barthel ($T_2$) | 11.85±8.05 | 13.32±8.40 | 0.33 |
| Median Delta Barthel | **9** | 12 | |
| BMI: | >30 Kg/m$^2$ (n=24) | ≤30 Kg/m$^2$ (n=94) | p-value |
| Pre-treatment Barthel ($T_1$) | 70.05±13.40 | 77.24±11.56 | 0.02* |
| Delta Barthel ($T_2$) | 13.32±8.29 | 10.39±7.05 | 0.11 |
| Median Delta Barthel | **9.5** | 11 | |
| Comorbidities: | Yes (n=61) | No (n=57) | p-value |
| Pre-treatment Barthel ($T_1$) | 73.44±13.35 | 74.40±14.00 | 0.70 |
| Delta Barthel ($T_2$) | 12.80±8.71 | 12.38±7.90 | 0.78 |
| Median Delta Barthel | 11 | 10 | |
| Multiple comorbidities: | Yes (n=24) | No (n=94) | |
| Pre-treatment Barthel ($T_1$) | 65.46±12.97 | 75.86±11.47 | 0.0002* |
| Delta Barthel ($T_2$) | 10.62±8.51 | 13.39±7.86 | 0.13 |
| Median Delta Barthel | **9.5** | 11.5 | |
| Respiratory Comorbidities: | Yes (n=13) | No (n=105) | |
| Pre-treatment Barthel ($T_1$) | 74.77±10.47 | 73.90±14.10 | 0.83 |
| Delta Barthel ($T_2$) | 13.00±7.23 | 12.50±8.36 | 0.84 |
| Median Delta Barthel | 10 | 12 | |
| Cardiovascular Comorbidities: | Yes (n=40) | No (n=78) | |
| Pre-treatment Barthel ($T_1$) | 70.95±13.68 | 75.44±13.39 | 0.09 |
| Delta Barthel ($T_2$) | 14.34±9.94 | 11.71±7.41 | 0.11 |
| Median Delta Barthel | 12 | 10 | |

Our study has the strength of being a prospective study enrolling a significant number of post COVID-19 patients of working age (i.e. <65 years). Data on patients aged 18 to 64 years are scarce (37). However, this age range represents the most productive life years of a population. Considering the high healthcare indirect costs deriving from the loss of their productive potential, rehabilitation of subjects aged between 18-65 years developing a long-lasting and debilitating disease assumes fundamental importance. Furthermore, the post COVID-19 population included in our study appears to be more representative of the actual real-world situation. Indeed, 65.2% of the enrolled subjects recovered by mild to moderate SARS-CoV2 infection not requiring hospitalization and/or respiratory support during the acute phase, while 34.7 % of them had severe SARS-CoV2 pneumonia. On the other hand, currently available studies and randomized controlled trial (RCT) evaluating the effectiveness of rehabilitation treatment in post COVID-19 patients are mainly related only to a severe infection requiring mechanical ventilation and/or invasive ICU treatments (21, 38-40). Finally, unlike other "low-intensity" rehabilitation programs that were undertaken at hospital discharge (21-23), our Spa treatment was started at least 3 months after the

acute phase. This allowed us to exclude the possibility of an improvement in symptoms not determined by the treatment but time-related.

Moreover, for the first time, we analyzed the relationship between the two main post COVID-19 symptoms (i.e. dyspnoea and fatigue) at the beginning and at the end of a respiratory rehabilitation treatment. Our results suggested that post COVID-19 dyspnoea and fatigue mostly improve together. On the other hand, BED and BPL were less mutually related. At the basis of this discrepancy, however, there may be the greater complexity of questionnaires, such as the Borg and the Barthel, in assessing exertion symptoms, compared to a "yes" or "no" type assessment used to confirm the presence of dyspnoea or fatigue.

While potential risk factors for the development of a severe COVID-19 are now almost known, studies assessing risk factors for post COVID-19 syndrome are contrasting (41-48). Therefore, in our study we tried to find eventual risk factors associated to the occurrence of post COVID-19 symptoms, as well as risk factors that may predict a lack of improvement in symptoms after treatment. No substantial risk factors were associated to a clinically relevant post COVID-19 dyspnoea, while obesity configured a risk factor for fatigue. Unexpectedly, patients with respiratory comorbidities were less likely for experiencing clinically important dyspnoea and fatigue. A possible explanation is that patients with chronic respiratory diseases are more used to having and chronically enduring the feeling of "short of breath" and related fatigue (49). Obesity, respiratory comorbidities and a previous severe acute COVID-19 (phenotype 4) configured risk factors for the lack of improvement of dyspnoea after treatment, while no risk factors were associated to improvement or lack of improvement of fatigue. Female patients showed a significantly lower pre-treatment BPL compared to male patients. This result agrees with other studies reporting a higher experience of physical limitation in female post COVID-19 patients (4, 50). On the other hand, male patients didn't reach a clinically meaningful improvement in BPL after treatment. As expected, a lower pre-treatment BPL was also recorded in obese patients and in patients with multiple comorbidities. Patients aged over 65 years, patients presenting a BMI>30 $Kg/m^2$ and patients with comorbidities didn't reach a clinically meaningful improvement in BED and BPL after intervention. Future studies are needed to confirm the possible influence of these clinical differences in post COVID-19 patients.

Although the exact mechanisms of post-COVID-19 fatigue and dyspnoea has yet to be recognized, several hypotheses have been produced. A first hypothesis consists in the presence of residual lung injury after the acute phase (51). However, this explanation fits well only a small percentage of post COVID-19 patients who experienced a severe acute disease and in which exertional dyspnoea can be well explained by persistent residual chest CT abnormalities and restricted pulmonary function (52). On the other hand, in a larger number of patients the causes of dyspnoea and fatigue remains enigmatic due to the absence of abnormalities in pulmonary function tests or chest imaging (11-13). Also in another study of ours we did not find important correlations with functional characterization in post COVID-19 subjects with dyspnoea (34).

A suggestive hypothesis comes from the study by Singh et al (53). This study examined 10 patients who recovered from a mild COVID-19 with invasive cardiopulmonary exercise testing (iCPET). Despite the absence of abnormalities in blood gases or any other pulmonary or cardiovascular parameter, these patients exhibited a condition of severe muscle deconditioning characterized by a peripheral decreased oxygen extraction ($EO_2$). Additionally, all patients demonstrated an exaggerated hyperventilatory response during exercise. This remarkable finding suggested that dyspnoea in post COVID-19 patients may occur because of an excessive stimulation of the respiratory centres in the brain stem, which, in turn, results from an altered peripheral metabolic situation in skeletal muscles. Several non-mutually exclusive pathobiologic mechanisms may underlie this condition. One of them would be related to a prolonged pro-inflammatory response (hyper-inflammatory cytokine storm) associated with SARS-CoV-2 infection (51, 54). Other hypotheses include clotting/coagulation issues, the establishment of a dysfunctional nerve signalling and a virus-mediated mitochondrial damage (55, 56). To this regard, Lam et al. (14) proposed the existence of a distinct emerging long COVID-19 phenotype with connotations yet to be verified.

On this background, rehabilitation programs including aerobic training, strengthening exercises, diaphragmatic breathing techniques, as well as mindfulness training addressing psychological aspects related to the disease, might represent effective treatment options in patients with persistent symptoms after COVID-19 (57, 58). Thermal waters may have a favourable additive effect to physiotherapy, due to the reduction of inflammation in the early airways

and the positive effect on the vascularisation of large bronchi induced by mineral-rich water inhalations. It is noteworthy to remember that the first damages induced by SARS-$CoV_2$ occur in the upper airways. The thermal water specifically used at the "Margherita di Savoia's Baths" come directly from the famous local salt deposits, presenting a high saline content, as well as other important substances including iodine and bromine and trace elements, such as sulphur. Treatment with inhaled salt-bromide-iodine thermal water has been shown to have vasodilating activity on the bronchial mucosa and stimulating action on the muco-ciliary clearance, at the same time increasing the production of secretory IgA (28, 59). Sulphur-rich water inhalation has been demonstrated to decrease the synthesis of pro-inflammatory cytokines and the inflammatory mucosal infiltration, and reduce the levels of elastase produced by the neutrophils (28, 60). Assisted breathing creates the conditions for the benefits of thermal water to reach the small airways, as well as promoting better chest expansion thanks also to the use of an end-expiratory pressure. This is important considering the scarring effects induced by COVID-19 affecting the interstitium and resulting in increased traction of the lung. Finally, hydrokinesitherapy combines the rehabilitative effect of physiotherapy on asthenic subjects with the physical effect of the heat of water, leading to an improvement in the vascularisation and tone of the striated muscles. Furthermore, immersions in mineral-rich waters seem to be effective in reducing pro-inflammatory cytokines, including IL-6 levels (28, 59, 60).

We have to acknowledge that the present study has some limitations.

The first limitation could be related to the shorter duration of our rehabilitation program. However, our Spa treatment consisted in about 2-3 hours of daily therapy for a total of 12 sessions disbursed in two weeks. The TERECO study (21) evaluated and remotely monitored the effectiveness of a pulmonary rehabilitation program held at home during 6 weeks, but consisting in about 3-4 weekly sessions, each lasting about 40-60 minutes. De Souza et al. (22) proposed a home-based rehabilitation program for a total duration of 6 weeks, but delivered with only a weekly session by videoconference. Paneroni et al. (23) investigated the efficacy of a one-month telerehabilitation program consisting of one hour of daily exercises monitored by twice a week video calls. Our rehabilitation treatment was, therefore, more intense. Furthermore, effectiveness data in our study were examined one month after the conclusion of the intervention. This allowed us to verify the long-term duration of benefits.

Second, although standardized tools were used for the assessment of dyspnoea and fatigue, all consisted of self-reported questionnaires. This may imply a bias due to the so-called "cognitive dissonance" (61), that is the cognitive need of participants to change the perception of symptoms even if they have not objectively improved after the completion of the rehabilitation program. Anyhow, also other works on rehabilitation treatment in post COVID-19 patients used the same evaluation questionnaires. For example, the TERECO study (21) assessed the post-treatment effectiveness using the mMRC dyspnoea scale, De Souza et al. (22) valued post-treatment patients' exertional dyspnoea using the Borg Dyspnoea Scale et al. (23) analyzed patients' post-treatment physical limitation using the Barthel Index. In this work we have not included functional data (i.e. $FEV_1$ and FVC values assessed on spirometry, desaturation and meters travelled assessed by 6MWT), but in another work of ours we assessed no correlation between functional parameters and post COVID-19 symptoms (34). Similarly, Lam et al (14) and Huang et al (62) have shown that there is no relationship between imaging, spirometric data and dyspnoea. Functional data would appear to be useful only in the early stages of recovery from COVID-19, when lung damage still persists. Our Spa rehabilitation treatment was started at least 3 months after the acute phase. Patients included in our study had no or only modest lung alterations correlated to previous COVID-19 pneumonia and only one of them was diagnosed with pre-existent pulmonary fibrosis. The functional evaluation at entry was, therefore, performed in our study only for the purpose of planning the rehabilitation intervention.

Third, we did not perform an a priori sample size calculation of participants included in the study. Anyhow, this limit is due to a lack of previously existing data in the literature on a Spa rehabilitation program for post COVID-19 patients.

Another limitation of our study might be a bias related to interventions in the Spa setting, because of the social atmosphere of health resorts producing positive effect on mood and cognitive function through the reduction of stress. To this regard we must add that our study lacks the inclusion of a comparator group that did not have suspected or confirmed SARS-$CoV_2$ infection. However, the potential presence of psychological confounding factors can also be considered a strength of a Spa rehabilitation treatment, increasing its effectiveness.

In conclusion, dyspnoea and fatigue were confirmed to be important post COVID-19 symptoms even in younger subjects of working age (i.e. <65 years) and subjects with absent or modest pulmonary alterations at distance from the acute episode. Our study suggested that Spa health resorts could be considered as an effective "low intensity" setting for a rehabilitation program of such subjects, allowing to reduce the pressure on "high intensity" hospital rehabilitation units and the economic expenses for the National Health System. Besides the assessment of presence or absence of fatigue and clinically meaningful dyspnoea with the mMRC scale, this work also wanted to evaluate the severity of patients' exertion dyspnoea (BED) and physical limitation (BPL). We found that there is a strong relationship in terms of improvement between dyspnoea and fatigue, even if risk factors for their occurrence appear to be different. The improvement in exertion dyspnoea and physical limitation seemed to be less mutually related. Anyhow, a possible explanation for this discrepancy may be that the Borg and Barthel questionnaires are more complex and articulated. In our study we also tried to verify the factors that predict a lack of improvement in symptoms after treatment. Obesity, respiratory comorbidities and a severe phenotype of acute COVID-19 configured risk factors for the lack of improvement of dyspnoea after treatment, while no risk factors were associated to the lack of improvement of fatigue. Older age, obesity and comorbidities may make a clinically meaningful improvement in BED and BPL after intervention more difficult. Gender differences seem to influence the perceived physical limitation, with women exhibiting worse BPL at entry, but men presenting less improvement in BPL after treatment.

Further studies on the topic are advised to properly investigate beneficial effect of a Spa-based rehabilitative programs in post COVID-19 patients.

**Declarations**

**Ethical approval and Consent to Participate:** The study was conducted in accordance to the amended Declaration of Helsinki and all patients signed a written informed consent to participate. Ethical approval was deemed unnecessary according to national regulations because the present study adheres to accepted ethical standards of treatment (Regional Council Resolution No. 963 of 16/06/2021, Apulia Region - Italy, supplemented by the Prot. AOO_183/PROT/10789 OF 06/30/2021, Executive Determination of the Department of Health - Health Promotion Department - Strategies and Supply Governance Service).

**Availability of Data and Materials:** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Consent for Publication:** Not applicable

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

**Competing interests**: The authors declare no competing interests

**Authors' Contribution:** E.R., O.R., M.P.F.B. and D.L. equally contributed to the study conception and design. Data collection were performed by E.R., C.M.I.Q., G.S., E.C., P.T., G.M., E.L., S.S., O.R., M.P.F.B., S.T. and D.L. The analysis was performed by C.M.I.Q. and O.R. The first draft of the manuscript was written by C.M.I.Q., O.R. and S.T. All authors commented on previous versions of the manuscript and contributed to the final version. All authors read and approved the final manuscript

## Riassunto

***Trattamento riabilitativo "a bassa intensità" per la dispnea persistente post COVID-19: il valore di un centro termale quale setting di cura appropriato***

**Introduzione.** La sindrome post COVID-19 consiste in una frequente e invalidante complicanza che si rende responsabile di un ritardo nel reinserimento sociale e nel ritorno alla vita lavorativa dei pazienti che ne sono affetti.

**Disegno dello studio.** Quello presentato è stato uno studio prospettico osservazionale di coorte. L'obiettivo principale è stato quello di esplorare l'efficacia di un trattamento riabilitativo termale sul miglioramento della dispnea e della stanchezza post COVID-19, analizzando contemporaneamente la relazione tra tali sintomi. Inoltre, è stato valutata la possibilità che diverse caratteristiche cliniche predispongano i pazienti a manifestare sintomi post COVID-19 o influenzino l'efficacia dell'intervento termale.

**Metodi.** Da luglio a novembre 2021, sono stati arruolati 187 pazienti con sindrome post COVID-19. Tutti i pazienti lamentavano dispnea persistente, il cui impatto sulle attività quotidiane è stato valutato utilizzando la scala modificata per la dispnea del Medical Research Council. 144 pazienti (77,0%) hanno riferito anche stanchezza persistente. Il trattamento termale è stato iniziato almeno 3 mesi dopo la fase acuta del COVID-19. Alla fine del trattamento, ai pazienti è stato chiesto di valutare il miglioramento nella sensazione di dispnea e di stanchezza. Per 118 pazienti sono stati inoltre impiegati la scala modificata per la Dispnea di Borg per la stima della gravità della dispnea da sforzo e l'indice Barthel per la stima della gravità della limitazione fisica.

**Risultati.** 165 pazienti su 187 (88,2%) hanno riportato un miglioramento della dispnea, mentre 116 pazienti su 144 (80,6%) hanno riportato un miglioramento sia della dispnea che della stanchezza. Su un totale di 118 soggetti, un miglioramento clinicamente significativo sulla scala modificata per la Dispnea di Borg (inteso come un Delta Borg uguale o superiore a -2,0 punti) è stato raggiunto dal 50,8% dei pazienti, mentre un miglioramento clinicamente significativo per l'indice Barthel (inteso come un Delta Barthel uguale o superiore a +10,0 punti) è stato raggiunto dal 51,7% di essi. Il 31,4% dei pazienti ha raggiunto un miglioramento minimo clinicamente importante sia per la scala modificata per la Dispnea di Borg che per l'indice Barthel. Nessun fattore di rischio è stato associato alla sensazione di dispnea clinicamente rilevante all'ingresso, mentre un BMI>30 $Kg/m^2$ è risultato il principale fattore di rischio per la stanchezza cronica. La presenza di comorbidità respiratorie, obesità e COVID-

19 acuto grave (fenotipo 4) hanno configurato fattori di rischio per il mancato miglioramento della dispnea dopo il trattamento, mentre nessun fattore di rischio è stato associato a un mancato miglioramento della stanchezza. L'età avanzata, l'obesità e la presenza di comorbidità sembravano rendere più difficile il raggiungimento di un miglioramento clinicamente significativo nella scala modificata per la Dispnea di Borg e nell'indice Barthel dopo il trattamento. Il sesso femminile potrebbe implicare una maggiore limitazione fisica all'ingresso, mentre i pazienti di sesso maschile sembrano mostrare un minore miglioramento nell'indice Barthel dopo il trattamento.

**Conclusioni.** Dispnea e stanchezza cronica hanno confermato di essere sintomi post COVID-19 importanti anche nei soggetti più giovani in età lavorativa e nei soggetti con alterazioni polmonari assenti o modeste a distanza dal COVID-19 acuto. Un centro termale sembrerebbe essere un ambiente efficace per un programma riabilitativo "a bassa intensità" in tali pazienti. Esiste una forte relazione in termini di miglioramento tra dispnea e stanchezza cronica, anche se i fattori di rischio per la loro insorgenza sembrano essere diversi. Il miglioramento della dispnea da sforzo e della limitazione fisica sembravano essere meno correlati tra loro, probabilmente a causa di una maggiore complessità nei questionari di valutazione. Alcuni fattori di rischio possono predire la mancanza di miglioramento dei sintomi dopo il trattamento.

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Ann Ig. 2024 Sep-Oct; 36(5): 614-618. doi: 10.7416/ai.2024.2629

# Why are rare diseases underdiagnosed? A clinical management study on detection of primary biliary cholangitis in primary care

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*Keywords: Rare diseases; primary care; chronic cholestasis; liver cirrhosis; alkaline phosphatase*
*Parole chiave: Malattie rare; assistenza primaria; colestasi cronica; cirrosi epatica; fosfatasi alcalina*

**Abstract**

***Background.*** *There are about 7,000 rare diseases that affect 10% of the world population. Primary biliary cholangitis, an autoimmune chronic liver disease of the interlobular bile ducts, is one of the most common causes of chronic cholestasis. However, it is a rare, often underdiagnosed and undertreated, disease which can lead to cirrhosis and liver failure. We aimed to assess the proportion of undetected primary biliary cholangitis patients in primary care through a clinical management process.*

***Methods.*** *We made two extractions of the clinical data concerning liver diseases, risk factors and laboratory tests from the databases of a sample of general practitioners, with a check and correction of mistakes. The clinical data of the patients without liver disease and major risk factors, and with serum Alkaline Phosphatase above the laboratory reference values, were re-evaluated by each general practitioner with an expert gastroenterologist. The patients with elevated Alkaline Phosphatase values and without evidence of intrahepatic or extrahepatic causes of cholestasis were considered suspected for primary biliary cholangitis and assessed for antimitochondrial antibodies test and specialist' s evaluation, according to present guidelines.*

***Results.*** *A total of 20,480 adults attending 14 general practitioners in the province of Brescia, Northern Italy, were included in the study. Nine patients had a prior primary biliary cholangitis diagnosis, with a prevalence of 43.9/100000. After excluding 2094 (10.2%) patient with liver diseases or other causes of cholestasis, 121 subjects with Alkaline Phosphatase above the reference values were re-evaluated by the general practitioners and gastroenterologist, and 27 patients without symptoms or signs of cholestasis were considered suspected for primary biliary cholangitis: 9 of them were tested for antimitochondrial antibodies, and three new primary biliary cholangitis cases were detected (+33%).*

***Discussion and Conclusions.*** *This study shows that there is a not negligible burden of undetected cases of adult rare diseases that can be diagnosed in primary care, through a disease management procedure, without modifying the routine clinical practice.*

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Annali di Igiene : Medicina Preventiva e di Comunità (Ann Ig)
ISSN 1120-9135 https://www.annali-igiene.it

## Introduction

Although the definition of what is a rare disease varies by geographical area and country, in the European Union a disease is considered rare when it affects fewer than 1 in 2,000 people (1). There are about 7,000 rare diseases that affect 10% of the world population (1), and many of them are usually underdiagnosed and undertreated.

Primary biliary cholangitis (PBC) is a chronic inflammatory, autoimmune, cholestatic liver disease that predominantly affects the interlobular bile ducts (2). It is one of the most common causes of chronic cholestasis among old women, with most patients aged 60 -79 years and a female-to-male ratio of 4–6:1 (2). PBC prevalence ranges from 3 to 40 per 100,000 worldwide, and from 12 to 58 per 100,000 in Europe, according to recent meta-analyses (3, 4). An Italian study recently reported a prevalence of 27.9 per 100,000 in the country, through the analysis of a large database of GPs' electronic medical records (5).

Early diagnosis of PBC is fundamental, as treatment with ursodeoxycholic acid, or second line therapy, prevents progression to liver cirrhosis and improves survival (6, 7). The proportion of subjects with early diagnosis of the disease has increased in last decades, probably due to increased routine testing of liver enzymes and awareness of the disease (8).

Current guidelines recommend a two-step approach for PBC diagnosis, consisting of: first, identifying adult asymptomatic subjects with cholestasis lasting 6 months and over by elevated levels of serum Alkaline Phosphatase (ALP) and/or gamma-glutamyltranspeptidase (GGT), and then, after excluding other liver and non-liver causes of ALP and/or GGT increase, determining serum antimitochondrial antibodies (AMA) and/or PBC-specific antinuclear antibodies (ANA) (6, 7). Since ALP can have various sources, also other intrahepatic and extrahepatic causes of ALP elevation must be considered for differential diagnosis (6, 9). However, data regarding guideline adherence in primary care settings and resulting PBC underdiagnosis are lacking.

This study aimed to assess the proportion of subjects with liver enzymes indicative of possible PBC but not investigated for the disease in primary care, leading to underdiagnosis and undertreatment of the disease.

## Methods

A few General Practitioners (GPs), an expert gastroenterologist and some University epidemiologists working in the province of Brescia, Italy, set up a Working Group to investigate the prevalence and clinical pattern of PBC in the general population.

Data on history of liver and non-liver chronic diseases, presence of risk factors for liver disease, US examinations and specialists' visits and the latest values of ALP, GGT and AMA, were extracted from the GP's electronic archives. PBC diagnosis was based on the International Classification of Diseases, IX Revision, code 571.6. Only laboratory data and specialists' evaluations performed in the last 5 years were considered. All the data were anonymised at each extraction and a code was randomly assigned to each subject. No change in the GPs' routine clinical activity was done before and after the data extraction and across the clinical management process.

The clinical management process included the following steps:

1. A first data extraction of all GPs' patients aged 18 years and over was made (June 2021). The data were checked, and evident mistakes and missing data were reported to each GP for his/her correction. A second data extraction then was performed.
2. Patients without diagnosis of liver disease and without major risk factors for liver disease (HBV and HCV chronic infections, alcohol abuse, use of drugs, etc.) (6) were considered for subsequent steps.
3. Complete clinical data of the patients with ALP values above the laboratory reference values were evaluated by GPs and the gastroenterologist together.
4. The patients with elevated ALP values and without evidence of intrahepatic or extrahepatic (causes of cholestasis (4) were considered suspected for PBC and recommended for AMA test and specialist' s assessment.
5. Among the AMA positive patients, new PBC cases were diagnosed.

## Results

A total of 20,480 adults attending 14 GPs in the province of Brescia, Northern Italy, with a mean age of 52.8 years (SD 19 years), 52.3% women, were included in the study. At the first data extraction, 9 patients with previous PBC diagnosis were identified, with a prevalence of 43.9/100.000 (95% confidence

interval, CIs: 20.1-83.4) (Figure 1). After excluding 2094 (10.2%) patients with liver diseases or with major hepatic risk factors for cholestasis, 121 subjects with ALP values above the reference values were re-evaluated by GPs and the gastroenterologist together. Among them, 94 patients who had hepatic or extrahepatic causes of ALP elevation were excluded from further evaluation, leaving 27 subjects with PBC suspicion. None of them had symptoms or signs of cholestasis. 18 of them were not tested for AMA/ANA due to very old age, presence of other severe diseases or refusal. Ultimately, 9 patients were tested for AMA: 4 were AMA positive and, after specialist's assessment, 3 of them had a definite diagnosis of PBC. One of the newly detected cases had already developed liver cirrhosis.

Overall, 12 patients were diagnosed with PBC after the clinical management procedure, with a mean age of 64 years (SD 13.3 years), 91.7% female. PBC prevalence was 58.6/100,000 (95% CIs: 30.3-102.4). About half of them (4 of 9) had had PBC diagnosis in the past 3 years, 4 (33.3%) had cirrhosis, and 2 (16.7%) PCB-related diseases (autoimmune atrophic gastritis and Crohn's disease).

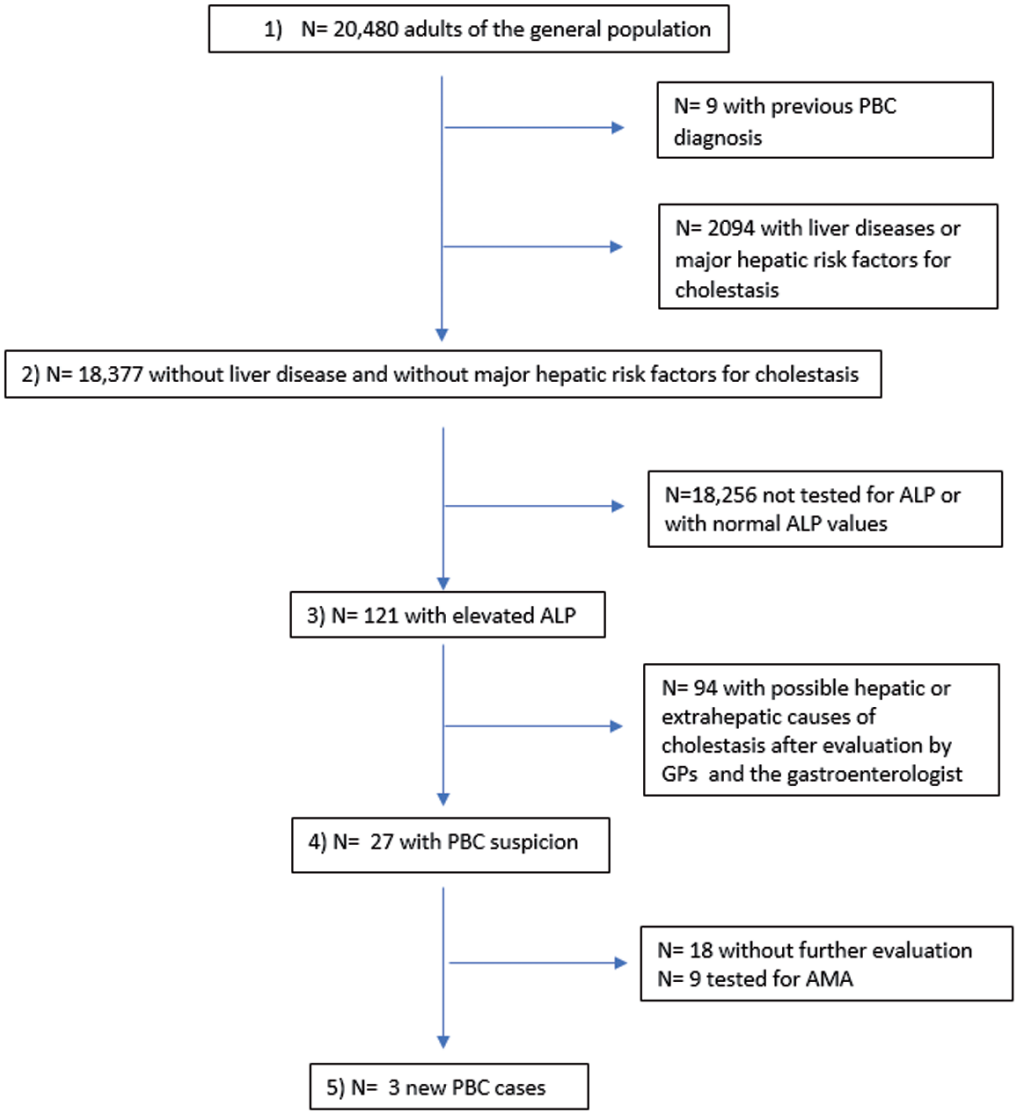


Figure 1 - Flow-chart of the clinical management procedure for detecting General Practitioners' patients with previously undiagnosed primary biliary cholangitis in the adult general population

## Discussion

The main finding of this study is the successful implementation of a clinical management procedure in primary care for detection of PBC, a relatively rare and often unrecognized liver disease, following present guidelines (6, 7). The procedure led to the detection of 3 new cases of PBC, with a 33% increase in the disease prevalence. However, other PBC cases probably remained undetected, including: a) subjects with early PBC who did not have an ALP test, or had ALP values within the normality range in past 5 years; b) subjects with ALP elevation but who were not tested for AMA/ANA because they had other possible causes of cholestasis, including hepatic or non-hepatic disease or risk factors for liver disease (6); c) subjects with PBC suspicion but not tested for AMA due to very old age, poor health conditions, or refusal.

The main strength of this study is the use of a population-based database, excluding possible selection bias of case-series. Indeed, demographic data and prevalence of some common diseases such as diabetes, hypertension, cardio-and cerebral-vascular and celiac diseases in the adult population were in line with another GPs' database study on PBC (5) and with Italian national data (10). A second strength of the study is the clinical management process, consisting of a critical assessment of GPs' data, with correction and integration of routinely registered data.

Nonetheless, this study has some limitations. First, the relatively small number of GPs involved in the study, who were volunteers. However, the small number of the participating GPs allowed us to maintain close contacts with each physician through multiple verbal and written communications. Second, only subjects with elevated ALP values in the past 5 years were selected to identify undetected PBC cases. However, the number of subjects with at least one ALP test in the past 5 years varied substantially among the GPs, suggesting differences in GPs' propensity to prescribe the test in clinical practice. Of note, more than half of ALP diagnoses were performed in recent years (2019-2021), probably due to an increase in disease awareness by GPs, in agreement with other studies (3).

Overall, this study on a relatively rare disease shows that underdetection of rare diseases is likely to occur in primary care, mainly due to lack of a comprehensive diagnostic approach, in spite of current guidelines. The recently proposed application of Artificial Intelligence (AI) in healthcare might be helpful to improve the detection of rare diseases and to identify health system barriers causing underdiagnosis in primary care (11).

## Conclusions

In conclusion, our study suggests that there is a non negligible proportion of rare diseases in the adult general population, such as PBC, that are underdiagnosed and undertreated in our country, despite the fact that the Italian Health System provides universal, free, primary healthcare and diagnostic approach for most diseases. The underestimation of rare diseases may be even higher in countries lacking a National Health System.

**Acknowledgments:** The authors thank Dr. Ovidio Brignoli for his thoughtful considerations and support to the study execution.

**Abbreviations:** ALP, alkaline phosphatase; AMA, antimitochondrial antibody; ANA, antinuclear antibody; GGT, gamma-glutamyl transferase; PBC, primary biliary cholangitis.

**Financial support and sponsorship:** This is a spontaneous study promoted by the Unit of Hygiene, Epidemiology and Public health, Department of Medical and Surgical Specialities, Radiological Sciences and Public Health, University of Brescia, together with the Gastrointestinal Unit, University of Brescia, and the School for GPs, Brescia area and the Protection Agency (ATS) of Brescia, with the non-conditioning support of Advanz Pharma Specialty Medicine.

**Conflicts of interest:** There are no conflicts of interest to declare.

**Ethics:** The project was approved by the Ethical Committee of Spedali Civili of Brescia, Italy (NP 3958) on 14th April 2021.

### Riassunto

***Perché le malattie rare sono sottodiagnosticate? Uno studio di management clinico sull'individuazione della colangite biliare primitiva in ambito di medicina generale***

**Introduzione**. Ci sono circa 7.000 malattie rare che colpiscono il 10% della popolazione mondiale. La colangite biliare primitiva, un'epatopatia infiammatoria autoimmune dei dotti intraepatici, è una delle cause più comuni di colestasi cronica, che può portare alla cirrosi e all'insufficienza epatica. Tuttavia la colangite biliare primitiva è una malattia rara, e pertanto è spesso sottodiagnosticata e sottotrattata. Lo scopo della ricerca era di stimare la proporzione di casi di colangite biliare primitiva nella popolazione generale non diagnosticati, mediante una procedura di clinical management.

**Metodi**. Sono state effettuate due estrazioni dei dati relativi a epatopatie, fattori di rischio ed esami di laboratorio presenti nei database di un campione di medici di medicina generale della provincia di Brescia, con controllo e correzione degli errori. I dati clinici dei pazienti senza malattie di fegato o fattori di rischio epatico, e con livelli di fosfatasi alcalina superiori ai valori di riferimento del laboratorio, sono stati rivalutati da ciascun medico di medicina generale

con un esperto gastroenterologo. I soggetti con elevati livelli sierici di fosfatasi alcalina e senza altre cause intraepatiche o extraepatiche di colestasi sono stati considerati sospetti per colangite biliare primitiva e sottoposti a determinazione degli anticorpi anti-mitocondri e ad una valutazione specialistica.

**Risultati**. Un totale di 20.480 assistiti adulti di 14 medici di medicina generale della provincia di Brescia è stato incluso nello studio. Nove pazienti avevano una diagnosi di colangite biliare primitiva, con una prevalenza di 43.9/100.000. Dopo avere escluso 2.094 (10.2%) pazienti con malattie di fegato o fattori di rischio per colestasi, 121 soggetti con fosfatasi alcalina superiore ai valori di riferimento del laboratorio sono stati rivalutati da ciascun medico di medicina generale e dal gastroenterologo. 27 pazienti senza sintomi o segni di colestasi sono stati presi in considerazione per il sospetto di colangite biliare primitiva: 9 sono stati sottoposti a test per gli anticorpi anti-mitocondri, e tre nuovi casi di colangite biliare primitiva sono stati individuati (+33%).

**Discussione e conclusioni.** Questo studio mostra che vi è un considerevole numero di casi di malattie rare dell'adulto non individuati, che possono essere riconosciuti in ambito di medicina generale mediante una procedura di management clinico, senza modificare la pratica clinica corrente.

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