ANNALI
DELL'ISTITUTO SUPERIORE DI SANITÀ

Volume **59** No. **3**
2023

A SCIENCE
JOURNAL *for*
PUBLIC
HEALTH

www.iss.it

Graphic design of the cover: Massimo Delle Femmine, Istituto Superiore di Sanità
The photograph is a double immunofluorescence staining of a post-mortem brain section from a person with multiple sclerosis for the T lymphocyte marker CD8 (green) and laminin (red). Image shows accumulation of cytotoxic CD8+ T lymphocytes in the perivascular space of a cerebral blood vessel.
Image is provided by Barbara Serafini, Department of Neuroscience, Istituto Superiore di Sanità, Rome, Italy.

ANNALI
dell'Istituto Superiore di Sanità

Vol. 59, No. 3 2023

Contents

EDITORIAL

Artificial intelligence in scholarly publishing: opportunities and concerns

Federica Napolitani[1], **Enrico Alleva**[2] **and Annarita Barbaro**[3]

[1]*Servizio Comunicazione Scientifica, Istituto Superiore di Sanità, Rome, Italy*
[2]*Formerly Director, Centro di Riferimento per le Scienze Comportamentali e la Salute Mentale, Istituto Superiore di Sanità, Rome, Italy*
[3]*Servizio Conoscenza, Istituto Superiore di Sanità, Rome, Italy*

The all-changing artificial intelligence (AI) revolution is currently underway. The sooner we recognize it, the better. As in all revolutions driven by technological progress and innovations, it is necessary to thoroughly discuss and to understand all surging developments and to address them, as soon as possible, by setting out standards, guidelines and policies.

Presumably AI will fully impact the generations to come. They will be able to experience its potentially infinite applications and unparalleled opportunities and, at the same time, will have the means to evaluate the consequences of what we now consider its potential benefits and threats. However, it is without doubt that at present we are witnessing an exponential proliferation of AI applications, tools and services and that AI itself is at the centre of the debate, in the general public and within the scientific and scholarly community. It is a hot topic which plays a growing role in different aspects of our society and is becoming relevant for all stakeholders in science communication: researchers, authors, editors, reviewers and publishers.

In scholarly publishing and in research practices, the potential impact of GPT models (Generative Pre-trained Transformer) recently emerged in a substantial number of discussions, conferences, webinars, editorials which always ended up by involving a plethora of different ethical implications.

One of these models is ChatGPT which is an AI chatbot tool for content creation produced by OpenAI, a research and deployment company working on artificial general intelligence (AGI). Among its limitations, as reported by the same producer, it "sometimes writes plausible-sounding but incorrect or nonsensical answers". ChatGPT is, de facto, already used by researchers for different purposes like translating, editing, drafting abstracts and for improving writing practices, and it potentially could be a valuable tool for ideation and writing while not being a source of original and reliable information. As recently reported, "ChatGPT and other LLMs (Large Language Models) produce text that is convincing, but often wrong, so their use can distort scientific facts and spread misinformation" [1].

Its misuse by authors is raising concerns among science editors who are already busy in trying to maintain the quality standards and high levels of integrity throughout the whole publication process of their journals, in an environment blurred by predatory publishers and paper mill organizations, which are profit-oriented and responsible for an increased number of fraudulent and fake publications.

To meet these concerns and advocate for a safe, transparent and sound use of AI tools in science communication, the International Committee of Medical Journal Editors (ICMJE) on May 2023 updated the *Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals* including a whole new section and a revision of other sections to provide guidance on how work conducted with the assistance of AI technology (including ChatGPT) should and should not be acknowledged: "At submission, the journal should require authors to disclose whether they used artificial intelligence (AI)–assisted technologies (such as Large Language Models [LLMs], chatbots, or image creators) in the production of submitted work. Authors who use such technology should describe, in both the cover letter and the submitted work, how they used it. Chatbots (such as ChatGPT) should not be listed as authors because they cannot be responsible for the accuracy, integrity, and originality of the work, and these responsibilities are required for authorship (see Section II.A.1). Therefore, human beings are responsible for any submitted material that included the use of AI-assisted technologies. Authors should carefully review and edit the result because AI can generate authoritative-sounding output that can be incorrect, incomplete, or biased. Authors should not list AI and AI-assisted technologies as an author or co-author, nor cite AI as an author. Authors should be able to assert that there is no plagiarism in their paper, including in text and images produced by the AI. Humans must ensure

there is appropriate attribution of all quoted material, including full citations" [2].

The Committee on Publication Ethics (COPE) recognising the value of AI tools for ideation and writing, issued a position statement clarifying that authors can use the AI tools, so long as they are properly credited and attributed, being fully responsible for the content of their manuscripts: "The use of artificial intelligence (AI) tools such as ChatGPT or Large Language Models in research publications is expanding rapidly. COPE joins organisations, such as WAME and the JAMA Network among others, to state that AI tools cannot be listed as an author of a paper (…) Authors who use AI tools in the writing of a manuscript, production of images or graphical elements of the paper, or in the collection and analysis of data, must be transparent in disclosing in the Materials and Methods (or similar section) of the paper how the AI tool was used and which tool was used. Authors are fully responsible for the content of their manuscript, even those parts produced by an AI tool, and are thus liable for any breach of publication ethics" [3]. COPE also started a discussion on March 2023 about AI and fake papers and ethical implications.

Many publishers have also inserted disclaimers or included specific guidelines for authors wishing to use AI in the production of articles or in the conduct of research. Elsevier addresses the use of AI and AI-assisted writing technologies in scientific writing [4]; Taylor & Francis clarifies the responsible use of AI tools in academic content creation [5]; journals like *JAMA* specify that Authors should include in their paper a description of the content created or edited by AI and the name of the AI model or tool used, including producer, version and extension numbers [6], and Springer Nature set down guidelines for its use [7]. The same European Commission posed some questions concerning the intellectual property of the ChatGPT-generated content (Who owns it? Is it possible to use it without infringing someone's copyright and so on) [8] and the European Union has prepared a general regulation on Artificial Intelligence, the EU AI Act, whose positions have been adopted by the MEPs on 14 June 2023 [9, 10] and which will continue to be discussed till approved in the final form of a law.

While AI is posing some threats, at the same time it might offer the way to overcome those same challenges, for instance to detect machine-created content or paper mill articles. It could also help in generating ideas, suggesting innovative methods of studies, help in bioimage analysis [11], increasing equity and inclusion for people with disabilities who might use AI tools as assistive technologies or for alleviating linguistic disparities [12]. An Artificial Intelligence Review Assistant (AIRA) is in use at Frontiers, a major Open Access scholarly Publisher, in its digital peer-review platform, enabling faster, more efficient quality control and manuscript handling [13].

Will it be beneficial in support of the many activities involved in the scientific reporting and publication process? Those who are already experimenting AI tools feel fascinated by its potential but, at the same time, rightly scared. What is clear is that nobody can stop this revolution but can try to make it as beneficial as possible for everyone and to prevent its misuse. This is precisely what *Annali ISS*, the journal for public health published by the Italian National Institute of Health, will try to do in the near future (Authors' Guidelines are being updated to cover the use of AI tools) in full compliance with the recommendations and best practices issued by international organizations to ensure quality standards, transparency and integrity in science reporting. We do not expect this to be our last change in policy on this topic and we welcome the opinions of our readers both at this stage and in the future.

Conflict of interest statement
The Authors declare that there are no conflicts of interest.

REFERENCES

1. van Dis EAM, Bollen J, Zuidema W, van Rooij R, Bockting CL. ChatGPT: five priorities for research. Nature. 2023;614(7947):224-6. doi: 10.1038/d41586-023-00288-7
2. International Committee of Medical Journal Editors. Recommendations for the conduct, reporting, editing and publication of scholarly work in medical journals [Internet]. May 2023. Available from: http://www.ICMJE.org.
3. COPE. Authorship and AI tools. COPE Position Statement. [Internet]. 13 February 2023. Available from: https://publicationethics.org/cope-position-statements/ai-author.
4. Elsevier. The use of AI and AI-assisted writing technologies in scientific writing. Frequently Asked Questions. [Internet]. Available from: https://www.elsevier.com/about/policies/publishing-ethics/the-use-of-ai-and-ai-assisted-writing-technologies-in-scientific-writing.
5. Taylor & Francis. Taylor & Francis Clarifies the Responsible use of AI Tools in Academic Content Creation. [Internet]. 17 February 2023. Available from: https://newsroom.taylorandfrancisgroup.com/taylor-francis-clarifies-the-responsible-use-of-ai-tools-in-academic-content-creation/#.
6. Journal of the American Medical Association. Instructions for authors. [Internet]. Available from: https://jamanetwork.com/journals/jama/pages/instructions-for-authors.
7. Springer Nature. Editorial policies: Artificial Intelligence (AI). [Internet]. Available from: https://www.nature.com/nature-portfolio/editorial-policies/ai.
8. European Commission. Intellectual property in ChatGPT. [Internet]. 20 February 2023. Available from: https://intellectual-property-helpdesk.ec.europa.eu/news-events/news/intellectual-property-chatgpt-2023-02-20_en.
9. European Union. EU AI Act: first regulation on artificial intelligence. European Parliament News. [Internet]. 14 June 2023. Available from: https://www.europarl.europa.eu/news/en/headlines/society/20230601STO93804/eu-ai-act-first-regulation-on-artificial-intelligence.

10. Gasser U. An EU landmark for AI governance. Science. 2023;380(6651):1203. doi: 10.1126/science.adj1627

11. Nogare DD, Hartley M, Deschamps J, et al. Using AI in bioimage analysis to elevate the rate of scientific discovery as a community. Nat Methods. 2023;20:973-5. https://doi.org/10.1038/s41592-023-01929-5

12. Berdejo-Espinola V, Amano T. AI tools can improve equity in science. Science. 2023;379(6636):991. doi: 10.1126/science.adg9714

13. Frontiers. Artificial Intelligence to help meet global demand for high-quality, objective peer-review in publishing. [Internet]. 1 July 2020. Available from: https://blog.frontiersin.org/2020/07/01/artificial-intelligence-peer-review-assistant-aira/.

ORIGINAL ARTICLES AND REVIEWS

Knowledge and behaviours associated with HIV infection and other sexually transmitted infections in blood donors in Italy

Vincenza Regine[1]*, **Lucia Pugliese**[1]*, **Alice Simonetti**[2], **Francesco Marchionni**[2], **Gianpietro Briola**[2], **Vincenzo Saturni**[2] and **Barbara Suligoi**[1]

[1]*Dipartimento di Malattie Infettive, Istituto Superiore di Sanità, Rome, Italy*
[2]*Associazione Volontari Italiani del Sangue (AVIS), Milan, Italy*
This Authors contributed equally to this manuscript as co-first Author

Abstract
Introduction. Sexually transmitted infections (STIs) represent a group of widespread infectious diseases. The objective of this study is to investigate the knowledge on HIV and STIs as well as sexual risk behaviours among blood donors in Italy.
Materials and methods. The study was carried out in 2017 among blood donors who accessed social media of the Italian Association of Blood Donors (Associazione Volontari Italiani del Sangue, AVIS), and answered to a questionnaire posted online.
Results. Participating blood donors were 9,021, median age 36 years (IQR 26-47), 53.9% males, 94.3% heterosexual, and 2.7% reported having a current occasional partner. Unprotected sex in the last 4 months was reported by 54.1% of participants. About half of the participants were not informed of most STIs, 11.0% reported never having searched for information on HIV and STIs, one third considered unlikely acquiring HIV through unprotected sex with a known person, 21.3% would stop having sex with a partner found to be HIV-positive, and 15.8% would be afraid to hug or kiss a person with HIV.
Discussion. Our results show that most blood donors have a stable partner and search actively for information on HIV and STIs. However, there is a proportion of them who engage in high-risk behaviours, have misconceptions on HIV and STIs transmission, reporting a stigmatising attitude towards people with HIV.
Conclusion. A more comprehensive and updated information on various STIs, transmission modes and safe sex should be provided to blood donors, not only to prevent the spread of these infections but also to avoid unjustified discrimination.

INTRODUCTION

Sexually transmitted infections (STIs) represent a group of highly spread infectious diseases, both in Italy and worldwide [1-4]. Their prevention is acknowledged to be a primary goal of the public healthcare system and it is crucial among blood donors in ensuring blood safety [5-7].

In Italy, about 2,000 new HIV diagnoses are reported each year and approximately 130,000 people are estimated to be living with HIV; out of these, about 15,000 are still undiagnosed [8-10].

The number of STIs cases showed a 42% increase between 2005 and 2019, according to data reported to the sentinel STIs surveillance system [11].

The spread of HIV and other STIs among blood donors is constantly monitored by the Information System of Transfusion Services (Sistema Informativo dei Servizi Trasfusionali, SISTRA) [12].

In 2020, SISTRA data reported 1,420 blood donors who tested positive for at least one of the four mandatory transfusion-transmissible infection markers. In 2020, among regular blood donors about 1.9 out of 100,000 blood donors tested positive for HIV, 12.6 for HBV, 1.0 for HCV and 9.3 for syphilis, whereas among first-time blood donors, 9 per 100,000 were positive for HIV, 109.8 for HBV, 45.5 for HCV and 96.2 for syphilis [12]. The number of blood donors positive to hepatitis B and C decreased in the last ten years whereas the number of blood donors positive to syphilis was stable, nevertheless prevalence of syphilis remains the highest

[13-15]. National data on mandatory notifiable syphilis show an increase in acute syphilis incidence since 2006 [16]. The incidence of HIV-positive blood donors remained stable in the last decade, differently from what observed in the national surveillance data that report a progressive decrease in the incidence of new diagnoses since 2012 [13-15]. However, a recent analysis showed that HIV rates observed among blood donors are only weakly associated with those observed in the general population [17]. This difference in HIV rates between blood donors and general population was compared internationally in a recent study. It is observed that Italy together with Spain have the highest HIV rates and authors attributed these differences to the donor deferral criteria which are based on a policy of gender neutrality, i.e. in both countries there are not differences based on sexual orientation in deferral policy of donors [17]. In this framework, it is undeniable that there is not only one way to remain alert on blood donation safety: alongside the deferral criteria, the knowledge of HIV/STIs at-risk behaviour and their prevention play a key role among blood donor population. An Italian study conducted among HIV-positive blood donors highlighted that the main reason for not having reported a risky behaviour in the pre-donation selection was "not realizing having engaged in a behaviour at risk infection" [18]. Behaviours at risk for HIV infection among blood donors were evidenced also in other Italian studies [19].

In this context, it is plausible that a proportion of the blood donor population has a poor knowledge of HIV/STIs sexual risk behaviour. The objective of this study is to investigate the knowledge on HIV and STIs as well as the frequency of sexual risk behaviours among blood donors in Italy.

MATERIALS AND METHODS

The study was carried out in 2017 by the Italian National Institute of Health (Istituto Superiore di Sanità, ISS) and by the Italian Association of Blood donors (Associazione Volontari Italiani del Sangue, AVIS) which is the largest Italian blood donor association, each year it contributes 70% of the national blood supply coming from blood donor associations, and the 37% of the national blood supply. The population was selected in the 3,300 AVIS seats located throughout the country. Each seat contacted its associates informing them of the survey and inviting them to participate. The survey was also disseminated among AVIS social media users by posting the invitation every two weeks. The study questionnaire was posted on the national AVIS website from February 28 to April 2, 2017. The survey was anonymous, in particular the system to collect data used set in order to prevent possible identification of the IP from which participants accessed to the survey.

The questionnaire included an initial question for the selection of blood donors and collected information on the following 4 field: demographic variables, sexual behaviours, level of knowledge on sexually transmitted infections, opinions and stigma towards HIV-positive people. Each field included about 10 open-ended or closed-ended or Likert scale questions. The questions on sexual behaviours were formulated taking into ac-

count the deferral criteria adopted in Italy (4 months from the last STIs sexual risk behaviour) if donors did not engage in "high risk behaviours" for which there is permanent deferral. Knowledge questions also included the sources of information: never get informed, family/friend comparison, in-depth internet searches, inquiries to doctors and specialists, scientific studies, participation in school/university/blood donor association training events. In this paper the answers were grouped into three modalities: No, never; Yes, a little, through internet search; Yes, a lot, through scientific sources.

The questions related to the opinions on STIs were formulated on a scale of 4 levels of agreement/probability (not at all, a little, enough, a lot), in this paper the answers were grouped into dichotomous variables (unlikely *vs* likely). The average time to complete questionnaire was approximately 15 minutes and 90% of the participants answered all the questions. Survey participants were 11,257 and of these 9,021 (80%) were blood donors. In this study, all the questionnaires filled in by people who declared to be a blood donor were included.

This work presents a description of HIV sexual risk behaviours among blood donors who participated in the survey. Specific differences for various subgroups have been evaluated using Chi-squared test: gender, age, geographical area, educational level, occupation, number of years from the first donation. In order to evaluate factors correlated to the never get informed on HIV and STIs, a multivariate logistic regression model was used. IBM SPSS v26 software was used for statistical analysis.

RESULTS
Population characteristics

This survey included 9,021 blood donors. *Table 1* describes demographic characteristics of participants, 29.7% of the interviewed declared to have been blood donor for less than 3 years while 37.6% for more than 10 years.

Sexual risk behaviours for HIV and other STIs

Table 2 shows sexual behaviours at risk of HIV infection and other STIs. About 80% of the blood donors interviewed had a stable partner and 94.3% declared to be heterosexual. More than a half (54.1%) had had unprotected sexual intercourse in the last 4 months, 96.5% of them were with a stable partner, 2.4% with an occasional partner, 1.1% of blood donors gave no information on partner status.

The main reason for not using of condom was both with stable and occasional partner the trust in their partner: 58.5% of answers for stable partner and 53.5% of answers for occasional partner. The use of drugs during sex was reported from 69 (0.8%) participants, 71.0% of them were blood donors less than 35 years old, 60.0% were males and 39.0% students (data not shown in the *Table*).

Knowledge on HIV and other STIs

Table 3 shows knowledge, opinions and false beliefs regarding HIV and STIs: 63.4% of blood donors declared to get informed a lot on HIV and STIs through scientific sources (papers, specialist books and conferences), a quarter of blood donors declared to get informed a

Table 1
Characteristics of 9,021 blood donors participating in the study, Italy, 2017

		N	%
Time elapsed from first blood donation	1-3 years	2,682	29.7
	4-6 years	1,599	17.7
	7-10 years	1,352	15.0
	>10 years	3,388	37.6
Gender	Male	4,864	53.9
	Female	4,157	46.1
Median Age (IQR[a])	36 (26-47)		
Age group (years)	<25	1,718	19.0
	25-34	2,408	26.7
	35-49	3,062	34.0
	≥50	1,833	10.3
Nationality	Italian	8,918	98.9
	Non-Italian	103	1.1
Area of residence	Northern Italy	5,895	65.3
	Central Italy	1,614	17.9
	Southern Italy and Islands	1,512	16.8
Education	Primary school	967	10.7
	Secondary school	5,095	56.5
	Degree	2,959	32.8
Occupation	Unemployed	803	8.9
	Employed	5,140	57.0
	Freelance	1,207	13.4
	Student	1,541	17.1
	Housewife/retired	330	3.6

[a]IQR = interquartile range.

Table 2
Sexual behaviour of 9,021 blood donors participating in the study, Italy, 2017

	N	%
Sexual orientation		
Heterosexual	8,506	94.3
Homo-bisexual	515	5.7
Current partner		
Stable (>6months)	7,101	78.7
Occasional	242	2.7
None	1,678	18.6
Condom use during sex in the last 4 months		
No sexual intercourse	1,946	21.6
Sexual intercourse always with condom	2,191	24.3
Sexual intercourse without condom	4,884	54.1
Sex without condom with		
Stable partner	4,711	96.5
Occasional partner	116	2.4
na	57	1.1
Reasons for not using condom (with a stable partner)[a]		
I trust my partner	3,444	58.5
I do not want to use contraceptives	1,732	29.4
I am taking the contraceptive pill	527	8.9
Other reasons (not having handy condom, cost, allergy)	186	3.1
Reasons for not using condom (with an occasional partner)[a]		
I trust my partner	77	53.5
I do not want to use contraceptives	33	22.9
I am taking the contraceptive pill	0	0.0
Other reasons (I do not have a condom, cost, allergy)	34	23.6
Use of drugs during sex		
No	8,952	99.2
Yes	69	0.8

[a]More than one answer allowed; na: not available.

little through internet search, while 11.0% declared to get never informed. The proportion of blood donors who inform themselves about HIV and STI changed by level of education. Higher proportion of people who inform themselves a lot from scientific sources were observed at high levels of education compared to people less educated: 54.0% among blood donors with primary school, 61.8% among those with secondary school and 69.1% among graduated blood donors (p-value <0.00). The multivariate regression logistic model showed that factors significantly correlated with never getting informed on HIV and STIs were: having a job compared to students (OR 1.75 CI 95% 1.27-2.41), having a middle and high school diploma compared to a degree (OR 1.74 CI 95% 1.39-2.18, OR 1.37 CI 95% 1.17-1.61, respectively), being heterosexual compared to MSM (OR 1.50 CI 95% 1.04-2.17), being male compared to female (OR 1.41 CI 95% 1.22-1.63), being aged between 25 and 49 years (OR 1.43 CI 95% 1.06-1.93) and older than 50 years (OR 2.18 CI 95% 1.55-3.05) compared to those younger than 25 years. The STIs known were as follows: HIV (90.8%), syphilis (39.5%), hepatitis B and C (27.6%), gonorrhoea (23.8%), whereas the least known STIs was Trichomonas infection (3.8%).

Opinions and stigma on HIV and other STIs

About a quarter of blood donors declared that it is unlikely to get infected during oral sex; this proportion was 30.4% among people over 50 years old and it is significantly higher (p-value <0.05) than in the lower age groups (22.0% among blood donors 25-49 years; 25.4% among blood donors <25 years) *(Figure 1)*. About 17% found it unlikely to be infected via anal intercourse; these percentages are significantly (p-value <0.05) higher among blood donors aged less than 25 years (20.3%) and among blood donors over the age of 50 years (21.1%) compared to the 25-49 age group (14.2%) *(Figure 1)*.

The proportion of blood donors who believe it is unlikely to get infected with an STI through either vaginal

Table 3
Knowledge on HIV and sexually transmitted infections (STIs) among 9,021 blood donors participating in the study, Italy, 2017

		N	%
Do you get informed on STIs?			
Yes, a lot, through scientific sources		5,724	63.4
Yes, a little, through internet search		2,308	25.6
No, never		989	11.0
The STIs I know are (open answer, % of total respondents)			
None		439	4.9
HIV/AIDS		8,187	90.8
Syphilis		3,566	39.5
Viral hepatitis (HBV, HCV)		2,486	27.6
Gonorrhoea		2,146	23.8
Genital herpes		1,515	16.8
Papilloma virus (HPV), ano-genital warts		1,052	11.7
Chlamydia, LGV		925	10.3
Other STIs (trichomonas, chancroid, etc.)		346	3.8
Can you acquire an STI through			
Vaginal sex	unlikely	364	4.0
	very likely	8,657	96.0
Vaginal sex during menses	unlikely	1,280	14.2
	very likely	7,741	85.8
Anal sex	unlikely	1,515	16.8
	very likely	7,506	83.2
Oral sex	unlikely	2,200	24.4
	very likely	6,821	75.6
HIV can be acquired through unprotected sex with			
Someone that you already known	unlikely	3,089	34.2
	likely	5,932	65.8
A new partner	unlikely	597	6.6
	likely	8,424	93.4
A partner who has same-sex	unlikely	1,133	12.6
	likely	7,888	87.4
Opinions and stigma			
Would you stop having sex if you find out that your partner is HIV+?	No	7,101	78.7
	Yes	1,920	21.3
Are you afraid of hugging or kissing an HIV+ friend?	No	7,599	84.2
	Yes	1,422	15.8
Would you share the room with an HIV+ person?	No	8,002	88.7
	Yes	1,019	11.3
Would you ban HIV+ children from public schools?	No	8,492	94.1
	Yes	529	5.9
Are you afraid of acquiring HIV in a public toilet?	No	7,713	85.5
	Yes	1,308	14.5
Do you agree in recording the names of HIV+ people in a national registry that can be accessed only by NHS workers?	No	3,417	37.9
	Yes	5,604	62.1

intercourse during menstruation, anal or oral sex, were significantly lower (p-value <0.05) in the 5,724 blood donors who declared to get informed on STIs through scientific sources (during menstruation 11.2%, anal 13.4%, oral 20.3%) compared to blood donors who declared to get informed a little on STIs or never (during menstruation 19.1%, anal 23.3%, oral 32.1%) (data not shown in *Table*).

Blood donors who considered it unlikely to be infected with HIV through unprotected sex with a person already known were 34.2%, with a partner who has same-sex sex 12.6% and with a new partner 6.6%. These proportions were significantly (p-value <0.05) higher in males compared to females *(Figure 2)*. The proportion of blood donors who considered it unlikely to be infected with HIV through unprotected sex with a new partner was significantly (p-value <0.05) lower in blood donors with a university degree (5.1%) compared to blood donors with a secondary school degree (11.4%). Significantly differences were observed in the proportion of blood donors who considered it unlikely to be infected with HIV through unprotected sex with a person who has same-sex sex in particular among blood donors with a degree was 9.5% while among blood donors with secondary school was 19.0% (p-value <0.05) (data not shown).

Table 3 shows stigmatizing opinions towards people with HIV. Blood donors stating that they would stop having sex if they found out that their partner was HIV positive were 21.3%, there were significantly (p-value <0.05) differences between males and females (23.3% *vs* 20.2%) (data not shown). Donors who would be afraid to hug or kiss an HIV positive friend were 15.8%, there were significantly differences in males compared to females (18.4% *vs* 14.1%) and in donors aged 50 and more compared to those younger (20.2% *vs* 15.3%) (data not shown). Donors that would not feel comfortable sharing common spaces with HIV positive people was 11.3%, there were no significant differences in terms of age, gender, level of education and occupation (data not shown).

DISCUSSION

The present study is the first large study that assessed knowledge, attitudes and opinions on HIV and other STIs among blood donors in Italy. Our survey shows that although a high percentage of blood donors declared to get informed through scientific sources on HIV and STIs mostly using reliable sources, there is still a proportion of them who engage in high-risk behaviours, have misconceptions on STIs and HIV transmission and report a stigmatising attitude towards people with HIV.

Regarding behaviours at risk of infection, it should be noted that 2% of participants had unprotected sex with occasional partners in the last 4 months. Attention should be paid to this proportion because these blood donors do not fulfil the selection criteria of eligible blood donors, underpinning that the selection process might not be flawless, and hence endanger blood safety. Blood donors who had unprotected sex in the last 4 months with occasional partners declared that they did not use
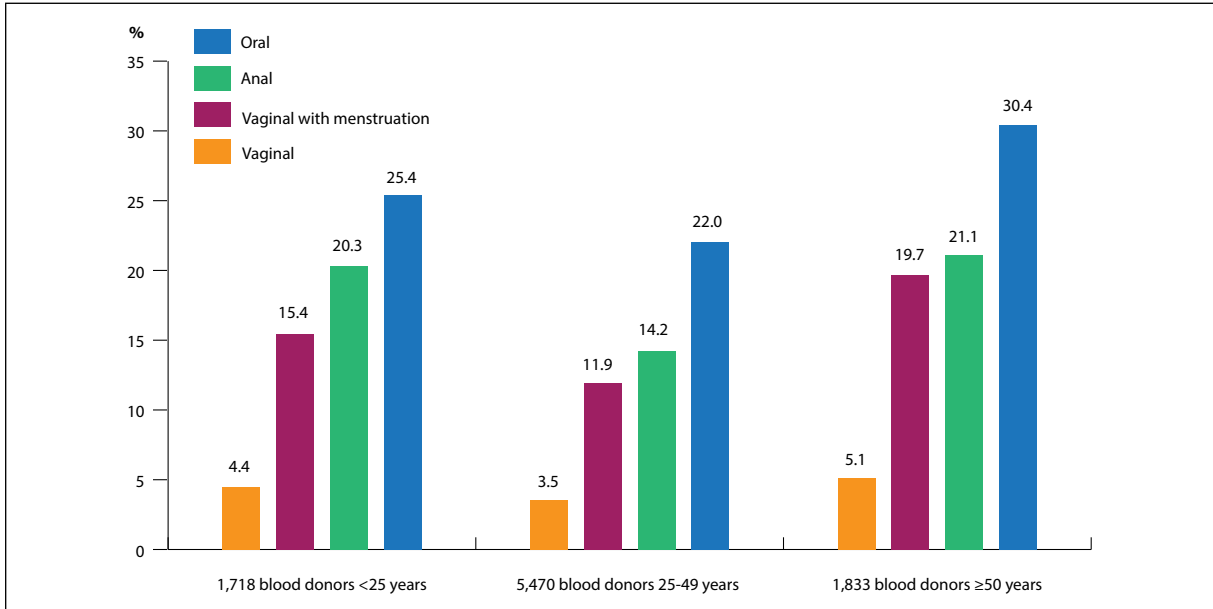
Figure 1
Proportion of blood donors who believe it unlikely to acquire an STI during sex (vaginal, vaginal with menstruation, anal, oral), by age group.

condoms because of their trust in their partners or because they used other contraceptive methods, such as oral contraceptives. The latter result clearly shows that condom is mainly considered a contraceptive rather than a protection also against infections, evidencing a poor knowledge on protection against STIs. Our study shows that more than 60% of the respondents get informed on STIs by consulting scientific sources. This result can be explained by the high awareness of blood donors who are motivated by the donation experience, and by the fact that our study sample was young and with a high education level. However, it should be noted that 11% of respondents reported never having looked for information on STIs.

Our study shows that a quarter of participants rate as unlikely acquiring an STI through oral sex, and one sixth through anal sex or vaginal intercourse during menstruation, therefore uncovering a poor knowledge on the risk of transmission modes. Specifically, unprotected anal sex implies the higher risk for HIV transmission [20-24]. Participants under 25 years and over 50 years of age showed the highest proportion of misleading information on STIs transmission. These results are important because the inadequate information on HIV/STIs might lead to engaging in unprotected sex [25-27]. Furthermore, our study shows that more than 90% of the respondents declared they knew HIV infection, while less than 40% knew other STIs. A
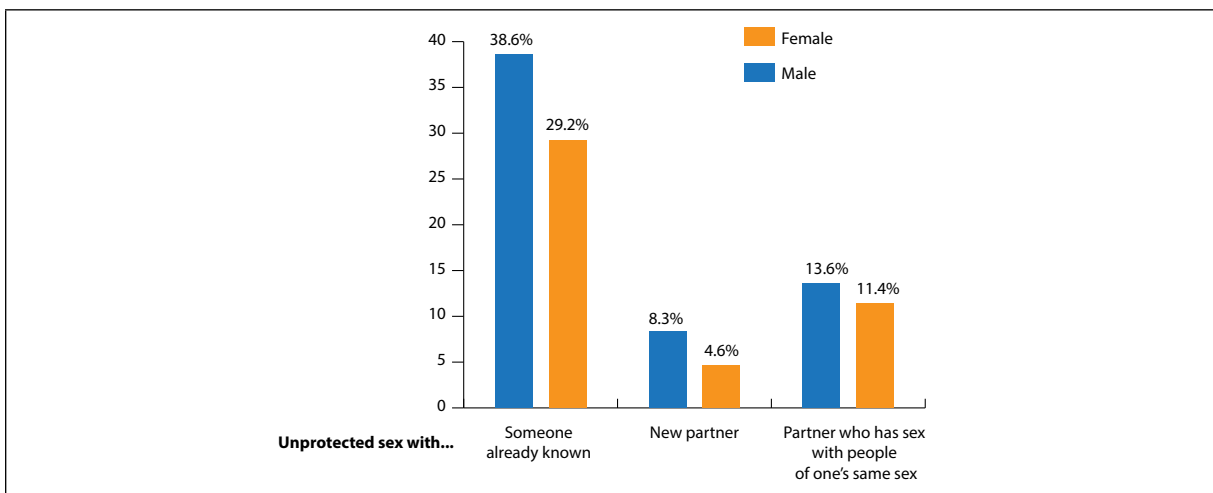
Figure 2
Proportion of blood donors who believe it unlikely to acquire HIV during unprotected sex with (someone already known, new partner, partner who has sex with people of one's same sex) by gender.

recent study carried out in Germany confirms similar findings [28].

We observed the highest percentages of misconception on STIs transmission among blood donors over 50 years of age. An insufficient knowledge on HIV/STI transmission is probably associated with the increasing HIV incidence trend among individuals older than 50 years reported both in Italy and in Europe in the last five years, as opposite to the decreasing trend observed in all other age groups [4, 8]. A systematic review showed that, compared to individuals under 45 years of age, heterosexuals aged between 45 and 64 years have a higher risk of acquiring an STI and among them, males have a higher risk of infection because of a lower condom use [29].

One fifth of respondents would stop having sex, even protected sex, if they would find out their partner as being HIV-positive, and one third would have unprotected sex with a partner if known. These results suggest that the risk of acquiring HIV/STIs is generally associated with a judgemental attitude towards "categories" of individuals (e.g., infected, friend, at risk, known person, trustful, etc.) rather than to at-risk sexual behaviour.

Stigmatizing beliefs emerged from a proportion of participants that stated being afraid of hugging or kissing an HIV-positive friend, or sharing a room with an HIV-positive person. Similar beliefs and stigmatising behaviours are still widespread in several countries. A study conducted in Spain showed that 50% of the population would feel uncomfortable having social relationships with HIV-positive people, although this percentage has decreased over time due to a number of information campaigns on the transmission mode of HIV infection [30, 31].

The added value of the study is having used Internet and the website of the largest Italian blood donor association to post the study questionnaire [32]. These options allowed to reach quickly and without costs a large number of blood donors all over the country. In addition, our sample is representative of the Italian population aged 18-65 years in terms of gender distribution, educational level and employment status. However, a selection bias towards a higher participation of individuals more sensitive to STIs prevention is to be considered [13, 33, 34].

CONCLUSION

Our findings stress the need to improve prevention policies and to increase awareness-raising campaigns on HIV/STIs transmission modes and the adoption of safe sexual behaviours among blood donors. Health staff operating in blood transfusion services have the opportunity to provide more in-depth information on HIV/STIs during the pre-screening procedures. Prevention initiatives using social media such as AVIS associative websites, newsletters and social webpages are extremely effective and should be incremented to facilitate the dissemination of correct health information and to achieve the highest quality standards in blood donations.

REFERENCES

1. World Health Organization. Sexually Transmitted Infections (STIs). Geneva: WHO; 2019. Available from: https://www.who.int/en/news-room/fact-sheets/detail/sexually-transmitted-infections-(stis).

2. World Health Organization. Global health sector strategy on sexually transmitted infections, 2016-2021. Geneva: WHO; 2016. Available from: https://apps.who.int/iris/bitstream/handle/10665/246296/WHO-RHR-16.09-eng.pdf?sequence=1.

3. Joint United Nations Programme on HIV/AIDS 2020. Global HIV & AIDS statistics. 2020 fact sheet. Geneva: UNAIDS; 2020. Available from: https://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf.

4. European Centre for Disease Prevention and Control/WHO Regional Office for Europe. HIV/AIDS surveillance in Europe 2020-2019 data. Copenhagen: WHO Regional Office for Europe; 2020. Available from: https://www.ecdc.europa.eu/en/publications-data/hivaids-surveillance-europe-2020-2019-data.

5. European Centre for Disease Prevention and Control. Long-term surveillance strategy 2014-2020. Stockholm: ECDC; 2013. Available from: https://www.ecdc.europa.eu/en/publications-data/long-term-surveillance-strategy-2014-2020-revised.

6. Ministero della Salute. Piano nazionale di interventi contro HIV e AIDS (PNAIDS). Rome: Ministero della Salute; 2017. Available from: http://www.salute.gov.it/imgs/C_17_pubblicazioni_2655_allegato.pdf.

7. Ministero della Salute. Piano Nazionale della Prevenzione 2020-2025. Rome: Ministero della Salute; 2020. Available from: http://www.salute.gov.it/portale/news/p3_2_1_1_1.jsp?lingua=italiano&menu=notizie&p=dalministero&id=5029-.

8. Regine V, Pugliese L, Boros S, et al. Aggiornamento delle nuove diagnosi di infezione da HIV e dei casi di AIDS in Italia al 31 dicembre 2020. Not Ist Super Sanità. 2021;34(11).

9. Mammone A, Pezzotti P, Regine V, et al. How many people

are living with undiagnosed HIV infection? An estimate for Italy, based on surveillance data. AIDS. 2016;30(7):1131-6. doi: 10.1097/QAD.0000000000001034

10. Regine V, Dorrucci M, Pezzotti P, et al. People living with undiagnosed HIV infection and a low CD4 count: estimates from surveillance data, Italy, 2012 to 2014. Euro Surveill. 2018;23(15). doi: 10.2807/1560-7917. ES.2018.23.15.17-00240

11. Salfa MC, Ferri M, Suligoi B. Le Infezioni Sessualmente Trasmesse: aggiornamento dei dati dei due sistemi di sorveglianza sentinella attivi in Italia al 31 dicembre 2019. Not Ist Super Sanità. 2021;34(7-8).

12. Catalano L, Piccinini V, Pati I, et al. Italian Blood System 2020: activity data, haemovigilance and epidemiological surveillance. Roma: Istituto Superiore di Sanità; 2021. (Rapporti ISTISAN 21/14).

13. Velati C, Romanò L, Pati I, et al. Studio di monitoraggio del rischio residuo di trasmissione trasfusionale delle infezioni da virus dell'immunodeficienza umana e virus dell'epatite B e C (Italia, 2009-2018). Roma: Istituto Superiore di Sanità; 2019. (Rapporti ISTISAN 19/26).

14. Velati C, Romanò L, Piccinini V, et al. Prevalence, incidence and residual risk of transfusion-transmitted hepatitis C virus and human immunodeficiency virus after the implementation of nucleic acid testing in Italy: a 7-year (2009-2015) survey. Blood Transfus. 2018;16:422-32. doi: 10.2450/2018.0069-18

15. Velati C, Romanò L, Pati I, et al. Prevalence, incidence and residual risk of transfusion-transmitted hepatitis B virus infection in Italy from 2009 to 2018. Blood Transfus. 2019;17:409-17. doi: 10.2450/2019.0245-19

16. European Centre for Disease Prevention and Control. Surveillance atlas of infectious diseases. Stockholm: ECDC; 2023. Available from: https://www.ecdc.europa. eu/en/surveillance-atlas-infectious-diseases.

17. Germain M, Grégoire Y, Custer BS, et al. An international comparison of HIV prevalence and incidence in blood donors and general population: a BEST Collaborative study. Vox Sang. 2021;116(10):1084-93. doi: 10.1111/vox.13107

18. Raimondo M, Facco G, Regine V, et al. HIV-positive blood donors unaware of their sexual at-risk behaviours before donation in Italy. Vox Sang. 2016;110(2):134-42. doi: 10.1111/vox.12328

19. Regine V, Raimondo M, Camoni L, et al. Low perception of sexual behaviours at risk for human immunodeficiency virus infection among blood donors who call the AIDS/STI Help Line in Italy. Blood Transfus. 2013;11(4):575-9. doi: 10.2450/2013.0257-12

20. Schöfer H. Sexuellübertragbare Infektionen der Mundhöhle [Sexually transmitted infections of the oral cavity]. Hautarzt. 2012;63(9):710-5. German. doi: 10.1007/s00105-012-2352-9

21. Ballini A, Cantore S, Fatone L, et al. Transmission of non-viral sexually transmitted infections and oral sex. J Sex Med. 2012;9(2):372-84. doi: 10.1111/j.1743-6109.2011.02515.x

22. Patel P, Borkowf CB, Brooks JT, et al. Estimating per-act HIV transmission risk: a systematic review. AIDS. 2014;28(10):1509-19. doi: 10.1097/QAD.0000000000000298

23. Nagelkerke N, Seedat S, Raddad A, et al. Sexual behaviour surveys should ask more: covering the diversity of sexual behaviours that may contribute to the transmission of pathogens. Sex Transm Dis. 2021;48(9):e119-e121. doi: 10.1097/OLQ.0000000000001347

24. Habel MA, Leichliter JS, Dittus PJ, et al. Heterosexual anal and oral sex in adolescents and adults in the United States, 2011-2015. Sex Transm Dis. 2018;45(12):775-82. doi: 10.1097/OLQ.0000000000000889

25. Mazzitelli M, Caridà G, Scigliano C, et al. Knowledge of HIV infection and transmission: a knowledge, attitudes, beliefs and practices (KABP) survey among a sample of students at the "Magna Graecia", University of Catanzaro. Ann Ist Super Sanità. 2016;52(4):530-5. doi: 10.4415/ANN_16_04_12

26. Copen CE. Condom use during sexual intercourse among women and men aged 15-44 in the United States: 2011-2015 National Survey of Family Growth. National health statistics reports n. 105. Hyattsville, MD: National Center for Health Statistics; 2017. Available from https://www.cdc.gov/nchs/data/nhsr/nhsr105.pdf.

27. Goldstein RL, Upadhyay UD, Raine TR. With pills, patches, rings and shots: Who still uses condoms? A longitudinal cohort study. J AdolescHealth. 2013;52(1):77-82. doi: 10.1016/j.jadohealth.2012.08.001

28. Skaletz-Rorowski A, Potthoff A, Nambiar S, et al. Age specific evaluation of sexual behaviour, STI knowledge and infection among asymptomatic adolescents and young adults. J Infect Public Health. 2020;13(8):1112-7. doi: 10.1016/j.jiph.2020.04.005

29. Monsell E, McLuskey J. Factors influencing STI transmission in middle-aged heterosexual individuals. Br J Nurs. 2016;25(12):676-80. doi: 10.12968/bjon.2016.25.12.676

30. Fuster MJ, Molero F, de Montes LG, et al. HIV- and AIDS-related stigma: psychosocial aspects in a representative Spanish sample. Span J Psychol. 2013;16:E30. doi: 10.1017/sjp.2013.52

31. Fuster-Ruizde Apodaca MJ, Molero F, Gil de Montes L, et al; Spanish Group for the Study of HIV-Related Stigma. Evolution of HIV-related stigma in Spain between 2008 and 2012. AIDS Care. 2014;26(Suppl. 1):S41-5. doi: 10.1080/09540121.2014.906557

32. Chiasson MA, Hirshfield S, Rietmeijer C. HIV prevention and care in the digital age. J Acquir Immune DeficSyndr. 2010;55(Suppl. 2):S94-7. doi: 10.1097/QAI.0b013e3181fcb878

33. Istituto Nazionale di Statistica. Censimento della popolazione e delle abitazioni: l'istruzione. Anno 2019. ISTAT; 15 dicembre 2020. Available from: https://www.istat.it/it/archivio/251658.

34. Istituto Nazionale di Statistica. Istruzione e formazione. Annuario Statistico Italiano 2020. Rome: ISTAT; 2020. Available from: https://www.istat.it/it/files//2020/12/C07.pdf.

Fluoro-edenite non-neoplastic diseases in Biancavilla (Sicily, Italy): pleural plaques and/or pneumoconiosis?

Caterina Bruno[1]*, Rosario Di Stefano[2], Vincenzo Ricceri[3], Mauro La Rosa[3],
Achille Cernigliaro[4], Paolo Ciranni[5], Giuseppe Di Maria[6], Daniele Mandrioli[7],
Amerigo Zona[1], Pietro Comba[1]* and Salvatore Scondotto[5]

[1]Dipartimento Ambiente e Salute, Istituto Superiore di Sanità, Rome, Italy
[2]Azienda Provinciale Sanitaria, Catania, Italy
[3]Divisione di Radiologia, Ospedale Maria Santissima Addolorata di Biancavilla, Azienda Provinciale
Sanitaria, Catania, Italy
[4]Unità Operativa Complessa di Patologia Clinica, Dipartimento di Scienze Radiologiche e Servizi, Ospedale
Sant'Antonio Abate, Azienda Sanitaria Provinciale, Trapani, Italy
[5]Dipartimento per le Attività Sanitarie e Osservatorio Epidemiologico, Assessorato della Salute, Regione
Siciliana, Palermo, Italy
[6]Dipartimento di Medicina Interna, Università di Catania, Catania, Italy
[7]Istituto Ramazzini, Bologna, Italy
*retired

Abstract
Background. A mesothelioma cluster in Biancavilla (Sicily, Italy), drew attention to fluoro-edenite, a fibre classified by International Agency for Research on Cancer as carcinogenic to humans. Significant excesses in mortality and morbidity were observed for respiratory diseases and a significant excess of pneumoconiosis hospitalizations was reported.
Objective. Aim of this study is to assess the characters of the lung damage in Biancavilla residents hospitalized with pneumoconiosis or asbestosis diagnoses.
Methodology. Medical records, available radiographs and computed tomography scans were collected. The obtained imaging was reviewed by a panel of three specialists and focused on pleural and parenchymal abnormalities. Cases with an ILO-BIT or ICOERD score equal or greater than 2 were considered positive for a pneumoconiosis-like damage, cases with a score lower than 2 or insufficient quality of imaging were considered inconclusive. If no pneumoconiotic aspects were present the cases were classified as negative.
Results. Out of 38 cases, diagnostic imaging for 25 cases were found. Ten cases out of 25 showed asbestosis-like features, nine subjects were considered negative. In six patients' results were inconclusive.
Conclusions. Asbestosis-like features were substantiated in Biancavilla residents without known occupational exposure to asbestos. Further studies to estimate population respiratory health are required. Experimental studies on the fibrogenic potential of fluoro-edenite are needed.

INTRODUCTION

A cluster of deaths from pleural malignant tumour was reported in Biancavilla (Sicily, Italy), 23,052 inhabitants, a municipality similar to the others scattered at the slopes of Etna Volcano with large areas occupied by orange and lemon trees [1, 2]. No industrial facilities are present, with the exception of a huge quarry were rocks containing a material similar to tuff was operating for several decades. This material was largely used in the local building industry and for road paving. No particular occupational exposures (direct or indirect) to asbestos have been reported either in Biancavilla or in the other Etnean municipalities. More specifically, no ascertained occupational exposure to asbestos was detected among the cases of mesothelioma interviewed by the investigators of the

Sicilian Mesothelioma Register in their permanent on-going routine survey.

The researchers' attention thus focused on a quarry material containing a previously unknown amphibole, identified as fluoro-edenite [3] and considered it to be related to the disease [4]. Experimental studies *in vivo* and *in vitro* [5-7] confirmed the fibre be able to induce mesotheliomas. The International Agency for Research on Cancer (IARC), on the basis of the mesothelioma incidence data in Biancavilla [8] and the aforementioned experimental data, classified fluoro-edenite as carcinogenic to humans (Group 1, sufficient evidence of carcinogenicity in humans) [9].

Epidemiological studies on the resident population carried out in order to detect the other diseases possibly related with exposure to the fluoro-edenite fibres [10] found out an excess of mortality from chronic obstructive pulmonary diseases.

Statistically significant excesses in mortality and morbidity were observed for respiratory diseases both in men and women [11], and a significant excess of hospitalization due to pneumoconiosis was reported [12-14].

Pleural plaques and lung parenchymal lesions were detected in 43 construction workers, all men, exposed to fluoro-edenite in Biancavilla. Pleural bilateral plaques were detected in 39 subjects out of 43, fibrosis was present in seven workers and a restrictive ventilatory defect in two subjects [15].

A retrospective cross-sectional study in inhabitants of Biancavilla exposed to fluoro-edenite, compared with a population living and working at least 30 km away from Biancavilla was performed, to assess the occurrence and the prevalence of pleural plaques. High-Resolution Computed Tomography (HRCT) chest scans carried out in Biancavilla municipality hospital site (exposed subjects) were compared with HRCT chest scans carried out in a hospital 30 km away from Biancavilla. The relative risk (RR) for pleural plaques in the "exposed" population was 6.74 CI 95% (4.47-9.58). Lung parenchymal abnormalities were observed in 11% of exposed group (fibrosis = 8%) *vs* 1% in the unexposed subjects (fibrosis = 0.5%) [16].

The aim of the present study was to assess the distinguishing characters of pleural and/or parenchymal damage, in resident in Biancavilla subjects, hospitalized and diagnosed with "pneumoconioses" in any part of the hospital discharge form, since pneumoconiotic diseases are unexpected in non-occupationally exposed populations.

MATERIALS AND METHODS

The present study comprises the series of residents in Biancavilla hospitalized since January 2006 to December 2013 in the Sicilian Region and diagnosed with "pneumoconioses or other lung diseases due to external agents" (500-508 codes, 9th revision of International Statistical Classification of Diseases, ICD) in any part of the hospital discharge form.

Medical records were searched for, and the available radiographs and Computed Tomography (CT) scans were collected. If available, additional personal information on patients was collected through family doc-

tors. Unfortunately, lung function tests were not available for a revision because of technical issues (faded thermal paper).

The obtained imaging was reviewed by a panel of three specialists (two skilled radiologists and one epidemiologist and occupational physician) and focused on pleural and parenchymal abnormalities. The panel was unaware of diagnoses reported in the personal records.

The International Labour Office-Bureau International du Travail (ILO-BIT) [17] criteria for the radiographs and the International Classification of HRCT for Occupational and Environmental Respiratory Diseases (ICOERD) [18] for CT scans were utilized.

We classified the results in a semi-quantitative approach considering positive for a parenchymal pneumoconiosis-like damage cases with an ILO-BIT or ICOERD score equal or greater than 2. Cases with score lower than 2 or with insufficient quality of imaging were classified as "doubtful cases". If no pneumoconiotic aspects were present or no parenchymal damage was found, the cases were classified as negative.

The study was performed in accordance with the Declaration of Helsinki of the World Medical Association [19] and the name and all birth/personal data were anonymised and each subject had a code assignment.

RESULTS

Thirty-eight patients were hospitalized in the observed period. One infant with aspiration pneumonia was excluded from the case series. Out of the 37 remaining patients, medical charts were recovered for 34 subjects (21 men and 13 women), aged between 42 to 88 (*Figure 1*).

The main cause of hospitalization was related to respiratory diseases in 26 patients, one being affected by mesothelioma, 12 recovered for asbestosis, one for silicosis, and two for unspecified pneumoconioses. One patient was hospitalized for ICD code 506 (respiratory conditions due to chemical fumes and vapours) and two of them for ICD code 507 (pneumonitis due to solids and liquids). Including the secondary diagnoses, asbestosis was reported in a total of 25 cases, pneumoconiosis due to silica and other silicates (silicosis) in three cases, and unspecified pneumoconiosis in two cases. Other main causes related to respiratory disease were pleuritis (one case), acute respiratory failure (three cases), and other respiratory abnormalities (two cases).

In 12 cases (6 men and 6 women) no diagnostic imaging were obtained, average age was 73.8 in men and 68.7 in women. Little information was found on previous occupations in two men (a quarryman and a house painter) in this group.

Diagnostic imaging to be examined by the panel were available for 25 cases (19 men and 6 women). Chest Rx were found for 10 subjects and CT scans for 19 patients (all but four have been subjected to both examinations).

In all subjects, pleural plaques were found, most of them (22 out 25) were calcified. All available images pointed to a diagnosis of asbestosis-like disease with diffuse and bilateral pleural plaques, very rare in silicosis. Subjects included in the study with a diagnosis of "aspiration pneumonia" also presented pleural plaques.
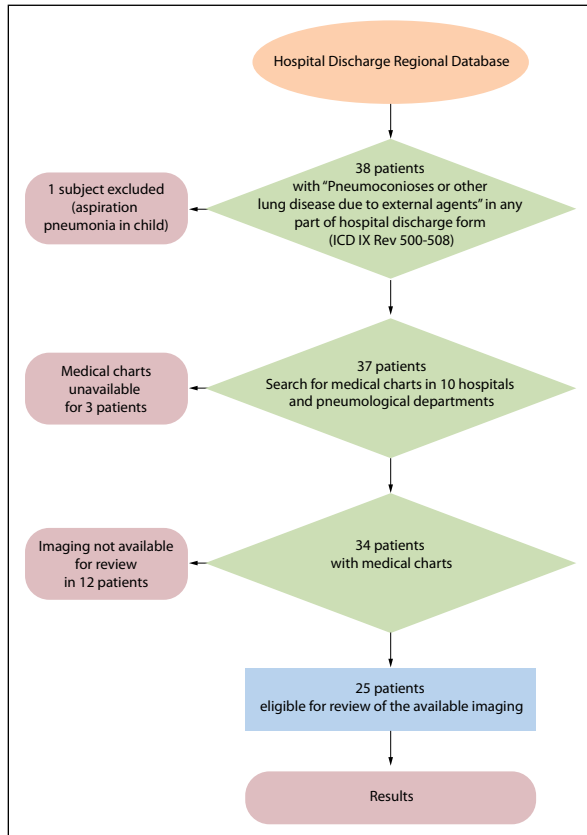
Figure 1
Selection of cases eligible for imaging review, flow chart.

Ten cases out of 25 showed asbestosis-like parenchymal features, nine subjects presenting lung alterations not related to pneumoconiosis or not presenting parenchymal damage were considered negative for imaging results. In further six patients imaging results were inconclusive because of insufficient quality or characteristics of imaging (*Table 1*).

In *Table 2* cases with parenchymal features suggestive for asbestosis-like pneumoconiosis with ICOER or ILO-BIT score equal or greater than were itemized. Average age was 63.1 (66.1 in men and 50 in women).

The negative cases were six men and three women: in four people no parenchymal damage was found (two men and two women); one man and one woman presented a CT suggesting old tuberculosis scar; two men were affected by mild emphysema and one man presented increased broncho-vascular markings and hyperlucency of lung middle zones. Average age was 57.6 (55.2 in men and 62.3 in women) (*Table 3*).

Cases presenting some features of pneumoconiotic damages but imaging characteristics insufficient for a definition of asbestosis-like pneumoconiosis were itemized in *Table 4*. Average age was 66.3 (64.4 in men).

DISCUSSION

In asbestos exposed workers the occurrence of asbestosis is related to an intense exposure (at least 25/fibres/mL/year) [20] with very few case studies reporting parenchymal fibrosis of the lung due to environmental exposure to asbestos [21, 22].

In Italy hospital discharge records are classified according to the International Statistical Classification of Diseases, 9th revision [23] and pleural plaques were not included as an item like in the 10th revision [24].

It is for that reason that we considered the possibility that pneumoconioses and asbestosis codes were utilised to encode merely pleural plaques or other pleural alterations commonly found in population environmentally exposed to asbestos [25-27] or other natural fibres [21, 22, 28]. Furthermore, we did not exclude other diseases, e.g., "inhalation pneumonia", that could be misclassified in other similar codes. For these reasons we decide to include in the analysis all the residents in Biancavilla, hospitalized in Sicily diagnosed with any disease included in "pneumoconioses or other lung diseases due to external agents" in any part of the hospital discharge form.

The Sicilian protocol about surveillance on asbestos exposed and former exposed subjects [29] provides chest radiographs as first level diagnostic exams, in accordance with the procedures of the ILO-BIT for the pneumoconiosis established by an international team [17] and updated by the Helsinki criteria update in 2014 [18]. Most of our recovered cases had undergone further medical examinations and were submitted to CT scan of the chest.

Chest radiographs were available in few cases, but with sufficient technical quality, except one case having only the postero-anterior projection, not sufficient for the ILO-BIT criteria for a pneumoconiosis diagnosis.

In our study most of CT scans presented a sufficient quality for the ICOERD criteria for imaging reading for pneumoconiosis. Reliability of the ICOERD proposed international classification of HRCT for occupational and environmental respiratory diseases had been tested, and evaluation of CT scans intra reader concordance had been investigated [30, 31]. Concordance between ILO-BIT criteria readings of radiographs and the results of CT scan readings by ICOERD criteria had been investigated [31, 32].

The goal of the present investigation was to evaluate if features of the imaging were coherent with a pneumo-

Table 1
Patients with available diagnostic imaging, period of observation 2006-2013

Patients	n	Monolateral pleural plaques	Bilateral pleural plaques	Asbestosis-like parenchymal features	Negative imaging results	Uncertain or complex parenchymal features
Men	19	2	17	8	6	5
Women	6	2	4	2	3	1
All	25	4	21	10	9	6

Table 2
Patients with asbestosis-like parenchymal findings, period of observation 2006-2013

Patient ID	Age	Rx	CT scan	Parenchymal features	Other information of interest
Men					
3	80	X	X	Bilateral ground glass opacities	
6	73	X	X	Bilateral ground glass opacities; large opacities	Farmer
11	74		X	Bilateral ground glass opacities; honeycombing	Former farmer
14	76		X	Bilateral small opacities; profusion 2	Farmer
17	62		X	Linear bilateral interlobular opacities	Office worker
24	61	X	X	Left lung atelectasis parenchimal inhomogeneus attenuation with both irregular and rounded small opacities. Fibrotic bands in lower lung zones. A large opacity in the left lung. Vicarious emphysema of right lung and mediastinal shift	Retired post office employee. Heavy smoker. Hospitalized for aspiration pneumonia
26	55		X	Fibrotic bands in lower lung zones. Large opacity of the left lung. Emphysema of right lung	Farmer
32	50	X	X	Interlobular bilateral linear opacities; parenchimal inhomogeneus attenuation; bilateral ground glass opacities of lower lung zones	House painter
Women					
30	53		X	Bilateral ground glass opacities	
34	47		X	Bilateral ground glass opacities	

Table 3
Patients without asbestosis-like parenchymal findings, period of observation 2006-2013

Patient ID	Age	Rx	CT scan	Parenchymal features	Monolateral pleural plaques	Bilateral pleural plaques	Pleural calcifications
Men							
18	64		X	Mild emphysema	X		
19	66	X		CT suggesting old healed tuberculosis		X	X
23	61		X	No parenchymal damage		X	X
25	55	X		Mild emphysema		X	X
33	42	X		Increased broncho-vascular markings and hyperlucency of lung middle zones		X	X
37	43		X	No parenchymal damage		X	
Women							
16	69		X	No parenchymal damage	X		X
20	65	X	X	CT suggesting old healed tuberculosis		X	X
29	53		X	No parenchymal damage		X	X

coniosis similar to asbestosis, so we were interested in a qualitative evaluation following the ILO-BIT and ICO-ERD criteria and we categorised the results of the panel reading in a simplified classification (pneumoconiotic features, not pneumoconiotic features and uncertain damages).

Our results underline that all the subjects reviewed, presented pleural plaques and this could be the main reason because code 501 (asbestosis) or 505 (pneumoconiosis) of 9th revision of ICD were utilized. However, ten subjects out of 25 showed imaging features similar to the asbestosis ones and in further six people presented insufficient but suggestive parenchymal abnormalities.

This appears to indicate that fluoro-edenite fibres inhalation can cause a pneumoconiotic disease similar to asbestosis.

Environmental exposures to asbestos and asbestiform fibres are, in general, considered not sufficient to cause pneumoconiosis even though several studies [27, 33-36] have reported the occurrence of lung fibrosis or pneumoconiosis in environmental contexts.

Occupational exposure to fibres in some cases might have been relevant, e.g., those related to earthmoving jobs in construction sites and in farming [37, 38]. In other cases (e.g., civil servants and housewives) environmental exposure circumstances should be hypothesized. Some similar-asbestosic patterns, furthermore, were observed in female patients in the total absence of conventional asbestos exposures.

The points of strength have already been introduced: a multidisciplinary study group, encompassing clinicians, epidemiologists, and public health professionals,

Table 4
Patients with asbestosis-like parenchymal findings not sufficient for a diagnosis, period of observation 2006-2013

Patient ID	Age	Rx	CT scan	Parenchymal features	Monolateral pleural plaques	Bilateral pleural plaques	Pleural calcifications	Other information of interest
Men								
8	73		X	Bilateral parenchimal inhomogeneus attenuation not sufficient quality of CT scan	X		X	Smoker
15	74		X	Available previous CT not related with hospitalization. Second CT not available with a detailed report in medical records		X	X	Former farmer
22	68	X	X	Rx series in one single projection. CT not available parenchymal thickening and undetermined pulmonary fibrosis		X		
27	59		X	Suggesting ground glass opacities. Obesity not sufficient quality of CT scan				
35	48		X	Available CT not related with hospitalization. Second available CT without parenchymal window. Right lung parenchymal opacity suggesting rounded atelectasis		X	X	Heavy smoker Former policeman
Woman								
10	76	X		Rounded opacities right lung parenchymal opacity in lower lung zone. Indicative CT imaging of not sufficient quality	X		X	

has had the opportunity to exhaustively explore the case-series of Biancavilla patients affected by pleural plaques and pulmonary fibrosis, isolating a group of them characterized by environmental exposure to fluoro-edenite in the absence of asbestos exposure.

This observation supports the notion of fluoro-edenite's fibrogenicity for residents in the area at study.

Three main limitations require to be mentioned as well. The study, for feasibility aspects, could not include a proper reference population, the information on environmental and occupational (or para-occupational) exposure to fluoro-edenite or other risk factors and confounding factors was unavoidably heterogeneous, and the low number of study subjects determined an overall low statistical power of the study. Notwithstanding these limitations, though, the study detected in Biancavilla a cluster of cases of a lung fibrosis similar to asbestosis, in addition to several cases of pleural plaques.

Fluoro-edenite capacity to induce fibrosis or pneumoconiosis was not specifically investigated and these results suggest the need of in vivo and in vitro experimental studies.

Regarding public health issues, further efforts are required to investigate respiratory conditions in Biancavilla residents through systematic prospective studies and examining in depth individual ways of exposure.

Even if recognizing the need for a continuing process of health surveillance and epidemiological monitoring in Biancavilla, the study findings can since now actively contribute to priority setting in environmental remediation, as extensively discussed in the WHO report "Urban redevelopment in contaminated sites"

[39] that includes a case study on Biancavilla, an area recognized since 2001 as National Priority Contaminated Site. The major effort supported by both National and Sicilian Regional Governments in order to reduce airborne fibre level is justified in light of both the well-recognized mesothelioma risk in this community and the emerging risk of environmental fibrosis and pneumoconiosis. The promotion of experimental, clinical, and epidemiological studies, together with the advancement of environmental clean-up, will also contribute to the most needed development of environmental health literacy and consequent resilience in the community.

CONCLUSIONS

In our clinical records, in addition to bilateral calcified pleural plaques, asbestosis-like parenchymal features were observed in patients' residents in Biancavilla town and without known occupational exposure to asbestos. These findings underline the requirement of further studies on the resident population to estimate their respiratory health, identify possibility of pneumoconiosis cases and the prevalence of pleural plaques and parenchymal impairment. The fibrogenic potential of fluoro-edenite fibres have to be tested by specific experimental studies.

Authors' contributions

Institutional review board statement

The study was conducted in accordance with the Declaration of Helsinki of the World Medical Association and performed according to the rules of the "Decreto Legislativo n. 196/2003, Codice in materia di protezione dei dati personali" (Legislative Decree n. 196/2003 Regulations on personal data protection). The name and all birth/personal data were anonymized and each subject had a code assignment.

Informed consent statement

Patient consent was waived due to reason: the study was a retrospective survey of anonymized medical and imaging records of patients previously discharged from several different hospitals.

Data availability statement

Data supporting reported results are archived in regional hospitalizations datasets and motivated request is needed to be obtained. Medical records and imaging are archived in hospitals involved in the study: only anonymised information can be given. Only anonymized data can be consulted.

Conflict of interest statement

The Authors declare no conflict of interest.

REFERENCES

1. Di Paola M, Mastrantonio M, Carboni M, Belli S, Grignoli M, Comba P, Nesti M (Eds). La mortalità per tumore maligno della pleura in Italia negli anni 1988-1992. Roma: Istituto Superiore di Sanità; 1996. (Rapporti ISTISAN, 96/40). p. 1-30.
2. Paoletti L, Batisti D, Gianfagna A, Mastrantonio M, Nesti M, Comba P. Unusual high incidence of malignant pleural mesothelioma in a town of eastern Sicily: an epidemiological and environmental study. Arch Environ Health. 2000;55:392-8. doi: 10.1080/00039890009604036
3. Gianfagna A, Oberti R. Fluoro-edenite from Biancavilla (Catania, Sicily, Italy): Crystal chemistry of a new amphibole end-member. Am Mineral. 2001;86;1489-93.
4. Comba P, Gianfagna A, Paoletti L. Pleural mesothelioma cases in Biancavilla are related to a new fluoro-edenite fibrous amphibole. Arch Environ Health. 2003;58:229-32. doi: 10.3200/AEOH.58.4.229-232
5. Soffritti M, Minardi F, Bua L, Degli Esposti D, Belpoggi F. First experimental evidence of peritoneal and pleural mesotheliomas induced by fluoro-edenite fibres present in Etnean volcanic material from Biancavilla (Sicily, Italy). Eur J Oncol. 2004;9:169-75.
6. Belpoggi F, Tibaldi E, Lauriola M, Bua L, Falcioni L, Chiozzotto D, Manservisi F, Manservigi M, Soffritti M. The efficacy of long-term bioassays in predicting human risks: mesotheliomas induced by fluoro-edenitic fibres present in lava stone from Etna volcano in Biancavilla Italy. Eur J Oncol. 2011;16:185-95.
7. Ballan G, Del Brocco A, Loizzo S, Fabbri A, Maroccia Z, Fiorentini C, Travaglione S. Mode of action of fibrous amphiboles: the case of Biancavilla (Sicily, Italy). Ann Ist Super Sanità. 2014;50:133-9. doi: 10.4415/ANN_14_02_05
8. Bruno C, Tumino R, Fazzo L, Cascone G, Cernigliaro A, De Santis M, Giurdanella MC, Nicita C, Rollo PC, Scondotto S, Spata E, Zona A, Pietro Comba P. Incidence of pleural mesothelioma in a community exposed to fibres with fluoro-edenitic composition in Biancavilla (Sicily, Italy). Ann Ist Super Sanità. 2014;50:111-8. doi: 10.4415/ANN_14_02_02
9. International Agency for Research on Cancer. Fluoro-edenite. In: Some nanomaterials and some fibres. Lyon: IARC; 2017. (IARC monographs on the evaluation of carcinogenic risks to humans, 111). p. 215-42. Available from: http://monographs.iarc.fr/ENG/Monographs/vol111/index.php.
10. Biggeri A, Pasetto R, Belli S, Bruno C, Di Maria G, Mastrantonio M, Trinca S, R Uccelli R, Comba P. Mortality from chronic obstructive pulmonary disease and pleural mesothelioma in a natural fibre (fluoro-edenite) contaminated area. Scand J Work Environ Health. 2004;30:249-52. doi: 10.5271/sjweh.786
11. Cernigliaro A, Fano V, Pollina Addario S, Caruso S, Pennisi P, Forastiere F, Perucci CA, Comba P, Scondotto S. Mortality and hospital discharges in the population of Biancavilla (Sicily) contaminated by natural fibres. Epidemiol Prev. 2006;30:227-31.
12. Achille Cernigliaro, Antonello Marras, Sebastiano Pollina Addario, Salvatore Scondotto, Daniela D'Ippoliti, Erica Santelli, Paola Michelozzi, Francesco Forastiere. Stato di salute della popolazione residente nelle aree a rischio ambientale e nei siti di interesse nazionale per le bonifiche della Sicilia analisi dei dati ReNCaM (anni 2004-2011) e dei ricoveri ospedalieri (anni 2007-2011) Rapporto 2012. Available from: https://www.salute.gov.it/portale/temi/documenti/investimenti/29.pdf.
13. Pirastu R, Comba P, Conti S, Iavarone I, Fazzo L, Pasetto R, Zona A, Crocetti E, Ricci P (Eds). SENTIERI - Studio epidemiologico nazionale dei territori e degli insediamenti esposti a rischio da inquinamento: Mortalità, incidenza oncologica e ricoveri ospedalieri [SENTIERI - Epidemiological study of residents in national priority contaminated sites: Mortality, cancer incidence and hospital discharges]. Epidemiol Prev. 2014;38(Suppl 1):43-8.
14. Zona A, Iavarone I, Buzzoni C, Conti S, Santoro M, Fazzo L, Pasetto R, Pirastu R, Bruno C, Ancona C, Bianchi F, Forastiere F, Manno V, Minelli G, Minerba A, Minichilli F, Stoppa G, Pierini A, Ricci P, Scondotto S, Bisceglia L, Cernigliaro A, Ranzi A, Comba P; Gruppo di lavoro SENTIERI; Gruppo di lavoro AIRTUM-SENTIERI; Gruppo di lavoro Malformazioni congenite-SENTIERI. SENTIERI: Studio epidemiologico nazionale dei territori e degli insediamenti esposti a rischio da inquinamento.

Quinto Rapporto [SENTIERI: Epidemiological Study of Residents in National Priority Contaminated Sites. Fifth Report]. Epidemiol Prev. 2019;43(2-3 Suppl 1):1-208. doi: 10.19191/EP19.2-3.S1.032. Erratum in: Epidemiol Prev. 2019 Jul-Aug;43(4):219.

15. Rapisarda V, Ledda C, Ricceri V, Arena F, Musumeci A, Marconi A, Fago L, Bracci M, Santarelli L, Ferrante M. Detection of pleural plaques in workers exposed to inhalation of natural fluoro-edenite fibres. Oncol Lett. 2015;9:2046-52. doi: 10.3892/ol.2015.2978

16. Ledda C, Pomara C, Bracci M, Mangano D, Ricceri V, Musumeci A, Ferrante M, Musumeci G, Loreto C, Fenga C, Santarelli L, Rapisarda V. Natural carcinogenic fiber and pleural plaques assessment in a general population: A cross-sectional study. Environ Res. 2016;50:23-9. doi: 10.1016/j.envres.2016.05.024

17. International Labour Office. Guidelines for the use of the ILO international classification of radiographs of pneumoconioses (Revised edition 2011). Geneva: ILO; 2011. (Occupational safety and health series, 22). Available from: https://www.ilo.org/wcmsp5/groups/public/---ed_protect/---protrav/---safework/documents/publication/wcms_168260.pdf.

18. Wolff H, Vehmas T, Oksa P, Rantanen J, Vainio H. Asbestos, asbestosis, and cancer, the Helsinki criteria for diagnosis and attribution 2014: recommendations. Consensus Report. Scand J Work Environ Health. 2015;41:5-15. doi:10.5271/sjweh.3462

19. World Medical Association. WMA Declaration of Helsinki - Ethical principles for medical research involving human subjects, adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and successive amendments. Available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/.

20. Glazer CS, Newman LS. Occupational interstitial lung disease. Clin Chest Med. 2004;25:467-78. doi: 10.1016/j.ccm.2004.04.004

21. Gräsel B, Kaya A, Stahl U, Rauber K, Kuntz C. Erionite-induced pleural plaques. Exposition to urban pollution in a female Turkish migrant in Germany. Der Chirurg. 2008;79:584-8. doi: 10.1007/s00104-008-1515-9

22. Kliment C.R, Clemens K, Oury TD. North American erionite-associated mesothelioma with pleural plaques and pulmonary fibrosis: a case report. Int J Clin Exp Pathol. 2009;2:407-10.

23. Ministero del Lavoro, della Salute e delle Politiche Sociali. Classificazione delle malattie, dei traumatismi, degli interventi chirurgici e delle procedure diagnostiche e terapeutiche. Versione italiana della ICD-9-CM. https://www.salute.gov.it/imgs/C_17_pubblicazioni_2251_allegato.pdf.

24. CDC National Center for Health Statistics. International Classification of Diseases,Tenth Revision (ICD-10). https://www.cdc.gov/nchs/icd/icd10.htm.

25. Rey F, Boutin C, Steinbauer J, Viallat JR, Alessandroni P, Jutisz P, Di Giambattista D, Billon-Galland MA, Hereng P, Dumortier P, De Vuyst P. Environmental pleural plaques in an asbestos exposed population of northeast Corsica. Eur Respir J. 1993;6:978-82.

26. Sichletidis L, Daskalopoulou E, Chloros D, Vlachogiannis E, Vamvalis C. Pleural plaques in a rural population in central Macedonia, Greece. Med Lav. 1992;83:259-65.

27. Metintas M, Metintas S, Hillerdal G, Ucgun I, Erginel S, Alatas F, Yildirim H. Nonmalignant pleural lesions due to environmental exposure to asbestos: a field-based, cross-sectional study. Eur Respir J. 2005;26:875-80. doi: 10.1183/09031936.05.00136404

28. Sullivan PA. Vermiculite, respiratory disease, and asbestos exposure in Libby, Montana: Update of a cohort mortality study. Environ Health Perspec. 2007;115(4):579-85. doi: 10.1289/ehp.9481

29. Regione Sicilia. Decreto 6 maggio 2016. Approvazione del Protocollo sanitario regionale standardizzato per gli accertamenti sanitari in materia di amianto. Gazzetta Ufficiale della Regione Siciliana n. 23, 27 maggio 2016. Available from: https://olympus.uniurb.it/index.php?option=com_content&view=article&id=15757:sic65-5-16&catid=27&Itemid=137.

30. Suganuma N, Kusaka Y, Hering KG, VehmasT, Kraus T, Parker JE, Shida H; International CT Classification Study Group. Selection of reference films based on reliability assessment of a classification of high-resolution computed tomography for pneumoconioses. Int Arch Occup Environ Health. 2006;79(6):472-6. doi: 10.1007/s00420-005-0067-2

31. Suganuma N, Kusaka Y, Hering KG, Vehmas T, Kraus T, Arakawa H, Parker JE, Kivisaari L, Letourneux M, Gevenois PA, Tuengerthal S, Crane MD, Shida H, Akira M, Henry DA, Nakajima Y, Hiraga Y, Itoh H, Hosoda Y. Reliability of the proposed international classification of high-resolution computed tomography for occupational and environmental respiratory diseases. J Occup Health. 2009;51:210-22. doi: 10.1539/joh.l8030

32. Tamura T, Suganuma N, Hering KG, Vehmas T, Itoh H, Akira M, Takashima Y, Hirano H, Kusaka Y. Relationships (I) of International Classification of Highresolution Computed Tomography for Occupational and Environmental Respiratory Diseases with the ILO International Classification of Radiographs of Pneumoconioses for parenchymal abnormalities. Ind Health. 2015;53(3):260-70. doi: 10.2486/indhealth.2014-0073

33. Baris YI, Sahin A, Ozesmi M, Kerse I, Ozen E, Kolacan B, Altinörs M, Göktepeli A. An outbreak of pleural mesothelioma and chronic fibrosing pleurisy in the village of Karain/Ürgüp in Anatolia. Thorax. 1978;33(2):181-92. doi: 10.1136/thx.33.2.181

34. Baris YI, Artvinli M, Sahin AA, Sebastien P, Gaudighet A. Diffuse lung fibrosis due to fibrous zeolite (erionite) exposure. Eur J Respir Dis. 1987;70:122-5.

35. Dumortier P, Göcmen A, Laurent K, Manço A, De Vuyst P. The role of environmental and occupational exposures in Turkish immigrants with fibre-related disease. Eur Respir J. 2001;17:922-7. doi: 10.1183/09031936.01.17509220

36. Lampert Naik S, Lewin M, Young R, Dearwent SM, Lee R. Mortality from asbestos-associated disease in Libby, Montana 1979-2011. J Expo Sci Environ Epidemiol. 2017;27(2):207-13.

37. Massaro T, Baldassarre A, Pinca A, Martina GLM, Fiore S, Lettino A, Cassano F, Musti M. Esposizione ad amianto in edilizia in aree della Basilicata caratterizzate dalla presenza di rocce contaminate da tremolite [Exposure to asbestos in buildings in areas of Basilicata characterized by the presence of rocks containing tremolite]. G Ital Med Lav Ergon. 2012;34(3 Suppl):568-70.

38. Massaro T, Dragonieri S, Martina GLM, Baldassarre A, Cassano F, Musti M. Amianto e agricoltura: nuove prospettive di rischio [Asbestos and agriculture: new perspectives of risk]. G Ital Med Lav Ergon. 2012;34(3 Suppl):581-2.

39. World Health Organization Regional Office for Europe. Urban redevelopment of contaminated sites: a review of scientific evidence and practical knowledge on environmental and health issues. Copenhagen: WHO Regional Office for Europe; 2021.

Guillain-Barré syndrome in patients dying with COVID-19 in Italy: a retrospective study

Elisa Colaizzo[1], **Maria Puopolo**[1], **Dorina Tiple**[1], **Luana Vaianella**[1], **Nicola Vanacore**[2], **Alberto Milanese**[3], **Luigi Palmieri**[4], **Cinzia Lo Noce**[4], **Marco Canevelli**[5], **Alessia Perna**[6], **Graziano Onder**[4] and the Italian National Institute of Health COVID-19 Mortality Group*

[1]*Dipartimento di Neuroscienze, Istituto Superiore di Sanità, Rome, Italy*
[2]*Centro Nazionale per la Prevenzione delle Malattie e Promozione della Salute, Istituto Superiore di Sanità, Rome, Italy*
[3]*Dipartimento di Sanità Pubblica e Malattie Infettive, Sapienza Università di Roma, Rome, Italy*
[4]*Dipartimento Malattie Cardiovascolari, Endocrino-Metaboliche e Invecchiamento, Istituto Superiore di Sanità, Rome, Italy*
[5]*Dipartimento di Neuroscienze Umane, Sapienza Università di Roma, Rome, Italy*
[6]*Istituto di Neurologia, Università Cattolica del Sacro Cuore, Rome, Italy*
*The members of the Italian National Institute of Health COVID-19 Mortality Group are reported before the References

Abstract
Introduction. We presented a four-case series of COVID-19 related deaths occurred in patients with Guillain-Barré syndrome (GBS) between February 2020 and January 2022 in Italy.
Methods. They were extracted from 8,436 medical charts of COVID-19 patients dying. All cases, ranged 48-73 years, showed classical GBS clinical onset – limb weakness, sensory deficits, hypoareflexia – and three of them were admitted in intensive care unit (ICU) for ventilator support.
Results. The cerebrospinal fluid showing albumin-cytological dissociation was performed in two cases. Nerve conduction studies supported the diagnosis in all cases. Interstitial pneumonia was documented by chest X-rays or CT scans in all cases: they were treated with intravenous immunoglobulin (IVIg) and the drugs used for COVID-19 infection.
Conclusions. Although the mechanism of GBS onset is still unclear in COVID-19, fatal cases may be more frequent than other virus-related GBS, so that strictly monitoring in high-risk patients could dramatically decrease the mortality of GBS.

INTRODUCTION

Guillain-Barré syndrome (GBS) is an acute acquired immune-mediated polyradiculoneuropathy [1], more frequent in males, with about 100,000 cases every year worldwide [2], diagnosed according to clinical findings and classified in several variants, such as acute inflammatory demyelinating polyradiculoneuropathy (AIDP), acute motor axonal neuropathy (AMAN) and acute motor sensory axonal neuropathy (AMSAN). Mortality rates in Europe and North America vary between 3% and 7% [2]. The etiology can be traced back to a viral illness in half of the cases, the onset typically occurs in one to two weeks after a Campylobacter jejuni, HIV, Influenza A virus, Cytomegalovirus, Mycoplasma Pneumoniae, Haemophilus Influenzae infection or Ar-

bovirus infection such as Zika and Chikungunya virus. The incidence rate of GBS in USA and Europe increases with age (0.6 per 100,000 per year in children and 2.7 per 100,000 per year in >80-year-old people) [2].

Between February 2020 and May 2022, COVID-19 has caused about 6 million deaths worldwide [3]. Most of these deaths were due to respiratory complications caused by SARS-CoV-2 infection, but non-respiratory complications, including cardiac, renal, and neurological are also commonly identified in persons dying of COVID-19 [4]. Recent studies demonstrated the occurrence of GBS in patients with SARS-CoV-2 infection [5-9]. GBS can therefore represent a complication related to SARS-CoV-2 which can contribute to COVID-19 mortality. We described a series of 4 cases of

patients dying of GBS occurring after SARS-CoV-2 infection observed in a survey of 8,436 patients dying of COVID-19 in Italy.

MATERIALS AND METHODS
Study population and data collection

Data were obtained from the Italian National Institute of Health (Istituto Superiore di Sanità, ISS) Integrated Surveillance System [4, 10]. COVID-19-related deaths were defined as those occurring in patients who tested positive for SARS-CoV-2, independent of pre-existing comorbidities possibly contributing to death. Medical charts and death certificates of patients dying in the hospital were sent to the Italian National Institute of Health by all the regions and autonomous provinces of Italy. At Italian National Institute of Health COVID-19 Mortality Group, medical charts were reviewed by medical researchers to collect detailed information. Beyond data on demographic characteristics (region of residence, gender, age) and COVID-19 related data symptoms (fever, dyspnea, cough, diarrhea, and hemoptysis), chest X-rays or CT chest scans, pharmacological treatments (antibiotics, antivirals, monoclonal antibodies, corticosteroids), need of respiratory assistance, admission to intensive care, results of repeated SARS-CoV-2 testing, pre-existing comorbidities (diagnosed before hospital admission based on anamnestic data), hospital complications with relative additional notes and death data were collected.

Medical charts of 8,436 COVID-19 related deaths occurring between February 21st 2020 and January 10th, 2022, were reviewed to extract the list of cases of GBS occurring after SARS-CoV-2 infection. GBS was identified if the diagnosis was reported in the medical chart or death certificate. Medical charts of patients experiencing GBS were further reviewed by neurologists at INIH to collect GBS specific data: clinical features (limb weakness, hypoareflexia, sensory disturbances), results of cerebrospinal fluid (CSF) analysis (albumincytological dissociation), nerve conduction studies, and therapy for GBS. Lag time between dates of onset of COVID-19 symptoms and GBS disease (symptom onset and diagnosis) have been obtained for GBS cases occurring post COVID-19 infection. Summary statistics data obtained: categorical variables are summarized by frequencies, and continuous variables by mean and standard deviation (SD).

RESULTS

As at date of 10th January 2022, in Italy, among 8,436 medical charts of COVID-19 related deaths referred to the COVID-19 mortality database at Italian National Institute of Health four patients with a history of GBS: 2 females, 2 males, mean age ± SD: 62.7±11 (73-48) were identified (prevalence of SARS-CoV-2 related GBS among patients dying of COVID-19=0.05%). Demographic and COVID-19 clinical characteristics of these patients, as well the GBS symptoms at the onset are reported in the *Table 1*. Fever and dyspnea were reported at hospitalization 4/4 and 3/4, respectively. All patients had pneumonia documented by chest X-rays or CT chest scans, mainly requiring respiratory as-

Table 1
Demographic and clinical characteristics of patients dying of SARS-CoV-2 related Guillain-Barré syndrome (GBS)

Number of patients (n)	**4**
Gender	
Female	2
Male	2
Age (years)* mean (SD)	62.7 (11.6)
COVID-19 symptom at hospitalization (n)	
Fever	4
Cough	1
Dyspnea	3
Diarrhea	1
Pneumonia (n)	**4**
Respiratory assistance	
No	0
Yes	
Mechanical ventilation	2
High flow oxygen	0
cPAP	1
NA	1
Admission to intensive care	
No	1
Yes	3
COVID-19 swab testing swabs at death (n)	
Positive	3
Negative	1
Acute respiratory failure	4
Brain damage	2
Superinfections	2
Shock	2
Others	0
Complication during hospitalization (n)	
Brain damage	2
Superinfections	2
Shock	2
Others	0
COVID-19 related therapy (n)	
Antibiotics	4
Antiviral	3
Corticosteroids	3
Monoclonal antibody	2
Onset of GBS symptoms	
Tetraparesis	
Yes	3
No	0
NA	1

Continues

Table 1
Continued

Number of patients (n)	**4**
Onset of GBS symptoms (continued)	
Paresthesia	
Yes	1
No	1
NA	2
Facial palsy	
Yes	0
No	2
NA	2
Electrodiagnostic patterns (VCN/EMG)	
Axonal damage	
Yes	2
No	2
Demyelination damage	
Yes	4
No	0
CFS analyzed	**2**
Albuminocytologic dissociation	2
Therapy for GBS	
Intravenous immunoglobulines	4

*Age at death in GBS patients diagnosed during COVID-19 disease onset: 48, 59, 71, 73.

sistance (2 mechanical ventilation, and 1 cPAP), and admission in intensive care (3/4). Complications during hospitalization were brain damage (2/4), superinfections (2/4), and shock (2/4). All patients received antibiotics, mainly in combination with corticosteroids (3/4) and antivirals (3/4). Two patients also received monoclonal antibody (tocilizumab). Only one patient tested negative to SARS-CoV-2 before dying.

GBS generally presented with muscle weakness (three patients) and less frequently with paresthesia (one patient). Electrophysiological studies were suggested for GBS showing demyelinating changes in all cases: also, only one patient showed axonal nerve damage. In patients with available lumbar puncture (two patients)

albumin-cytological dissociation was reported. All patients were treated with intravenous immunoglobulin.

In the *Figure 1*, lag time of onset of GBS symptoms, diagnosis, and death after onset of COVID-19 symptoms are shown: since COVID-19 onset, one patient developed GBS after three days, one patient after 29 days and two patients after 31 days. For these patients, death occurred after 8, 74, 63 and 73 days after COVID-19 onset, respectively.

DISCUSSION

We described 4 cases of patients dying of SARS-CoV-2 related GBS identified in a sample of 8,436 COVID-19 related deaths. Based on these data it can be estimated that 0.05% of all COVID-19 deaths are associated with SARS-CoV-2 related GBS. Limited data on characteristics of fatal SARS-CoV-2 related GBS are available so far [4]. The four cases we described were older when compared to an international COVID-19 related GBS cohort (61 *vs* 56) and with an Italian one (61 *vs* 59) [3, 11]. Furthermore, their age was increased if compared to pre-pandemic cases (age of greatest incidence was 30-50 years) [12]. The most frequently described causes of death in GBS are respiratory failure, pneumonia, cardiac arrest, and autonomic dysfunction [4]. As reported, we also observed in all four our cases pneumonia and respiratory failure. Considering neurophysiological features, in all our patients demyelinating findings were detected as generally reported in COVID-19 related GBS [3]. Although axonal form as AMAN or ASMAN are generally associated with a poor prognosis, only two of our patients had a mixed form, demyelinating and axonal, the other two had only demyelinating as in COVID-19 related GBS demyelinating form may be severe or fatal. Severe forms of GBS described are associated with COVID-19 [6].

All our GBS patients were treated with intravenous immunoglobulin and with COVID-19 therapy, the cases were very severe and unfortunately the use of intravenous immunoglobulins, the treatment of choice for GBS, have not had effect. No patients with fatal GBS were vaccinated. The GBS patients were cases that date back to before the vaccination in Italy and one case when vaccination was available knowing that the vaccine campaign in Italy had started. GBS is considered a post-infectious neuropathy, developing 2-4 weeks after an acute infection [13]. The absence of SARS-CoV-2 RNA in CSF and the consideration that COVID-19
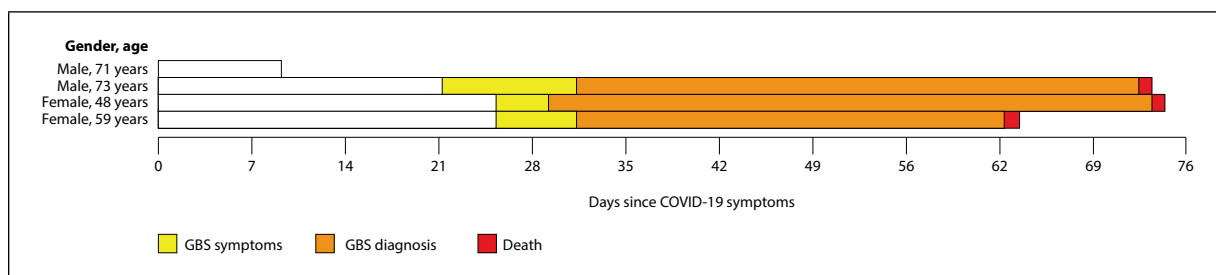
Figure 1
Lag time of onset of Guillain-Barré Syndrome (GBS) symptoms, diagnosis, and death after COVID-19 onset.

can initially be asymptomatic, which makes the latency duration longer than thought, [11] may suggest a prominent post-infectious immune-mediated mechanism rather than direct neuronal damage or a para-infectious one [14].

In our study GBS may be considered a para-infectious event, it occurred in one case 3 days after COVID-19 onset, in other patients after 29 days and in the other two patients after 31 days. Similar cases with para-infective disease caused by Borrelia Burgdorferi, Brucella and West Nile virus have been reported in different countries, because of the effect of the agent or an hyperimmune response [12]. It is probable that COVID-19-related respiratory impairment has determined the severity of the disease course [4] and respiratory failure due to GBS may get fast worse [15, 16].

The main limitation of this study relates to the fact that we only described cases of SARS-CoV-2 associated with GBS resulting in patients' death and therefore we cannot estimate the frequency of GBS in COVID-19 patients, nor the mortality associated with this condition, as we have not access to information/data of GBS diagnoses post COVID not followed by death. In addition, we based our analysis on a retrospective assessment of medical charts and an underestimation of GBS cases is possible. At last, our study was limited to cases occurred in 2020 and 2021, before new antiviral treatments became available on the market.

Although the mechanism of GBS onset is still unclear in COVID-19, fatal cases may be more frequent than other virus-related GBS [15, 16]. Clinician should be aware to promptly diagnose and treat this condition to understand if strictly monitoring patients with a high-risk profile could dramatically decrease the mortality of GBS.

The Italian National Institute of Health COVID-19 Mortality Group

The members of the Italian National Institute of Health COVID-19 Mortality Group are:

Luigi Palmieri, Elvira Agazio, Pierfrancesco Barbariol, Antonino Bella, Eva Benelli, Luigi Bertinato, Matilde Bocci, Stefano Boros, Marco Bressi, Giovanni Calcagnini, Federica Censi, Alessandra Ciervo, Elisa Colaizzo, Cecilia Damiano, Martina Del Manso, Corrado Di Benedetto, Chiara Donfrancesco, Massimo Fabiani, Francesco Facchiano, Marco Floridia, Fabio Galati, Marina Giuliano, Tiziana Grisetti, Cecilia Guastadisegni, Cinzia Lo Noce, Pietro Maiozzi, Valerio Manno, Margherita Martini, Alberto Mateo Urdiales, Eugenio Mattei, Claudia Meduri, Paola Meli, Giada Minelli, Graziano Onder, Daniele Petrone, Patrizio Pezzotti, Flavia Pricci, Ornella Punzo, Flavia Riccardo, Chiara Sacco, Paolo Salerno, Debora Serra, Matteo Spuri, Marco Tallon, Manuela Tamburo De Bella, Dorina Tiple, Brigid Unim, Luana Vaianella, Maria Fenicia Vescio, Liliana Elena Weimer, Silvio Brusaferro.

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

REFERENCES

1. Fokke C, van den Berg B, Drenthen J, et al. Diagnosis of Guillain-Barré syndrome and validation of Brighton criteria. Brain. 2014;137:33-43. doi: 10.1093/brain/awt285

2. Willison HJ, Jacobs BC, van Doorn PA. Guillain-Barré syndrome. Lancet. 2016;388(10045):717-27. doi: 10.1016/S0140-6736(16)00339-1

3. Filosto M, Cotti Piccinelli S, Gazzina S, et al. Guillain-Barré syndrome and COVID-19: an observational multicentre study from two Italian hotspot regions. J Neurol Neurosurg Psychiatry 2021;92(7):751-6. doi: 10.1136/jnnp-2020-324837

4. van den Berg B, Bunschoten C, van Doorn PA, et al. Mortality in Guillain-Barre syndrome. Neurology. 2013;80:1650-4. doi: 10.1212/WNL.0b013e3182904fcc

5. Uncini A, Vallat JM, Jacobs BC. Guillain-Barré syndrome in SARS-CoV-2 infection: an instant systematic review of the first six months of pandemic. J Neurol Neurosurg Psychiatry. 2020;91(10):1105-10. doi: 10.1136/jnnp-2020-324491

6. Palmieri L, Vanacore N, Donfrancesco C, et. al. Clinical characteristics of hospitalized individuals dying with COVID-19 by age group in Italy. J Gerontol A Biol Sci Med Sci. 2020;75(9):1796-800. doi: 10.1093/gerona/glaa146

7. d'Orsi G, Sica S, Maiorano A, et al. Guillain-Barré syndrome as only manifestation of COVID-19 infection. Clin Neurol Neurosurg. 2021;207:106775. doi: 10.1016/j.clineuro.2021.106775

8. van Doorn PA, Ruts L, Jacobs BC. Clinical features, pathogenesis, and treatment of Guillain-Barré syndrome. Lancet Neurol. 2008;7(10):939-50. doi: 10.1016/S1474-4422(08)70215-1

9. Sejvar JJ, Baughman AL, Wise M, et al. Population incidence of Guillain-Barré syndrome: a systematic review and meta-analysis. Neuroepidemiology. 2011;36(2):123-33. doi: 10.1159/000324710

10. Desforges M, Le Coupanec A, Stodola JK, Meessen-Pinard M, Talbot PJ. Human coronaviruses: viral and cellular factors involved in neuroinvasiveness and neuropathogenesis. Virus Res. 2014;194:145-58. doi: 10.1016/j.virusres.2014.09.011

11. Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, et al. Neurological associations of COVID-19. Lancet Neurol. 2020;19(9):767-83. doi: 10.1016/S1474-4422(20)30221-0

12. Aladawi M, Elfil M, Abu-Esheh B, et al. Guillain Barré syndrome as a complication of COVID-19: A systematic review. Can J Neurol Sci. 2022;49(1):38-48. doi: 10.1017/cjn.2021.102

13. Zhou Z, Kang H, Li S, et al. Understanding the neurotropic characteristics of SARS-CoV-2: from neurological manifestations of COVID-19 to potential neurotropic mechanisms. J Neurol. 2020;267(8):2179-84. doi: 10.1007/s00415-020-09929-7

14. De Sanctis P, Doneddu PE, Viganò L, et al. Guillain

Barré syndrome associated with SARS-CoV-2 infection. A systematic review. Eur J Neurol. 2020;27:2361-70. doi: 10.1111/ene.14462

15. Beghi E, Feigin V, Caso V, Santalucia P, Logroscino G. COVID-19 infection and neurological complications: Present findings and future predictions. Neuroepidemiology. 2020;54(5):364-9. doi: 10.1159/000508991

16. Palmieri L, Palmer K, Lo Noce C, et al.; Italian National Institute of Health COVID-19 Mortality Group. Differences in the clinical characteristics of COVID-19 patients who died in hospital during different phases of the pandemic: national data from Italy. Aging Clin Exp Res. 2021;33(1):193-9. doi: 10.1007/s40520-020-01764-0

Culture, religion and gender: considerations in facing migration related health inequalities in Italy

Claudio Giovannini[1]*, **Leuconoe Grazia Sisti**[2]*, **Raffaella Michieli**[3],
Maria Augusta Angelucci[4], **Walter Ricciardi**[5] and **Walter Malorni**[1]

[1]*Centro per la Salute Globale Ricerca e Studi, Università Cattolica del Sacro Cuore, Rome, Italy*
[2]*Istituto Nazionale per la Salute, Migrazione e Povertà (INMP), Rome, Italy*
[3]*Collegio Italiano di Medicina Generale, Venice, Italy*
[4]*Azienda Ospedaliera S. Camillo Forlanini, Rome, Italy*
[5]*Dipartimento di Scienze della Vita e Sanità Pubblica, Università Cattolica del Sacro Cuore, Rome, Italy*
To be considered as first Authors

Abstract
Background. The presence in Italy of a significant foreign population (5-6 million including both formally residents and not officially registered ones) introduces significant transformations in the Italian demography with important challenges on ensuring fundamental rights including work, education and above all, health.
Access to healthcare. Issues common to the entire migrant population concern the difficulty of accessing the health system of the host country due to the lack of knowledge of its rules and its functioning, the linguistic and cultural barriers and the distrust towards a system that is not recognized as his own, as well as the difficulties and misunderstandings encountered in the relationship with health professionals. Religion, culture and gender may even increase these difficulties.
Conlusion and future perspective. Culture and religion should be taken into account when designing and implementing healthcare services and healthcare workers need to be trained in acknowledging these challenges. The National Health Service should become more sensitive to the increasing cultural and religious pluralism of patients starting with investing more in the training of health professionals.

INTRODUCTION

One of the challenges for the Italian National Health Service (NHS) is the fight against health inequalities which also includes the promotion of the health of all fragile minorities present in the national territory. As foreseen by the Italian constitution, the aim is to provide adequate prevention, diagnosis and treatment services to all people. Compared to what happened in other European countries, migration in Italy has some peculiarities: the short period (just over thirty years) in which it developed and took root to become a structural datum of the country; the great diversity of origin of immigrants (over 200 countries from all continents) and the belonging of immigrants to religious confessions other than Catholic.

FOREIGN POPULATION IN ITALY
Key data on the Italian situation (at 1st January 2022)

Italy has witnessed a relevant flow of immigrants in the recent decades. According to the Initiatives and Studies on Multiethnicity (ISMU) Foundation elaborations and estimates [1] on National Institute of Statistics (ISTAT) data [2], the total number of foreigners regularly present in Italy at 1st January 2022 are 6,003,000 of whom 5,194,000 residents, 303,000 non-residents (but with a regular residence-permit) and 506,000 (estimates) non-regular foreigners without a residence permit.

Immigrant women and men are almost in the same percentage in Italy, while minors represent 20.3% of the total. Only about 30% of the foreigners residing in Italy come from a country of the European Union. The largest groups of immigrants are Romanians (1,138,000), followed by Moroccans (408,000), Albanians (about 397,000), Chinese (291,000), Ukrainians (230,000), Indians (162,000), Filipinos (155,000), Egyptians and Bangladeshi (about 150,000), Pakistanis (123,000) *(Figure 1)*.

The foreign population is notoriously young. The age group between 15 and 39 year old accounts for about

Address for correspondence: Claudio Giovannini, Centro per la Salute Globale Ricerca e Studi, Università Cattolica del Sacro Cuore, Largo Francesco Vito 1, 00168 Rome, Italy. E-mail: clagiovn@gmail.com.
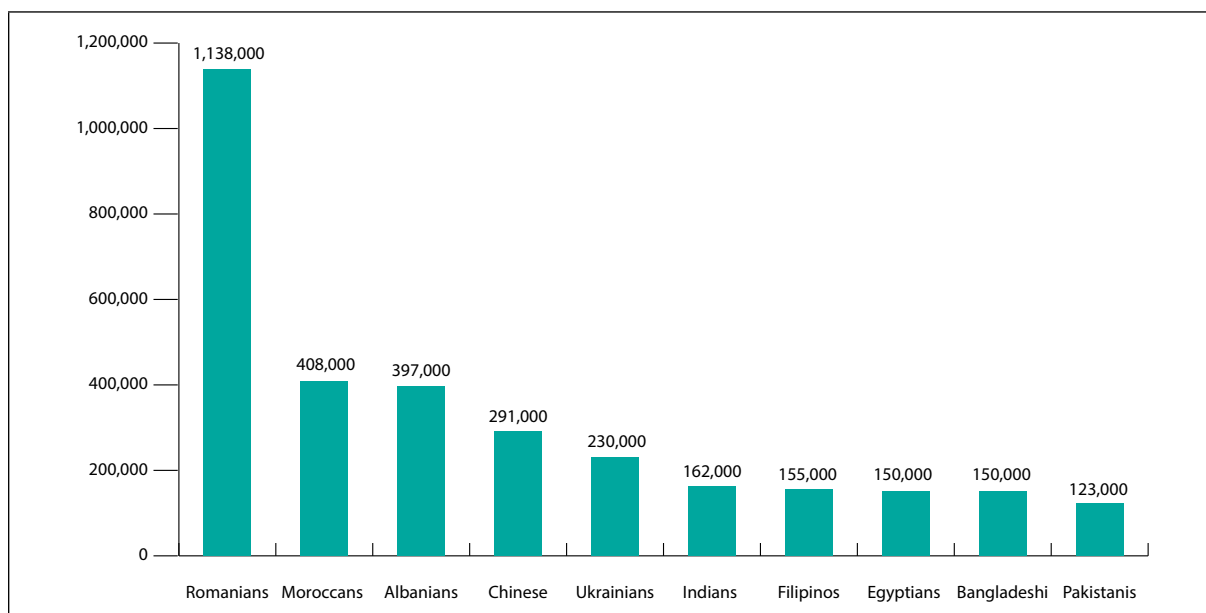
Figure 1
Largest groups of residing immigrants in Italy.

45% of the total foreign population, *vs* 26.2% for Italians. Among residents over 65 years old, 3% is made-up of foreigners and 23.7% of Italians [1].

Non-Italian citizen students

Students with non-Italian citizenship in the 2020/2021 school year are, in absolute values, 865,388, 10.3% of the total, of which 66.7% were born in Italy but did not have access to citizenship. Almost a quarter of the children of immigrants, aged 3-5 years, do not attend kindergarten; 27% of foreign studentsare late in school compared to 7.5% of Italians; 32% of foreign boys between the ages of 18 and 24 drop out of school against 10.7% of Italian boys [1].

Professed religions

Table 1 shows professed religions of immigrants. As reported, it is estimated (1th July 2022) that among the majority of foreigners currently residing in Italy, almost 2,780,000 (53.1%) belong to Christian religions and 1,539,000 (29.4%) to the Islamic religion. Buddhists, Hindus and Sikhs follow with lower percentages between 3 and 2%, then the native religions, while atheists and agnostics are considerably represented (9.9%).

Socio-economic conditions

87% of immigrants are employees, concentrated mainly in some sectors: collective and personal services (642,000 employees), agriculture (584,000), industry (466,000), hotels and restaurants (263,000), commerce (260,000) and construction (235,000) followed by care workers (179,500), domestic collaborators and similar professions (111,500). Temporary contractual forms are preponderant [3].

In the last years, due to the economic crises to the COVID-19 pandemic and ultimately to the war in Europe, the number of destitute, homeless, new poor

Table 1
Religions professed by immigrants [1]

Religion	% of total	N	Country of origin
Christian	53.1	2,784,000	
Ortodox	29.1	1,524,000	Romania, Ukraine, Moldova, Albania
Catholic	17.1	898,000	Fhilippines, Albania, Polland, Peru
Evangelic	2.8	145,000	Nigeria, Romania,China, Ghana
Coptic	1.5	81,000	Egypt, Ethiopia
Other	3.0	136,000	–
Muslim	29.4	1,539,000	Morocco, Albania, Bangladesh
Buddhist	3.5	182,000	China, Sri Lanka
Hindu	2.1	109,000	India
Sikh	1.7	88,000	India
Other religions	0.4	22,000	–
No religion	9.9	518,000	China, Romania, Albania

among both Italian and foreign citizens has increased.

The immigrant population was the most exposed to poverty: today more than one in four families are destitute compared to an incidence of 6% recorded among Italian families.

The unemployment rate of foreign citizens (13.1%) is higher than that of Italian citizens (8.7%), while the employment rate of foreigners (60.6%) fell more intensely [3]. Young people and women are the most disadvantaged groups. More than 9 out of 10 young people are in low-skilled, low-paying jobs. Immigrant women have

suffered the most from the crisis, so much that the reduction in the female employment rate among foreigners is twice as high as that of males [3].

KEY HEALTH ASPECTS OF IMMIGRANTS

Generally, immigrants show a mortality advantage respect to the native population as also found in Italy [4]. However, the literature highlights that many chronic diseases, such as hypertension, diabetes, chronic kidney disease, obesity and metabolic syndrome have a higher prevalence in immigrants than in the native population due to the interplay between genetic and, mostly, behavioural factors.

In Italy, refugees and immigrants from sub-Saharan African and south Asian countries were found to have a higher risk of cardiovascular diseases than native population. In this regard, South Asians, particularly when living in high-income countries, are at a substantially elevated risk of type 2 diabetes (T2DM) compared with white Europeans, and typically develop the disease 5-10 years earlier and at a lower BMI [5]. According to the Italian Diabetes Society, the risk of developing T2DM is 3 to 5 times higher for those coming from Southeast Asia, 2 to 4 times higher for those coming from the Middle East and North Africa, and 2-3 times higher for those coming from Sub-Saharan Africa [5]. Overall, the risk of developing T2DM diabetes among immigrants is 55% higher than in Italians with similar characteristics [5].

Among respiratory diseases [6] as a whole, the prevalence of asthma and allergic diseases in immigrants from less wealthy countries is lower than in high-income host countries, but the risk of developing these diseases increases with the length of stay in the host country, demonstrating that in addition to genetic predisposition, environmental factors also play a decisive role in the development of atopy.

As concern cancer, it should be noted that most immigrants come from geographical areas (i.e Africa, Central and South America, many Asian regions and Eastern Europe) where cancer screening attitudes and services versus a higher prevalence of risk factors are not yet strongly consolidated, e.g., human papilloma infection in Sub-Saharan Africa and Eastern Europe, areas that represent most of the origin countries of immigrants in Italy. Moreover, also chronic infections predisposing to cancers, such as hepatitis B and C, and Helicobacter Pylori infection, have greater prevalence in Eastern and sub-Saharan Africa for hepatitis B, in Eastern Mediterranean and European countries for hepatitis C, in Africa, Eastern Europe, Asia and Latin America for Helicobacter pylori, respectively [6].

Other chronic diseases frequently observed are mental disorders, musculoskeletal and gastrointestinal disorders, genetic diseases and immune-mediated inflammatory diseases [7].

CULTURAL RELIGIOUS AND GENDER ASPECTS OF IMMIGRANTS IMPACTING HEALTHCARE

The right to access health care is a principle that finds its foundation in the Italian Constitution. Nevertheless, there are several obstacles that prevent immigrants from accessing the services they are entitled to: linguistic and cultural barriers, administrative barriers, limited knowledge of the rules and functioning of the NHS, distrust of a health system that is not recognized as his own, as well as difficulties and misunderstandings encountered in the relationship with health professionals.

Culture, religious affiliation, family and social relationships, gender issues, education level, economic situation, degree of inclusion in the host society necessarily shape health seeking behaviors and the access to healthcare [8]. For example, religious beliefs influence the choices regarding procreation, organ donation and transplantation; palliative care and end of life; the compliance with pharmacological treatments and dietary prescriptions, and the prevention attitudes, to cite a few [8].

Also gender inequalities may have crucial implications for health. In many cultures, women depend on males for the interaction with the health professionals (e.g., personal history and description of symptoms) and encounter difficulties to be visited by male professionals. In this regard, Hindu women generally do not go to the gynecologist until the end of their pregnancy [9]; Muslim generally agree to be examined only by same sex professionals; Buddhist women wish to be visited only by same-sex personnel, and monks are prohibited from being cared by female personnel [10]. Furthermore, male individuals belonging to some immigrant groups often avoid seeking healthcare, even in emergency situation, fearing this would diminish their social role in the community.

These cultural customs and systems of values are often unknown to Italian health professionals and stereotypes and prejudices could persist, hampering the patient-doctor communication and relationship nourishing the distrust towards host health systems and sometimes western medicine at a large, resulting in low health services seeking. In addition, the lack of migrant-sensitive information on rights and health services available on the territory was also observed.

Recently, Italy has seen a significant increase in the female share of migratory flows. Previously, female migration was essentially pushed by family reunification. Starting from the 90s, the increasing demand for elderly and home care drew working migrant women, especially from the Eastern Europe. Today, women represent, on average, about half of the immigrant population in the country. The share of women ranges from values below 30% of immigrants from Bangladesh or Egypt, up to over 78% in the case of Ukrainian immigration.

Immigrant women carry out fewer visits during pregnancy and fewer ultrasound scans than Italian women. Moreover, they carry out the first prenatal visit later (11.5% of foreigners carry it out after the 12th week *vs* 2.65% of Italians) risking to fail the early diagnosis and monitoring of potential pathological conditions. An effort by the NHS is therefore needed to promote prenatal care and screenig services offered to immigrant women.

Further, the adherence to screening programs for breast cancer and cervical cancer, even if rising, is still low as the engagement in conscious motherhood and

family planning counselling. Language, cultural, but also administrative and logistic barriers are some of the factors called upon to explain this evidence.

Also noteworthy is the persistence of traditional surgical practices, declared illegal worldwide, often due to misinterpretations of religions, such as circumcisions and partial or total mutilation of the female genitals (FGM) [11]. These practices are still in use mainly in some populations of northern Africa, the Horn of Africa and the sub-Saharan belt.

The United Nations International Emergency Children's Fund (UNICEF) estimates that there are 125 million women in the world living with the consequences of genital mutilations. According to UN estimates, 200 million women and girls worldwide have suffered from various forms of genital mutilation [12]. In Italy, estimates indicate that about 80,000 women and 7,000 minors have undergone FGM [13, 14]. Italy is one of the countries hosting the largest number of excised women, due to the consistent female migration flow from countries with a high prevalence of FGM such as Egypt, Nigeria, Ethiopia and Senegal It is obviously not known if and how many of these practices were carried out in Italy or in the country of origin. Italian law (Law January 9th 2006, n. 7) is particularly severe and provides for imprisonment from 4 to 12 years for those who practice mutilations, even when the operation is performed abroad on an Italian or foreign citizen residing in Italy, increase of the penalty by one third when the victim is a minor. If FGM is performed by medical personnel there is disqualification from the register and suspension of the practice. Article 6 also provides for the obligation for health personnel to report to the competent authorities, an action that can allow immigrant women to acquire refugee status, even if healthcare professionals are often not adequately trained in informing victims of FGM about their right to apply for asylum [15].

However, the records of the presence of FGM in women who have given birth represents the first tool for the protection of newborn girls. The consequent passage of information to the pediatrician allows the latter to maintain surveillance over the time, necessary to prevent repetition of the practice on girls.

Other challenges for the Italian Health Service are male ritual circumcisions, which concern a large segment of the immigrant population, mostly Muslim, and which are partly carried out clandestinely with serious health consequences for the boys and children.

No official data is available on the extent of the phenomenon of ritual non-therapeutic circumcisions in Italy. Some data can be implicitly derived from the numbers of migrants from some areas of Africa reported in the annual Immigration Reports of Italian Caritas and Fondazione Migrantes. According to estimates by the Association of Doctors of Foreign Origin in Italy (AMSI) and the Community of the Arab World in Italy (CO-MAI), around 11,000 children are circumcised each year, 6,000 of which in the countries of origin and 5,000 in Italy [16]. At least one third of the 5,000 circumcision operations carried out in Italy take place outside the structures of the National Health Service in clandestine circuits, at home or in any case in unprotected environments, and often by non-medical personnel despite being a practice with a high risk of damage (early or late) and may even lead to the death of the child [16, 17]. In recent years there have been numerous news reporting the death of children due to the execution of circumcision by unqualified people without adequate medical training and in hygienically unsafe environments.

One of the reasons that drives families to entrust their children to inadequate personnel is the absence of non-therapeutic circumcision within the Essential Levels of Assistance (LEA) so that the surgery, not being paid by the Italian NHS, has prohibitive costs [17]. The economic possibilities of many immigrant families (especially African ones) do not allow them to face the cost of intervention in the health sector or the expense of a trip to their country of origin.

CONCLUSIONS

Access to care for the immigrant population in Italy is protected by one of the most inclusive legislations in the European and global panorama. Despite this, the interpretation and application of the legislation on the access to care for foreign people are highly uneven on the territory, both nationally and within the Regions/Autonomous Provinces themselves. It therefore becomes necessary to reaffirm that the fundamental principles of the NHS (universality, globality and equity) are the basis for the realization of the right to health protection, as foreseen by Art. 32 of the Italian Constitution. The aim is to provide adequate prevention, diagnosis and treatment services to all people regardless of religion, ethnicity, culture of the country of origin, economic and social condition and, last but not least, gender.

Inadequate or insufficient information of immigrant citizens is cause of limited access and improper use of services offered by NHS. The scarcity of cultural-linguistic mediators in most healthcare facilities but also scarce availability of the rules in force in a multilingual version are obstacles for accessing NHS services. It is necessary that all the Regional Health Services standardize, and guarantee detailed information on the services offered to all the people present on the Italian territory.

The religious restrictions, concerning for example the type of food that can be accepted, the type of medicine that can be prescribed, the health problems in the long periods of fasting prescribed by one's religions, the behaviors and the different needs regarding gender belonging, dangerous practices such as "homemade" circumcisions, or even the illegal surgery practices of cultural nature, as FGM, make the immigrant-NHS relationship difficult and find our healthcare workers unprepared for adequate responses.

Cultural realities, traditions and systems of values of immigrants are often unknown to Italian health operators. The lack of knowledge of both the spiritual and cultural expectations of the immigrant patient can lead to difficulties of interaction, misunderstanding, and even of lower levels of quality of care and assistance, poor patient satisfaction, limited adherence to

established care which can even lead to worse health outcomes. It therefore appears mandatory to organize training and updating activities aimed at the plurality of social and health figures who interact in various capacities with the foreign population.

All the critical aspects described here pose particularly complex questions in relation with immigrant populations and imply the need for a specific attention to their Country of origin, their religious belief and their traditional medical interventions (e.g., MGF and circumcision). Hence, personalized strategies should be implemented in order to establish a correct dialogue and a fruitful relationship of trust with patients with such different cultural features and religious creeds. Knowledge of all the critical issues can also offer the necessary tools to guarantee the overcoming of any discrimination. A collective effort is needed to lay the foundations for a public health system centered on the person as a whole, a transcultural health system capable of welcoming and providing preventive, diagnostic and treatment services to all people, regardless of whether they belong to a minority or not. On the other hand, the need to increase communication strategies in order to improve immigrant awarness of the Italian NHS, i.e. how does it works in terms of access and on the rights the immigrants have, also represents a mandatory task.

Authors' contributions

Conceptualization: CG, LGS, WM; investigation: CG, LGS, RM, MAA; supervision: WM, WR; writing - original draft: CG, RM, MAA; writing- review and editing: LGS, WM.

All Authors have read and agreed to the published version of the manuscript.

Conflict of interest statement

The Authors declare to have no conflict of interest.

REFERENCES

1. Fondazione ISMU ETS. Ventottesimo Rapporto sulle Migrazioni 2022. Milano: Franco Angeli Ed; 2023. Available from: www.ismu.org/ventottesimo-rapporto-sulle-migrazioni-2022/.

2. Istituto Nazionale di Statistica. Rapporto annuale 2022. La situazione del Paese. ISTAT; 2022. Available from: www.istat.it/it/archivio/271806.

3. Caritas Italiana e Fondazione Migrantes. XXXI Rapporto immigrazione 2022. Costruire il futuro con i migranti. Teu Ed; 2022.

4. Pacelli B, Zengarini N, Broccoli S, Caranci N, Spadea T, Di Girolamo C, Cacciani L, Petrelli A, Ballotari P, Cestari L, Grisotto L, Giorgi Rossi P; IN-LiMeS Group. Differences in mortality by immigrant status in Italy. Results of the Italian Network of Longitudinal Metropolitan Studies. Eur J Epidemiol. 2016;31(7):691-701. doi: 10.+1007/s10654-016-0177-z

5. Sattar N, Gill JMR. Type 2 diabetes in migrant south Asians: mechanisms, mitigation, and management. Lancet Diabetes Endocrinol. 2015;3(12):1004-16. doi: 10.1016/S2213-8587(15)00326-5

6. Petrelli A, Di Napoli A, Perez M, Gargiulo L. Lo stato di salute della popolazione immigrata in Italia: evidenze dalle indagini multiscopo istat. E&P. 2017;41(3-4, Suppl. 1):11-7.

7. World Health Organization. World report on the health of refugees and migrants. WHO; 2022. Available from: www.who.int/publications/i/item/9789240054462.

8. Insieme per prenderci cura. Salute e identità religiose. Per un approccio multiculturale nell'assistenza alla persona. Induismo - Buddhismo - Ebraismo - Cristianesimo - Islam. Veneranda Biblioteca Ambrosiana, Associazione Medica Ebraica (AME), Comunità Religiosa Islamica Italiana (COREIS), Ordine Professioni Infermieristiche Milano, Lodi, Monza e Brianza (OPI); 2020. Available from: https://moked.it/ame/files/2020/04/Saluteidentita-religiose_nov_2020.pdf.

9. Queensland Health. Health care providers' handbook on Hindu patients. Brisbane: Division of the Chief Health Officer, Queensland Health; 2011. Available

from: https://www.health.qld.gov.au/__data/assets/pdf_file/0024/156255/hbook-hindu.pdf.

10. Harvey C. A Buddhist perspective on health and spirituality. Scottish Journal of Healthcare Chaplaincy. 2006;9(1). doi: https://doi.org/10.1558/hscc.v9i1.33

11. World Health Organisation. Female genital mutilation 2022. WHO; 2023. Available from: www.who.int/news-room/fact-sheets/detail/female-genital-mutilation.

12. UNICEF. Female genital mutilation. UNICEF; 2022. Available from: https://data.unicef.org/topic/child-protection/female-genital-mutilation.

13. Farina P, Ortensi LE, Menonna A. Estimating the number of foreign women with female genital mutilation/cutting in Italy. Eur J Public Health. 2016;26(4):656-61.doi: 10.1093/eurpub/ckw015

14. Ortensi LE, Farina P, Leye E. Female genital mutilation/cutting in Italy: an enhanced estimation for first generation migrant women based on 2016 survey data. BMC Public Health. 2018;18(1):129. doi: 10.1186/s12889-017-5000-6

15. United Nations High Commissioner for Refugees. Emersione e referral delle persone sopravvissute a – o a rischio di – violenza di genere nel contesto della procedura di asilo. Procedure operative standard per le commissioni territoriali per il riconoscimento della protezione internazionale. UNHCR; 2021. Avaiable from: www.unhcr.org/it/wp-content/uploads/sites/97/2022/07/SOPs_web.pdf.

16. Associazione medici di origine straniera in Italia (AMSI) in collaborazione con l'area rapporti con i Comuni e Affari Esteri e Area riabilitazione dell'Ordine dei Medici di Roma. Dati sulla circoncisione in Italia. OMCEO Newsletter; 25 March 2019. Available from: www.dire.it/news-letter/odm/anno/2019/marzo/25/?news=N01.

17. Italia. Senato della Repubblica, Camera dei Deputati. Commissione Parlamentare per l'Infanzia e l'Adolescenza. Relazione sulle problematiche connesse alle pratiche di circoncisione rituale dei minori. XVIII Legislatura – disegni di legge e relazioni. 2021. Available from: https://www.senato.it/service/PDF/PDFServer/DF/362164.pdf.

ORIGINAL ARTICLES AND REVIEWS

Compliance with hand-hygiene guidelines among healthcare workers: a cross-sectional study at the Umberto I teaching hospital of Rome, Italy

Martina Antinozzi, Mariateresa Ceparano, Vincenzo Cammalleri, Valentina Baccolini, Daniela Tufi, Maria De Giusti, Paolo Villari and Carolina Marzuillo

Dipartimento di Sanità Pubblica e Malattie Infettive, Sapienza Università di Roma, Rome, Italy

Abstract
Introduction. Healthcare-associated infections are often associated with poor hand hygiene (HH) by healthcare workers (HCWs). The objective of this cross-sectional study at the Umberto I teaching hospital in Rome was to quantify compliance with HH by direct observation following a multimodal strategy devised by the World Health Organisation and to map critical areas for improvement.
Methods. Predictors of HH compliance were identified using a multivariable logistic regression model. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were calculated.
Results. Eighty-four trained observers from 50 wards collected 4,081 observations showing that overall HH compliance was 71.9%. The multivariable analysis found a positive association with the outcome for midwives compared to physicians (aOR=2.5, 95% CI: 1.5-4.1), and a negative association for healthcare assistants (aOR=0.5, 95% CI: 0.3-0.8). There was greater compliance during public holidays and weekends (aOR=1.5, 95% CI: 1.1-2.1), but compliance was lower for external staff (aOR=0.7, 95% CI: 0.5-0.9). We found a positive association with all HH indications after interaction with a patient or with patient surroundings compared with the indication "before touching a patient" (all p<0.001); the highest association was with the indication "after contact with biological fluids" (aOR=7.7, 95% CI: 4.7-12.5).
Conclusion. Overall, we observed reasonable compliance levels, but it is important to increase adherence to HH practice and monitor any behaviour change.

INTRODUCTION

Healthcare-associated infections (HAIs) are a threat to patient safety and public health [1]. In Italy, the National Institute of Health estimated a prevalence of patients with HAI in acute care hospitals of 8.03% [2]. According to the guidelines of many international institutions, such as the European Centre for Disease Prevention and Control (ECDC), the World Health Organization (WHO) and the US Centers for Disease Control and Prevention (CDC), the best way to reduce HAIs is the strict adherence of healthcare workers to standard hygiene precautions [3, 4]. Hand hygiene (HH) has indeed been found to be a cost-effective intervention that reduces the incidence of HAIs in hospitals [5], particularly if founded on the promotion of HH among healthcare workers (HCWs), coupled with assessment of the practice [6].

Nevertheless, compliance of HCWs with all standard hygiene precautions remains a long-standing challenge [7]. Indeed, studies have highlighted that relatively few HCWs follow the correct hygiene procedures [8]; for example, albeit limited, the data on the appropriate use of gloves are not reassuring [9, 10]. Several monitoring systems analyse how well staff follow HH precautions, there are direct and indirect methods for hand hygiene monitoring: direct methods include direct observation, patient assessment or HCWs self-reporting, whereas indirect methods include monitoring consumption of soap or handrub, or the use of automated monitoring of the use of sinks and handrub dispensers. In 2009, the WHO developed an evidence-based guideline that recommends direct observation as the gold standard for monitoring HCWs compliance with good HH practice. Personnel education and training, along with staff eval-

uation and performance feedback, are also necessary to achieve the highest compliance rates [3]. However, applying this WHO strategy showed that adherence to good HH practice depends on various factors, including the country, setting, habit, culture, and resource availability [11].

In Italy, a few studies have analysed compliance with HH guidelines, returning a different picture according to the setting, but showing an increase in overall compliance rates over the years [7, 12, 13]. However, most studies focused on single wards or settings, whereas data across an entire hospital are limited [14]. Moreover, HH compliance has to be contextualized, for example, taking into account the important effect of the COVID-19 pandemic on the behaviour of healthcare professionals. As underlined by Vicentini *et al.* [15] "HH has received much attention in the context of the COVID-19 pandemic as an important tool for both HCWs and patient safety"; thus, the pandemic has increased the awareness of HCWs of this topic. At the same time, in response to the current shortage of essential hospital personnel, many recently graduated HCWs entered the wards with very little work experience and were immediately required to deal with the pandemic. Consequently, it was difficult to ensure widespread control of compliance with good HH practice [15]. Therefore, the aim of this study was to evaluate HCWs compliance with HH guidelines in a large teaching hospital in Rome, Italy, comparing settings and mapping critical areas for improvement.

METHODS
Setting

The study was conducted at the Umberto I teaching hospital of Rome, one of the largest public hospitals in Italy. The hospital is composed of 54 buildings and hosts 1,235 beds, with a staff of approximately 4,700 HCWs. The hospital's Ethics Committee approved the study protocol (reference number: 4707/2021).

Study design and observation strategy

The study was made up of two phases: a training webinar on the Zoom platform (11th November 2021) to train the HCW staff in charge of conducting direct observations on standard hygiene precautions and a second phase of three weeks (from 6th to 31st December 2021) to perform data collection.

The HCWs participating in the webinar were those who agreed to serve as anonymous observers of HH compliance and to monitor their colleagues during daily care activities. They had been previously identified by the hospital management department in October 2021 among those involved in clinical risk-management activities. Next, during the one-day webinar, these HCWs had a lecture on the definition, impact and burden of HAIs, with a focus on pathogen transmission and the importance of compliance with good HH practice in reducing infection rates. They were then trained to conduct anonymous direct observations of HH compliance using the "My five moments for hand hygiene" approach [16]. Specifically, to avoid overloading the participants, each observer was asked to conduct at least

50 observations over a three-week period, with a total of at least 100 observations per ward (i.e., two observers per ward), using a paper-based checklist provided by the Section of Hygiene of the Department of Public Health and Infectious Diseases of the Sapienza University of Rome.

The anonymous checklist was divided into two sections. The first section contained data about the observer, including gender and job category (i.e., physician, nurse, healthcare assistant, other), and information to identify the hospital wards and the date of observation (i.e., weekday or weekend day/holiday). The second section collected information on adherence to the five moments for hand hygiene according to the WHO guidelines: 1) before touching a patient; 2) before an aseptic procedure; 3) after body fluid exposure; 4) after touching a patient; and 5) after touching a patient's surroundings [3]. For each one of these, four actions were considered: 1) handwashing with soap and water; 2) hand rubbing with the hydroalcoholic solution; 3) inappropriate use of gloves (i.e., without a previous action of HH); and 4) nothing (i.e., missed HH action and no gloves used). The anonymous checklist also required the following information: work shift (i.e., morning, afternoon, night), observed HCW job category (physician, nurse, healthcare assistant, or other HCW categories, such as medical student, technician, therapist), observed HCW gender, observed HCW staff type (i.e., internal or external to the ward), and context of delivered care (clinical area, surgical area, intensive area).

At the beginning of December 2021, all hospital staff received a formal communication from the Medical Director of the Umberto I teaching hospital about the objectives and methodology of the study. Therefore, the HCWs were aware that they were being observed for compliance with HH guidelines, but they were not told who the observers were or when the observations would occur.

Statistical analysis

Descriptive statistics were obtained using mean and standard deviation (SD) for continuous variables and proportions for dichotomous and categorical variables. The rate of compliance with HH guidelines was measured as the sum of the number of HH actions performed using soap and water plus those performed using an alcohol-based formulation against the total number of opportunities recorded. The recommended rate of HH compliance should be ≥81.0% according to WHO guidelines [17]. In the univariate analysis, Pearson's χ^2 test was used to assess possible associations between independent variables and overall HH compliance. Pearson's χ^2 test was also used to compare indications for HH before and after patient contact. Then, a multivariable logistic regression model was built to identify factors independently associated with HH compliance. Only variables with $p \leq 0.05$ after univariate were retained in the full multivariate model. Multicollinearity was checked using as a threshold a variance inflation factor of 5. The Hosmer-Lemeshow test was used to evaluate the goodness of fit of the model. As a result, the following variables were used to build the

model: observer gender, observer job category, observed HCW gender, observed HCW job category, staff type (i.e., internal, or external), work shift, day of the week, and context of delivered care (medical, surgical, or intensive area). Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were calculated. All statistical analyses were performed with Stata version 17.0 (StataCorp LLC, 4905 Lakeway Drive, College Station, Texas, USA). A two-tailed p-value less than 0.05 was considered statistically significant.

RESULTS
Setting

The observations were carried out in 50 out of 60 wards (83.3%), with 10 wards not available for data collection because of COVID-19 isolation precautions. The wards analysed belong to the following integrated activities Departments: Haematology, Oncology and Dermatology (2.9%); Head-Neck (3.3%); Internal Medicine, Endocrine-Metabolic Sciences and Infectious Diseases (7.9%); Emergency-Acceptance, Critical Areas and Trauma (10.4%); General Surgery, Plastics and Orthopaedics (10.5%); Cardio-Thoraco-Vascular and Organ Transplant Surgery (15.2%); Maternal, Childhood and Urogynaecology Sciences (15.5%); Internal Medicine and Medical Specialities (15.6%); and Neuroscience and Mental Health (18.9%). Overall, the checklist was filled in by 84 observers out of the 120 initially identified by the hospital management department, with a response rate of 70%. In 60.7% of cases, observers represented the clinical area, followed by surgical (25.0%) and intensive (14.3%) areas.

Characteristics of recorded observations

We collected a total of 5,385 observations out of the 6,000 expected (89.8%), with an average number of observations per observer of 64.1 (SD: 38.2). However, only 4,081 (68.0%) could be analysed (i.e., where just one HH indication was observed) *(Table 1)*. Observations were collected mostly by female HCWs (70.8%). Concerning job categories involved in the collection of data, a similar number were made by physicians and nurses (47.8% and 47.3%, respectively), followed by midwives (4.8%), healthcare assistants (0.1%) and others (0.1%).

Regarding the observed staff, 61.2% were females. Most of the observations involved physicians (42.1%), followed by nurses (35.2%), healthcare assistants (11.4%) and students (3.7%), with only a minority being relatives (0.8%) or midwives (0.6%). Almost all the observed HCWs belonged to the department where the surveys were carried out (90.8%). As for work shifts, observations were mainly made during the morning (57.4%), followed by the afternoon (35.7%) and night (6.8%). Most observations were collected from Monday to Friday (85.8%), with only a small portion on weekend days or public holidays (14.2%). Slightly more than half of the observations (54.8%) were recorded in the clinical area, followed by the surgical area (31.6%), while the remaining was collected in the intensive area (13.6%).

The most frequently recorded indication was "before touching a patient" with 1,518 observations collected,

Table 1
Characteristics of recorded observations (N=4,081)

	N (%)
Observer gender	
Male	1,140 (27.9)
Female	2,889 (70.8)
Missing	52 (1.3)
Observer job category	
Physician	1,951 (47.8)
Nurse	1,929 (47.3)
Midwife	196 (4.8)
Healthcare assistant	4 (0.1)
Other	1 (0.1)
Observed HCW gender	
Male	1,575 (38.6)
Female	2,497 (61.2)
Observed HCW job category	
Physician	1,716 (42.1)
Nurse	1,435 (35.2)
Midwife	24 (0.6)
Healthcare assistant	465 (11.4)
Student	153 (3.7)
Relative	32 (0.8)
Other	164 (4.0)
Missing	92 (2.2)
Observed ward staff	
Internal	3,705 (90.8)
External	376 (9.2)
Work shift	
Morning	2,342 (57.4)
Afternoon	1,460 (35.7)
Night	277 (6.8)
Missing	2 (0.1)
Day	
Weekday	3,503 (85.8)
Weekend day/holidays	578 (14.2)
Ward area	
Clinical area	2,235 (54.8)
Surgical area	1,292 (31.6)
Intensive area	554 (13.6)
Indication type	
Before touching a patient	1,518 (37.2)
Before clean/aseptic procedure	359 (8.8)
After touching a patient	1,138 (27.9)
After body fluid exposure	436 (10.7)
After touching a patient's surroundings	630 (15.4)

HCW: healthcare worker.

accounting for 37.2% of the total, followed by "after touching a patient" (27.9%), "after touching a patient's surroundings" and "after body fluid exposure risk" (15.4% and 10.7%, respectively). The least frequently observed indication was "before clean/aseptic procedure" (8.8%).

Compliance with HH guidelines and its predictors

Overall compliance with HH guidelines using an alcohol-based formulation (38.3%) or soap and water (32.7%) was 71%. As for the indication, the observed staff showed the highest adherence rates to HH practice (i.e., alcohol rubbing or washing with soap and water) "after contact with a patient's surroundings", "after contact with a patient" or "after contact with biological fluids" (75.1%, 79.9% and 91.5%, respectively; p<0.001) (Figure 1). The use of soap and water was preferred "before clean/aseptic procedure" (46.5%) and "after being exposed to body fluid" (72.0%), whereas for "before touching a patient", "after touching a patient" and "after touching a patient's surroundings", the observed staff mostly used an alcohol-based formulation (33.0%, 49.8% and 52.1%, respectively). The incorrect use of gloves (i.e., without previous HH) was more frequently reported "before touching a patient" (28.3%) and "before aseptic procedure" (27.3%), while doing nothing (i.e., no HH and no gloves) appeared to be more common "after touching patient's surroundings" (20.5%), followed by "before touching a patient" (14.8%) and "after touching a patient" (13.8%).

In the univariable analysis, we found that compliance rates with HH procedures were significantly different according to the gender (p<0.001) and job category (p=0.024) of the observers who collected the observations, with females and midwives registering the highest rates of compliance (72.8% and 81.1%, respectively) (Table 2). As for the HCW job category, midwives re-

ported the highest compliance (91.7%), followed by relatives (87.5%), nurses and physicians (74.0% and 71.0%, respectively), students (69.3%) and healthcare assistants (62.6%) (p<0.001). Female HCWs generally showed better compliance than males (72.7% vs 68.5%, respectively), and internal HCWs were more compliant than external personnel (71.8% vs 63.0%, respectively). Higher compliance rates were also reported during night shifts (80.5%), weekend days and public holidays (77.8%), and in the surgical area (77.9%).

In the multivariable analysis (Table 3), compared to physicians, being a midwife or a patient's family member was positively associated with the outcome (aOR=2.5, 95% CI: 1.5-4.1 and aOR=4.5, 95% CI: 1.2-17.9, respectively), while being a healthcare assistant yielded a negative association (aOR=0.5, 95% CI: 0.3-0.8). Considering the observed ward staff, being an external staff member seemed to play a negative role concerning HH adherence compared to being an internal staff member (aOR=0.7, 95% CI: 0.5-0.9), whereas observations collected on holidays or weekends showed higher HH compliance compared to weekdays (aOR=1.5, 95% CI: 1.1-2.1). Additionally, all HH indications after interaction with the patient or the patient's surroundings had a positive association with HH compared with the indication "before touching a patient" (all p<0.001), with the highest association being with "after contact with biological fluids" (aOR=7.7, 95% CI: 4.7-12.5). Lastly, the gender and job category of the observer, gender of observed staff, work shift and ward area showed no association with the outcome.

DISCUSSION

The present study quantified the adherence of HCWs to HH guidelines in the vast majority of wards of the Umberto I teaching hospital of Rome and found overall compliance of 71%. This value aligns with data in the
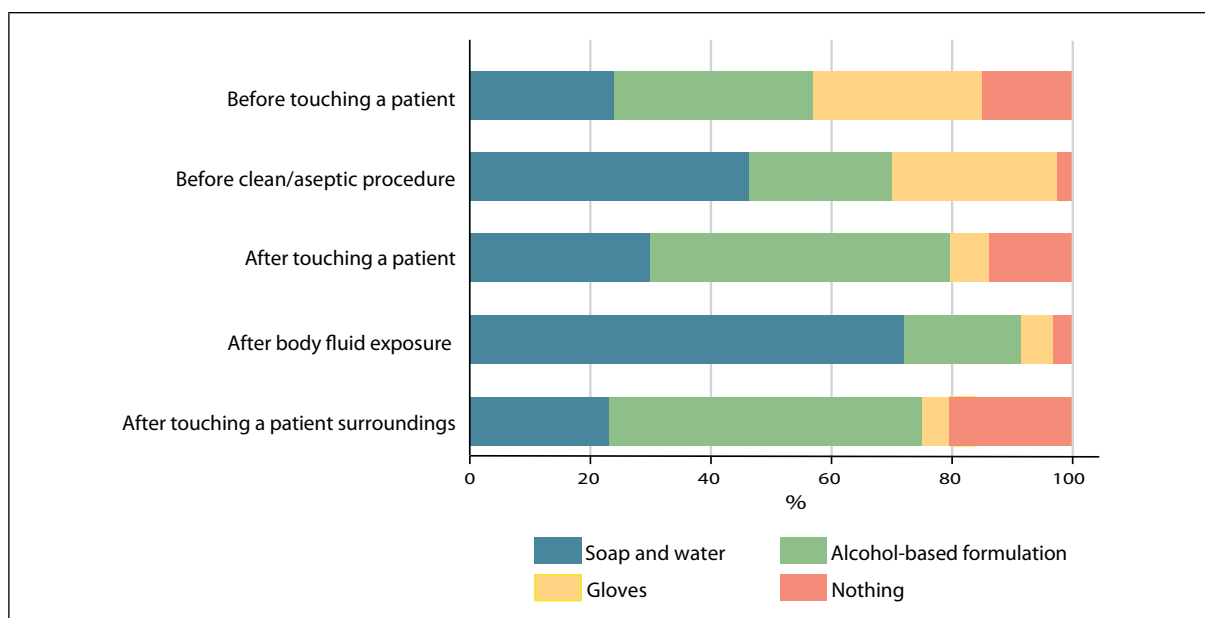
Figure 1
Compliance with hand-hygiene guidelines by indication (N=4,081).

Table 2
Univariable analysis of compliance with hand-hygiene (HH) guidelines

	HH non-compliance	HH compliance	p-value
Observer gender (N= 4,029)			<0.001
Male	393 (34.5)	747 (65.5)	
Female	785 (27.2)	2,104 (72.8)	
Observer job category (N=4,081)			0.024
Physician	566 (29.0)	1,385 (71.0)	
Nurse	580 (30.1)	1,349 (69.9)	
Midwife	37 (18.9)	159 (81.1)	
Healthcare assistant	1 (25.0)	3 (75.0)	
Other	0 (0.0)	1 (100.0)	
Observed HCW gender (N=4,072)			0.004
Male	496 (31.5)	1,079 (68.5)	
Female	682 (27.3)	1,815 (72.7)	
Observed HCW job category (N=3,989)			<0.001
Physician	497 (29.0)	1,219 (71.0)	
Nurse	373 (26.0)	1,062 (74.0)	
Midwife	2 (8.3)	22 (91.7)	
Healthcare assistant	174 (37.4)	291 (62.6)	
Student	47 (30.7)	106 (69.3)	
Relative	4 (12.5)	28 (87.5)	
Other	57 (34.8)	107 (65.2)	
Observed ward staff (N=4,081)			<0.001
Internal	1,045 (28.2)	2,660 (71.8)	
External	139 (37.0)	237 (63.0)	
Work shift (N=4,079)			<0.001
Morning	728 (31.1)	1,614 (68.9)	
Afternoon	402 (27.5)	1,058 (72.5)	
Night	54 (19.5)	223 (80.5)	
Day (N=4,081)			<0.001
Weekday	1,056 (30.2)	2,447 (69.8)	
Weekend day/Holiday	128 (22.2)	450 (77.8)	
Ward area (N=4,081)			<0.001
Clinical area	713 (31.9)	1,522 (68.1)	
Surgical area	286 (22.1)	1,006 (77.9)	
Intensive area	185 (33.4)	369 (66.6)	

HCW: healthcare worker.

literature reporting HH compliance rates among hospital HCWs usually between 60% and 70% [15, 18, 19]. As stated before, it should be noted that in healthcare facilities there were improvements in HH compliance rates during the pandemic [20, 21], probably induced by the fear and increased awareness of the importance of HH associated with the pandemic [22].

Although our hospital's HH compliance rate reflects the data in the literature, it should be remembered that, historically, the prevalence of HAIs at the Umberto I teaching hospital of Rome has been quite high compared to the European average [23]. This may have

worsened during the COVID-19 pandemic, so monitoring HH and promoting the training of health workers are key factors in preventing and containing the spread of nosocomial infections [24]. In line with previous studies, we also found significant differences in HH adherence rates in relation to several factors. As consistently reported [7, 25], HCWs showed a tendency to adhere more frequently to the practice of HH when protecting themselves, as underlined by the greater adherence to HH procedures after exposure to the patient, to body fluids, or to the patient's surrounding environment. On the other hand, the indication "before touching a pa-

Table 3

Multivariable logistic regression model for compliance with hand-hygiene (HH) procedures

	HH compliance	
	aOR (95% CI)	*p*-value
Observer gender		
Male	Ref.	
Female	1.3 (0.7-2.2)	0.425
Observer job category		
Physician	Ref.	
Nurse	1.1 (0.6-1.9)	0.688
Midwife	1.3 (0.6-2.7)	0.554
Healthcare assistant	1.0 (0.4-2.2)	0.934
Observed HCW gender		
Male	Ref.	
Female	1.3 (0.7-2.2)	0.425
Observed HCW job category		
Physician	Ref.	
Nurse	1.0 (0.7-1.5)	0.916
Midwife	2.5 (2.5-4.1)	<0.001
Healthcare assistant	0.5 (0.3-0.8)	0.002
Student	0.8 (0.5-1.2)	0.269
Relative	4.5 (1.2-17.9)	0.031
Other	0.7 (0.4-1.3)	0.260
Observed ward staff		
Internal	Ref.	
External	0.7 (0.5-0.9)	0.022
Work shift		
Morning	Ref.	
Afternoon	1.1 (0.9-1.3)	0.458
Night	1.7 (0.9-3.1)	0.092
Day		
Weekday	Ref.	
Weekend day/Holiday	1.5 (1.1-2.1)	0.004
Ward area		
Clinical area	Ref.	
Surgical area	1.6 (0.8-3.3)	0.163
Intensive area	1.0 (0.4-2.5)	0.954
Indication type		
Before touching a patient	Ref.	
Before clean/aseptic procedure	1.6 (0.9-3.1)	0.130
After touching a patient	3.1 (2.0-4.8)	<0.001
After body fluid exposure	7.7 (4.7-12.5)	<0.001
After touching a patient's surroundings	2.6 (1.6-4.2)	<0.001

aOR: adjusted odds ratio. CI: confidence interval. HCW: healthcare worker.

tient" showed the lowest compliance rate, but this poor result might have been an effect of the pandemic (during which the survey was conducted), when healthcare personnel was particularly focused on self-protection rather than preventing cross-transmission between patients [22, 26, 27].

As for the HCW job category, there were some discrepancies, with midwives achieving higher levels of compliance, similar to family members of hospitalized patients, with the latter possibly showing particular care in their contact with their relatives. This attitude translates into immense benefits for patients, considering that family members usually have no formal training in infection control and are mostly unaware of their role in the nosocomial transmission of infections [28]. In contrast to other studies [8, 25, 29], which report a higher degree of HH compliance by nurses than by physicians, we did not document any significant differences in compliance rates between the two professional categories. Probably, with the outbreak of the pandemic, medical staff in our hospital also paid more attention to HH, as reported in a recent review that showed an improvement in the degree of compliance by physicians [30]. However, being external to the ward appeared to negatively affect compliance, confirming the hypothesis that being psychologically involved with patients is a driver of HH compliance [31].

Another factor that seemed to affect compliance was the day of the observation. Specifically, observations recorded during holidays or weekend days showed higher adherence to good HH practice, a factor that could be related to a lower workload during these periods. In fact, several studies have shown that an increased workload reduces HH compliance in HCWs [32, 33]. By contrast, work shifts and ward areas did not show any association with the outcome, similar to the observed HCW gender, highlighting how an educational intervention can boost compliance rates uniformly. This is particularly important in intensive care units, which represent critical areas where HH compliance levels are required to reach a benchmark of 90% [34], given the high incidence of HAIs often seen in these departments. In the Umberto I teaching hospital, for example, both adult and neonatal intensive care units are monitored using an active HAI surveillance system [26, 35, 36].

Lastly, regarding the use of gloves, the present survey points out how they were often worn as a substitute for handwashing, which is inappropriate behaviour considering that the indications for HH are independent of those justifying the use of gloves (sterile or unsterile) [37]. This may be due to the mistaken belief that glove use alone is sufficient to limit the spread of microorganisms; since this indicates poor HH compliance, further training of HCWs on proper glove use is needed [7].

This study has some strengths and limitations. The main strength is that it included a large number of wards across medical, surgical and intensive areas, making it possible to draw comparisons between settings and to map critical areas for improvement. Secondly, the survey was performed according to a standardized protocol recommended by the WHO [3]. In this regard, despite direct observation being considered the "gold

standard" method of monitoring HH compliance, our results may suffer from the Hawthorne effect, where HCWs may improve their practice under observation, despite not knowing the identities of the observers and which practices were recorded. However, it has previously been shown that the Hawthorne effect can also be used in a positive way to encourage compliance with HH [38]. Moreover, enrolling HCWs to collect data and perform the observations on their own wards might have made them inclined to rate their co-workers differently than outside observers would. In addition, differences among observers might also have affected accuracy. However, we tried to limit the impact of these potential biases as much as possible during the one-day educational intervention. Another limitation relates to the period in which the survey was conducted, which coincided with an increase in COVID-19 cases and a consequent increase in hospitalizations. For this reason, a few wards were not able to provide the number of observations requested. Lastly, some of the observations collected could not be analysed due to incorrectly completed forms. For these reasons, it will be essential to repeat this survey over time and to improve HCW training in conducting direct observations of HH compliance.

CONCLUSION

This study represents a starting point for the monitoring of HCW behaviour toward good HH practice. It will be essential to repeat this survey routinely so that the analysis of HH compliance over time can help identify any major critical issues and evaluate the effectiveness of the interventions that will be carried out. Since the hands of HCWs play a fundamental role in the transmission of microorganisms during daily care activities [35, 39], monitoring HCWs' compliance with HH guidelines and promoting a culture of safety through repeated interventions are key for improving the clinical care pathway for patients.

REFERENCES

1. Migliara G, Di Paolo C, Barbato D, Baccolini V, Salerno C, Nardi A, Alessandri F, Giordano A, Tufi D, Marinelli L, Cottarelli A, De Giusti M, Marzuillo C, De Vito C, Antonelli G, Venditti M, Tellan G, Ranieri MV, Villari P. Multimodal surveillance of healthcare associated infections in an intensive care unit of a large teaching hospital. Ann Ig. 2019;31:399-413. doi: https://doi.org/10.7416/ai.2019.2302

2. Dipartimento Scienze della Salute Pubblica e Pediatriche, Università degli Studi di Torino. Secondo studio di prevalenza italiano sulle infezioni correlate all'assistenza e sull'uso di antibiotici negli ospedali per acuti – Protocollo ECDC. Università degli Studi di Torino; 2018.

3. World Health Organization. Patient safety: WHO guidelines on hand hygiene in health care: first global patient safety challenge clean care is safer care. WHO; 2009.

4. Boyce JM, Pittet D. Guideline for hand hygiene in healthcare settings. Recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force Centers for Disease Control and Prevention. 2002.

5. Luangasanatip N, Hongsuwan M, Lubell Y, Limmathurotsakul D, Srisamang P, Day N P J, Graves N, Cooper BS. Cost-effectiveness of interventions to improve hand hygiene in healthcare workers in middle-income hospital settings: a model-based analysis. J Hosp Infect. 2018;100:165-75. doi: https://doi.org/10.1016/j.jhin.2018.05.007

6. Guest JF, Keating T, Gould D, Wigglesworth N. Modelling the costs and consequences of reducing healthcare-associated infections by improving hand hygiene in an average hospital in England. BMJ Open. 2019;9. doi: https://doi.org/10.1136/bmjopen-2019-029971

7. Baccolini V, D'Egidio V, De Soccio P, Migliara G, Massimi A, Alessandri F, Tellan G, Marzuillo C, De Vito C, Ranieri M V, Villari P. Effectiveness over time of a multimodal intervention to improve compliance with standard hygiene precautions in an intensive care unit of a large teaching hospital. Antimicrob Resist Infect Control. 2019;8. doi: https://doi.org/10.1186/s13756-019-0544-0

8. Erasmus V, Daha TJ, Brug H, Richardus JH, Behrendt MD, Vos MC, van Beeck EF. Systematic review of studies on compliance with hand hygiene guidelines in hospital care. Infect Control Hosp Epidemiol. 2010;31:283-94. doi: https://doi.org/10.1086/650451

9. Picheansanthian W, Chotibang J. Glove utilization in the prevention of cross transmission: a systematic review. JBI Database System Rev Implement Rep. 2015;13:188-230. doi: https://doi.org/10.11124/jbisrir-2015-1817

10. Trick WE, Vernon MO, Welbel SF, DeMarais P, Hayden

MK, Weinstein RA. Multicenter intervention program to increase adherence to hand hygiene recommendations and glove use and to reduce the incidence of antimicrobial resistance. Infect Control Hosp Epidemiol. 2007;28:42-9. doi: https://doi.org/10.1086/510809

11. Allegranzi B, Gayet-Ageron A, Damani N, Bengaly L, McLaws ML, Moro ML, Memish Z, Urroz O, Richet H, Storr J, Donaldson L, Pittet D. Global implementation of WHO's multimodal strategy for improvement of hand hygiene: A quasi-experimental study. Lancet Infect Dis. 2013;13:843-51. doi: https://doi.org/10.1016/S1473-3099(13)70163-4

12. Bert F, Giacomelli S, Ceresetti D, Zotti CM. World Health Organization Framework: multimodal hand hygiene strategy in Piedmont (Italy) health care facilities. J Patient Saf. 2019;15:317-21. doi: https://doi.org/doi:10.1097/PTS.0000000000000352

13. Ragusa R, Giorgianni G, Lupo L, Sciacca A, Rametta S, La Verde M, Mulè S, Marranzano M. Healthcare-associated Clostridium difficile infection: role of correct hand hygiene in cross-infection control. 2018;59:145-52.

14. Kopsidas I, De Luca M, Bielicki J, Blázquez-Gamero D, Von Both U, Ciliento G, Epalza C, Goycochea Valídivia WA, Kolberg L, Lutsar I, MacHaira M, Neth O, Oletto A, Tsolia MN, Viltrop AL, Zaoutis T, Spyridis N. Hand hygiene compliance rates in 9 pediatric intensive care units across Europe: results from the reducing antimicrobial use and nosocomial infections in kids network. Pediatr Infect Dis J. 2022;41:E434-E437. doi: https://doi.org/10.1097/INF.0000000000003658

15. Vicentini C, Libero G, Bordino V, Zotti C M. Hand hygiene practices during the COVID-19 pandemic in Northern Italy: assessment of compliance rates measured by direct observation and alcohol-based handrub usage. Antibiotics. 2022;11:1510. doi: https://doi.org/10.3390/antibiotics11111510

16. Sax H, Allegranzi B, Uçkay I, Larson E, Boyce J, Pittet D. "My five moments for hand hygiene": a user-centred design approach to understand, train, monitor and report hand hygiene. J Hosp Infect. 2007;67:9-21. doi: https://doi.org/10.1016/j.jhin.2007.06.004

17. Rayson D, Basinda N, Pius RA, Seni J. Comparison of hand hygiene compliance self-assessment and microbiological hand contamination among healthcare workers in Mwanza region, Tanzania. Infect Prev Pract. 2021;3:3(4):100181. doi: 10.1016/j.infpip.2021.100181

18. Mouajou V, Adams K, DeLisle G, Quach C. Hand hygiene compliance in the prevention of hospital-acquired infections: a systematic review. J Hosp Infect. 2022;119:33-48. doi: https://doi.org/10.1016/j.jhin.2021.09.016

19. Ojanperä H, Kanste OI, Syrjala H. Hand-hygiene compliance by hospital staff and incidence of healthcare-associated infections, Finland. Bull World Health Organ. 2020;98:475-83. doi: https://doi.org/10.2471/BLT.19.247494

20. Wong SC, AuYeung CHY, Lam GKM, Leung EYL, Chan VWM, Yuen KY, Cheng VCC. Is it possible to achieve 100 percent hand hygiene compliance during the coronavirus disease 2019 (COVID-19) pandemic? J Hosp Infect. 2020;105:779-81. doi: https://doi.org/10.1016/j.jhin.2020.05.016

21. Makhni S, Umscheid CA, Soo J, Chu V, Bartlett A, Landon E, Marrs R. Hand hygiene compliance rate during the COVID-19 pandemic. JAMA Intern Med. 2021;181:1006-8. doi: 10.1001/jamainternmed.2021.1429

22. Moore LD, Robbins G, Quinn J, Arbogast JW. The impact of COVID-19 pandemic on hand hygiene perfor-

mance in hospitals. Am J Infect Control. 2021;49:30-3. doi: https://doi.org/10.1016/j.ajic.2020.08.021

23. Barbato D, Castellani F, Angelozzi A, Isonne C, Baccolini V, Migliara G, Marzuillo C, De Vito C, Villari P, Romano F, De Giusti M. Prevalence survey of healthcare-associated infections in a large teaching hospital. Ann Ig. 2019;31:423-35. doi: https://doi.org/10.7416/ai.2019.2304

24. Angelozzi A, Caminada S, Dorelli B, Sindoni A, Baccolini V, Di Paolo C, Mele A, Salvatori LM, Alessandri F, Marzuillo C, De Vito C, Tellan G, De Giusti M, Villari P. Knowledge, attitude, barriers, professional behaviour and possible interventions: a survey on healthcare-associated infections among the healthcare workers of an intensive care unit in a large teaching hospital in Rome. Ann Ig. 2021;33:628-43. doi: https://doi.org/10.7416/ai.2021.2461

25. Randle J, Arthur A, Vaughan N. Twenty-four-hour observational study of hospital hand hygiene compliance. J Hosp Infect. 2010;76:252-5. doi: https://doi.org/10.1016/j.jhin.2010.06.027

26. Baccolini V, Migliara G, Isonne C, Dorelli B, Barone LC, Giannini D, Marotta D, Marte M, Mazzalai E, Alessandri F, Pugliese F, Ceccarelli G, De Vito C, Marzuillo C, De Giusti M, Villari P. The impact of the COVID-19 pandemic on healthcare-associated infections in intensive care unit patients: a retrospective cohort study. Antimicrob Resist Infect Control. 2021:10. doi: https://doi.org/10.1186/s13756-021-00959-y

27. Ceparano M, Baccolini V, Migliara G, Isonne C, Renzi E, Tufi D, De Vito C, De Giusti M, Trancassini M, Alessandri F, Ceccarelli G, Pugliese F, Villari P, Angiulli M, Battellito S, Bellini A, Bongiovanni A, Caivano L, Castellani M, Coletti M, Cottarelli A, D'agostino L, De Giorgi A, De Marchi C, Germani I, Giannini D, Mazzeo E, Orlandi S, Piattoli M, Ricci E, Siena LM, Territo A, Vrenna G, Zanni S, Marzuillo C. Acinetobacter baumannii isolates from COVID-19 patients in a hospital intensive care unit: molecular typing and risk factors. Microorganisms. 2022:10. doi: https://doi.org/10.3390/microorganisms10040722

28. Biswal M, Angrup A, Rajpoot S, Kaur R, Kaur K, Kaur H, Dhaliwal N, Arora P, Gupta, AK. Hand hygiene compliance of patients' family members in India: importance of educating the unofficial "fourth category" of healthcare personnel. J Hosp Infect. 2020;104:425-9. doi: https://doi.org/10.1016/j.jhin.2019.09.013

29. Le CD, Lehman EB, Nguyen TH, Craig TJ. Hand hygiene compliance study at a large central hospital in Vietnam. Int J Environ Res Public Health. 2019;16. doi: https://doi.org/10.3390/ijerph16040607

30. Wang Y, Yang J, Qiao F, Feng B, Hu F, Xi ZA, Wu W, Ni Z, Liu L, Yuan Y. Compared hand hygiene compliance among healthcare providers before and after the COVID-19 pandemic: A rapid review and meta-analysis. Am J Infect Control. 2022;50:563-71. doi: https://doi.org/10.1016/j.ajic.2021.11.030

31. Montagnani C, Cocchi P, Lega L, Campana S, Biermann KP, Braggion C, Pecile P, Chiappini E, De Martino M, Galli L. Serratia marcescens outbreak in a neonatal intensive care unit: Crucial role of implementing hand hygiene among external consultants. BMC Infect Dis. 2015;15. doi: https://doi.org/10.1186/s12879-014-0734-6

32. Chang NCN, Schweizer ML, Reisinger HS, Jones M, Chrischilles E, Chorazy M, Huskins WC, Herwaldt L. The impact of workload on hand hygiene compliance: Is 100% compliance achievable? Infect Control Hosp Epidemiol. 2022;43:1259-61 doi: https://doi.org/10.1017/ice.2021.179

33. Dhar S, Marchaim D, Tansek R, Chopra T, Yousuf A, Bhargava A, Martin ET, Talbot TR, Johnson LE, Hingwe A, Zuckerman JM, Bono BR, Shuman EK, Poblete J, Tran M, Kulhanek G, Thyagarajan R, Nagappan V, Herzke C, Perl TM, Kaye KS. Contact precautions more is not necessarily better. Infect Control Hosp Epidemiol. 2014;35:213-9. doi: https://doi.org/10.1086/675294

34. Chavali S, Menon V, Shukla U. Hand hygiene compliance among healthcare workers in an accredited tertiary care hospital. Indian J Crit Care Med. 2014;18:689-93. doi: https://doi.org/10.4103/0972-5229.142179

35. Isonne C, Baccolini V, Migliara G, Ceparano M, Alessandri F, Ceccarelli G, Tellan G, Pugliese F, De Giusti M, De Vito C, Marzuillo C, Villari P, Barone LC, Giannini D, Marotta D, Marte M, Mazzalai E, Germani I, Bellini A, Bongiovanni A, Castellani M, D'Agostino L, De Giorgi A, De Marchi C, Mazzeo E, Orlandi S, Piattoli M, Ricci E, Siena LM, Territo A, Zanni S. Comparing the occurrence of healthcare-associated infections in patients with and without COVID-19 hospitalized during the pandemic: a 16-month retrospective cohort study in a hospital intensive care unit. J Clin Med. 2022:11. doi: https://doi.org/10.3390/jcm11051446

36. Ceparano M, Sciurti A, Isonne C, Baccolini V, Migliara G, Marzuillo C, Natale F, Terrin G, Villari P. Incidence of healthcare-associated infections in a neonatal intensive care unit before and during the COVID-19 pandemic: a four-year retrospective cohort study. J Clin Med. 2023;12:2621. doi: https://doi.org/10.3390/jcm12072621

37. Wilson J, Prieto J, Singleton J, O'Connor V, Lynam S, Loveday H. The misuse and overuse of non-sterile gloves: application of an audit tool to define the problem. J Infect Prev. 2015;16:24-31. doi: https://doi.org/10.1177/1757177414558673

38. Pittet D. Promotion of didand hygiene: magic, hype, or scientific challenge? Infect Control Hosp Epidemiol. 2002;23:118-9. doi: https://doi.org/10.1086/502019

39. Allegranzi B, Pittet D. Role of hand hygiene in healthcare-associated infection prevention. J Hosp Infect. 2009;73:305-15. doi: https://doi.org/10.1016/j.jhin.2009.04.019

Effects of combined strength and endurance training on exercise capacity in kidney transplant cyclists and runners

Valentina Totti[1], **Rocco Di Michele**[2], **Giulio Sergio Roi**[3], **Sandro Bartolomei**[2], **Giovanni Mosconi**[4], **Gianluigi Sella**[5], **Alessandro Nanni Costa**[6], **Gabriela Sangiorgi**[7], **Manuela Trerotola**[1], **Lia Bellis**[1], **Franco Merni**[2] and **Massimo Cardillo**[1]

[1]*Centro Nazionale Trapianti, Istituto Superiore di Sanità, Rome, Italy*
[2]*Dipartimento di Scienze per la Qualità della Vita, Università di Bologna, Bologna, Italy*
[3]*Scuola di Specializzazione in Medicina dello Sport e dell'Esercizio Fisico, Università di Bologna, Bologna, Italy*
[4]*Unità Operativa di Nefrologia e Dialisi, Ospedale Morgagni-Pierantoni, AUSL Romagna, Forlì, Italy*
[5]*Unità Operativa di Medicina dello Sport, CMP Centro di Medicina e Prevenzione, AUSL della Romagna, Ravenna, Italy*
[6]*IRCCS Azienda Ospedaliero Universitaria di Bologna, Policlinico di Sant'Orsola, Bologna, Italy*
[7]*Centro Riferimento Trapianti della Regione Emilia-Romagna, Bologna, Italy*

Abstract

Introduction. After transplantation, engaging in regular physical activity (PA) or sport is recommended for health. Participation to competitive sports is increasingly common among kidney transplant recipients while little is known on how training affects the physical performance in transplanted athletes.

Aim. The purpose of this case study was to assess the effects of a tailored training program on exercise parameters in kidney transplant cyclists (CKTRs) and runners (RKTRs).

Methods. Twelve male transplanted athletes were enrolled. The workload at aerobic and anaerobic thresholds, the submaximal aerobic power (V'O$_2$ stage) and rate of perceived exertion (RPE) during an incremental cycling or running test, and the peak instantaneous force (PIF) during a countermovement jump were assessed at baseline (T$_0$) and after 6 months of tailored training (T$_6$) consisting in strength and aerobic exercises. Exercise adherence, blood lipid profile and renal function were also investigated.

Results. Eight CKTRs and 4 RKTRs completed the 6-month training period, with a significant increase of training volume (minutes/week). The exercise adherence was met by 90% in both groups. At T$_6$, there were significant (p<0.05) improvements of maximum workload attained, the workload corresponding to the aerobic threshold and PIF, while workloads at anaerobic threshold, V'O$_2$ stage and RPE were unchanged. Blood cholesterol significantly decreased (p<0.01), while the other blood parameters were unchanged.

Conclusions. These findings indicate that the combined strength and endurance training is well tolerated and may improve exercise performance in this selected population of KTRs.

INTRODUCTION

Kidney transplantation is the standard treatment for end-stage renal disease and can offer a new independence from the disease process. After transplantation, engaging in regular physical activity is recommended to counteract the effects side of the immunosuppressive therapy as weight gain and represents in all respects a therapeutic intervention for improving health [1]. Contrary to what is commonly thought, sport can also be practiced after a solid organ transplantation. Indeed, participation to recreational and competitive sports activities is increasingly common among kidney trans-

Address for correspondence: Valentina Totti, Centro Nazionale Trapianti, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy. E-mail: valentina.totti@iss.it

plant recipients (KTRs). Totti *et al.* showed that transplant recipients practicing football are able to attain energy expenditure levels and quality of life similar to healthy controls [2]. Moreover, it was shown that well-trained KTRs can safely participate to a long-distance road cycling race without acute signs of kidney damage and can benefit from physical activity, even at a competitive level [2-4].

The increasing interest on the benefits of physical activity in transplant recipients has led to a number of studies showing the effects of different exercise training programs on health and exercise capacity in this population [5]. Nevertheless, most studies focused on sedentary or moderately active transplant recipients, while still little is known on how training affects the physical performance in transplanted competitive athletes.

Conditioning programs including a combination of strength and endurance training are known to impact performance-related parameters such as running or cycling economy and the power output associated to the maximum oxygen uptake in healthy competitive cyclists and runners [6]. While this kind of training may be used also by competitive KTRs, some aspects specific of that population might lead to a sub-optimal training stimulus and adaptation. Indeed, reduced muscle mass and strength are common conditions during dialysis and muscle wasting is major clinical problem due to the dialysis [7]. As a consequence, perceived muscular fatigue may be increased with possible inability to maintain a given force or power output [8]. Furthermore, immunosuppressive therapy as cyclosporine reduces oxidative activity and capillarity of some muscles, possibly contributing to reduce exercise tolerance [9]. The long-term systematic combination of immunosuppressive drug and glucocorticoid therapy may also induce muscle atrophy and bone loss [10].

To investigate the impact of combined strength and endurance training in competitive KTRs athletes, the purpose of the present case study was to assess the effects of a tailored training program on a selection of performance parameters on kidney transplant cyclists and runners.

MATERIALS AND METHODS
Patients' information

CKTRs and RKTRs were recruited from a national association who organize sport events for transplant recipients (ANED Sport, Associazione Nazionale Emodializzati, Dialisi e Trapianto). All participants regularly practiced sports before enrolment in the study and were declared eligible by the Sport Physicians. The following inclusion criteria were used: age 18-60 years, at least 6 months after organ transplantation and regularly trained. Exclusion criteria were orthopaedic limitations, psychiatric or neurological disorders, proteinuria within nephrotic range, sedentary lifestyle and any cardiovascular contraindication to exercise testing and training. Twelve KTRs – 8 male cyclists (CKTRs), 4 male runners (RKTRs) – provided informed consent before inclusion according to the procedures approved by the local Ethics Committee and following all the guidelines for experimental investigation required by the institu-

tions. The study conformed to the policy statement with respect of Declaration of Helsinki. Subjects were informed about the nature of the research and the assurances of anonymity.

Diagnostic assessment

Information on medical illness, pathologies leading to renal disease, dialysis vintage and medications were collected using structured questionnaires.

Renal function and blood lipid profile were recorded from the last medical check from each participant. Fat mass percentage (FM%) was determined by the Jackson & Pollock equation using seven skinfolds (abdominal, thigh, triceps, bicep, subscapular, suprailiac, chest) measured with a Harpenden calliper [11].

In relation to the practiced sport, an incremental cycling or treadmill exercise protocol were used to determine the aerobic and anaerobic thresholds. For cyclists, the cycling exercise protocol started with a workload of 25 W and increased by 50 W every 3 minutes, while, for runners, the treadmill exercise protocol started with a speed of 10 km/h and was increased by 1 km/h every 4 minutes. At every stage, a capillary blood sample from the earlobe was taken to measure blood lactate concentration (YSI Model 1500 Sport Lactate Analyser; Yellow Springs Instrument Co, Yellow Springs, Ohio, USA) to estimate the workload associated to the aerobic and anaerobic thresholds, corresponding to 2 and 4 mmol of lactate, respectively. The test was ended when lactate was >4mmol/L. The rate of perceived exertion (RPE) was recorded at each step using 0-10 visual analogue scale. The oxygen consumption ($V'O_2$) was measured using an open-circuit spirometry system (Sensor Medics Corp., Anaheim, CA, USA), which was carefully calibrated before each test. Respiratory gases were analysed for volume and fractions of oxygen and carbon dioxide, and the steady state $V'O_2$ expressed in terms relative to body mass (mLO_2/kg/min) averaged over the final two minutes of the first stage of the incremental test, was used to calculate the $V'O_2$ stage.

Finally, countermovement jumps (CMJ) were performed on a dual-force platform system (Kistler Instruments Ltd., Farnborough, United Kingdom). The peak instantaneous force (PIF) of the lower limbs was considered as the outcome measure over three attempts. Training volume was recorded by direct interviews before the tests. Adherence to the exercise program and eventual adverse events were also recorded.

"Therapeutic" intervention

After testing, a tailored training program was given to each participant. Each training program included 3 sessions/week of aerobic exercise (cycling or running) and 2 sessions/week of strength exercises that included isometric squats (4 sets of 10 seconds), lunges (3 sets of 10 repetitions) and plantar flexors (3 sets of 10 repetitions). Warm-up, cool-down and stretching exercises were included in each training sessions. All training sessions were not directly supervised, anyway all KTRs were contacted after 3 and 6 months by phone to assess progress and adherence to the program. The same testing protocol was repeated after 6 months of training.

Data were analyzed with descriptive statistics. Differences between T_0 and T_6 were assessed by paired t-tests, assuming as significant a value of $p < 0.05$.

RESULTS

Follow-up and outcomes

The demographic and clinic characteristics of the participants are shown in *Table 1*. All KTRs were assuming regular immunosuppressive therapy. The exercise program adherence, defined as compliance in executing the assigned exercise program (total number of session n=72) during the 6-month period was met by 7 out of 8 CKTRs and 3 out of 4 RKTRs, i.e., 83% of the subjects. The training volume showed increases of 77±40% at T_6 (*Table 2*; $p < 0.01$), without reporting adverse events.

No changes were observed for FM% that remained stable in both groups at T_6 ($p > 0.05$; *Table 2*). The workloads associated to the aerobic and anaerobic thresholds showed improvements in CKTRs of 22±32% and 11±26% respectively and in RKTRs of 5±5% and 0±6% respectively at T_6 ($p > 0.05$; *Figure 1*). RPE measured at the end of the last stages of the tests non significantly increased in both groups. Furthermore, in both groups, a higher workload at the end of the tests was observed at T_6 (+13±15%; $p < 0.05$).

PIF showed improvements of 6±11% ($p < 0.05$). $V'O_2$ stage remained unchanged at T_6 (*Figure 2*).

Blood cholesterol showed a significant decrease (-8±9%, $p < 0.01$) while the other blood parameters remained unchanged (*Table 2*).

DISCUSSION

This case series showed that competitive KTRs were able to complete a 6-month training including 3 sessions/week of aerobic exercise and 2 sessions/week of strength exercises without any evident adverse effects. Moreover, the majority of athletes showed overall improvements in the workload associated to the aerobic thresholds and the maximum sustained workload, with a slightly increased exercise tolerance. The wide range of performances of this small group of subjects affected the standard deviation around the mean (i.e., the coefficient of variation) and also the presence of opposite trends in some subjects confirmed the physiological variability present even in healthy subjects, as reported by the literature [12]. Regarding the PIF, the study group showed a significant improvement at T_6, as a pos-

sible effect of strength exercises on the muscles of the lower limbs also in KTRs. Chan *et al.* showed that KTRs were mostly capable of generating muscular power similar to healthy subjects, corroborating that fatigue is not only explained by deficits in the muscular and cardiovascular systems [13]. The same mechanisms were showed in elite healthy cyclists, where adding strengthening to endurance training can increase strength and rate of force development as appear in CKTRs [14]. In the present study, the $V'O_2$ stage, which can be roughly considered an indicator of economy of cycling or running, did not show significant improvements. However, considering the three subjects who achieved more than 1,500 minutes/week of training volume, we found a significant decrease of the $V'O_2$ stage ($p < 0.05$), indicating that the effects of an adequate volume of combined endurance and strength training tends to improve the economy of locomotion, as already reported in healthy cyclists [14]. Furthermore, Montero *et al.* showed that exercise programs including strength training improve the energy cost of cycling and shows a superior effect compared with endurance training alone [15]. The present findings confirm that, despite the intake of immunosuppressive therapies often associated with glucocorticoid, KTRs may improve the exercise performance by combined endurance and strength trainings, counteracting the side effects of the pharmacological therapies, and may reduce the muscle atrophy and weakness. Moreover, immunosuppressive therapy alone seems to have no inhibitory effect on the physiological factors related to the aerobic and muscular metabolism and regular training could be considered as a therapy that counteract the side effects of other drugs on aerobic capacity and muscle strength. Future studies are needed to more deeply investigate this aspect in larger samples of subjects. The limitations of the study are represented by the lack of data on renal function (e.g., creatinine), hydration status and training volume at the time of enrolment in the study. Another limitation is the small sample of subjects and the absence of a specific questionnaire to assess the exercise program adherence, as we used self-reported interviews.

CONCLUSIONS

The outcomes of this case study demonstrate that combined endurance and strength training is overall well tolerated in this sample and may improve sport

Table 1
Demographic and clinical characteristics of cyclists (CKTRs) and runners (RKTRs) kidney transplant recipients

	CKTRs								RKTRs				Mean±SD
Patient (n)	1	2	3	4	5	6	7	8	1	2	3	4	n=12
Dialysis vintage (months)	126	72	0	66	96	24	13	48	48	24	6	7	44.2±39.6
Age (years)	54	45	44	40	49	51	50	61	33	50	45	60	48.5±7.9
Time from transplant (years)	15	3	6	5	17	4	12	22	4	10	7	17	10.2±6.3
Body Mass Index (kg/m²)	24.7	26.5	23.1	24.1	22.4	22.3	22.4	30.5	23.7	20.6	22.6	22.7	23.8±2.6
Pathologies leading to renal disease	G	P	G	G	G	G	N	P	G	P	G	G	--

G: glomerulonephritis; P: polycystic kidney disease; N: nephropathy.

Table 2
Fat mass, training volume, performance parameters, rate of perceived exertion (RPE), blood lipid profile and renal function in cyclists (CKTRs) and runners (RKTRs) kidney transplant recipients at baseline (t0) and after 6 months of training (t6)

Patient (n)		CKTRs								RKTRs				Mean±SD
		1	2	3	4	5	6	7	8	1	2	3	4	n=12
Fat mass (%)	T_0	11.9	17.5	8.6	20.6	11.2	15.0	8.5	23.3	18.0	7.6	21.8	11.2	14.6±5.5
	T_6	12.5	22.9	9.7	17.3	13.1	13.7	8.8	23.8	20.2	8.5	19.4	10.0	15.0±5.5
Training volume (min/week)	T_0	120	240	720	1620	540	234	552	720	240	150	180	480	483±419
	T_6	180	480	480	2,880	1,620	720	600	1,620	240	100	270	600	816±822**
V'O₂ stage (mL/min/kg)	T_0	19.79	22.18	23.66	23.99	24.53	24.93	25.83	18.10	30.72	35.01	35.89	38.31	26.9±6.5
	T_6	19.66	19.41	25.08	22.01	22.07	27.87	25.67	17.56	31.59	33.45	36.76	39.30	26.7±7.2
S2 - Workload (W)	T_0	171	100	143	100	165	93	168	58	--	--	--	--	125±43
S2 - Workload (W)	T_6	167	108	158	136	172	150	145	102	--	--	--	--	142±26
S2 - Workload (km/h)	T_0	--	--	--	--	--	--	--	--	9.7	9.3	12.0	10.7	10.4±1.2
S2 - Workload (km/h)	T_6	--	--	--	--	--	--	--	--	10.0	10.0	12.0	11.8	11.0±1.1
S4 - Workload (W)	T_0	247	215	231	176	211	132	215	97	--	--	--	--	191±52
S4 - Workload (W)	T_6	239	163	238	203	226	208	203	136	--	--	--	--	202±36
S4 - Workload (km/h)	T_0	--	--	--	--	--	--	--	--	12.1	12.7	13.7	15.4	13.5±1.4
S4 - Workload (km/h)	T_6	--	--	--	--	--	--	--	--	13.0	12.0	14.3	14.7	13.5±1.2
Max workload (W)	T_0	250	250	250	200	250	200	250	125	--	--	--	--	222±45
Max workload (W)	T_6	250	250	300	200	300	250	250	150	--	--	--	--	256±50*
Max workload (km/h)	T_0	--	--	--	--	--	--	--	--	12.0	13.0	14.0	15.0	13.5±1.3
Max workload (km/h)	T_6	--	--	--	--	--	--	--	--	13.0	13.0	14.5	16.0	14.1±1.4
RPE (0-10 scale)	T_0	5	5	4	5	6	6	4	4	5	5	3	4	4.7±0.9
	T_6	5	5	5	5	7	7	5	7	4	5	2	5	5.2±1.4
Peak instantaneous force (N)	T_0	1,598	1,841	1,574	1,659	1,504	1,509	1,285	1,427	1,330	1,351	1,692	1,326	1,508±172
	T_6	1,698	2,006	1,437	1,810	1,759	1,710	1,209	1,489	1,385	1,314	2,178	1,239	1,602±308*
Total Cholesterol (mg/dL)	T_0	178	220	237	261	195	211	230	217	173	174	168	171	203±31
	T_6	161	222	200	244	170	193	160	210	164	165	164	172	185±28**
Triglycerides (mg/dL)	T_0	87	280	99	199	55	249	115	93	126	145	61	145	138±71
	T_6	87	282	98	157	37	250	105	90	166	122	60	144	133±73
Creatinine (mg/dL)	T_0	1.58	1.68	1.84	1.10	1.34	1.82	1.70	1.05	0.92	1.30	1.00	1.31	1.39±0.33
	T_6	1.54	1.56	1.88	1.07	1.47	1.89	1.48	1.05	0.89	1.43	1.00	1.23	1.37±0.33
eGFR (mL/min/1.73mq)	T_0	49	47	43	79	60	42	46	76	101	62	86	59	62.5±19.1
	T_6	50	51	42	81	54	40	50	76	104	55	86	64	62.8±19.8
Glucose (mg/dL)	T_0	65	85	85	114	101	100	99	91	79	84	90	79	89.3±12.9
	T_6	71	76	87	116	92	107	102	85	81	77	79	83	88.0±13.7

*$p<0.05$; **$p<0.01$.
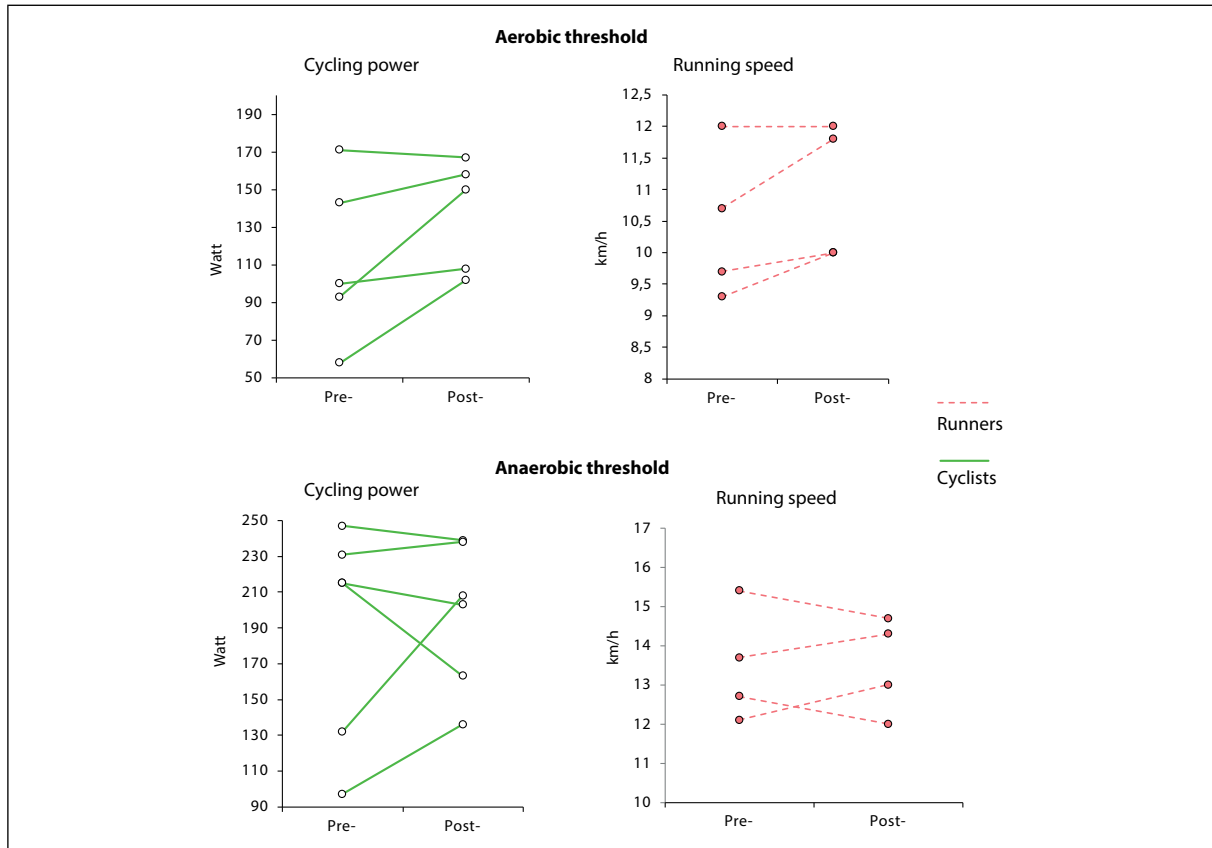
Figure 1
Scatterplot of cycling power and running speed at aerobic (95% CI diff standard: from 0.12 to 0.76, p<0.05) and anaerobic thresholds (95% CI diff standard: from -0.25 to 0.55, ns) pre- and post-training in kidney transplant recipients cyclists and runners respectively.
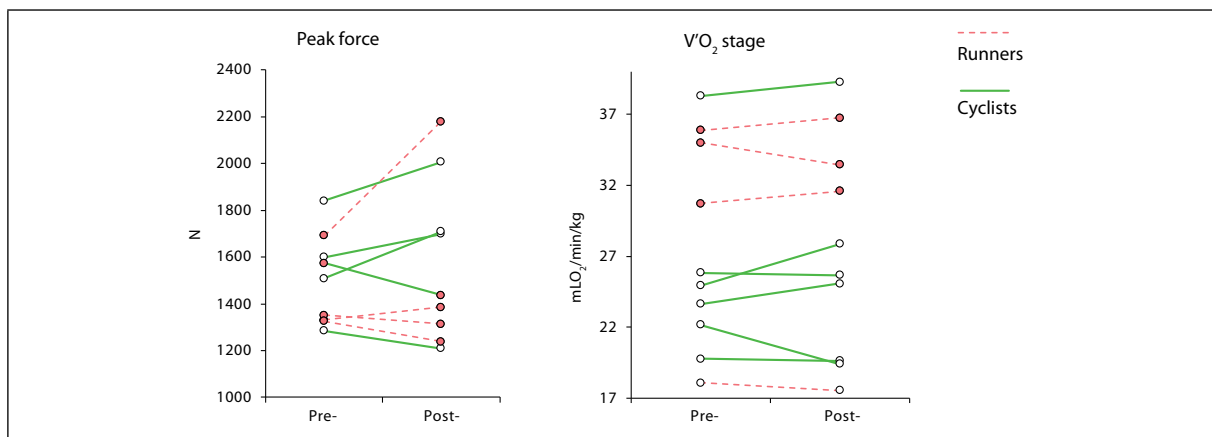
Figure 2
Scatterplot of peak force (N) (95% CI diff standard: from -0.27 to 1.03, ns) and V'O$_2$ stage (mLO$_2$/min/kg) (95% CI diff standard: from -0.14 to 0.16, ns) in kidney transplant recipients cyclists and runners pre- and post-training.

performance capacity of cyclist and runner KTRs. Referring to the scientific literature on healthy competitive athletes, physiological responses seem to appear comparable to the study group [16, 17]. Further research is needed to investigate the hydration status of transplant recipients who regularly practice sport, which is closely related to renal function. Anyway, these findings can help design future studies to determine the opti-

mal training load to improve performance and reduce fatigue in KTRs practicing physical activity or sports.

Authors' contributions
V. Totti and R. Di Michele have participated in research design, in drafting the paper, in the performance of the research in data analysis and statistics and in critical revision of the paper; GS. Roi, S. Bartolomei, G.

REFERENCES

1. Gordon EJ, Prohaska T, Siminoff LA, Minich PJ, Sehgal AR. Needed: tailored exercise regimens for kidney transplant recipients. Am J Kidney Dis. 2005;45(4):769-74. doi: 10.1053/j.ajkd.2005.01.002
2. Totti V, Zancanaro M, Trerotola M, Nanni Costa A, Antonetti T, Anedda A, Roi GS. Quality of life and energy expenditure in transplant recipient football players. Transplant Proc. 2013;45(7):2758-60. doi: 10.1016/j.transproceed.2013.07.027
3. Cappuccilli M, Mosconi G, Roi GS, De Fabritis M, Totti V, Merni F, Trerotola M, Marchetti A, La Manna G, Nanni Costa A. Inflammatory and adipose response in solid organ transplant recipients after a marathon cycling race. Transplant Proc. 2016;48(2):408-14. doi: 10.1016/j.transproceed.2016.02.001
4. Mosconi G, Roi GS, Totti V, Zancanaro M, Tacconi A, Todeschini P, Ramazzotti E, Di Michele R, Trerotola M, Donati C, Nanni Costa A. Transplant Direct. 2015;1(9):e36. doi: 10.1097/TXD.0000000000000546
5. Neale J, Smith AC, Bishop NC. Effects of exercise and sport in solid organ transplant recipients: a review. Am J Phys Med Rehabil. 2017;96(4):273-88. doi: 10.1097/PHM.0000000000000599
6. Rønnestad BR, Mujika I. Optimizing strength training for running and cycling endurance performance: A review. *Scand J Med Sci Sports.* 2014; 24(4):603-12. doi: 10.1111/sms.12104
7. Chen CT, Lin SH, Chen JS, Hsu YJ. Muscle wasting in hemodialysis patients: new therapeutic strategies for resolving an old problem. ScientificWorldJournal. 2013;2013:643954. doi: 10.1155/2013/643954
8. Schillings ML, Hoefsloot W, Stegeman DF, Zwarts MJ. Relative contributions of central and peripheral factors to fatigue during a maximal sustained effort. Eur J Appl Physiol. 2003;90(5-6):562-8. doi: 10.1007/s00421-003-0913-4
9. Biring MS, Fournier M, Ross DJ, Lewis MI. Cellular adaptations of skeletal muscles to cyclosporine. J Appl Physiol. 1985;84(6):1967-75. doi: 10.1152/jappl.1998.84.6.1967
10. Schakman O, Gilson H, Thissen JP. Mechanisms of glucocorticoid-induced myopathy. J Endocrinol. 2008;197(1):1-10. doi: 10.1677/JOE-07-0606
11. Jackson AS, Pollock ML. Generalized equations for predicting body density of men. Br J Nutr. 1978;40:497-504. doi: 10.1079/bjn19780152
12. Nimmo MA, Leggate M, Viana JL, King JA. The effect of physical activity on mediators of inflammation. Diabetes Obes Metab. 2013;15(Suppl. 3):51e60. doi: https://doi.org/10.1111/dom.12156
13. Chan W, Jones D, Bosch JA, McPhee J, Crabtree N, McTernan PG, Kaur O, Inston N, Moore S, McClean A, Harper L, Phillips A, Borrows R. Cardiovascular, muscular and perceptual contributions to physical fatigue in prevalent kidney transplant recipients. Transpl Int. 2016;29(3):338-51. doi: 10.1111/tri.12727
14. Rønnestad BR, Hansen J, Hollan I, Ellefsen S. Strength training improves performance and pedalling characteristics in elite cyclist. Scand J Med Sci Sports. 2015;25:e89-e98. doi: 10.1111/sms.12257
15. Montero D, Lundby C. The effect of exercise training on the energetic cost of cycling. Sports Med. 2015;45(11):1603-18. doi: 10.1007/s40279-015-0380-1
16. Mosconi G, Roi GS, Totti V, Zancanaro M, Tacconi A, Todeschini P, Ramazzotti E, Di Michele R, Trerotola M, Donati C, Nanni Costa A. Renal function in kidney and liver transplant recipients after a 130-km road cycling race. Transplant Direct. 2015;1(9):e36. doi: 10.1097/TXD.0000000000000546
17. Mosconi G, Angelini ML, Balzi W, Totti V, Roi GS, Cappuccilli M, Tonioli M, Storani D, Trerotola M, Costa AN. Can solid-organ-transplanted patients perform a cycling marathon? Trends in kidney function parameters in comparison with healthy subjects. Transplant Proc. 2016;48(2):415-9. doi: 10.1016/j.transproceed.2015.12.042

Smoking intensity changes during the COVID-19 pandemic waves in a cohort of smokers in Italy

Giulia Carreras[1], Filippo Monti[1], Alessandra Lugo[2], Silvano Gallus[2], Chiara Stival[2], Sabrina Molinaro[3], Sonia Cerrai[3], Anna Odone[4], Luisa Mastrobattista[5], Claudia Mortali[5], Giuseppe Gorini[1] and the "LOST IN TOSCANA" Study Investigators*

[1]*Istituto per lo Studio, la Prevenzione e la Rete Oncologica (ISPRO), Florence, Italy*
[2]*Dipartimento di Ricerca Epidemiologia Medica, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy*
[3]*Consiglio Nazionale delle Ricerche (CNR), Istituto di Fisiologia Clinica (IFC), Pisa, Italy*
[4]*University of Pavia, Department of Public Health, Pavia, Italy*
[5]*Centro Nazionale Dipendenze e Doping, Istituto Superiore di Sanità, Rome, Italy*
**The members of the "LOST IN TOSCANA" Study Investigators are listed before the references*

Abstract
Introduction. COVID-19 lockdown in Italy resulted in increased smoking consumption, mainly associated with mental distress. This study aims to update previous findings investigating changes in smoking intensity during the whole COVID-19 pandemic.
Methods. This analysis was carried out within the "LOST IN ITALY" ("LOckdown and lifeSTyle IN ITALY") and "LOST IN TOSCANA" studies on 880 smokers with information collected during main pandemic peaks. Changes in cigarettes/day were investigated in association with survey-periods, socio-demographic and psychological characteristics through a linear mixed-model.
Results. Net of psychological distress and socio-demographic variables, in comparison to pre-pandemic period cigarettes/day increased by 1.16 during lockdown, and remained over half higher subsequently. In the overall period, an increase of >1 cigarette/day was also associated to lower education, older age, male gender and psychotropics drugs use.
Conclusions. After 2 years of pandemic, cigarettes/day have not yet returned to the pre-pandemic levels, mainly due to socio-demographic factors, but also to nicotine addiction, that tends to stabilize consumption.

INTRODUCTION

The coronavirus disease (COVID-19), firstly identified in December 2019, has spread worldwide causing almost 700 million cases and 6 million deaths in January 2023 [1]. At the beginning, many countries worldwide implemented lockdown interventions to detain the virus spread [2]. However, several COVID-19 waves were recorded [3]. After the initial wave which comprised a pre-pandemic phase in January-May 2020 and a first wave in June 2020-February 2021, the COVID-19 pandemic comprised other three global waves up to the beginning of 2022: the second, March-June 2021; the third, July-October 2021; the fourth, November 2021-March 2022 [3]. Each of these waves was associated with different restriction policies that varied from country to country.

The isolation measures implemented during the first wave were linked to a general declining mental health [4] and lifestyles changes, comprising smoking habits, related both to mental distress and to a large amount of time spent at home [5]. The impact of the COVID-19 pandemic on smoking habits is complex and uncertain [6]. Most studies found a reduction of smokers; however, among smokers, contrasting results were found, with a recent meta-analysis reporting a reduced and an increased consumption respectively among 21% and 27% of smokers, and quitting smoking among 4% [7]. In Italy, results from the "LOckdown and lifeSTyle IN ITALY" (LOST IN ITALY) project, a cross-sectional study investigating changes in smoking habits during lockdown, showed a huge effect of the 2020 lockdown in increasing smoking consumption. In fact, despite a reduced prevalence in younger ages, maybe due to the social role of smoking among youth, a consumption increase accounted for most changes, with 36% of

Address for correspondence: Giulia Carreras, Istituto per lo Studio, la Prevenzione e la Rete Oncologica (ISPRO), Via Cosimo il Vecchio 2, 50139 Florence, Italy. E-mail: g.carreras@ispro.toscana.it.

smokers reporting a higher consumption [5]. Most of the determinants of such increase were related to mental distress, such as insufficient amount of sleep and anxiety and depression symptoms. In addition, among those who continued smoking during the first pandemic phase, there were more frequently novel product users, i.e. electronic cigarette (e-cigarette) and heated tobacco product (HTP) users [8].

In the framework of the "LOST IN ITALY" project and its extension "LOST IN TOSCANA", the aim of this study was to update previous results by investigating how smoking intensity changed during the COVID-19 pandemic waves following lockdown.

METHODS

The "LOST IN ITALY" study cohort, described in detail elsewhere [5, 9] is based on a cross-sectional survey on 6,003 participants representative of the Italian adult population who completed a web-based interview during the Italian lockdown (April 27-May 3, 2020). The fieldwork was conducted by Doxa, the Italian branch of the Worldwide Independent Network/Gallup International Association.

Within the "LOST IN ITALY" study, about half of the initial cohort was re-contacted during the first and the second COVID-19 waves (3,185 in November 27-December 20, 2020, and 3,000 in May 7-18, 2021). Finally, 4,831 participants (80.4%) were re-contacted during the last COVID-19 wave (February 24-March 21, 2022) within the "LOST IN TOSCANA" study. For the purpose of this analysis, only respondents who were current smokers at all waves and that have information in at least two surveys (the first, with the pre-lockdown and lockdown measurements, and another survey) were kept into the analysis (N=880). Each subject included has a number of measurements that goes from three to five, resulting in an unbalanced design.

In all surveys, participants completed a questionnaire on socio-demographic information, lifestyle habits and mental distress. Moreover, at the first survey, changes before and during the lockdown were recorded. Current smokers were defined as respondents who reported having smoked ≥100 cigarettes during their life and that were current smokers (i.e., smoked >0 cigarettes per day – cig/day) at the time of the interview. Current e-cigarette or HTP users were defined as respondents using e-cigarettes or HTP occasionally or regularly. The dual use was defined as smokers using either e-cigarettes or HTP. The use of psychotropic drugs was registered and sleep disorders and anxiety or depression symptoms were recorded using validated tools [4, 10-12].

Changes in the number of cig/day were investigated in association with survey time, socio-demographic variables (sex, education, age at baseline), use of e-cigarettes or HTPs, use of psychotropic drugs, sleep disorders and anxiety or depression symptoms. In order to take into account for the repeated measures design and considering dependency of observations within subjects, and also allowing the inclusion of individuals who participated to different number of surveys, i.e., unbalanced design, linear mixed models were used. A random intercept model was implemented, with socio-demographic variables as time-invariant and variables on mental distress and novel products use as time-varying covariates. Since the psychological distress variables were not correlated (Pearson-R=0.18, R=0.21 for anxiety or depression and respectively sleep disorders and drugs use, and R=-0.02 for sleep disorders and drugs use), a model which adjusted for all those variables was used.

The Intraclass Correlation Coefficient (ICC) was calculated to estimate the percentage of the total variance that was explained by between-subjects variance.

RESULTS

A comparison of smokers who were retained *versus* lost to follow-up showed significant differences in age suggesting a missing at random mechanism *(Supplementary Table 1S available online)*. Thus, fitting a linear mixed model to the observed data can produce valid inference [13].

For each subject the number of measurements goes from three to five, resulting in an unbalanced design. An increase in psychological distress and psychotropic drugs use was observed during the lockdown with a subsequent decrease up to the last survey, reaching pre-pandemic levels for the drugs use only. The mean number of cig/day was 11.7 before lockdown, 13.0 during lockdown and it reached 12.3 in the last survey *(Supplementary Table 2S available online)*.

The ICC was 83.6% (95% CI: 81.4%-85.6%), implying that the measures were quite stable within subjects and suggesting that the use of random intercept models would be a good approximation to model such correlation. Net of psychological distress and socio-demographic variables, in comparison to the period before the lockdown, the number of cig/day significantly increased by 1.16 (95% CI 0.89, 1.44) during lockdown, by 0.62 (95% CI 0.31, 0.92) in November-December 2020, by 0.69 (95% CI 0.37, 1.02) in May 2021, and by 0.57 (95% CI 0.28, 0.86) in February-March 2022 *(Table 1)*.

Statistical evidence of association was observed between sleep disorders and cig/day, with those reporting inadequate sleep smoking 0.32 (95% CI 0.03, 0.60) cig/day more than people with adequate sleep. Moreover, smokers using psychotropic drugs reported over 1 cig/day more than people not using drugs (coefficient 1.07, 95% CI 0.48, 1.67). A significant association with gender was also observed, with men smoking 1.48 cig/day more than women (95% CI 0.60, 2.36), and also for people with low education level smoking 1.44 (95% CI 0.10, 2.78) cig/day more than people highly educated. People aged 35-54 and 55-74 years smoked respectively 1.56 (95% CI 0.47, 2.66) and 2.96 (95% CI 1.75, 4.17) cig/day more than younger respondents. No significant changes in cig/day among people who also use novel products were observed in comparison to exclusive conventional cigarette smokers.

DISCUSSION

After 2 years of pandemic, smoking intensity have not yet returned to the pre-pandemic levels. The greater increase was observed during lockdown, with respondents

Table 1
Association between number of cigarettes smoked per day and survey period, socio-demographic characteristics, novel (tobacco) product use, psychotropic drugs use and mental distress variables (anxiety or depression symptoms and sleep disorders). Coefficients and 95% confidence intervals (CI) from the random intercept model

Variables		Coefficient (95% CI)
Survey*	Pre lockdown	Ref.
	Lockdown	1.16 (0.89, 1.44)
	Survey 2	0.62 (0.31, 0.92)
	Survey 3	0.69 (0.37, 1.02)
	Survey 4	0.57 (0.28, 0.86)
Sex	Female	Ref.
	Male	1.48 (0.60, 2.36)
Level of education	High	Ref.
	Medium	0.90 (-0.05, 1.85)
	Low	1.44 (0.10, 2.78)
Age	18-34 years	Ref.
	35-54 years	1.56 (0.47, 2.66)
	55-74 years	2.96 (1.75, 4.17)
Dual use**	Yes	Ref.
	No	0.28 (-0,06; 0.63)
Use of psychotropic drugs**	No	Ref.
	Yes	1.07 (0.48, 1.67)
Anxiety or depression symptoms***	No	Ref.
	Yes	0.30 (-0.01, 0.62)
Sleep disorders****	No	Ref.
	Yes	0.32 (0.03, 0.60)

*Pre-lockdown and lockdown: survey carried out in April-May 2020 referring respectively to the pre lockdown period and to the pre-pandemic COVID-19 wave; Survey 2: carried out in November-December 2020 referring to the COVID-19 wave 1; Survey 3: carried out in May 2021 referring to the COVID-19 wave 2; Survey 4: carried out in February-March 2022 referring to the COVID-19 wave 4.
**Dual use: smokers using either e-cigarettes or heated tobacco products.
***Use of psychotropic drugs: respondents using at least one drug among antidepressants, anxiolytics/benzodiazepine, hypnotics, antipsychotics and mood stabilizers [4].
****Anxiety or depression symptoms: respondents with value higher than 3 in the 2-item generalized anxiety disorder scale [10] or in the 2-item Patient Health Questionnaire scale [11].
*****Sleep disorders: respondents who reported to sleep less than 7 hours per night or who evaluated their overall sleep as quite bad or very bad [12].

smoking 1.16 cig/day more than before. These results confirmed the initial trend observed in the previous "LOST IN ITALY" analysis [5]. Moreover, this study shows that in the subsequent COVID-19 waves, the initial increase halved, remaining around 0.6 cig/day more than before the pandemic.

These results suggest that the restrictions imposed during the lockdown resulted in changes in smoking intensity mainly related to mental distress [5]. Then, during the subsequent COVID-19 waves, mental distress had not yet returned to the pre-pandemic levels, but this had no direct impact on tobacco consumption, which was mainly associated to socio-demographic factors usually related to tobacco addiction [14], such as a lower education, older age and being male, and to the use of psychotropic drugs. Therefore, once smoking intensity increases, it is not easy to come back to initial levels for smokers with specific socio-demographic characteristics, probably also due to tobacco and nicotine addiction themselves that tends to stabilize consumption [14].

Finally, our results did not support the harm reduction theory, which suggests that novel product use should determine a decrease in smoking intensity [15]. In fact, in our study, the dual use of novel products and traditional cigarettes was not associated with a decrease in cig/day.

Limitations of our study include the possible information bias due to the self-reported responses and, more importantly, a possible selection bias, being this study based on a sample of online panelists, characterized by a higher socioeconomic level compared with the general population. Moreover, we did not include quitters, since there are many differences between determinants of decreasing smoking intensity and of smoking cessation [16].

This study has several strengths. First of all, the statistical modelling allowed to take into account for the longitudinal structure of the data by considering the correlation within individuals. Moreover, despite the limitation of having a reduced number of observations in the two middle COVID-19 waves, the modeling strategy allowed to include all the observations coming from surveys with different sample sizes in an unbalanced design, without loss of power, and with not equally spaced measurements. Finally, the surveys were carried out during most of the COVID-19 pandemic waves (i.e. all except the third between July and October, 2021), allowing thus to capture the possible effect of the pandemic peaks on the population psychological distress and lifestyle changes.

CONCLUSIONS

After 2 years of pandemic, smoking intensity has not yet returned to the pre-pandemic levels, and this is explained mainly by socio-demographic factors, but also by tobacco and nicotine addiction, that tends to stabilize consumption.

Data availability
The data underlying this article will be shared on reasonable request to the corresponding Author.

The members of the "LOST IN TOSCANA" Study Investigators are:
Silvia Biagioni (CNR, Pisa, Italy); Fabio Voller, Elena Andreoni, Martina Pacifici (ARS Toscana, Florence, Italy); Valentino Patussi, Chiara Cresci, Donatello Cirone (Azienda Ospedaliero-Universitaria Careggi, Florence, Italy)

REFERENCES

1. World Health Organization. WHO Coronavirus (COVID-19) Dashboard. Available from: https://covid19.who.int/.
2. Lewnard JA, Lo NC. Scientific and ethical basis for social-distancing interventions against COVID-19. Lancet Infect Dis. 2020;20:631-3. doi: 10.1016/S1473-3099(20)30190-0
3. Gao L, Zheng C, Shi Q et al. Evolving trend change during the COVID-19 pandemic. Front. Public Health. 2022;10:957265. doi: https://doi.org/10.3389/fpubh.2022.957265
4. Amerio A, Lugo A, Stival C, Fanucchi T, Gorini G, Pacifici R, Odone A, Serafini G, Gallus S. COVID-19 lockdown impact on mental health in a large representative sample of Italian adults. J Affect Disord. 2021;292:398-404. doi: 10.1016/j.jad.2021.05.117
5. Carreras G, Lugo A, Stival C, Amerio A, Odone A, Pacifici R, Gallus S, Gorini G. Impact of COVID-19 lockdown on smoking consumption in a large representative sample of Italian adults. Tob Contr. 2022;31:615-22. doi: 10.1136/tobaccocontrol-2020-056440
6. Almeda N, Gómez-Gómez I. The impact of the COVID-19 pandemic on smoking consumption: A systematic review of longitudinal studies. Front Psychiatry. 2022;13:941575. doi: 10.3389/fpsyt.2022.941575
7. Sarich P, Cabasag CJ, Liebermann E, et al. Tobacco smoking changes during the first pre-vaccination phases of the COVID-19 pandemic: A systematic review and meta-analysis. eClinicalMedicine. 2022;47:10137.5. doi: https://doi.org/10.1016/j.eclinm.2022.101375
8. Gallus S, Stival C, McKee M, Carreras G, Gorini G, Odone A, van den Brandt PA, Pacifici R, Lugo A. Impact of electronic cigarette and heated tobacco product on conventional smoking: an Italian prospective cohort study conducted during the COVID-19 pandemic. Tob Control. 2022;tobaccocontrol-2022-057368. doi: 10.1136/tc-2022-057368
9. Odone A, Lugo A, Amerio A, Borroni E, Bosetti C, Carreras G, Cavalieri d'Oro L, Colombo P, Fanucchi T, Ghislandi S, Gorini G, Iacoviello L, Pacifici R, Santucci C, Serafini G, Signorelli C, Stival C, Stuckler D, Tersalvi CA, Gallus S. COVID-19 lockdown impact on lifestyle habits of Italian adults. Acta Biomed. 2020;91:87-9. doi: 10.23750/abm.v91i9-S.10122
10. Kroenke K, Spitzer RL, Williams JB, Monahan PO, Lowe B. Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. Ann Intern Med. 2007; 146:317-25. doi: 10.7326/0003-4819-146-5-200703060-00004
11. Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: validity of a two-item depression screener. Med. Care. 2003;41:1284-92. doi: 10.1097/01.MLR.0000093487.78664.3C
12. Buysse DJ 3rd, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28:193-213. doi: 10.1016/0165-1781(89)90047-4
13. Cnaan A, Laird N M, Slasor P. Using the general linear mixed model to analyse unbalanced repeated measures and longitudinal data. Stat Med. 1997;16:2349-80. doi: 10.1002/(sici)1097-0258(19971030)16:20<2349::aid-sim667>3.0.co;2-e
14. Institute of Medicine (US) Committee on Preventing Nicotine Addiction in Children and Youths; Lynch BS, Bonnie RJ (Eds). Growing up tobacco free: preventing nicotine addiction in children and youths. Washington (DC): National Academies Press (US); 1994.
15. World Health Organization. WHO Report on the global tobacco epidemic 2019: offer help to quit tobacco use. WHO; 2019. Available from: www.who.int/teams/health-promotion/tobacco-control/who-report-on-the-global-tobacco-epidemic-2019.
16. Prochaska JO, Di Clemente CC. Stages and processes of self-change of smoking: toward an integrative model of change. J Consulting Clin Psychol. 1983;51:390-5. doi: 10.1037//0022-006x.51.3.390

Vaccination against human papilloma virus in a Northeastern Italian area

Francesca Valent, Laura Deroma and Giulia Degani

SOC Igiene e Sanità Pubblica, Azienda Sanitaria Universitaria Friuli Centrale, Udine, Italy

Abstract

Objectives. Vaccination against human papilloma virus (HPV) in adolescents and persons at increased risk of infection and related consequences is an effective strategy to prevent genital cancers. The objective of this study was to assess vaccination activity and coverages in a Northeastern Italian area.

Methods. Anonymous data from various health administrative databases of the Italian 530,000-inhabitant Health Authority "Azienda Sanitaria Universitaria Friuli Centrale" were deterministically linked at the individual level through an anonymous stochastic key. Doses of HPV vaccine administered by year and coverages in different birth cohorts were calculated. Vaccinations of women treated for a CIN2+ lesion were also identified.

Results. The number of doses administered by year followed the evolution of national and regional laws. A steep drop was observed in 2020 and 2021 in both males and females (from 6,907 in 2019 to 5,027 in 2020 in males and from 6,989 in 2019 to 4,348 in 2020 in females). Coverages in adolescents were variable across Vaccination Services located in different sub-areas (complete cycle coverage in the 2008 cohort ranged from <40% in some Districts to >70% in others). Vaccination doses administered in adult women have increased almost steadily since 2018. One third of women treated for a CIN2+ were vaccinated.

Conclusions. In this area, efforts must be done to catch-up with doses missed during the pandemic and to overcome differences among different sub-areas.

INTRODUCTION

Human papilloma virus (HPV) is the most common sexually transmitted disease. Transmission may occur through either genital or skin contact. This infection is considered responsible for almost all cervical cancers and for a part of cancers of the vagina, vulva, penis, anus, rectus and oropharynx [1, 2].

More than 200 HPV strains exist. Of those that are sexually transmitted, some do not usually cause any disease and are defined as low risk; others, at high risk, have an effect on cancer incidence (for example, types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68). In particular, HPV16 e HPV18 are responsible for 66% of cervical cancers [3].

Since 2006, various vaccines against HPV have been approved in the European Union: a 2-valent vaccine (effective against types 16 and 18), a 4-valent one (types 6, 11, 16, 18), and, in 2015, a 9-valent one (types 6, 11, 16, 18, 31, 33, 45, 52, 58).

The Italian National Vaccine Prevention Plan (Piano Nazionale Prevenzione Vaccinale, PNPV) which is currently in force (PNPV 2017-19) sets a 95% coverage goal for HPV vaccination among boys and girls in their twelfth year of age [4], i.e., before there are expected to encounter the virus through sexual activity. HPV vaccination is effective in reducing the incidence of genital warts, pre-cancer lesions, malignant cervical cancer and related deaths [3]. All types of HPV vaccine (2-valent, 4-valent, and 9-valent) were shown to be cost-effective in Italy when used in adolescents [5, 6].

PNPV 2017-19 also recommends the HPV vaccination in all women (in co-payment, and according to regional guidelines) and suggests taking advantage of the first invitation to the cervical cancer screening program to catch the 25-year-olds. Finally, the vaccination is recommended in men having sex with men (MSM) as a specific risk group [4].

The US CDC also recommend vaccination in unvaccinated persons up to 26 years of age but not in those between 27 and 45, unless a careful medical assessment is carried out. In fact, in such age group the efficacy of the vaccine may be reduced because most people have already encountered the virus [7]. In persons >45, the vaccine is not considered cost-effective in the USA and is not covered by health insurance. Cost-effectiveness is actually dubious starting from 30 year of age [8]. In the UK, HPV vaccination is offered free of charge to MSM, trans women and men up to age 45 [9].

In accordance with the Italian PNPV, the Italian Friuli Venezia Giulia (FVG) Region, approximately

1,200,000 inhabitants, HPV vaccination is offered free of charge to adolescents (boys and girls) and to several risk groups: HIV subjects, patients undergoing immunomodulating or immunosuppressive therapy that may increase the risk of HPV infection (e.g., chronic inflammatory bowel disease, multiple sclerosis, etc.), MSM and, since 2018, women previously treated for CIN2+ lesions [10, 11]. The vaccine offered at the beginning of the HPV vaccination campaign, in 2008, was the 2-valent one; in 2011, the 4-valent vaccine became the mostly used one, whereas the 9-valent one was used almost universally in FVG≥ from 2018. The FVG Region started to recommend and offer the HPV vaccine free of charge to boys as early as 2015, from the birth cohort of 2004 [12], before the national recommendation was issued in 2017 [4].

Regarding women treated for CIN 2+, an Italian health technology assessment (HTA) was published in 2019 [13]. Such HTA was mostly based on the results of the SPERANZA project [14] and concluded that the HPV vaccine could decrease the risk of relapses in women undergoing surgery for HPV-related lesions. Thus, its use should be increased, although it is less cost-effective than if administered in pre-adolescence.

However, the efficacy or cost-effectiveness of the vaccination in some risk groups was questioned by recently published studies [15, 16].

The Vaccination Service of the Local Health Authority of Udine (Azienda Sanitaria Universitaria Friuli Centrale, ASUFC), FVG, Italy, provides all the vaccinations recommended in the PNPV and in the regional documents, for a catchment area of approximately 530,000 inhabitants, corresponding to the former province of Udine. The health emergency due to the COVID-19 pandemic, which lasted more than 2 years and officially ended in Italy on March 31st, 2022, caused interruptions or delays of normal preventive activities because of the restrictions imposed by the national and local health authorities on one side [17] and of the diversion of healthcare resources to COVID-19 responses on the other (e.g., contact tracing and COVID mass vaccination).

The objective of this study was to quantify the doses of HPV vaccine administered by the Vaccination Service of the ASUFC from the vaccine approval by the European Medical Agency to the end of 2022 (i.e., to examine the HPV-vaccine-related workload from the Vaccination Service perspective) and to describe the persons vaccinated against HPV and the vaccination coverage in target populations (i.e., to examine the public health performance, the temporal and the geographical variability from a population perspective). In addition, we aimed to assess the impact of the COVID pandemic on the HPV vaccination activity and to evaluate any differences in the coverage of adolescents across different subareas or pediatricians.

METHODS

This population-based retrospective cohort study used the Regional Health Information System (RHIS) of FVG as the source of information. The RHIS is a data warehouse including many anonymized health-related administrative databases which can be determin-

istically linked to one another through a stochastic key that is univocal at the person level in all databases. In detail, in this study, we used the list of all the potential healthcare beneficiaries, the residence database, the vaccination database, and the cervical cancer screening and cervical histology databases.

The study was focused on the subset of the FVG Region corresponding to the former administrative province of Udine.

Two different analyses were conducted. In the first, we extracted data on all the HPV vaccination doses administered from 2008 (when it started being offered in FVG) to 2022 (the most recent complete year with available data) and stratified them by calendar year, age, and sex of the vaccinated person. The purpose of this analysis was to describe the HPV vaccination-related activity in the ASUFC Vaccination Services, to highlight modifications and peculiarities in the age at administration, to show differences by sex, and to identify temporal fluctuations in the number of administered doses (Vaccination Service perspective).

The second analysis aimed to show HPV vaccination coverage among the population born between 1998 and 2009 and living in the ASUFC area as of December 31st, 2022. Only vaccinations administered to persons in the cohort were included in the analysis (population perspective). HPV vaccination cycles were considered complete if two doses were administered to adolescents <15 years of age or if three doses were administered to older young persons (i.e., 15-24 years of age). We calculated the coverage with complete cycles as well as coverage with at least one HPV vaccine dose (incomplete cycle). Coverages were expressed as percentages of the population as of December 31st, 2022 and were calculated by birth cohort, sex, District and primary care paediatrician. Although the HPV vaccination is a Vaccination Service's responsibility, we were interested to assess the variability across primary care paediatricians because they can influence coverages, either recommending or discouraging vaccination.

We also quantified women who started a vaccination cycle after receiving a diagnosis of CIN2+ lesion through the screening program and assessed whether their number changed in time.

All analyses were conducted using SAS Enterprise Guide v 7.15 (SAS Institute Inc., Cary, NC, USA).

The study was approved by the Ethics Committee of the Friuli Venezia Giulia Region on March 14th, 2023 (Parere CEUR-2023-Os-40). All the data in the data warehouse used in the analysis were anonymous, thus subjects could not be identified and no informed consent could be sent.

RESULTS

The Vaccination Services of the ASUFC administered 82,279 HPV vaccine doses to females ≥10 years of age from 2008 to 2022 and 25,724 doses to males ≥10 years of age from 2015 to 2022 (*Tables 1* and *2*). Approximately 1.5% of the overall doses administered to females and 3.3% of those administered to males regarded persons >45 years of age; the maximum age of persons being vaccinated was 78 in women and 84

Table 1
Human papilloma virus (HPV) vaccination doses administered by the Vaccination Services of ASUFC in the former Italian province of Udine, females

Age	Calendar year															Total
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	
10	73	1,386	672	442	589	425	186	168	41	13	18	20	2	2	12	4,049
11	1,011	3,655	2,378	2,721	3,037	3,022	2,677	1,991	1,856	992	990	1,027	384	141	163	26,045
12	37	975	711	805	1,073	798	813	598	540	1,164	1,902	1,515	801	435	1,554	13,721
13	17	109	173	160	273	170	176	133	93	258	191	500	350	643	1,922	5,168
14	396	2,220	1,900	1,343	285	186	220	109	103	238	163	113	47	221	903	8,447
15	2,287	2,916	2,234	2,611	941	157	175	106	81	282	188	102	54	38	113	12,285
16	90	686	350	275	332	111	80	73	44	249	210	140	64	43	83	2,830
17	76	214	103	81	98	108	46	39	41	180	148	89	61	41	53	1,378
18	34	74	42	46	72	61	16	22	19	61	91	34	33	27	36	668
19	16	27	22	13	31	29	10	6	6	32	52	41	27	18	30	360
20	8	14	12	16	14	15	16	6	15	17	28	42	25	21	33	282
21	8	9	10	9	26	19	12	7	5	23	31	49	13	19	20	260
22	7	5	6	10	13	10	13	5	8	7	41	57	28	15	45	270
23	3	7	7	7	13	11	21	17	10	14	46	57	32	17	38	300
24	8	5	4	5	13	5	11	9	9	34	46	69	57	48	45	368
25	3	10	2	11	10	19	20	37	19	44	71	48	46	33	60	433
26	6	2	2	3	5	9	15	29	32	33	51	50	33	37	26	333
27	1	0	0	3	4	13	11	18	23	14	36	62	34	23	21	263
28	0	0	1	1	3	3	9	18	18	21	40	75	62	32	29	312
29	0	3	0	3	2	1	8	16	9	11	31	58	66	43	40	291
30	0	4	1	2	1	4	3	9	9	10	23	33	47	45	64	255
31	0	1	1	0	5	1	7	4	15	10	29	35	49	33	52	242
32	0	0	0	0	3	1	3	10	1	6	21	41	29	38	60	213
33	0	0	0	0	1	5	5	5	10	10	25	36	40	26	38	201
34	0	0	0	2	5	5	2	15	10	7	31	42	36	22	45	222
35	2	1	0	0	4	1	0	7	11	7	33	35	40	27	35	203
36	0	0	0	0	2	2	1	7	9	6	27	19	35	33	34	175
37	0	1	0	0	2	3	2	4	4	14	33	39	26	32	41	201
38	0	0	0	0	0	0	1	4	11	10	11	37	36	33	39	182
39	0	0	0	2	2	0	0	2	6	12	27	36	36	18	52	193
40	0	0	0	0	1	1	3	6	9	8	20	36	36	21	29	170
41	0	0	0	0	2	0	0	0	3	4	18	37	24	36	26	150
42	0	0	0	0	1	0	2	5	5	8	14	32	31	14	41	153
43	0	0	0	0	0	6	5	10	6	9	14	24	26	13	25	138
44	0	0	0	0	2	1	1	2	2	9	16	16	28	24	32	133
45	0	0	0	1	0	5	1	3	0	4	15	33	29	23	35	149
>45	0	0	0	1	0	0	1	12	18	40	119	206	240	235	364	1,236
Total	**6,091**	**14,333**	**10,641**	**10,584**	**8,877**	**7,220**	**6,586**	**5,527**	**5,117**	**5,878**	**6,868**	**6,904**	**5,027**	**4,591**	**8,260**	**82,279**

ASUFC: Azienda Sanitaria Universitaria Friuli Centrale.

in men. In the first years, the maximum number of doses were administered to 11-year-olds; however, progressively more and more doses were administered to 12-year-olds, and since 2017 the maximum number of doses have been administered at age 12.

In 2020 and 2021 there was a sharp decrease in HPV vaccination activity, as shown by the number of admin-istered doses in females (from 6,904 in 2019 to 5,027 in 2020 and 4,591 in 2021), and even more in males (from 6,989 in 2019 to 4,384 in 2020 and 3,812 in 2021). Surprisingly, vaccinations in women >45 were not reduced during the pandemic.

From 2015 to 2022, 651 women started their HPV vaccination cycle after a diagnosis of CIN2, CIN3 or

Table 2
Human papilloma virus (HPV) vaccination doses administered by the Vaccination Services of ASUFC in the former Italian province of Udine, males

Age	Calendar year								Total
	2015	2016	2017	2018	2019	2020	2021	2022	
10	54	39	10	19	19	2	1	12	156
11	578	1,423	922	991	960	350	128	150	5,502
12	7	666	1,227	1,865	1,526	681	398	1,477	7,852
13	13	58	357	226	510	364	596	1,777	3,903
14	5	41	197	179	84	41	221	893	1,665
15	5	39	146	304	246	39	21	99	899
16	5	23	130	306	409	118	37	79	1,107
17	1	21	68	196	198	117	39	60	700
18	0	5	42	111	110	44	43	30	385
19	0	3	14	53	74	34	21	33	232
20	1	4	5	41	49	31	19	15	165
21	0	2	16	47	41	39	18	41	204
22	2	0	13	38	60	29	16	23	182
23	0	1	7	31	70	44	18	22	197
24	2	3	21	47	65	39	27	23	227
25	3	7	13	35	43	42	21	27	192
26	0	10	9	21	25	16	18	16	118
27	2	1	4	19	19	9	10	10	74
28	3	6	1	17	14	20	4	15	82
29	1	3	2	6	17	12	7	14	63
30	0	2	6	15	10	8	5	12	58
31	0	3	7	17	13	11	5	11	67
32	2	1	6	18	13	13	2	28	83
33	3	5	6	21	17	6	5	19	82
34	0	2	3	16	15	4	7	7	54
35	0	1	13	12	12	10	9	4	61
36	0	5	7	21	7	7	2	12	61
37	0	2	4	12	13	3	7	7	48
38	2	1	6	7	19	10	8	8	64
39	0	4	1	16	15	3	2	7	48
40	2	3	4	8	21	5	1	3	48
41	2	1	14	17	10	18	5	7	74
42	1	2	6	18	12	13	9	2	65
43	1	2	3	17	14	7	4	12	60
44	0	3	12	10	21	18	5	8	77
45	0	0	6	18	15	8	5	6	58
>45	3	35	112	226	204	113	47	100	842
Total	**2,713**	**4,443**	**5,437**	**7,039**	**6,989**	**4,348**	**3,812**	**7,091**	**25,755**

ASUFC: Azienda Sanitaria Universitaria Friuli Centrale.

infiltrating cancer and their median age at administration of the first dose of vaccine was 40 years (25th percentile: 33; 75th percentile: 48). Median time from diagnosis to administration of the first vaccine dose was 199 days (25th percentile: 83; 75th percentile: 595). Of 304 women with a diagnosis of CIN2+ in 2022, 102 started a vaccination cycle after being treated (33.5%):

28 out of 75 women with a CIN2 diagnosis (37.3%), 73 out of 196 with a CIN3 diagnosis (37.2%), and 1 out of 33 with infiltrating cancer (3.0%).

Figure 1 shows the increase in time in the number of cycles started in women >45, among whom the cost-effective of the vaccine has not been proved. The number increased steeply from 2018, when the vaccine was
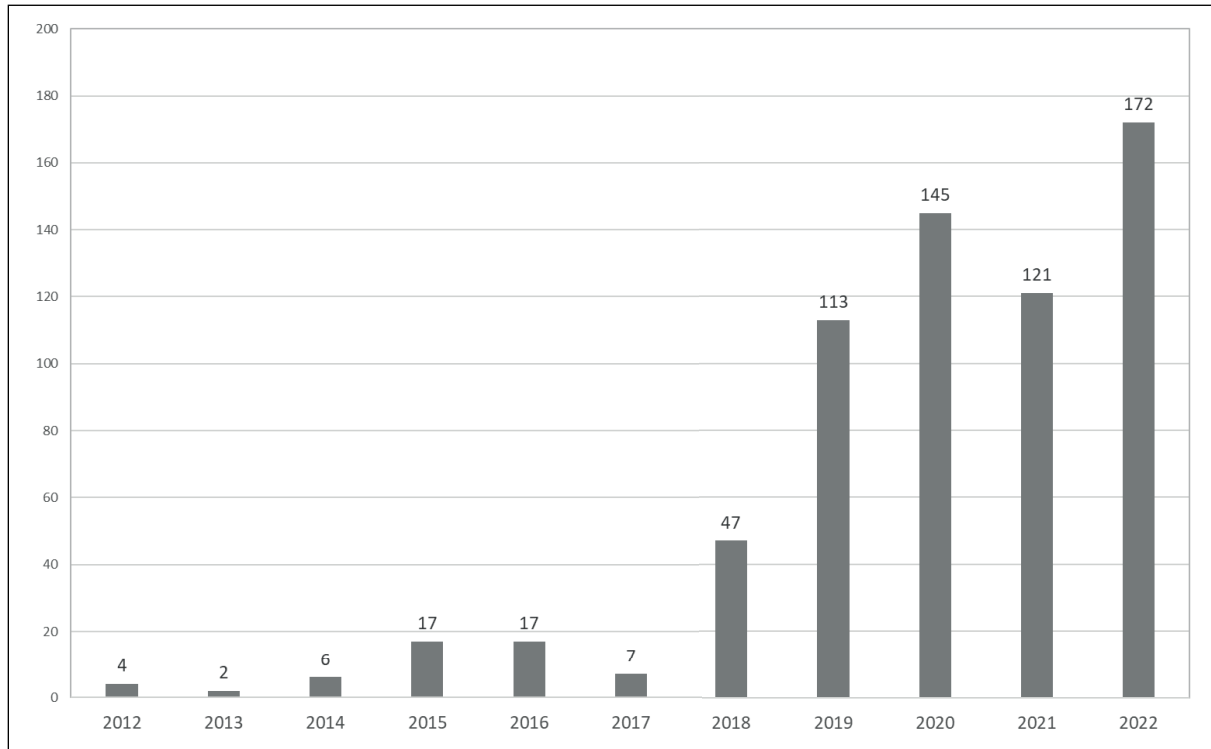
Figure 1
Number of human papilloma virus (HPV) vaccination cycles started among women >45 years of age by year, former province of Udine, Italy.

offered free of charge in the FVG Region, and only slightly decreased in 2021 during the COVID pandemic (on the other hand, the number of CIN2+ diagnoses did not show an increasing pattern: 280 in 2018, 278 in 2019, 270 in 2020, 271 in 2021, and 304 in 2022). Of 479 HPV vaccine cycles started before 2022 in women >45, which were expected to be complete at the end of 2022, only 56 (11.7%) were not.

Table 3 shows vaccination coverage among young females and males born between 1988 and 2009 and living in the ASUFC catchment area as of December 31st, 2022. Relatively good coverages with complete vaccination cycles were obtained starting with the birth cohort of 1993 (≥60% up to the cohort of 2007, with a peak of 72% in the cohorts of 2005 and 2006). Among males, coverages started to increase very slowly up to the cohort of 2004, in which 56% of males were vaccinated with complete cycle, and reached a peak of 67% in the cohort of 2006. The coverage with incomplete cycles was always higher, indicating that, in every cohort, a part of the persons interrupted the cycle. Coverages were slightly decreased in boys and girls from the cohorts of 2008, who were expected to be fully vaccinated during the pandemic, and 2009, who missed the second dose and were planned to be caught up in 2023 for cycle completion.

Figure 2 shows the differences across sub-areas (Health Districts A-I) in the coverage with complete cycles for the 2006 cohort, registering the highest values ever in the ASUFC area, the cohort 2007, which should have started the cycle before the pandemic and concluded it before or during the pandemic, and the 2008 cohort, which should have received the complete cycle during the pandemic. In the 2006 cohort, the differences among Districts were slight, although becoming much more evident in the two younger cohorts, indicating a differential capacity of maintaining or recovering the activities during and after the pandemic. If we consider coverage with ≥1 dose, however, differences among Districts are smaller (2006 cohort: 64.6%-89.2%; 2007 cohort: 63.4%-82.4%; 2008 cohort: 44.8%-82.0%).

High variability was also observed in coverage across paediatricians; the full-cycle coverage for the 2008 cohort, for example, ranges between 30.0% and 81.6% (data not shown).

DISCUSSION

This analysis shows that in a few years after the approval of the HPV vaccine by EMA, vaccination activity increased dramatically in this Northeastern Italian area, with coverages among adolescents and young adults reaching higher and higher values from the oldest cohorts, vaccinated in the initial period, and the younger ones. In this area, complete cycle coverages were similar to those reported for the larger FVG Region at the end of 2021, and for most cohorts higher than Italian values [18]. Our coverages are also consistent with those reported in a US survey [19], and even higher in some female cohorts.

Our data show very clearly that vaccination in boys started with a delay of several years after girls started to be vaccinated, consistently with the evolution of the im-

Table 3

Coverage with complete human papilloma virus (HPV) vaccination cycles and with ≥1 HPV vaccine dose in the population of the ASUFC catchment area born from 1988 to 2009 and living in the former Italian province of Udine as of December 31st, 2022, by birth cohort and sex

Birth cohort	Females			Males		
	Population Dec 31, 2022	Coverage complete cycle	Coverage at least 1 dose	Population Dec 31, 2022	Coverage complete cycle	Coverage at least 1 dose
1988	2,607	3.2%	4.0%	2,643	0.3%	0.4%
1989	2,555	3.1%	3.9%	2,584	0.3%	0.7%
1990	2,474	5.1%	6.7%	2,583	0.9%	1.2%
1991	2,460	6.0%	7.1%	2,536	0.4%	0.7%
1992	2,466	8.6%	9.9%	2,568	0.9%	1.4%
1993	2,152	60.2%	62.6%	2,445	0.9%	1.5%
1994	2,226	61.1%	62.8%	2,424	1.4%	1.9%
1995	2,287	61.7%	64.0%	2,479	1.9%	2.4%
1996	2,210	63.8%	65.9%	2,512	2.1%	2.9%
1997	2,231	68.1%	70.5%	2,479	1.5%	2.5%
1998	2,247	70.1%	72.4%	2,544	2.1%	3.1%
1999	2,195	69.7%	71.6%	2,449	2.7%	3.9%
2000	2,314	71.3%	73.9%	2,549	4.6%	6.6%
2001	2,222	70.7%	72.5%	2,428	7.7%	9.8%
2002	2,270	70.0%	72.7%	2,423	10.9%	14.0%
2003	2,224	70.5%	74.2%	2,601	13.0%	19.5%
2004	2,278	71.2%	75.9%	2,435	55.9%	59.9%
2005	2,241	72.2%	76.8%	2,411	65.1%	69.1%
2006	2,255	72.4%	77.6%	2,394	67.3%	71.9%
2007	2,267	67.1%	75.6%	2,322	63.0%	72.8%
2008	2,221	59.3%	71.6%	2,276	53.0%	64.8%
2009	2,304	43.4%	67.2%	2,312	39.4%	61.9%

ASUFC: Azienda Sanitaria Universitaria Friuli Centrale.

munization schedules of the FVG Region [12], which anticipated the national schedule extending to boys the recommendation of HPV vaccination [3]. However, soon since 2015, coverages approached those obtained among girls. In 2019, the number of HPV doses administered was virtually identical among males and females, but the impact of the COVID pandemic on HPV vaccination was much more evident among males (from almost 7,000 doses in 2019 to less than 4,500 in 2020 and less than 4,000 in 2021) than among females (from almost 7,000 in 2019 to 5,000 in 2020 and approximately 4,600 in 2021). The impact of the COVID pandemic on HPV vaccination in boys, as well as the need to catch up on adolescents that missed doses during the pandemic, were also highlighted in Germany [20]. In 2022 the activity returned to pre-pandemic levels in males (7,000 doses) and even higher in females (more than 8,000 doses), indicating the catch-up implementation in the ASUFC area was effective.

Interestingly, more than 3% of all doses administered in 2022 regarded persons >45 years of age.

Vaccinations in persons >45 decreased during the

COVID pandemic among men, but not among women. In fact, adult women who were vaccinated likely belonged to the group that was diagnosed and treated for a CIN2+ cervical lesion (more than 600 were diagnosed thanks to the organized regional screening program as well as in other circumstances): although screening activity was also reduced during the pandemic [21], the program was completely interrupted in Friuli Venezia Giulia only for few months, so CIN2+ lesions continued to be detected. On the other hand, adult men requesting HPV vaccination were more likely to be MSM or other groups with high-risk behaviours, among whom the need for vaccination could have been reduced during the pandemic because of the restriction imposed by Governments regarding travelling and social events [22].

Our data also show that even within a relatively small study area (approximately 530,000 inhabitants on 5,000 km^2), high variability may exist in vaccination coverage and in the ability to catch up on boys and girls with missed doses. Baseline coverage differences may depend on organizational differences in the local
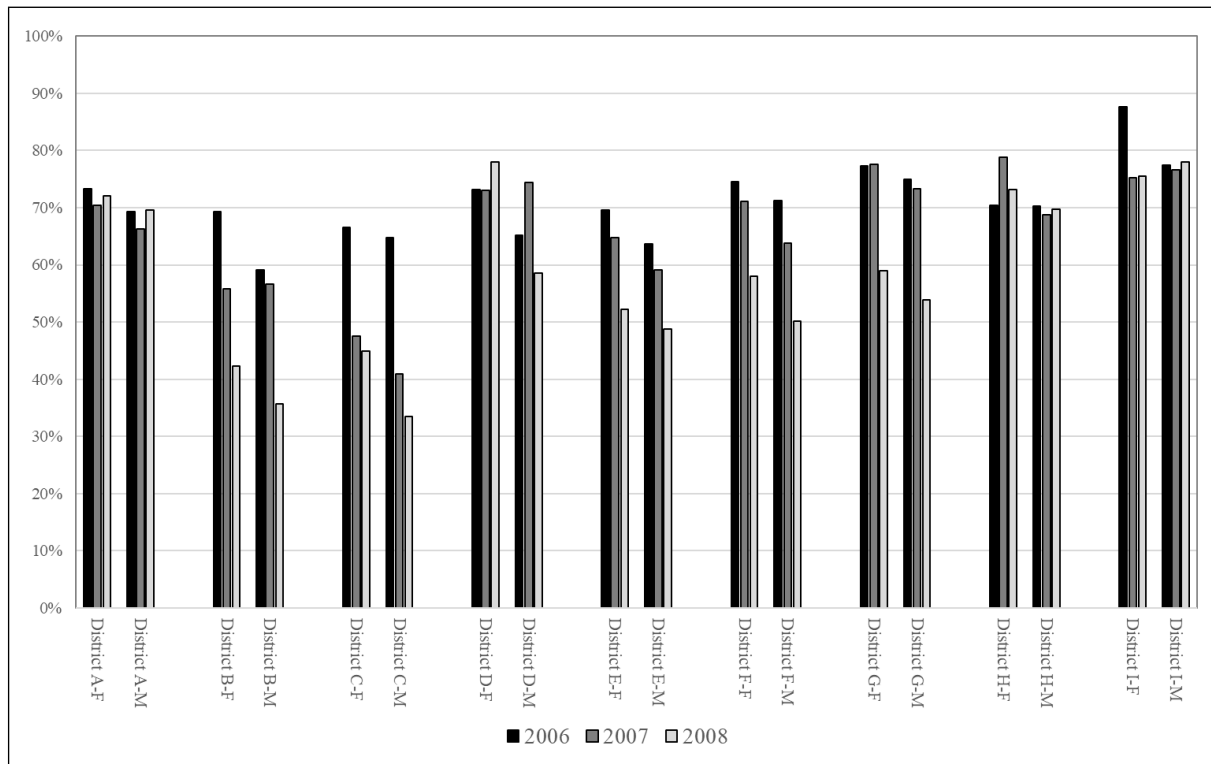
Figure 2
Coverage with complete human papilloma virus (HPV) vaccination cycles among female and male adolescents born in 2006, 2007, and 2009 as of December 31st, 2022 in 9 Health Districts of the Italian former province of Udine.

Vaccination Services, the size of their target population, the persuasive ability of paediatricians and general practitioners, and cultural differences, including the population's attitude towards vaccination. The local Vaccination Services of the different sub-area also showed different abilities to catch up on boys and girls with missed vaccine doses. Organizational issues may explain this difference (target population, number of available vaccinal ambulatories, human resources). As an alternative, the staff of the different Services may have been differently involved in the COVID-related activities management. Such activities regarded virtually all the healthcare professionals of all sub-areas in the first months of the pandemic but, during the last months, were gradually centralized in specific areas, where the return to normality was postponed. Finally, during the COVID pandemic, a different resource allocation characterized the various Services, with only some of them having to interrupt adult vaccinations.

Regardless of the reasons for the delay in HPV vaccinations, in the Health Districts with the lowest coverages, we must actively call on the telephone the boys and girls of the 2009 cohort with missed doses and invite them to special massive catch-up vaccination sessions. In doing so, we must pay attention to timing since we ideally want to administer second doses to teens before they turn 15. Afterwards, 3 doses are needed to complete the cycle, despite the most recent World Health Organization recommendations including a two-dose schedule, and even an off-label one-dose schedule, for girls and women from 9 to 20 years [23]. In fact, according to current evidence, a single dose shows comparable efficacy and duration of protection as two doses. As a matter of fact, coverages with ≥1 dose were very high in all adolescent cohorts and differences across Health Districts were less evident, suggesting that single-dose coverage is easier to obtain and allows for equity. Thus, the Italian Ministry of Health and Regions should consider the tradeoff of switching to the single-dose schedule in adolescents and to the two-dose schedule in the age group 15-20. Furthermore, a two-dose schedule in women >21 may also increase vaccine take-up in adulthood, especially among persons to whom the vaccine is not offered free of charge.

Vaccination after treatment for cervical lesions only occurs in one-third of women. Thus, efforts are needed to inform women with a CIN2+ diagnosis of the potential benefits of being vaccinated and to schedule an appointment to start the cycle. For this aim, a close collaboration with gynaecologists is crucial.

The pandemic slowed down most of our routine schedules. Nonetheless, it also taught us to be quicker and more flexible, manage larger vaccination sessions, and pay more attention to communication than before. Thus, we are confident we will successfully catch up on most missed doses and return to pre-pandemic HPV vaccine coverage during 2023. For the most effective prevention of cervical cancer, we will also work to strengthen complementary and synergic public health programs such as educational interventions and cervical screening, as recommended by the World Health Organization [23].

ORIGINAL ARTICLES AND REVIEWS

REFERENCES

1. Centers of Disease Control and Prevention. HPV and cancer. Available from: https://www.cdc.gov/cancer/hpv/statistics/cases.htm.
2. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. A review of human carcinogens. Part B: Biological agents. Lyon: IARC; 2009.
3. Centers for Disease Control and Prevention; Hall E., Wodi AP, Hamborsky J, et al. (Eds). Epidemiology and prevention of vaccine-preventable diseases. 14th ed. Washington, DC: Public Health Foundation; 2021.
4. Ministero della Salute. Piano Nazionale Prevenzione Vaccinale 2017-19. Available from: https://www.salute.gov.it/imgs/C_17_pubblicazioni_2571_allegato.pdf.
5. La Torre G, de Waure C, Chiaradia G, Mannocci A, Capri S, Ricciardi W. The health technology assessment of bivalent HPV vaccine cervarix in Italy. Vaccine. 2010;28(19):3379-84. doi: 10.1016/j.vaccine.2010.02.080
6. Mennini FS, Bonanni P, Bianic F, de Waure C, Baio G, Plazzotta G, Uhart M, Rinaldi A, Largeron N. Cost-effectiveness analysis of the nine-valent HPV vaccine in Italy. Cost Eff Resour Alloc. 2017;15:11. doi: 10.1186/s12962-017-0073-8
7. Meites E, Szilagyi PG, Chesson HW, Unger ER, Romero JR, Markowitz LE. Human Papillomavirus Vaccination for Adults: Updated recommendations of the Advisory Committee on Immunization Practices MMWR. 2019;68(32);698-702.
8. Kim JJ, Simms KT, Killen J, Smith MA, Burger EA, Sy S, Regan C, Canfell K. Human papillomavirus vaccination for adults aged 30 to 45 years in the United States: A cost-effectiveness analysis. PLoS Med. 2021;18(3):e1003534. doi: 10.1371/journal.pmed.1003534
9. NHS. HPV vaccine overview. Available from: https://www.nhs.uk/conditions/vaccinations/hpv-human-papillomavirus-vaccine/.
10. Regione Autonoma Friuli Venezia Giulia. Aggiornamento dell'offerta vaccinale per adulti, anziani e soggetti a rischio nella Regione Friuli Venezia Giulia - 2019. Allegato alla Delibera della Giunta Regionale n. 2425 del 21 dicembre 2018. Available from: https://www.regione.fvg.it/rafvg/export/sites/default/RAFVG/salute-sociale/promozione-salute-prevenzione/FOGLIA5/allegati/Allegato_2_alla_Delibera_2425-2018.pdf.
11. Regione Autonoma Friuli Venezia Giulia. Aggiornamento dell'offerta vaccinale per infanzia e adolescenza nella Regione Friuli Venezia Giulia. Allegato alla Delibera n. 1919 del 16 dicembre 2022. Available from: http://mtom.regione.fvg.it/storage//2022_1919/Allegato%201%20alla%20Delibera%201919-2022.pdf.
12. Regione Autonoma Friuli Venezia Giulia. Offerta vaccinale regionale: Infanzia e adolescenza. Allegato alla Delibera n. 2535 del 18 dicembre 2014. Available from: http://mtom.regione.fvg.it/storage//2014_2535/Allegato%201%20alla%20Delibera%202535-2014.pdf.
13. Basile M, Bonanni P, Calabrò GE, Carini E, Cicchetti A, Conversano M, De Vincenzo R, Favaretti C, Ghelardi A, Tafuri S. Report di approfondimento e valutazione, con metodologia HTA (Health Technology Assessment), della vaccinazione anti-HPV nelle donne trattate per lesioni HPV-correlate. QIJPH. 2019;8(7):1-76. Available from: https://www.ijph.it/hta-vaccinazione-antiHPV.
14. Ghelardi A, Parazzini F, Martella F, Pieralli A, Bay P, Tonetti A, Svelato A, Bertacca G, Lombardi S, Joura EA. SPERANZA project: HPV vaccination after treatment for CIN2. Gynecol Oncol. 2018;151(2):229-34. doi: 10.1016/j.ygyno.2018.08.033
15. Eriksen DO, Jensen PT, Schroll JB, Hammer A. Human papillomavirus vaccination in women undergoing excisional treatment for cervical intraepithelial neoplasia and subsequent risk of recurrence: A systematic review and meta-analysis. Acta Obstet Gynecol Scand. 2022;101(6):597-607. doi: 10.1111/aogs.14359
16. Vargas Parada C, Lennert Veerman J. Cost-effectiveness study of HPV vaccination as a primary prevention strategy for anal cancer in HIV-positive men in Chile. Value Health Reg Issues. 2016;11:17-23. doi: 10.1016/j.vhri.2015.12.002
17. Ministero della Salute. Covid-19: Norme, circolari e ordinanze. Available from: https://www.salute.gov.it/portale/nuovocoronavirus/archivioNormativaNuovoCoronavirus.jsp.
18. Ministero della Salute. Direzione generale della prevenzione sanitaria. Ufficio 5 Prevenzione delle malattie trasmissibili e profilassi internazionale. Coperture vaccinali al 31.12.2021 per HPV (aggiornamento ottobre 2022). Available from: https://www.salute.gov.it/imgs/C_17_tavole_27_1_7_file.pdf.
19. Pingali C, Yankey D, Elam-Evans LD, Markowitz LE, Valier MR, Fredua B, Crowe SJ, Stokley S, Singleton JA. National Vaccination Coverage Among Adolescents Aged 13-17 years - National Immunization Survey-Teen, United States, 2021. MMWR Morb Mortal Wkly Rep. 2022;71(35):1101-8. doi: 10.15585/mmwr.mm7135a1
20. Wähner C, Hübner J, Meisel D, Schelling J, Zingel R, Mihm S, Wölle R, Reuschenbach M. Uptake of HPV vaccination among boys after the introduction of gender-neutral HPV vaccination in Germany before and during the COVID-19 pandemic. Infection. 2023;10:1-12. doi: 10.1007/s15010-023-01978-0
21. Osservatorio Nazionale Screening. Rapporto sui ritardi accumulati dai programmi di screening italiani in seguito alla pandemia da Covid 19. Terzo rapporto aggiornato al 31 Dicembre 2020. Available from: https://www.osservatorionazionalescreening.it/sites/default/files/allegati/Rapporto%20ripartenza-12_20.pdf.
22. Ministero della Salute. Covid-19 - Situazione in Italia. Available from: https://www.salute.gov.it/portale/nuovo-coronavirus/dettaglioContenutiNuovoCoronavirus.jsp?area=nuovoCoronavirus&id=5351&lingua=italiano&menu=vuoto.
23. World Health Organization. Human papillomavirus vaccines: WHO position paper (2022 update). Weekly epidemiological record. 2022;50:645-72.

Sarcopenic obesity and hypertension in elderly patients: a narrative review of pathophysiology and management strategies

Mihaela Jurdana[1] and Lovro Žiberna[2]

[1]*Faculty of Health Sciences, University of Primorska, Izola, Slovenia*
[2]*Faculty of Pharmacy, University of Ljubljana, Ljubljana, Slovenia*

Abstract
Introduction. Sarcopenic obesity and hypertension are a public health problem that is increasing worldwide due to the progressive aging of the population and the increasing prevalence of obesity and physical inactivity. Sarcopenic obesity is characterized by the simultaneous presence of sarcopenia (loss of muscle mass) and adiposity (increase in fat mass). Because symptoms are not specific, sarcopenic obesity remains largely undiagnosed. This review explores the latest research on sarcopenic obesity and its association with hypertension, with a focus on arterial stiffness.
Methods. A comprehensive narrative review was conducted by systematically searching PubMed and Scopus databases for relevant scientific literature.
Results. Sarcopenic obesity and hypertension are closely linked, sharing common factors such as inflammation, insulin resistance, and oxidative stress, with arterial stiffness playing a crucial role.
Discussion. Given the lack of specific symptoms for sarcopenic obesity, early diagnosis and management are crucial. Treatment strategies should prioritize weight loss, adequate protein intake, and regular physical activity. Further investigation is warranted for pharmacological interventions.
Conclusion. Sarcopenic obesity and hypertension present significant challenges to global public health. Addressing arterial stiffness is paramount in managing these conditions effectively. Lifestyle modifications, including weight management and physical activity, remain central to the treatment of sarcopenic obesity, while additional research is needed to explore potential pharmacological options.

INTRODUCTION

Sarcopenic obesity is an emerging public health problem related to the accelerated global ageing of the world population, which has increased rapidly over the past three decades [1]. Baumgartner was the first to propose the term sarcopenic obesity [2] as a clinical and functional condition characterized by the coexistence of sarcopenia (low skeletal muscle mass and function) and obesity (excessive fat mass). Sarcopenic obesity is considered a unique clinical condition, distinct from obesity and sarcopenia alone.

Loss of skeletal muscle mass and function usually occurs with advancing age and is accompanied by a relative or absolute increase in body fat. This process favors the development and occurrence of sarcopenic obesity and leads to many negative clinical complications such as frailty, falls, disability, immobility, fractures, cardiometabolic and respiratory diseases, cancer, and increased mortality [3-5]. Furthermore, obesity, particularly abdominal obesity, can independently lead to loss of muscle mass and function due to the negative effects of oxidative stress, inflammation, insulin resistance, and the presence of chronic non-communicable diseases, all of which negatively impact muscle mass [6].

The decline in physical activity and loss of skeletal muscle mass and function that accompanies ageing is well documented and appears to occur even in relatively weight-stable healthy individuals. Physical inactivity is both a major cause and consequence of sarcopenia and obesity, which can lead to sarcopenic obesity that can be exacerbated by concomitant diseases [7]. Importantly, therapeutic weight loss targeting excess fat

Address for correspondence: Mihaela Jurdana, Faculty of Health Sciences, University of Primorska, Izola, Polje 42, SI-6310 Izola, Slovenia. E-mail: mihaela.jurdana@fvz.upr.si.

inevitably leads to greater loss of skeletal muscle mass, which may be more pronounced in individuals with predisposing catabolic conditions (ageing, chronic diseases) or with persistent inadequate diet (especially low protein intake) and weight fluctuations [8, 9].

However, the lack of universally accepted diagnostic criteria for sarcopenic obesity affects patient identification and has strong negative implications for prevention and treatment strategies for sarcopenic obesity. The diagnosis requires the presence of both altered (i.) skeletal muscle function and (ii.) body composition [7].

Assessment of skeletal muscle functional parameters is critical to treatment protocols for sarcopenic obesity because it affects patients' quality of life. Muscle strength (e.g., handgrip strength, HGS) and knee extensor strength (adjusted for body mass in the population for which data are available) should be the functional parameters of choice for the diagnosis of sarcopenic obesity [10, 11]. In addition, the chair-stand test (5 times sit-stand; 30 s chair-stand test) is used to measure physical performance and muscle strength. When low skeletal muscle function is detected, the diagnosis is followed up by body composition determination.

Various definitional and diagnostic criteria for body composition have been used to estimate the prevalence of sarcopenic obesity. Several studies have detected sarcopenic obesity using dual-energy x-ray absorptiometry (DEXA), which is appropriate for laboratory practice but requires expensive equipment that may not always be available [4]. In clinical practice, sarcopenic obesity is defined by higher fat mass (FM) relative to fat-free mass (FFM). The ratio of FM to FFM (FM /FFM) >0.8 has been established as an index of sarcopenic obesity [12]. FM and FFM are determined clinically using bioelectrical impedance analysis (BIA), a technique widely used in clinical practice [5, 12-17].

Our study aims are to investigate the relationship between sarcopenic obesity and hypertension and explore potential therapeutic strategies. This is motivated by the known association between sarcopenic obesity and hypertension and the higher prevalence of sarcopenic obesity in hypertensive patients.
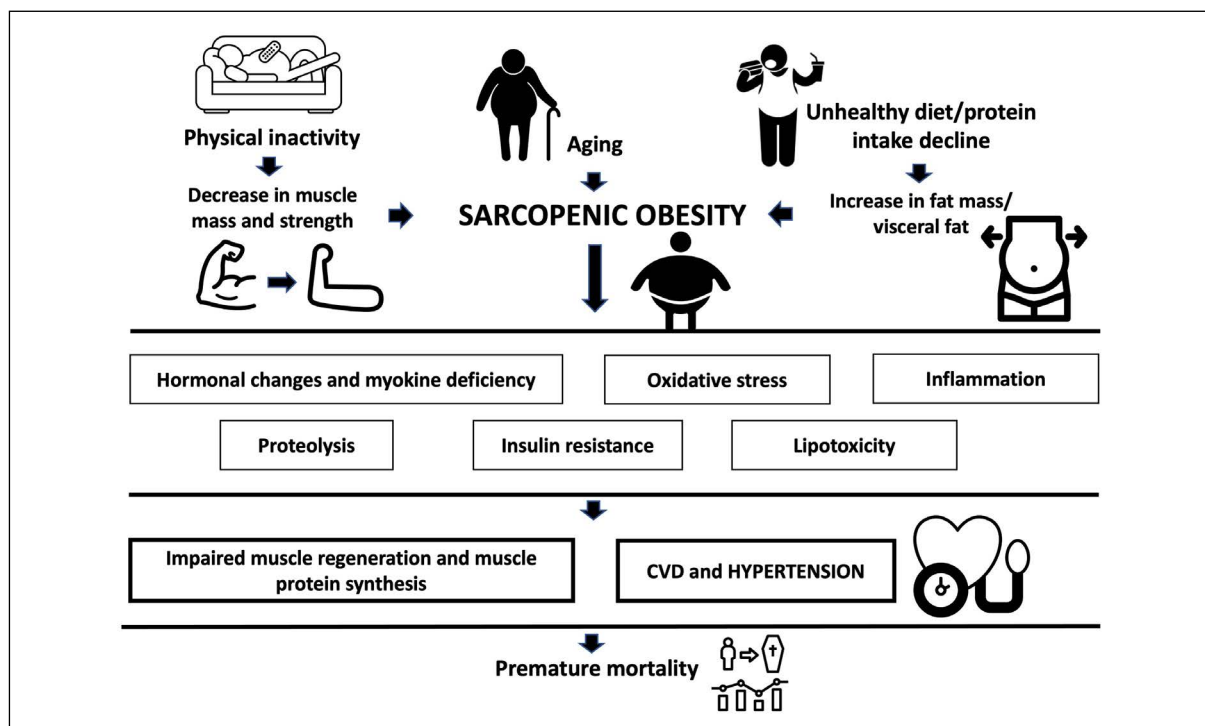
PATHOPHYSIOLOGICAL PATHWAY OF SARCOPENIC OBESITY

Several mechanisms underlie age-related muscle loss, including hormonal and neuronal changes, poor nutrition, physical inactivity, inflammation, and chronic diseases [18]. In addition, the quality of muscle mass decreases due to a decrease in fiber size and the number of fast-type II muscle fibers, a decrease in muscle protein synthesis, and mitochondrial function [4]. The increasing prevalence of obesity in the elderly independently leads to a loss of muscle mass and function, as adipose tissue negatively affects skeletal muscle mass [4].

In a large sample of men and women, the degree of obesity and waist circumference has been shown to directly influence inflammation, which in turn contributes to the development of sarcopenia [19]. Catabolic pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor α (TNF-α), and hormones

such as leptin and resistin are preferentially released from abdominal adipose tissue and can stimulate protein catabolism in skeletal muscle, which promotes the occurrence of sarcopenic obesity [16]. In addition, muscle unloading and physical inactivity in older adults increase abdominal fat accumulation and associated systemic inflammation, oxidative stress, and consequently muscle wasting [16, 20].

On the other hand, sarcopenia can directly increase fat accumulation by decreasing overall energy expenditure. Obesity and sarcopenia can therefore synergistically reinforce each other, with a vicious cycle of fat accumulation and loss of skeletal muscle mass leading to immobility, independence, and disability [2, 3, 7]. In addition, further increases in hormone levels of leptin, which are at least partially dependent on age-related increases in fat mass, may lead to leptin resistance and consequently to a reduction in fatty acid oxidation in muscle. Subsequently, fat deposition in skeletal muscle and other organs such as the heart and liver contributes to loss of muscle quality in obese older adults and negatively affects sarcopenia [4, 21]. Deposition of intramuscular fat promotes lipotoxicity and inflammation, leading to impaired muscle recovery, which in turn can promote fibrosis, and thus insulin resistance.

Contractile skeletal muscle produces and releases anti-inflammatory myokines and plays an important role in counteracting pro-inflammatory effects [22]. Anti-inflammatory myokines, including muscle-derived interleukin 6 (IL-6), interleukin 8 (IL-8), interleukin 15 (IL-15), and interleukin-1 receptor antagonist (IL-1ra), act as antagonists of the overall pro-inflammatory burden [23]. Muscle IL-6 was the first myokine identified and the most-studied myokine exerting extensive anti-inflammatory effects [24]. Interestingly, IL-6 from adipose tissue has a pro-inflammatory effect, whereas IL-6 from skeletal muscle has an anti-inflammatory effect [25]. Therefore, the release of IL -6 during physical activity leads to an increase in the anti-inflammatory IL -1ra and IL-10. In most studies dealing with exercise, TNF-α does not change and is likely suppressed by muscle-derived IL-6, as shown by a modest decrease in TNF-α after exercise [21]. This confirms that the anti-inflammatory effects of regular exercise may protect against systemic inflammation [25]. Furthermore, intracellular fat deposition in skeletal muscle is characterized by a decrease in anti-inflammatory myokines (IL-15, IL-8, IL-6), leading to sarcopenia [18]. A vicious cycle between skeletal muscle loss and fat gain can lead to more sarcopenia and further weight gain. The negative clinical consequences of sarcopenic obesity are of paramount importance. A progressive increase in fat mass is a strong risk factor for poor health status and has significant implications for the development of hypertension and other cardio-metabolic risk factors [10, 6]. These risks may increase with additional loss of muscle mass [26]. Consequently, lower muscle mass has been repeatedly associated with cardiovascular risk factors, including arterial stiffness, suggesting the additive effects of low muscle mass on blood pressure [26]. Thus, sarcopenic obesity and hypertension share common etiologic mechanisms *(Figure 1)*.

Figure 1

Pathophysiological mechanisms and consequences of sarcopenic obesity.

Schematic biological pathways leading to sarcopenic obesity during ageing. Ageing is associated with physical inactivity and inadequate food intake. These changes contribute to age-related decreases in muscle mass and strength and increases in body fat, as well as unfavorable changes such as increased inflammation, oxidative stress, insulin resistance, and an imbalance of pro- and anti-inflammatory cytokines. In addition, this can impair skeletal muscle mass and function and lead to numerous adverse cardiometabolic effects and hypertension, which in turn contributes to poor health.

SARCOPENIC OBESITY AND HYPERTENSION

The interaction of skeletal muscle and adipose tissue has been found to play a key role in the regulation of blood pressure and the development of hypertension. Few studies have investigated and confirmed the association between sarcopenic obesity and hypertension, as the ratio of fat mass to fat-free mass is an important predictor of hypertension [26, 27]. In addition, low muscle mass has been directly associated with cardiovascular risk factors, including arterial stiffness [26, 28, 29], suggesting the effects of low muscle mass on blood pressure.

Sarcopenic obesity and its association with arterial stiffness suggest that individuals with lower muscle mass and higher fat mass in the general population are more likely to have higher blood pressure and sarcopenic obese individuals tend to consume higher amounts of antihypertensive drugs [30]. There was a significant difference in the prevalence of hypertension in older adults with sarcopenic obesity compared with individuals without sarcopenic obesity [31]. In women, a strong association was found between sarcopenic obesity and hypertension [32]. In postmenopausal women with sarcopenic obesity, hypertension was the most prevalent chronic morbidity [33]. These findings are consistent with other cross-sectional studies showing that individuals with sarcopenic obesity have higher cardio-metabolic risk [34].

The KNHANES series of cross-sectional studies by Park [26] found a 6.5-fold higher risk of hypertension in sarcopenic obese participants, who had higher systolic and diastolic blood pressure than participants with normal body composition. These results confirm the association between sarcopenic obesity and an increased risk of hypertension. In this study, the risk of hypertension associated with sarcopenic obesity was reduced by 30% after controlling for physical activity.

Several studies have previously reported the beneficial effects of physical activity on hypertension, with both systolic and diastolic blood pressure being reduced by 5-7 mmHg in people with hypertension [35]. This suggests that the pathway by which sarcopenic obesity affects hypertension is related in part to physical activity. On the other hand, it is also possible that physical inactivity leads to sarcopenic obesity, which in turn contributes to the risk of hypertension. One possible mechanism by which physical activity affects hypertensive patients is by increasing the quantity or quality of skeletal muscle.

In addition, abdominal obesity and sarcopenia negatively affect hypertension. The inflammatory status of older adults is associated with higher circulating levels of catabolic pro-inflammatory cytokines, even in the absence of chronic disease [36]. The previously described myokine concept suggests that the long-term anti-inflammatory effects of physical activity are mediated via

the effects of exercise leading to a reduction in visceral fat mass [21]. Interestingly, a negative correlation was found between plasma concentrations of muscle IL-15 and visceral fat mass [21]. IL-15 inhibits lipid accumulation in adipose tissue, supporting the idea that IL-15 is involved in reducing visceral fat mass and may play an important role in reducing inflammation. Therefore, physical activity and the resulting release of myokines provide the maintenance of fat stores, muscle mass, and metabolic homeostasis, as well as blood pressure [34, 37]. Based on these findings, abdominal obesity and sarcopenia might potentiate each other to induce hypertension.

TREATMENT STRATEGIES FOR LIFESTYLE MODIFICATIONS

Lifestyle interventions, including physical activity and caloric restriction, are the hallmark of treatment for sarcopenic obesity. Weight loss or physical activity alone has been reported to improve physical function. However, a combination of weight loss and physical activity was the more effective method for improving physical function and frailty [38].

PHYSICAL ACTIVITY

Physical activity is important to maintain skeletal muscle mass. In particular, aerobic exercise and resistance training are the most beneficial types of exercise to reduce fat mass and increase lean mass in overweight and obese individuals of all ages and genders [39]. Aerobic exercise, resistance training, and their combination have been shown to increase muscle protein synthesis in older adults despite age-related decreases in anabolic signaling [40]. In addition, aerobic activity and resistance training counteract inflammation and improve glucose metabolism, and insulin sensitivity, which may attenuate the progression of sarcopenic obesity [40, 41]. Aerobic activity decreases the negative effects of fat deposition in skeletal muscle and promotes lipolysis, leading to an increase in capillary density, which in turn stimulates mitochondrial production [41-45]. Importantly, 24 weeks of aerobic and resistance training in older women with sarcopenic obesity reduced carotid intima-media thickness and improved carotid flow velocity, resulting in a lower risk of cardiovascular disease [46].

SMOKING AND PSYCHOLOGICAL DISTRESS

Cigarette smoking contributes to the development of sarcopenia [47], obesity [48], and hypertension [49]. Therefore, smoking cessation is an important intervention step for this specific patient population.

Psychological distress leads to elevated cortisol levels and promotes adipogenic processes, as well as excessive consumption of high-calorie, high-fat, and high-sugar foods [50]. Recently, several interventions that combined cognitive behavioral therapy with mindfulness reported successful weight loss during the 18-month follow-up period [51].

NUTRITION-RELATED INTERVENTIONS

Strategies that optimize protein anabolism during weight loss, such as consumption before exercise or distribution of protein intake throughout the day, can prevent weight loss-induced sarcopenia [52, 38]. An adequate protein intake of 1.0-1.2 g/kg body weight per day should be provided for healthy non-geriatric individuals, while a higher intake of 1.2-1.5 g/kg body weight per day is recommended for high-risk patients with acute or chronic diseases [53, 54]. Higher doses of up to 2.2 g/kg/day are used only in obese patients under acute metabolic stress in the intensive care unit [54]. The general approach to nutrition in sarcopenic obese patients is to decrease caloric intake (hypocaloric diet) while increasing protein intake to prevent further loss of muscle mass [55]. The use of protein supplements is recommended when adequate food intake is not possible [56, 57].

Omega-3 long chain polyunsaturated fatty acids supplementation has been shown to enhance lower-body strength and functionality in older adults, without impacting lean mass, walking performance, or upper body strenght [58, 59]. Additionally, the inclusion of creatine supplementation in resistance training for older adults has resulted in increased lean tissue mass and significant improvements in both upper and lower body muscular strength [60]. On the other hand, there is insufficient evidence to support the use of β-hydroxy-β-methyl butyrate (HMB) supplementation for increasing or retaining skeletal muscle mass, enhancing muscle strength, or improving physical function in patients with sarcopenia or older individuals [61]. Similarly, vitamin D supplementation has not been shown to improve lower extremity function [62]. The use of coenzyme Q10, which has potential muscle-specific antioxidant and anti-inflammatory effects, in patients with sarcopenia is subject to an ongoing debate, as there is currently a lack of clinical trials confirming these effects [63].

In addition, some studies have shown that increased consumption of vegetables and fruits [64], dietary fiber [65], carotenes, and vitamins C and E [66] may also lead to a lower risk of sarcopenia. Interestingly, regular coffee consumption has been associated with a lower prevalence of sarcopenia [67]. Moreover, chronic coffee consumption has not been associated with an increased risk of hypertension [68], and several studies have shown no significant increase in systolic and diastolic blood pressure among hypertensive patients [69].

POTENTIAL PHARMACOLOGICAL APPROACHES

Currently, there is no specific pharmacological treatment for sarcopenic obesity. However, several potential pharmacological approaches have been proposed and discussed for patients with sarcopenic obesity and hypertension.

The drugs most commonly used in hypertension therapy are inhibitors of angiotensin converting enzyme (ACE), which converts angiotensin I to angiotensin II. Angiotensin II binds to AT1 receptors and leads to generalized vasoconstriction, increased noradrenaline release, secretion of aldosterone from the adrenal cortex, tubular reabsorption of Na^+ ions, and growth of cardiac and vascular cells [70]. Thus, ACE inhibitors reduce

arterial pressure in hypertensive patients by affecting capacitance and resistance vessels and reducing cardiac workload. Interestingly, the common isoform of ACE is found on the surface of endothelial cells, thus particularly abundant in lungs due to the large endothelial surface area. However, ACE is also found in other vascular tissues, including striated muscle, and is not restricted to endothelial cells. Moreover, angiotensin receptors are not only bound to cell membranes but have also been identified on mitochondrial membranes [71]. Altered mitochondrial angiotensin signaling leads to changes in angiotensin receptor expression, mitochondrial nitric oxide production, and altered cellular respiration associated with age-related mitochondrial dysfunction [71].

ACE inhibitors and angiotensin receptor blockers (ARBs) are discussed as potential therapies to reduce the development of sarcopenia [72]. In fact, ACE inhibitors are safe, approved, and widely-used drugs and, therefore, are probably the preferred therapeutic option for sarcopenic obesity with hypertension. Indeed, some studies have shown that hypertensive patients treated with ACE inhibitors have a significantly slower decline in muscle strength and higher lower limb muscle mass compared with patients treated with other antihypertensive agents [73]. One study also showed an improvement in physical performance on the 6-minute walk distance test in the elderly [74]. However, ACE inhibitors did not provide additional benefits to physical function when added to a standard exercise training program in functionally impaired older people [75]. A study in sarcopenic elderly patients receiving perindopril, an ACE inhibitor, over a 12-month period showed no improvement in physical performance or muscle mass [76]. Another trial (The ACES Trial, NCT03295734) is currently underway to evaluate the effect of three first-line antihypertensive agents: the ACE inhibitor perindopril, the angiotensin AT1 receptor antagonist losartan, and the thiazide diuretic hydrochlorothiazide on potential improvement in the self-paced gait speed [77]. In summary, the existing evidence does not support the use of ACE inhibitors or angiotensin receptor blockers as a single intervention to improve sarcopenia or exercise capacity in elderly obese patients.

Treatment with anabolic androgenic steroids such as testosterone improved muscle performance in elderly men with sarcopenia, as described by increases in maximal voluntary muscle strength [78], improvement in 6-minute walk test distance, and self-reported walking ability [79, 80]. However, the risk of adverse events associated with testosterone use must be considered, such as increased risk for thrombosis and cardiovascular events, prostatic hyperplasia with related urinary tract symptoms, and prostate cancer, among others [81, 82].

The antidiabetic drug metformin can slow the progression of sarcopenia by inhibiting NFkappaB inflammation, reducing oxidative stress, regulating lipid metabolism, and activating AMPK-dependent signaling, leading to the restoration of muscle size and function [83, 84].

There are also several experimental drugs in the pipeline that may be useful as potential therapeutics in the future. Ghrelin mimetics can reduce muscle loss under catabolic conditions by increasing pulsatile growth hormone secretion and decreasing inflammatory cytokines secretion [85]. Thus, ghrelin mimetics can increase fat-free mass and improve muscle function [86]. Another attractive approach is the inhibition of myostatin signaling pathways, either by monoclonal antibodies targeting myostatin or by antagonists of activin receptors. Myostatin is a negative regulator of muscle mass and transmits its effects by binding to activin receptors on the muscle membrane. Indeed, anti-myostatin antibodies have increased muscle mass and strength in mice [87]. Unfortunately, clinical trials have not been successful to date.

In the context of pharmacotherapy of sarcopenic obesity, we should also consider anti-obesity drugs. However, many appetite suppressants were withdrawn from clinical use due to serious adverse effects, such as dexfenfluramine, fenfluramine, and sibutramine. Their mechanism of action is to inhibit the noradrenaline and serotonin reuptake transporters, thereby increasing the levels of both neurotransmitters in the neuronal synapses of the hypothalamic region that controls food intake [88]. Similarly, lorcaserin acts as a selective agonist of serotonergic receptors $5HT_{2C}$ in the hypothalamus and suppresses appetite. It is used as an adjunctive pharmacotherapy to diet and improved weight loss, but patients regained weight after discontinuation [88, 89]. Another approach is to inhibit pancreatic lipases, which break down dietary fat into fatty acids and glycerol in the gastrointestinal tract. One such drug is orlistat, which is currently the only approved drug for the treatment of obesity. Orlistat inhibits intestinal absorption of 30% of triglycerides, and resulted in 5-10% greater weight loss than in the placebo group [90].

While several potential pharmacological approaches have been proposed and discussed for sarcopenic obesity, none have been fully successful to date.

CONCLUSIONS

One of the main reasons for the growing research interest in sarcopenic obesity is the increasing ageing of the world population associated with chronic diseases that share common pathophysiological aspects. According to the results of the studies included in this review, both sarcopenic obese men and sarcopenic obese women have higher blood pressure than individuals who are only obese or sarcopenic. Further studies are needed to develop an effective treatment for sarcopenic obesity in clinical practice.

Conflict of interest statement
The Authors report no conflict of interest.

REFERENCES

1. Barazzoni R, Bischoff S, Boirie Y, Busetto L, Cederholm T, Dicker D, Toplak H, Van Gossum A, Yumuk V, Vettor R. Sarcopenic obesity: time to meet the challenge. Obes Facts. 2018;11(4):294-305. doi: 10.1159/000490361

2. Baumgartner RN. Body composition in healthy aging. Ann NY Acad Sci. 2000;904:437-48. doi: 10.1111/j.1749-6632.2000.tb06498.x

3. Baumgartner RN, Wayne SJ, Waters DL, Janssen I, Gallagher D, Morley JE. Sarcopenic obesity predicts instrumental activities of daily living disability in the elderly. Obes Res. 2004;12(12):1995-2004.

4. Zamboni M, Mazzali G, Fantin F, Rossi A, Di Francesco V. Sarcopenic obesity: a new category of obesity in the elderly. Nutr Metab Cardiovasc Dis. 2008;18(5):388-95. doi: 10.1016/j.numecd.2007.10.002

5. Donini LM, Busetto L, Bauer JM, Bischoff S, Boirie Y, Cederholm T, Cruz-Jentoft AJ, Dicker D, Frühbeck G, Giustina A, Gonzalez MC, et al. Critical appraisal of definitions and diagnostic criteria for sarcopenic obesity based on a systematic review. Clin Nutr. 2020;39(8):2368-88. doi: 10.1016/j.clnu.2019.11.024

6. Hong SH, Choi KM. Sarcopenic obesity, insulin resistance, and their implications in cardiovascular and metabolic consequences. Int J Mol Sci. 2020;21(2):494. doi: 10.3390/ijms21020494

7. Donini LM, Busetto L, Bischoff SC, Cederholm T, Ballesteros-Pomar MD, Batsis JA, Bauer JM, Boirie Y, Cruz-Jentoft AJ, Dicker D, et al. Definition and diagnostic criteria for sarcopenic obesity: ESPEN and EASO consensus statement. Obes Facts. 2022;15(3):321-35. doi: 10.1159/000521241

8. Rossi AP, Rubele S, Calugi S, Caliari C, Pedelini F, Soave F, Chignola E, Vittoria Bazzani P, Mazzali G, Dalle Grave R, Zamboni M. Weight cycling as a risk factor for low muscle mass and strength in a population of males and females with obesity. Obesity (Silver Spring). 2019;27(7):1068-75. doi: 10.1002/oby.22493

9. Wang M, Tan Y, Shi Y, Wang X, Liao Z, Wei P. Diabetes and sarcopenic obesity: pathogenesis, diagnosis, and treatments. Front Endocrinol (Lausanne). 2020;11:568. doi: 10.3389/fendo.2020.00568

10. Ha YC, Hwang SC, Song SY, Lee C, Park KS, Yoo JI. Hand grip strength measurement in different epidemiologic studies using various methods for diagnosis of sarcopenia: a systematic review. Eur Geriatr Med. 2018;9(3):277-88. doi: 10.1007/s41999-018-0050-6

11. Jones CJ, Rikli RE, Beam WC. A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. Res Q Exerc Sport. 1999;70(2):113-9. doi: 10.1080/02701367.1999.10608028

12. Prado CM, Wells JC, Smith SR, Stephan BC, Siervo M. Sarcopenic obesity: A critical appraisal of the current evidence. Clin Nutr. 2012;31(5):583-601. doi: 10.1016/j.clnu.2012.06.010

13. Norman K, Stobäus N, Pirlich M, Bosy-Westphal A. Bioelectrical phase angle and impedance vector analysis--clinical relevance and applicability of impedance parameters. Clin Nutr. 2012;31(6):854-61. doi: 10.1016/j.clnu.2012.05.008

14. Thibault R, Genton L, Pichard C. Body composition: why, when and for who? Clin Nutr. 2012;31(4):435-47. doi: 10.1016/j.clnu.2011.12.011

15. Khadra D, Itani L, Tannir H, Kreidieh D, El Masri D, El Ghoch M. Association between sarcopenic obesity and higher risk of type 2 diabetes in adults: A systematic review and meta-analysis. World J Diabetes. 2019;10(5):311-23. doi: 10.4239/wjd.v10.i5.311

16. Biolo G, Di Girolamo FG, Breglia A, Chiuc M, Baglio V, Vinci P, Toigo G, Lucchin L, Jurdana M, Pražnikar ZJ, Petelin A, Mazzucco S, Situlin R. Inverse relationship between "a body shape index" (ABSI) and fat-free mass in women and men: Insights into mechanisms of sarcopenic obesity. Clin Nutr. 2015;34(2):323-7. doi: 10.1016/j.clnu.2014.03.015

17. Tomažič A, Žvanut B, Grbac LV, Jurdana M. Identification of sarcopenic obesity in adults undergoing orthopaedic surgery: Relationship between "a body shape index" (ABSI) and fat-free mass. A cross-sectional study. PLoS One. 2022;17(6):e0269956. doi: 10.1371/journal.pone.0269956

18. Ji T, Li Y, Ma L. Sarcopenic obesity: an emerging public health problem. Aging Dis. 2022;13(2):379-88. doi: 10.14336/AD.2021.1006

19. Schrager MA, Metter EJ, Simonsick E, Ble A, Bandinelli S, Lauretani F, Ferrucci L. Sarcopenic obesity and inflammation in the InCHIANTI study. J Appl Physiol. 2007;102(3):919-25. doi: 10.1152/japplphysiol.00627.2006

20. Jurdana M, Jenko-Pražnikar Z, Mohorko N, Petelin A, Jakus T, Šimunič B, Pišot R. Impact of 14-day bed rest on serum adipokines and low-grade inflammation in younger and older adults. Age (Dordr). 2015;37(6):116. doi: 10.1007/s11357-015-9848-z

21. Murton AJ, Marimuthu K, Mallinson JE, Selby AL, Smith K, Rennie MJ, Greenhaff PL. Obesity appears to be associated with altered muscle protein synthetic and breakdown responses to increased nutrient delivery in older men, but not reduced muscle mass or contractile function. diabetes. 2015; 64(9):3160-71. doi: 10.2337/db15-0021

22. Pedersen BK. Muscle as a secretory organ. Compr Physiol. 2013;3(3):1337-62. doi: 10.1002/cphy.c120033

23. Ostrowski K, Rohde T, Asp S, Schjerling P, Pedersen BK. Pro- and anti-inflammatory cytokine balance in strenuous exercise in humans. J Physiol. 1999;515:287-91. doi: 10.1111/j.1469-7793.1999.287ad.x

24. Pedersen BK, Febbraio MA. Muscle as an endocrine organ: focus on muscle-derived interleukin-6. Physiol Rev. 2008;88(4):1379-406. doi: 10.1152/physrev.90100.2007

25. Jurdana M. Physical activity and cancer risk. Actual knowledge and possible biological mechanisms. Radiol Oncol. 2021;55(1):7-17. doi: 10.2478/raon-2020-0063

26. Park SH, Park JH, Song PS, Kim DK, Kim KH, Seol SH, Kim HK, Jang HJ, Lee JG, Park HY, et al. Sarcopenic obesity as an independent risk factor of hypertension. J Am Soc Hypertens. 2013;7(6):420-5. doi: 10.1016/j.jash.2013.06.002

27. Yin T, Zhang JX, Wang FX, Zhao JH, Zhao Y, Liu L, Liu XY, Zhang YH, Zhao Y. The association between sarcopenic obesity and hypertension, diabetes, and abnormal lipid metabolism in chinese adults. Diabetes Metab Syndr Obes. 2021;14:1963-73. doi: 10.2147/DMSO.S308387

28. Ferreira I, Snijder MB, Twisk JW, van Mechelen W, Kemper HC, Seidell JC, Stehouwer CD. Central fat mass *versus* peripheral fat and lean mass: opposite (adverse *versus* favorable) associations with arterial stiffness? The Amsterdam Growth and Health Longitudinal Study. J Clin Endocrinol Metab. 2004;89(6):2632-9. doi: 10.1210/jc.2003-031619

29. Snijder MB, Henry RM, Visser M, Dekker JM, Seidell JC, Ferreira I, Bouter LM, Yudkin JS, Westerhof N, Stehouwer CD. Regional body composition as a determinant

of arterial stiffness in the elderly: The Hoorn Study. J Hypertens. 2004;22(12):2339-47. doi: 10.1097/00004872-200412000-00016

30. Ohara M, Kohara K, Tabara Y, Ochi M, Nagai T, Igase M, Miki T. Sarcopenic obesity and arterial stiffness, pressure wave reflection and central pulse pressure: the J-SHIPP study. Int J Cardiol. 2014;174(1):214-7. doi: 10.1016/j.ijcard.2014.03.194

31. Lu CW, Yang KC, Chang HH, Lee LT, Chen CY, Huang KC. Sarcopenic obesity is closely associated with metabolic syndrome. Obes Res Clin Pract. 2013;7(4):e301-7. doi: 10.1016/j.orcp.2012.02.003

32. Kreidieh D, Itani L, El Masri D, Tannir H, Citarella R, El Ghoch M. Association between sarcopenic obesity, type 2 diabetes, and hypertension in overweight and obese treatment-seeking adult women. J Cardiovasc Dev Dis. 2018;5(4):51. doi: 10.3390/jcdd5040051

33. Kang SY, Lim GE, Kim YK, Kim HW, Lee K, Park TJ, Kim J. Association between sarcopenic obesity and metabolic syndrome in postmenopausal women: a cross-sectional study based on the Korean national health and nutritional examination surveys from 2008 to 2011. J Bone Metab. 2017;24(1):9-14. doi: 10.11005/jbm.2017.24.1.9

34. Choi KM. Sarcopenia and sarcopenic obesity. Korean J Intern Med. 2016;31(6):1054-60. doi: 10.3904/kjim.2016.193

35. Hegde SM, Solomon SD. Influence of physical activity on hypertension and cardiac structure and function. Curr Hypertens Rep. 2015;17(10):77. doi: 10.1007/s11906-015-0588-3

36. Brüünsgaard H, Pedersen BK. Age-related inflammatory cytokines and disease. Immunol Allergy Clin North Am. 2003;23(1):15-39. doi: 10.1016/s0889-8561(02)00056-5

37. Chen K, Zhou M, Wang X, Li S, Yang D. The role of myokines and adipokines in hypertension and hypertension-related complications. Hypertens Res. 2019;42(10):1544-51. doi: 10.1038/s41440-019-0266-y

38. Batsis JA, Gill LE, Masutani RK, Adachi-Mejia AM, Blunt HB, Bagley PJ, Lopez-Jimenez F, Bartels SJ. Weight loss interventions in older adults with obesity: a systematic review of randomized controlled trials since 2005. J Am Geriatr Soc. 2017;65(2):257-68. doi: 10.1111/jgs.14514

39. Lopez P, Taaffe DR, Galvão DA, Newton RU, Nonemacher ER, Wendt VM, Bassanesi RN, Turella DJP, Rech A. Resistance training effectiveness on body composition and body weight outcomes in individuals with overweight and obesity across the lifespan: A systematic review and meta-analysis. Obes Rev. 2022;23(5):e13428. doi: 10.1111/obr.13428.

40. Hood DA. Mechanisms of exercise-induced mitochondrial biogenesis in skeletal muscle. Appl Physiol Nutr Metab. 2009;34(3):465-72. doi: 10.1139/H09-045

41. Mooren FC, Krüger K. Exercise, autophagy, and apoptosis. Prog Mol Biol Transl Sci. 2015;135: 407-22. doi: 10.1016/bs.pmbts.2015.07.023

42. Beyer I, Mets T, Bautmans I. Chronic low-grade inflammation and age-related sarcopenia. Curr Opin Clin Nutr Metab Care. 2012;15(1):12-22. doi: 10.1097/MCO.0b013e32834dd297

43. Woods JA, Wilund KR, Martin SA, Kistler BM. Exercise, inflammation and aging. Aging Dis. 2012;3(1):130-40.

44. Visser M, van Venrooij LM, Vulperhorst L, de Vos R, Wisselink W, van Leeuwen PA, de Mol BA. Sarcopenic obesity is associated with adverse clinical outcome after cardiac surgery. Nutr Metab Cardiovasc Dis. 2013;23(6):511-8. doi: 10.1016/j.numecd.2011.12.001

45. Bruunsgaard H, Bjerregaard E, Schroll M, Pedersen BK. Muscle strength after resistance training is inversely correlated with baseline levels of soluble tumor necrosis factor receptors in the oldest old. J Am Geriatr Soc. 2004;52(2):237-41. doi: 10.1111/j.1532-5415.2004.52061.x

46. Park J, Kwon Y, Park H. Effects of 24-week aerobic and resistance training on carotid artery intima-media thickness and flow velocity in elderly women with sarcopenic obesity. J Atheroscler Thromb. 2017;24(11):1117-24. doi: 10.5551/jat.39065

47. Steffl M, Bohannon RW, Petr M, Kohlikova E, Holmerova I. Relation between cigarette smoking and sarcopenia: meta-analysis. Physiol Res. 2015;64(3):419-26. doi: 10.33549/physiolres.932802

48. Sun M, Jiang Y, Sun C, Li J, Guo X, Lv Y, Yu Y, Yao Y, Jin L. The associations between smoking and obesity in northeast China: a quantile regression analysis. Sci Rep. 2019;14;9(1):3732. doi: 10.1038/s41598-019-39425-6

49. Virdis A, Giannarelli C, Neves MF, Taddei S, Ghiadoni L. Cigarette smoking and hypertension. Curr Pharm Des. 2010;16(23):2518-25. doi: 10.2174/138161210792062920

50. Kumar R, Rizvi MR, Saraswat S. Obesity and stress: A contingent paralysis. Int J Prev Med. 2022;13:95. doi: 10.4103/ijpvm.IJPVM_427_20

51. Ogata K, Koyama KI, Amitani M, Amitani H, Asakawa A, Inui A. The effectiveness of cognitive behavioral therapy with mindfulness and an internet intervention for obesity: A case series. Front Nutr. 2018;5:56. doi: 10.3389/fnut.2018.00056

52. Villareal DT, Aguirre L, Gurney AB, Waters DL, Sinacore DR, Colombo E, Armamento-Villareal R, Qualls C. Aerobic or resistance exercise, or both, in dieting obese older adults. N Engl J Med. 2017;376(20):1943-55. doi: 10.1056/NEJMoa1616338

53. Deutz NE, Bauer JM, Barazzoni R, Biolo G, Boirie Y, Bosy-Westphal A, Cederholm T, Cruz-Jentoft A, Krznariç Z, Nair KS, Singer P, Teta D, Tipton K, Calder PC. Protein intake and exercise for optimal muscle function with aging: recommendations from the ESPEN Expert Group. Clin Nutr. 2014;33(6):929-36. doi: 10.1016/j.clnu.2014.04.007

54. Bauer J, Biolo G, Cederholm T, Cesari M, Cruz-Jentoft AJ, Morley JE, Phillips S, Sieber C, Stehle P, Teta D, Visvanathan R, Volpi E, Boirie Y. Evidence-based recommendations for optimal dietary protein intake in older people: a position paper from the PROT-AGE Study Group. J Am Med Dir Assoc. 2013;14(8):542-59. doi: 10.1016/j.jamda.2013.05.021

55. Yumuk V, Tsigos C, Fried M, Schindler K, Busetto L, Micic D, Toplak H; Obesity management task force of the European Association for the Study of Obesity. European guidelines for obesity management in adults. Obes Facts. 2015;8(6):402-24. doi: 10.1159/000442721

56. Nazri NSM, Vanoh D, Soo KL. Natural food for sarcopenia: a narrative review. Malays J Med Sci. 2022;29(4):28-42. doi: 10.21315/mjms2022.29.4.4

57. Kim J, Lee Y, Kye S, Chung YS, Kim KM. Association between healthy diet and exercise and greater muscle mass in older adults. J Am Geriatr Soc. 2015;63(5):886-92. doi: 10.1111/jgs.13386

58. Cornish SM, Cordingley DM, Shaw KA, Forbes SC, Leonhardt T, Bristol A, Candow DG, Chilibeck PD. Effects of omega-3 supplementation alone and combined with resistance exercise on skeletal muscle in older adults: a systematic review and meta-analysis. Nutrients. 2022;14 (11):2221. doi: 10.3390/nu14112221

59. Dupont J, Dedeyne L, Dalle S, Koppo K, Gielen E. The role of omega-3 in the prevention and treatment of sar-

copenia. Aging Clin Exp Res. 2019;31(6):825-36. doi: 10.1007/s40520-019-01146-1

60. Chilibeck PD, Kaviani M, Candow DG, Zello GA. Effect of creatine supplementation during resistance training on lean tissue mass and muscular strength in older adults: a meta-analysis. Open Access J Sports Med. 2017;8:213-26. doi: 10.2147/OAJSM.S123529

61. Phillips SM, Lau KJ, D'Souza AC, Nunes EA. An umbrella review of systematic reviews of β-hydroxy-β-methyl butyrate supplementation in ageing and clinical practice. J Cachexia Sarcopenia Muscle. 2022;13(5):2265-75. doi: 10.1002/jcsm.13030

62. Bischoff-Ferrari HA, Dawson-Hughes B, Orav EJ, Staehelin HB, Meyer OW, Theiler R, Dick W, Willett WC, Egli A. Monthly high-dose vitamin d treatment for the prevention of functional decline: a randomized clinical trial. JAMA Intern Med. 2016;176(2):175-83. doi: 10.1001/jamainternmed

63. Guescini M, Tiano L, Genova ML, Polidori E, Silvestri S, Orlando P, Fimognari C, Calcabrini C, Stocchi V, Sestili P. The combination of physical exercise with muscle-directed antioxidants to counteract sarcopenia: a biomedical rationale for pleiotropic treatment with creatine and coenzyme Q10. Oxid Med Cell Longev. 2017;2017:7083049. doi: 10.1155/2017/7083049

64. Koyanagi A, Veronese N, Solmi M, Oh H, Shin JI, Jacob L, Yang L, Haro JM, Smith L. Fruit and vegetable consumption and sarcopenia among older adults in low- and middle-income countries. Nutrients. 2020;12(3):706. doi: 10.3390/nu12030706

65. Montiel-Rojas D, Nilsson A, Santoro A, Franceschi C, Bazzocchi A, Battista G, de Groot LCPGM, Feskens EJM, Berendsen A, Pietruszka B, et al. Dietary fibre may mitigate sarcopenia risk: findings from the NU-AGE cohort of older European adults. Nutrients. 2020;12(4):1075. doi: 10.3390/nu12041075

66. Welch AA, Jennings A, Kelaiditi E, Skinner J, Steves CJ. Cross-sectional associations between dietary antioxidant vitamins C, E and carotenoid intakes and sarcopenic indices in women aged 18-79 years. Calcif Tissue Int. 2020;106(4):331-42. doi: 10.1007/s00223-019-00641-x

67. Chung H, Moon JH, Kim JI, Kong MH, Huh JS, Kim HJ. Association of coffee consumption with sarcopenia in Korean elderly men: analysis using the Korea national health and nutrition examination survey, 2008-2011. Korean J Fam Med. 2017;38(3):141-7. doi: 10.4082/kjfm.2017.38.3.141

68. Grosso G, Micek A, Godos J, Pajak A, Sciacca S, Bes-Rastrollo M, Galvano F, Martinez-Gonzalez MA. Long-term coffee consumption is associated with decreased incidence of new-onset hypertension: A dose-response meta-analysis. Nutrients. 2017;9(8):890. doi: 10.3390/nu9080890

69. Mesas AE, Leon-Muñoz LM, Rodriguez-Artalejo F, Lopez-Garcia E. The effect of coffee on blood pressure and cardiovascular disease in hypertensive individuals: a systematic review and meta-analysis. Am J Clin Nutr. 2011;94(4):1113-26. doi: 10.3945/ajcn.111.016667

70. Epstein BJ, Leonard PT, Shah NK. The evolving landscape of RAAS inhibition: from ACE inhibitors to ARBs, to DRIs and beyond. Expert Rev Cardiovasc Ther. 2012;10(6):713-25. doi: 10.1586/erc.12.63

71. Abadir PM, Foster DB, Crow M, Cooke CA, Rucker JJ, Jain A, Smith BJ, Burks TN, Cohn RD, Fedarko NS, Carey RM, O'Rourke B, Walston JD. Identification and characterization of a functional mitochondrial angiotensin system. Proc Natl Acad Sci USA. 2011;108(36):14849-54. doi: 10.1073/pnas.1101507108

72. Kingsley J, Torimoto K, Hashimoto T, Eguchi S. Angiotensin II inhibition: a potential treatment to slow the progression of sarcopenia. Clin Sci (Lond). 2021;135(21):2503-20. doi: 10.1042/CS20210719

73. Onder G, Penninx BW, Balkrishnan R, Fried LP, Chaves PH, Williamson J, Carter C, Di Bari M, Guralnik JM, Pahor M. Relation between use of angiotensin-converting enzyme inhibitors and muscle strength and physical function in older women: an observational study. Lancet. 2002;359(9310):926-30. doi: 10.1016/s0140-6736[02]08024-8

74. Hutcheon SD, Gillespie ND, Crombie IK, Struthers AD, McMurdo ME. Perindopril improves six minute walking distance in older patients with left ventricular systolic dysfunction: a randomised double blind placebo controlled trial. Heart. 2002;88(4):373-7. doi: 10.1136/heart.88.4.373

75. Sumukadas D, Band M, Miller S, Cvoro V, Witham M, Struthers A, McConnachie A, Lloyd SM, McMurdo M. Do ACE inhibitors improve the response to exercise training in functionally impaired older adults? A randomized controlled trial. J Gerontol A Biol Sci Med Sci. 2014;69(6):736-43. doi: 10.1093/gerona/glt142

76. Sumukadas D, Witham MD, Struthers AD, McMurdo ME. Effect of perindopril on physical function in elderly people with functional impairment: a randomized controlled trial. CMAJ. 2007;177(8):867-74. doi: 10.1503/cmaj.061339

77. LACE study group, Achison M, Adamson S, Akpan A, Aspray T, Avenell A, Band MM, Bashir T, Burton LA, Cvoro V, Donnan PT, et al. Effect of perindopril or leucine on physical performance in older people with sarcopenia: the LACE randomized controlled trial. J Cachexia Sarcopenia Muscle. 2022;13(2):858-71. doi: 10.1002/jcsm.12934

78. Harper SA, Baptista LC, Roberts LM, Wherry SJ, Boxer RS, Hildreth KL, Seay RS, Allman PH, Carter CS, Aban I, et al. Angiotensin converting enzyme inhibitors combined with exercise for hypertensive seniors (The ACES Trial): Study protocol of a randomized controlled trial. Front Med (Lausanne). 2020;6:327. doi: 10.3389/fmed.2019.00327

79. LeBrasseur NK, Lajevardi N, Miciek R, Mazer N, Storer TW, Bhasin S. Effects of testosterone therapy on muscle performance and physical function in older men with mobility limitations (The TOM Trial): design and methods. Contemp Clin Trials. 2009;30(2):133-40. doi: 10.1016/j.cct.2008.10.005

80. Bhasin S, Ellenberg SS, Storer TW, Basaria S, Pahor M, Stephens-Shields AJ, Cauley JA, Ensrud KE, Farrar JT, Cella D, et al. Effect of testosterone replacement on measures of mobility in older men with mobility limitation and low testosterone concentrations: secondary analyses of the Testosterone Trials. Lancet Diabetes Endocrinol. 2018;6(11):879-90. doi: 10.1016/S2213-8587[18]30171-2

81. Dias JP, Melvin D, Shardell M, Ferrucci L, Chia CW, Gharib M, Egan JM, Basaria S. Effects of transdermal testosterone gel or an aromatase inhibitor on prostate volume in older men. J Clin Endocrinol Metab. 2016;101(4):1865-71. doi: 10.1210/jc.2016-1111

82. Corona G, Torres LO, Maggi M. Testosterone therapy: what we have learned from trials. J Sex Med. 2020;17(3):447-60. doi: 10.1016/j.jsxm.2019.11.270

83. Lyu Q, Wen Y, He B, Zhang X, Chen J, Sun Y, Zhao Y, Xu L, Xiao Q, Deng H. The ameliorating effects of metformin on disarrangement ongoing in gastrocnemius muscle of sarcopenic and obese sarcopenic mice. Biochim Bio-

phys Acta Mol Basis Dis. 2022;1868(11):166508. doi: 10.1016/j.bbadis.2022.166508

84. Kulkarni AS, Brutsaert EF, Anghel V, Zhang K, Bloomgarden N, Pollak M, Mar JC, Hawkins M, Crandall JP, Barzilai N. Metformin regulates metabolic and nonmetabolic pathways in skeletal muscle and subcutaneous adipose tissues of older adults. Aging Cell. 2018;17(2):e12723. doi: 10.1111/acel.12723

85. Dixit VD, Schaffer EM, Pyle RS, Collins GD, Sakthivel SK, Palaniappan R, Lillard JW Jr, Taub DD. Ghrelin inhibits leptin- and activation-induced proinflammatory cytokine expression by human monocytes and T cells. J Clin Invest. 2004;114(1):57-66. doi: 10.1172/JCI21134

86. Nass R, Gaylinn BD, Thorner MO. The ghrelin axis in disease: potential therapeutic indications. Mol Cell Endocrinol. 2011;340(1):106-10. doi: 10.1016/j.mce.2011.02.010

87. Camporez JP, Petersen MC, Abudukadier A, Moreira GV, Jurczak MJ, Friedman G, Haqq CM, Petersen KF, Shulman GI. Anti-myostatin antibody increases muscle mass and strength and improves insulin sensitivity in old mice. Proc Natl Acad Sci USA. 2016;113(8):2212-7. doi: 10.1073/pnas.1525795113

88. Moon JH, Oh CM, Kim H. Serotonin in the regulation of systemic energy metabolism. J Diabetes Investig. 2022;13(10):1639-45. doi: 10.1111/jdi.13879

89. Smith SR, Garvey WT, Greenway FL, Zhou S, Fain R, Pilson R, Fujioka K, Aronne LJ. Coadministration of lorcaserin and phentermine for weight management: A 12-week, randomized, pilot safety study. Obesity (Silver Spring). 2017;25(5):857-65. doi: 10.1002/oby.21811

90. Son JW, Kim S. Comprehensive review of current and upcoming anti-obesity drugs. Diabetes Metab J. 2020;44(6):802-18. doi: 10.4093/dmj.2020.0258

BOOK REVIEWS, NOTES AND COMMENTS

Edited by
Federica Napolitani Cheyne
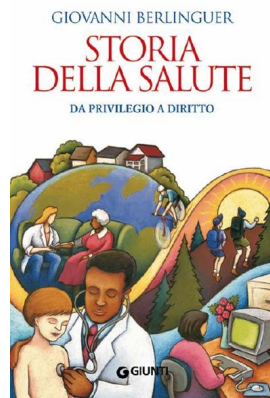
STORIA DELLA SALUTE
Da privilegio a diritto
Giovanni Berlinguer
Firenze: Giunti Editore; 2011.
312 p.
ISBN 978-88-0905-365-6
€ 16,00

LA SALUTE SOSTENIBILE
Perché possiamo
permetterci un Servizio
sanitario equo ed efficace
Marco Geddes da Filicaia
Roma: Il Pensiero Scientifico;
2018.
180 p.
ISBN 978-8849006117
€ 18,00

In the last months, the Ministry of Health initiated a general reflection on some of the most relevant and urgent issues dealing with continuous transformation of the Italian National Health System (NHS). Analogous changes and ongoing discussions are underway in most of the National Health Systems at European and international level.

The Italian National Institute of Health (Istituto Superiore di Sanità, ISS) is actively participating in the debate, given its role as the technical biomedical branch of the Italian NHS. At least from an historical point of view, we found worth mentioning those two books, whose editorial roles may represent a sort of landmark, useful for the ongoing present discussions. The COVID pandemics triggered a series of debates, therefore its formal end is witnessing some substantial changes of perspectives and planned strategies at national, supranational and global level. These two books may therefore be helpful to the present discussion, despite their point of view and resulting perspectives may appear biased or even old-fashioned for some.

Giovanni Berlinguer exerted a major technical and political role in the years when the NHS was established (Law n. 833, 1978). A Medical Doctor, he covered the chair of Physiology and Occupational Hygiene (Fisiologia e Igiene del Lavoro) at "La Sapienza" University of Rome. Senator of the Italian Republic for a long time since 1983, he was a very active member of the International Committee of Bioethics of UNESCO (2001-2007) and in the Commission on the social determinants of Health (World Health Organization - WHO, 2005-2008).

His book is a rather exhaustive, yet brief compendium of the history of the social relevance of health, starting from the Middle-Age times, reviewing major historical epidemics, emerging diseases, and the origin and development of the WHO, including some hints on the role exerted by scientific biomedicine and social sciences in the recognition and coping with occupational diseases.

Marco Geddes da Filicaia's book is instead an attempt to reasoning on the recent economical, strategical and social factors having shaped and still shaping our national NHS. It reviews a few recent trends of the Italian NHS, such as level of general taxation, expenses due to personnel, the necessities of minor or major adjustments, etc. The economical calculations fade in some hot ethical aspects of contemporary biomedicine and public health. It may sound a rather biased (for some critics, a slightly superficial) analysis, however its reading may be useful since it represents a rather shared perspective among those active within the NHS itself.

Enrico Alleva* and Stella Falsini
Centro di Riferimento per le
Scienze Comportamentali e la Salute Mentale
Istituto Superiore di Sanità, Rome, Italy
*Vice-President of Consiglio Superiore di Sanità

enrico.alleva@iss.it

AGRUMI: UNA STORIA DEL MONDO
Giuseppe Barbera
Milano: Il Saggiatore; 2023
288 p.
ISBN 9788842831815
€ 25,00

Why reviewing a book about citrus in a public-health journal? Because what was called "the disease of the sea", which affected for a very long-time scores of sailors after long navigation, and which was added to typhus and dysentery infections, is definitely part of the history of medicine. "*Sovratutte le altre sciagure questa che era la pegiore*", ("above all other misfortunes this was the worst"), as judged by Antonio Pigafetta in the report vividly narrating the journey he made around the world between 1519 and 1522 by Ferdinando Magellano.

The scurvy symptoms he described were: "*cressivano le gengive sovra li denti, così de soto como de sovra, che per modo alguno non potevano magiare e cossì morivano*" ("the gums grew over the teeth, both below and above, so that in no way they could eat and so they died").

The deaths have been estimated around two million, and it was a disease known from ancient times, perhaps already defined in the symptomatology by Hippocrates himself, which explodes in the centuries 500 and 600 in the long-lasting navigations to trace merchant routes, looking for lands to explore and colonize, new "exotic" goods to trade. It scourged the most important travels.

During the globe circumnavigation of Magellan attended by Pigafetta, 80% of the sailors died. As with many illnesses that have tormented the history of medicine, in reality, the remedies were (very) partially known and the demand from orange by patients was one of the main therapeutic cornerstones.

The fruits of the citrus were particularly effective (especially lemons). They resisted inside the galley for long navigations and could be cultivated in the tropical lands that the routes lined. It was thanks to the Jesuits that citrus fruits arrived in Brazil, but also in Madagascar and Saint Helena. In the following century, the British found out the specificity of the disease and its possible remedies after George Andson's expedition from Portsmouth in 1740 had lost 1300 sailors out of 2000 in the first ten months. Attention grew after 133,708 deaths, mainly from this pathological condition among sailors enlisted by the Royal Navy (184,899).

However, the "formalized" discovery was thanks to the clinical trial conducted by the Scottish physician James Lind, based on a clever comparison of different therapies. The experiment, with a group of "supercontrol" which was provided with cider, while other control groups (two individuals each) of patients were administered vinegar. Only the lemon-fed pair recovered symptoms.

But still the success of citrus fruits was not immediately recognized and several alternative treatments proliferated, none supported by the tests of an experimental method. In the meantime, however, the times of navigation changed and the principle responsible for defending against scurvy was eventually found by Albert Szent-Györgyi who in his studies of organic chemistry had isolated from orange an acid that was called "vitamin C". He received therefore a deserved Nobel Prize in 1937.

It is a history of experimental medicine that must be celebrated, and this beautiful book by Barbera makes it an acute and truly flowing narrative. It indeed represents a crucial step while enlightening on the methodological paths still covered by contemporary biomedicine.

By the way, the book does much more than simply prospect the "medical role" of the citrus fruits. It is pleasantly about the history and myths of those fruits, from the garden of Hesperides to Alexander the Great, Theophrastus and the Holtzman biblical tradition. The role of oranges and other citrus fruits as ornamental plants is nicely described as central scenario of the Amalfi and Sorrento landscapes and the contemporary role of oranges in the United States closes the book. As a whole, its reading is recommended.

Enrico Alleva and Stella Falsini
Istituto Superiore di Sanità
Rome, Italy

enrico.alleva@iss.it

PUBLICATIONS FROM INTERNATIONAL ORGANIZATIONS ON PUBLIC HEALTH

Edited by
Annarita Barbaro

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS (FAO)

Contribution of terrestrial animal source food to healthy diets for improved nutrition and health outcomes. An evidence and policy overview on the state of knowledge and gaps. Rome: Food and Agriculture Organization of the United Nations 2023; 296 p. ISBN 978-92-5-137536-5. FAO's Committee on Agriculture requested a comprehensive, science- and evidence-based global assessment of the contribution of livestock to food security, sustainable food systems, nutrition and healthy diets, considering environmental, economic and social sustainability. The assessment follows an agrifood systems approach and applies a One Health perspective to the economic, social and environmental dimensions when reviewing how the livestock sector contributes to the 2030 Agenda for Sustainable Development. It will consist of four component documents. This first component document focuses on the downstream impacts of terrestrial animal source food consumption as part of healthy diets and provides a robust systematic review of the evidence for its contribution to health and nutrition outcomes.

The State of Food and Agriculture 2022. Leveraging agricultural automation for transforming agrifood systems. Rome: Food and Agriculture Organization of the United Nations 2022; 182 p. ISBN 978-92-5-136043-9. The State of Food and Agriculture 2022 looks into the drivers of agricultural automation, including the more recent digital technologies. Based on 27 case studies, the report analyses the business case for adoption of digital automation technologies in different agricultural production systems across the world. It identifies several barriers preventing inclusive adoption of these technologies, particularly by small-scale producers. Key barriers are low digital literacy and lack of an enabling infrastructure, such as connectivity and access to electricity, in addition to financial constraints. Based on the analysis, the publication suggests policies to ensure that disadvantaged groups in developing regions can benefit from agricultural automation and that automation contributes to sustainable and resilient agrifood systems.

The impact of microplastics on the gut microbiome and health – A food safety perspective. Food Safety and Quality Series, No. 21. Rome: Food and Agriculture Organization of the United Nations 2023; 58 p. ISBN 978-92-5-137807-6. With a food safety focus, a scientific literature review was conducted to characterize the current understanding about the effects of microplastics on the gut microbiome and potential health implications. The main aspects analysed are the effects of microplastics on the composition, diversity and function of gut microbiome using in vitro and in vivo models; health implications resulting from the microplastic–microbiome interactions and underlying mechanisms; the establishment of causality; and influence of the gut microbiome on microplastic biodegradation. The research was also scoped to identify current gaps, limitations and needs for the eventual consideration of microbiome-related data in chemical risk assessment. This work contributes to the FAO global programme on the impact of food systems on NCDs and obesity, by understanding the potential health implications of gut microbiome–microplastic interactions. The outcomes will provide information which can be used to improve food safety policies.

UNITED NATIONS EDUCATIONAL, SCIENTIFIC AND CULTURAL ORGANIZATION (UNESCO)

Open data for AI: what now? Paris: UNESCO Publishing 2023; 64 p. ISBN 978-92-3-100600-5. The aim of these guidelines is to apprise Member States of the value of open data, and to outline how data are curated and opened. Member States are encouraged not only to support openness of high-quality data, but also to embrace the use of AI technologies and facilitate capacity building, training and education in this regard, including inclusive open data as well as AI literacy. The report has been produced through an extensive literature review and consultations with stakeholders, followed by a peer review process. It outlines concrete steps that can assist Member States in opening up their data, divided into three phases: preparation; opening of the data; and follow up for reuse and sustainability; with each phase consisting of four steps. These guidelines follow up on the UNESCO Recommendation on the Ethics of Artificial Intelligence.

JOINT UNITED NATIONS PROGRAMME ON HIV/AIDS (UNAIDS)

UNAIDS data 2022. Geneva: United Nations Programme on HIV/AIDS 2022; 446 p. Every year UNAIDS provides revised global, regional and country-specific modelled estimates using the best available epi-

demiological and programmatic data to track the HIV epidemic. Modelled estimates are required because it is not possible to count the exact number of people living with HIV, people who are newly infected with HIV or people who have died from AIDS-related causes in any country: doing so would require regularly testing every person for HIV and investigating all deaths, which is logistically infeasible and ethically problematic. Modelled estimates—and the lower and upper bounds around these estimates—provide a scientifically appropriate way of describing HIV epidemic levels and trends.

INTERNATIONAL LABOUR ORGANIZATION (ILO)

The value of essential work. World Employment and Social Outlook 2023. Geneva: International Labour Organization 2023; 281 p. ISBN 978-92-2-036650-9 (print) ISBN 978-92-2-036651-6 (web PDF). The COVID-19 pandemic has underscored the extent to which economies and societies depend on key workers. It has also highlighted how undervalued most key jobs are. Across the world, these workers produced, distributed and sold food, cleaned streets and buses to minimize the spread of the pandemic, ensured public safety, transported essential goods and workers to their jobs, and cared for and healed the sick. The COVID-19 pandemic has also made evident how undervalued most key jobs are, raising concerns about the sustainability of these essential activities, especially given the possibility of future shocks. This report calls for a revaluation of the work of key workers to reflect their social contribution and greater investment in key sectors. In addition to addressing an important, long-standing deficit in social justice, doing so will help to ensure the continuity of essential economic activities during future shocks and crises.

WORLD HEALTH ORGANIZATION (WHO)

Red and processed meat in the context of health and the environment: many shades of red and green. Information brief. Geneva: World Health Organization 2023; 66 p. ISBN 978-92-4-007482-8 (electronic version) ISBN 978-92-4-007483-5 (print version). Globally, production and consumption of all types of meat has increased substantially in the last 50 years, and – although red meat consumption is now plateauing in high-income countries (HICs) – is predicted to increase by a further 50% by 2050. Meat consumption remains highly unequal both between and within countries, and animal-source food intakes, including red meat, are lowest among those at most risk of undernutrition. This information brief synthesizes the evidence on the role of red and processed meat production and consumption in health and environmental outcomes, and in different social and political contexts. It does not give consumption recommendations, but, rather, represents the first stage in a scoping process

that could lead to World Health Organization (WHO) guidance on the role of red and processed meat in healthy diets from sustainable food systems. This brief is concise, easy to read and includes a summary and the key messages for each chapter. It is a useful resource for both advocates and the general public interested in this topic as well as technical staff, programme managers and decision makers who need to have a quick overview on what the main issues and gaps are on the role of red and processed meat for human and planetary health.

Carbohydrate intake for adults and children: WHO guideline. Geneva: World Health Organization 2023; 100 p. ISBN 978-92-4-007359-3 (electronic version) ISBN 978-92-4-007360-9 (print version). This guideline provides updated, evidence-informed guidance on the intake of carbohydrates to reduce the risk of diet-noncommunicable diseases in adults and children, with a particular focus on carbohydrate "quality". Carbohydrate quality refers to the nature and composition of carbohydrates in a food or in the diet, including the proportion of sugars, how quickly polysaccharides are metabolized and release glucose into the body (i.e., digestibility), and the amount of dietary fibre. The quality of carbohydrates in the diet can broadly impact health. This guideline is intended for a wide audience involved in the development, design and implementation of policies and programmes in nutrition and public health. This guideline includes recommendations on preferred food sources of carbohydrates, and recommended levels of intake for fruits and vegetables, and dietary fibre which can be used by policy-makers and programme managers to address various aspects of carbohydrate intake in their populations through a range of policy actions and public health interventions. The guidance in this guideline replaces previous WHO guidance on carbohydrate intake, including that from the 1989 WHO Study Group on Diet, Nutrition and the Prevention of Chronic Diseases and the 2002 Joint WHO/FAO Expert Consultation on Diet, Nutrition and the Prevention of Chronic Diseases. The guidance in this guideline should be considered in the context of that from other WHO guidelines on healthy diets.

Total fat intake for the prevention of unhealthy weight gain in adults and children: WHO guideline. Geneva: World Health Organization 2023; 66 p. ISBN 978-92-4-007365-4 (electronic version) ISBN 978-92-4-007366-1 (print version). The objective of this guideline is to provide updated guidance on the intake of total fat in the diet to reduce the risk of unhealthy weight gain. It is intended to be used by policymakers, programme managers, health professionals and other stakeholders in efforts to promote healthy diets. The guidance was formulated based on evidence for unhealthy weight gain only. The guideline was developed following the WHO guideline development process, as outlined in the WHO handbook for guideline development. This process includes a review of systematically gathered evidence by an international, multidisciplinary group of experts; assessment of the quality of that evidence via the Grading of Recom-

mendations Assessment, Development and Evaluation (GRADE) framework; and consideration of additional, potentially mitigating factors when translating the evidence into recommendations. The guidance in this guideline replaces previous WHO guidance on total fat intake, including that from the 1989 WHO Study Group on Diet, Nutrition and the Prevention of Chronic Diseases and the 2002 Joint WHO/FAO Expert Consultation on Diet, Nutrition and the Prevention of Chronic Diseases.

Instructions to Authors

Annali dell'Istituto Superiore di Sanità is a peer reviewed quarterly science journal which publishes research articles in biomedicine, translational research and in many other disciplines of the health sciences. The journal includes the following material: original articles, reviews, commentaries, editorials, brief and technical notes, book reviews. The publication of Monographic Sections on *Annali ISS* has been discontinued. In case you wish to present a limited number of coordinated contributions on specific themes concerning priorities in public health, please contact the Editorial office. *Annali* follows the Recommendations for the Conduct, Reporting, Editing, and Publications of Scholarly Work in Medical Journals, issued by the International Committee of Medical Journal Editors (ICMJE) recently updated with a specific section II.A.4. on Artificial Intelligence (AI)–Assisted Technology. www.icmje.org.

MANUSCRIPT SUBMISSION

Manuscripts should be submitted online to https://annali.iss.it/. The submission should include:
• cover letter where the authors declare that the manuscript has not been published or submitted for publication elsewhere;
• manuscript;
• tables and figures;
• author's contribution statement (individual contribution to the manuscript);
• conflict of interest statement (a conflict of interest exists when authors or their institutions have financial or personal relationship with other people or organizations that could inappropriately bias conduct and findings of the study);
• permission to reproduce figures, if appropriate.
Receipt of author's paper will be acknowledged by an e-mail containing an identification number which should be used in future correspondence.

NOTE FOR ISS AUTHORS

Authors whose affiliation is Istituto Superiore di Sanità can submit their paper only after completing the usual ISS authorization procedure (Infoweb).

REVIEW PROCEDURE

Each paper submitted to *Annali* is subjected to the following procedures:
• it is reviewed by the Editor-in-Chief for general suitability;
• if it is judged suitable, qualified referees are selected and a peer review process takes place;
• based on the recommendations of the referees and replies of the authors, the Editor-in-Chief decides whether the article should be accepted, modified or rejected;
• once the paper has been accepted, authors will receive proofs from the editorial office, which should be corrected and returned (usually within three working days).

MANUSCRIPT PRESENTATION

Please ensure that your manuscript follows these guidelines.
Manuscripts should be written in good English, as concisely as possible to allow a clear understanding of the text.
The title should be followed by the complete name of the authors, their affiliations – only one per author and in the original language – town and country. The name of the Working Group should appear at the end of the by-line; its composition should be reported before the References, names and affiliations of each member are required. The name and address, telephone and e-mail of the corresponding author should also be indicated. On the same page a running head of no more than 40 characters (including spaces) should be included.

Original articles should normally be organized into different sections (*i.e.*: Introduction, Materials and methods, Results, Discussion, Conclusions). In the Methods section a specific paragraph on the adopted statistical analysis should necessarily be included.
Each article should be accompanied by:
• an abstract of about 150 words; the abstract should be structured when required (such as in original articles);
• key words up to a maximum number of five (MeSH headings, whenever possible. Refer to: www.nlm.nih.gov/mesh/meshhome.html).
Tables and figures should be kept to a minimum and be presented only if necessary.
Authors should deal responsibly and effectively with security issues that might be raised by their papers (see: Statement on Scientific Publication and Security *Science* 2003;299:1149).
This journal has adopted the SAGER reporting Guidelines for Sex and Gender Equity in Research.
These guidelines apply to original research articles and review papers. Authors should use the terms sex and gender carefully in order to avoid confusing both terms. Where subjects can also be differentiated by gender (shaped by social and cultural circumstances), the research should be conducted similarly at this additional level of distinction. Where the subjects of research comprise organisms capable of differentiation by sex, the research should be designed and conducted in a way that can reveal sex-related differences in the results, even if these were not initially expected.
Please consult the guidelines (https://researchintegrity-journal.biomedcentral.com/articles/10.1186/s41073-016-0007-6).
Authors are also encouraged to use fair, accurate and respectful language, but preferences can change and vary across groups and individuals and can also evolve overtime. The following guidelines may help in use of a

correct terminology in the area of HIV: https://www.cdc.gov/stophivtogether/library/stop-hiv-stigma/fact-sheets/cdc-lsht-stigma-factsheet-language-guide.pdf
https://www.hptn.org/resources/HIVLanguageGuide
https://unesdoc.unesco.org/ark:/48223/pf0000144725
The name of the bioresource (and identifier, if available) which provided samples/data useful for the conduct of the study should be reported in extense, either in the Material and methods section or in the Acknowledgements.

LENGTH OF THE TEXT
To provide a text that meets the requirements of our publication:
• the *letter* to the Editor should be about 450 words; it does not need an abstract. Please contact the editorial office in advance if you wish to submit a Letter;
• the *editorial* should be no longer than 1,000 words; editorials are submitted on invitation. Please contact the editorial office in advance if you wish to submit an editorial;
• the *commentary,* 2,000 words; the commentary is an opinion piece or reflection on recent papers previously published on *Annali ISS* or elsewhere; an abstract is required; please contact in advance the editorial office;
• the *brief note*, 3,000 words, including about 15 references, one table and one figure;
• the *article,* 6,000 words, including about 40 references, three tables and two figures;
• the *review* should be no longer than 10,000 words, including no more than 100 references up to a maximum of four tables and three figures.
• *Supplementary materials* should be no longer than two printed pages. If necessary, authors could invite readers to contact them.

FORMATTING GUIDELINES
Text
• Use Times New Roman font, 10 point, single spaced;
• do not use the automated features of your application (endnotes, headers, footers, especially for references);
• avoid using bold characters to emphasise words or sentences within the text;
• indicate clearly titles of chapters and subchapters avoiding numbering.

Tables and figures
They should be understandable also without reference to the text and should be numbered in Arabic numerals in a consecutive and independent way according to their citation within the paper.
Tables should be presented on a separate sheet and preceeded by a title. Each column within the table should have a heading. Abbreviations should be reported in full in the legend.
Figures should be loaded as separate files. The following file formats are acceptable: JPEG, TIFF or EPS. Vectorial images (graphs, flow charts, schemes, and other non bitmap material) should be in Excel, Adobe Illustrator, Microsoft Power Point so as to allow the editorial formatting of the material.
Figures are redrawn into the *Annali* style by our in-house illustrators.
Photographs must have a minimum resolution of 300 dpi.

Captions should be presented on a separate sheet and contain a sufficient explanation of their object. They should be concise but comprehensive.

REFERENCES
All references in the text must be numbered in square brackets, *i.e.* [1, 2, 3-6], and mentioned at the end of the article in the order in which they are quoted. They should conform to the "Recommendations for the Conduct, Reporting, Editing, and Publications of Scholarly Work in Medical Journals" (www.icmje.org), according to the following examples.
Titles of periodicals should be abbreviated in accordance with the Medline abbreviation of the US National Library of Medicine (www.nlm.nih.gov/bsd/aim.html). Online journal articles can be cited using, in addition to the complete citation, the DOI number. Do not insert websites among the References but directly in the text in parentheses, where necessary.

Articles in journal
Bozzuto G, Ruggieri P, Molinari A. Molecular aspects of tumor cell migration and invasion. Ann Ist Super Sanità. 2010;46(1):66-80. doi: 10.4415/ANN_10_01_09

Books and chapters in a book
Godlee F, Jefferson T. Peer review in health sciences. London: BMJ Books; 1999.
Van Weely S, Leufkens HGM. Background paper: orphan diseases. In: Kaplan W, Laing R (Eds). Priority medicines for Europe and the world – a public health approach to innovation. Geneva: World Health Organization; 2004.

Proceedings
Fadda A, Giacomozzi C, Macellari V. Comparative measurements to validate a new telemetric pressure insoles system. In: 2. International Symposium on measurement, analysis and modelling of human functions. 1. Mediterranean Conference on measurement. Workshop on evaluation check of traceability. Proceedings. Genova: June 14-16, 2004. p. 425-7.

Technical reports
Della Seta M, Di Benedetto C, Leone L, Pizzarelli S, Siegmund U. ETHICSWEB technical guides. Manual for the creation of standards and guidelines for sharing information about knowledge organization systems on ethics and science. Roma: Istituto Superiore di Sanità; 2011. (Rapporti ISTISAN, 11/32).

Legislation
Italia. Decreto legislativo 29 ottobre, n. 419. Riordinamento del sistema degli enti pubblici nazionali, a norma degli articoli 11 e 14 della legge 15 marzo 1997, n. 59. Gazzetta Ufficiale – Serie Generale n. 268, 15 ottobre 1999.
US Social Security Administration. Evidentiary requirements for making findings about medical equivalence. Final rules. Fed Reg. 2006 Mar 1;71(40):10419-33.
The authors should check that each reference cited in the text appears in the reference list and viceversa. References should not include works submitted for publication but

not yet accepted or unpublished results, etc. These can be mentioned in the text in parentheses.

CONVENTIONS
All Latin or foreign words should be in italics. The authors should use internationally accepted abbreviations. All abbreviations should be spelled out in full the first time they occur in the text, followed by the shortened term in parentheses; afterwards use the abbreviation only. Avoid abbreviations in the title of the manuscript.
For writing symbols, quantities and units of measurements refer to the International Systems of Units (SI) and the ISO standards.

LICENSES AND AGREEMENTS
Extended quotations and illustrative material taken from other publications must be accompanied by the original permission granted by the Authors and by the publisher or in accordance with the copyright policy of the original publication and the Creative Commons.
Responsibility for the contents and opinions expressed on this journal rests solely with the Author(s).