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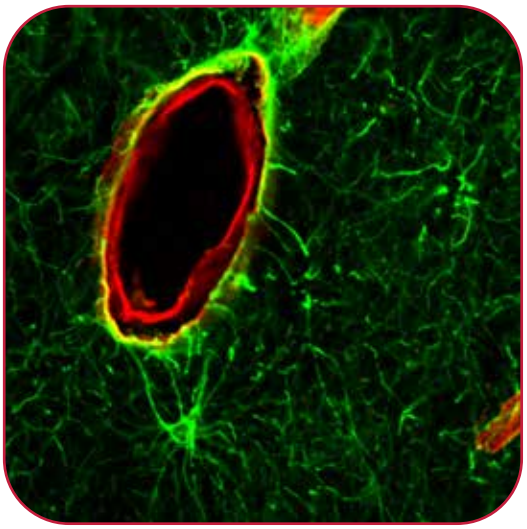
The photograph is a double immunofluorescence staining of a post-mortem human brain section for the astrocyte marker GFAP (green) and laminin (red). Image shows astrocyte end-feet contacting the basal lamina of a cerebral blood vessel. Image is provided by Barbara Serafini, Department of Neuroscience, Istituto Superiore di Sanità, Rome, Italy.



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COMMENTARY
Health in contaminated sites: the contribution of epidemiological surveillance to the detection of causal links

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Abstract
The search for cause-effect relationships is a central aspect of epidemiological surveillance programs applied to populations living close to contaminated sites. Here are described needs for assessing causality in using different epidemiological study designs in association with the aim of promoting environmental public health, where uncertainties should be considered under a precautionary driven approach.

Key words
- contaminated sites
- epidemiological monitoring
- causality
- precautionary principle
- environment and public health

Several scientific papers and reviews published in the last few years have dealt with the health impact of residence in the neighborhood of industrial contaminated sites. The journal *Annali dell'Istituto Superiore di Sanità* has contributed to this exercise by publishing studies concerning contaminated areas both in Italy and abroad [1-11]. The purpose of the present Commentary is to examine one specific and to some extent controversial issue, that is the contribution of epidemiological surveillance to the detection of certain or suspected causal agents amenable to preventive action.

In Europe, earlier industrialization and poor environmental management practices have left a legacy of thousands of contaminated sites and the issue of contaminated sites has been included among the priorities of the Declaration of the Sixth Ministerial Conference on Environment and Health of the European Region of WHO [12].

Estimates of the overall health impact of contaminated sites in Europe are not yet available. Nevertheless, a series of documents provided by the COST Action Industrial Contaminated Sites and Health Network (a collaborative effort coordinated by the Istituto Superiore di Sanità – ISS, that involved experts and practitioners in the environmental and health fields of about 30 countries in the years 2014-2018 www.icshnet.eu), reported some tools for the assessment of health risk and impact associated to single contaminated sites including how to develop and feed communication strategies. A compilation of reviews on the main approaches to study health risks and impacts from industrially contaminated sites resulting from the ICSHNet activities are documented within a collection of articles published in a special issue dedicated to "environmental health challenges from industrial contamination" [13, 14].

When considering both the available evidence of an ascertained health impact of contaminated sites on the population living in their surroundings and the aims and procedures of *ad hoc* epidemiological surveillance programs, a red thread connecting the two issues is undoubtedly represented by the search for cause-effect relationships.

There is consensus in the international scientific literature about the requirements that epidemiological studies should meet to corroborate or confute a specific etiological hypothesis concerning the association between environmental exposures and health outcomes, and the criteria for such evaluation have been defined. A comprehensive discussion of such issues is included within the latest edition of the preamble of the IARC monographs on the evaluation of carcinogenic risk to humans [15].

The availability of a body of epidemiological evidence in assessing causal hypotheses has been thoroughly debated. The heart of the matter is that the possibility that bias, confounding or misclassification of exposure

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and outcome that could explain the observed association should be ruled out with reasonable confidence. This generally implies that the epidemiological evidence be based on analytical studies adopting a cohort, case-control or other study designs with direct observation of the individual study subjects, rather than on geographic studies where the unit of observation is represented by spatially aggregated data [16]. Nevertheless, in the context of contaminated sites, optimal study designs for contributing to assessing causality are often infeasible due to scarce resources in economic, technical and temporal terms. In fact, analytical epidemiological studies are quite complex, generally designed to respond to single specific research questions, require years to be finished and are always expensive.

Epidemiological study models applied in contaminated sites are often based on descriptive approaches useful for generating hypotheses, while analytic studies are mainly used for testing hypotheses, though each type of study can be used for both purposes [17].

Some study designs applicable in contaminated sites can potentially be used for epidemiological surveillance, that is, the capacity to assess the evolution of health risk and impact over time. Such models are principally based on cross-sectional area-based designs, while the best option among analytical designs is essentially based on a (residential) cohort approach that can be eventually modelled by combining different designs (e.g., with a nested biomonitoring study for a fine-grained evaluation of chemical exposure, if appropriate) [4, 14].

The key points to be considered in deciding on epidemiological study designs and their potential application to a given contaminated site are the following:

- the need to set goals before selecting the study design. This point, apparently obvious, is not always fulfilled since it is not rare to see chosen a study design before setting the goals because of previous knowledge and confidence with that design;
- the need to assess the feasibility of the study design in a given context;
- the validity of exposure assessment, considering that it is essential in weighing the value of results, in particular, if the study is chosen to verify a given hypothesis;
- the fact that "before initiating a new epidemiological study in a contaminated site, it is important to be certain that the expected goals are attainable and that the research itself will support – rather than interfere with – pursuit of needed public health actions" [18];
- the fact that "where data systems are in place, risk assessment combined with epidemiological surveillance may often be the most efficient, informative response to the exposure event in a contaminated site" [18].

As described above, the most common study design adopted in contaminated sites is represented by the analysis of current health information systems or data from pathology registries (e.g., cancer registries), often based on aggregated data (geographic or micro-geographic approaches).

In Italy, for example, an epidemiological surveillance project (Progetto SENTIERI) is being applied to monitor cause-specific mortality and hospitalization, cancer incidence and prevalence of malformations at birth in 46 among the main Italian sites of interest for remediation activities (almost all of them, with few exemptions mainly due to feasibility aspects) [19, 20].

In this frame, it should be stressed that in SENTIERI both environmental and health data are aggregated at the municipality level (around 310 out of a total of about 8,000 in Italy at large). Municipalities are characterized in terms of the presence/absence of the main sources of contaminants. For some contaminated sites, health outcomes are defined considering priority index contaminants identified through data and information collection on contamination, followed by an indepth analysis of intrinsic toxicological profiles of single contaminants and the likelihood of exposure for the population [20].

Some authors have criticized the geographic epidemiological study design adopted in SENTIERI, stating that "Establishing causal links between specific environmental exposures and complex, multifactorial diseases and conditions is a challenging endeavor and requires stronger evidence than the one provided by studies based on aggregated data" [21].

Soskolne, *et al*. [22] have criticized this last paper speaking of research financially supported by special interests as a common and worrisome practice.

Since, in this frame, we are dealing with epistemological, not deontological, issues, it seems appropriate to refer to the underlying selected study design in terms of the methodology of scientific research.

Some authors suggest adopting a consequential epidemiological approach that extends beyond etiologic studies to test and document solutions [23]. Galea [24] stated that the purpose of epidemiology has to do with health organization and disease reduction, where methods are tools convenient only insofar as they help us get there. Brownson, *et al*. [25] had previously raised the point that the natural observation unit is made not at the individual level but rather at multiple levels of an ecologic framework. This last point perfectly fits with the contribution of epidemiological surveillance based on aggregate data to causal inference: "Epidemiological surveillance should integrate general systems of observation at macro-area level with particular systems of observation at local level... Regulatory guidelines and adequate financial support would make possible the implementation of cohort or other analytical studies apt to pursue the epidemiological characterization of a given area" [26].

Epidemiological evidence generated by health information systems available at different levels of geographic aggregation may contribute to detecting causal links in the frame of an integrated multidisciplinary approach. The "epidemiological characterization" of a given contaminated area resulting from the application of different study models is apt to assess causal links at a local level and can be seen as analogous to "triangulation" in aetiological epidemiology, that is the practice of obtaining more reliable answers to research questions through integrating results from several different approaches, where each approach has different key sources of potential bias that are unrelated to each other [27].

For the evaluation of causal links, the gold standard remains the aforementioned IARC Monograph paradigm. In particular settings, geographic epidemiologi-

cal methods and case series can constitute sufficient evidence of cancer risk in humans, as it was for fluoroedenite, the asbestiform fibre naturally occurring in soils at the slopes of the Etna Volcano in Sicily initially reported by ISS (see Bruno, *et al.* 2017 for a thorough reconstruction of the whole issue) and subsequently recognized by IARC as carcinogenic to humans with sufficient evidence [28].

The publication of the WHO Report "Urban redevelopment of contaminated sites" [29] has recently contributed to the increase in collective awareness about the relevance of the health impact of contaminated sites in Europe and the need to develop appropriate strategies of monitoring and intervention. Among the key messages, it is important to translate scientific evidence into practical action and provide competent authorities with financial resources and operational tools to evaluate the success (in terms of health) of remediation interventions.

Epidemiological surveillance may thus contribute to priority setting for prevention and health promotion, assessment of the decreased occurrence of diseases regarded as being of etiological interest (based on *a priori* knowledge), with a specific focus on vulnerable subpopulations [19, 20].

Geographic epidemiological studies, conducted in the context of a permanent updating of environmental characterization of the contaminated sites, have the potential to indicate both preventive action of ascertained effectiveness and, in front of uncertainties, interventions justified in terms of the precautionary principle. Adopting a precautionary-driven approach is of great interest considering promoting public health in contaminated sites, especially in those areas where polluting industrial activities have operated for decades. In these places, whatever study design recently implemented would be unable to assess causal links without any uncertainties. Nevertheless, in such sites, the final aims of epidemiological studies from a public health perspective should be to promote actions to prevent future risks, that is, considering partial and uncertain evidence on observed past and present risks as signals (i.e., facts) when giving recommendations for interventions.

Another final aspect being highlighted is that epidemiological surveillance studies and systems, if appropriately designed, can be used not only for assessing the risks and impacts associated with contamination but also for considering issues arising from an environmental justice perspective [30].

Communities living where polluting human activities are located often show disadvantages associated with exposure to noxious environmental contaminants and socioeconomic deprivation [31]. For such communities, there is a need to assess inequalities and inequities associated with contaminated sites in terms of distributive and procedural injustice [32]. National assessments based on country surveillance systems like SENTIERI, can thus be designed to assess the presence of distributive injustices at a country level and by geographical macro-area. This means identifying communities close to contaminated sites where the potential exposure to harmful contaminants is combined with the presence of socioeconomic deprivation and with health profiles showing higher than expected observed risks [33]. The primary aim of such efforts is thus not to assess causal links between environmental exposure, socioeconomic deprivation and health profiles, but to identify the communities with an overburden of fragilities, while local surveillance systems can be developed to assess the contribution of different factors to health risks thus allowing specific actions to reduce them.

In different contexts, e.g., toxic torts litigations or criminal prosecution, the aim may be to pursue the identification of causal links, respectively "more likely than not" and "beyond any reasonable doubt". This may occur in some particular settings. For public health goals, though, the priority is to throw light on complex causal webs with the aim of reducing the likelihood of occurrence of environmentally-related adverse health effects with different degrees of credibility.

Conflict of interest statement

No potential conflict of interest.

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Characteristics of COVID-19 cases in Italy from a sex/gender perspective

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Abstract

Introduction. Coronavirus disease 19 (COVID-19) is an infectious disease caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). To date, few data on clinical features and risk factors for disease severity and death by gender are available.

Aim. The current study aims to describe from a sex/gender perspective the characteristics of the SARS-CoV-2 cases occurred in the Italian population from February 2020 until October 2021.

Method and results. We used routinely collected data retrieved from the Italian National Surveillance System. The highest number of cases occurred among women between 40 and 59 years, followed by men in the same age groups. The proportion of deaths due to COVID-19 was higher in men (56.46%) compared to women (43.54%). Most of the observed deaths occurred in the elderly. Considering the age groups, the clinical outcomes differed between women and men in particular in cases over 80 years of age; with serious or critical conditions more frequent in men than in women.

Conclusions. Our data clearly demonstrate a similar number of cases in women and men, but with more severe disease and outcome in men, thus confirming the importance to analyse the impact of sex and gender in new and emerging diseases.

Key words

- gender
- sex
- COVID-19
- SARS-CoV-2 infection
- coronavirus
- public health

INTRODUCTION

Coronavirus disease 19 (COVID-19) is an infectious disease caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), a newly discovered human coronavirus. It was first reported in December 2019 in China [1], and then spread rapidly worldwide, being declared by the World Health Organization (WHO) a public health emergency of international concern on 30 January 2020 [2]. As to date (30 July 2021) it caused about 200 million cases and more than 4 million deaths worldwide. Most people affected by COVID-19 develop a mild to moderate respiratory illness and they recover without any specific treatment. However, older people and those with pre-existing and/or underlying medical problems, like cardiovascular disease, diabetes, obesity, chronic respiratory disease, and cancer are more likely to develop severe respiratory illness that often requires admission to an intensive care unit (ICU) [1].

Global data strongly indicates that a sex/gender-based disparity exists, with men being at higher risk of infection by SARS-CoV-2, hospitalisation, poor clinical outcomes and death due to COVID-19 than women [3]. Several international studies have reported a male/female ratio of COVID-19 infections and a Case Fatality Rate (CFR, percentage of deaths out of the number of observed cases of infection) that are higher in men as compared to women [4, 5]. In particular, two epidemiological studies from 38 countries reported a mean CFR in men 1.7 times higher than in women [6, 7]. In addition, long-term COVID-19 outcomes after intensive care unit (ICU) admission are worse in critically ill men compared to their female counterparts [8]. Similar sex-based disparities have been previously observed with the Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) epidemics [9, 10].

Many factors can contribute to the disparity in disease outcomes observed between adult men and women, including intrinsic differences in innate and adaptive immunity, the role of sex hormones, as well as gender specific differences in behaviours [11]. All these factors confer a protective advantage against COVID-19 to women, which have been reported to have lower viral loads, lesser inflammation, better clinical outcomes and lower mortality as compared to men. Furthermore, it is

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also important to underline that sex differences in COVID-19 clinical outcomes could reflect the difference between women and men in pre-existing comorbidity rates.

To date, data on clinical features and risk factors for disease severity and death in infants, children, and adolescents are still limited, while sex/gender analyses and comparisons with clinical characteristics, disease progression, and outcome, in both adults and children, are almost completely missing. However, it has recently been suggested that male gender is not an independent risk factor of severe COVID-19 in children [12]. Children appear to be less commonly affected by SARS-CoV-2 infection than adults, with a clinical course milder than adults [13, 14], even if a minority of children with COVID-19 require hospitalization, and severe cases have also been reported [15].

Collection, integration and sharing of disaggregated epidemiological data must be promoted to allow the analysis of the risk factors associated to COVID-19, including those related to sex and gender. This could help in the development of adequate therapeutic protocols, more targeted care and prevention strategies for specific groups of patients and population.

In this vein, the current study aims to describe from a sex perspective the characteristics of the SARS-CoV-2 cases occurred in the Italian population from the beginning of its spread in February 2020 until 31 May 2022, and provides insight into sex related issues to explain the disease dynamic in the Italian population.

MATERIAL AND METHODS

Data sources

We used routinely collected data retrieved from the Italian National Surveillance System of confirmed SARS-CoV-2 infections until 31 May 2022. The Istituto Superiore di Sanità coordinates this system, established on 27 February 2020. Data are collected and entered daily on a secure online platform by the 19 Italian regions and the two Autonomous Provinces (AP), according to an increasingly harmonized track-record [16]. As previously described [17], this surveillance system collects data on all SARS-CoV-2 confirmed cases, following the international case definition that considers as a confirmed case any person with laboratory confirmation of SARS-Cov-2 virus, irrespective of clinical signs and symptoms [18]. Data collected include information on the demographics, clinical outcomes, date of diagnosis, and geographical area of diagnosis. All records are checked for inconsistencies and duplicate by the coordinating centre. The scientific dissemination of anonymised COVID-19 surveillance data was authorised by the Italian Presidency of the Council of Ministers, thus no specific ethics approval was needed.

Data on co-morbidities were available only for deceased patients, for whom a detailed analysis of medical records was carried out by experienced clinicians.

Study population and endpoints

The cases were divided by age from 0 to 90 and over in ten age groups. The case distributions in the study period (epidemic curve) were made by dates of diagnosis and symptom onset. The primary outcome of the study was to outline the epidemiological and clinical characteristics of COVID-19 cases in Italy by sex.

The epidemiological characteristics described were:

1. distribution of the cases in the study period (epidemic curve) and reporting rate of infections (n. of reported cases per 1,000 inhabitants) by region, age and sex;
2. CFR as percentage of deaths among the cases, in general and by age and sex.

Basic clinical information was routinely collected by public health officers through telephone interviews to the cases, usually at the beginning of the quarantine and at the end. Symptoms were self-reported by cases during telephone interview. Clinicians assessed patients with more severe disease. The clinical severity was classified as:

- *asymptomatic*: a case positive to the SARS-CoV-2 molecular testing but without clinical signs;
- *mild:* a case with stable and within normal limit vital signs, and excellent indicators for recovery;
- *severe*: according to WHO (www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-2), severe COVID-19 was defined as the presence of any of the following: oxygen saturation <90% on room air; in adults, signs of severe respiratory distress and, in children, very severe chest wall indrawing, grunting, central cyanosis, or presence of any other general danger signs (inability to breastfeed or drink, lethargy or reduced level of consciousness, convulsions) in addition to the signs of pneumonia;
- *critical*: according to WHO critical COVID-19 was defined by the presence of acute respiratory distress syndrome (ARDS), sepsis, septic shock, or other conditions that would normally require the provision of life-sustaining therapies such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy.

A patient was considered recovered from the infection if tested negative to a follow up swab.

Statistical analysis

We described the main demographic and clinical characteristics and the distribution of cases over time by sex using counts with percentages and median for categorical and continuous variables, respectively. The comparison by sex and age groups of the main endpoints using Chi-square tests for categorical variables to detect the significant differences ($p < 0.05$) between groups. The statistical package used for the analysis was Stata 16.1 (StataCorp 4905 Lakeway Drive, College Station, Texas 77845 USA). The infection rates were calculated by using the data on the January 1st 2020 Italian population divided by sex and age groups provided by the Italian National Institute of Statistics (www.istat.it/en/). CFR, not accounting for delays, were calculated by age and sex. Chloropleth maps were built with QGIS version 3.10 (https://qgis.org).

RESULTS

In the period 17 February 2020 to 31 May 2022 in Italy 17,542,535 cases of COVID-19 and 164,071 deaths among cases were reported. On 31 May, 15,448,821 out of 17,542,535 (88.06%) recovered from the infection.

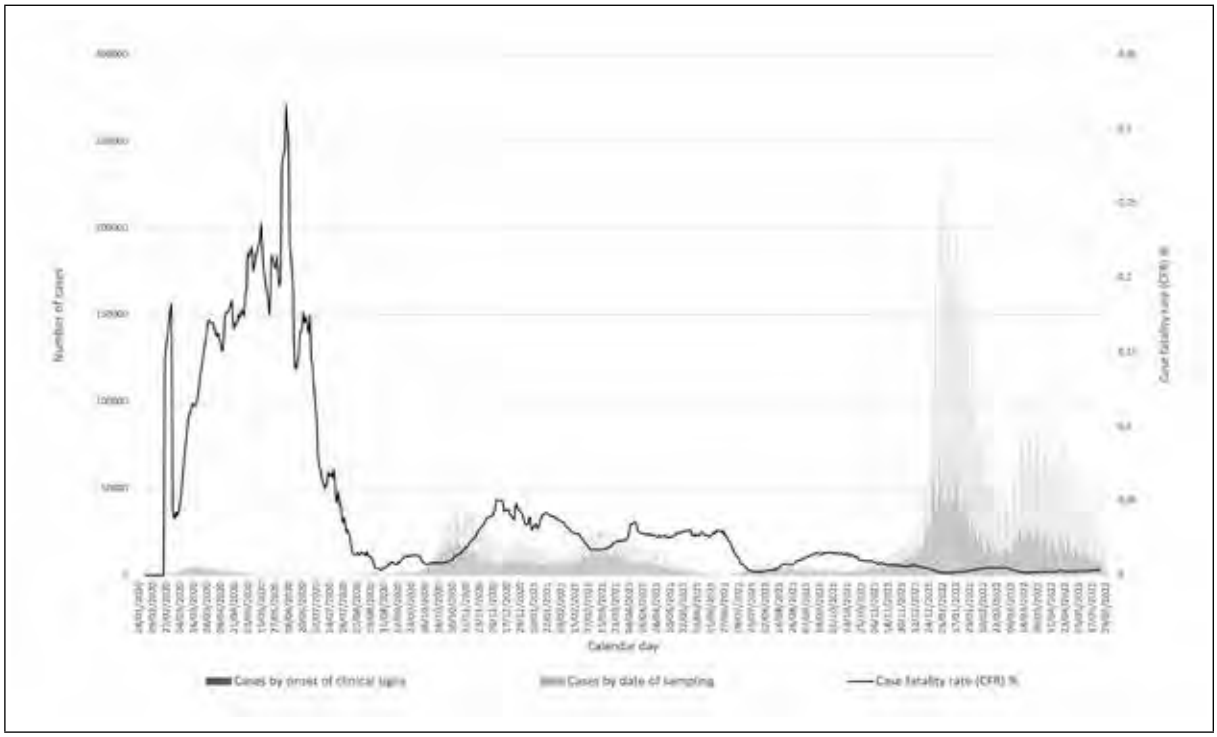

Figure 1
SARS-CoV-2/COVID-19 infections from 17 February 2020 to 31 May 2022 in Italy.
Number of cases of SARS-CoV-2/COVID-19 infection diagnosed from 17 February 2020 to 31 May 2022 in Italy (Data from the Italian National Surveillance System of confirmed SARS-CoV-2 infections, Istituto Superiore di Sanità). The number of cases are reported by date of sampling (light grey) and by onset of clinical signs (dark grey). The black line represents the percentage of case fatality rate (CFR).

The distribution of the COVID-19 cases in Italy by date of symptoms onset and by date of sampling is shown in *Figure 1*. As observed in most of the Western European countries, also in Italy the epidemic showed five main waves, with the peak in January 2022. The relatively low number of cases during the first pandemic wave was due to the shortage of diagnostic tests, which were conducted mainly in symptomatic patients. On the contrary, from July 2020 the availability of more testing options (molecular and antigenic) and the abundance of diagnostic kits allowed to extend the screening to positive case contacts and suspected people, even if asymptomatic, consequently the number of positive cases increased. The trend of the weekly-diagnosed cases was similar in male and female patients throughout the observation period, except for the first three months, when there was first an increase in male cases, immediately followed by an increase in female ones (data not shown).

The cumulative COVID-19 infection rate assessed by Italian region *(Figure 2)* showed that the North Western regions were the most affected by the pandemic while the Southern regions were those where the virus circulated the less. The only exception is Valle d'Aosta, the smallest Italian region located in the North-West, mostly covered by Alps Mountains.

The median age of diagnosed cases was 45 years, with no differences between males and females except for the initial period between March and April 2020, when the median age was significantly higher in female (80 years) with respect to male (70 years).

The proportion of the 164,130 deaths due to COVID-19 was higher in men (55.94%) compared to women (44.06%), with the highest number of deaths observed in males aged 80-89 (35,572) *(Table 1)*.

The overall reporting rate in Italy was 290.70 cases/1000 inhabitants, with the highest one (406.67) observed in women aged 10-19. The reporting rates were statistically different between males and females in each age group, as shown in *Table 1*.

The overall CFR was 0.93%, however great differences were observed when age and sex were considered *(Table 1)*. The CFR was substantially <1% in both sexes until the age of 50 years. Over 50 years, the CFR was always higher in men than in women, and this difference increased according to age (from 2.67% at 70 years to 7.66% at 90 years).

From January 2021 the vaccination campaign started and the CFR decreased in both sexes, in particular from July 2021, when the administered vaccine doses were more than 25 million.

In a subset of 8,436 deceased SARS-CoV-2 patients the most common comorbidities diagnosed before the infection were described *(Table 2)*. The mean number of comorbidities was 3.7 (median = 3, SD = 2.1). Overall, 2.9% of the patients presented no comorbidities, 11.3% one comorbidity, 17.9% two, and 67.8% three or more comorbidities. In women (n = 3,424) the average num-

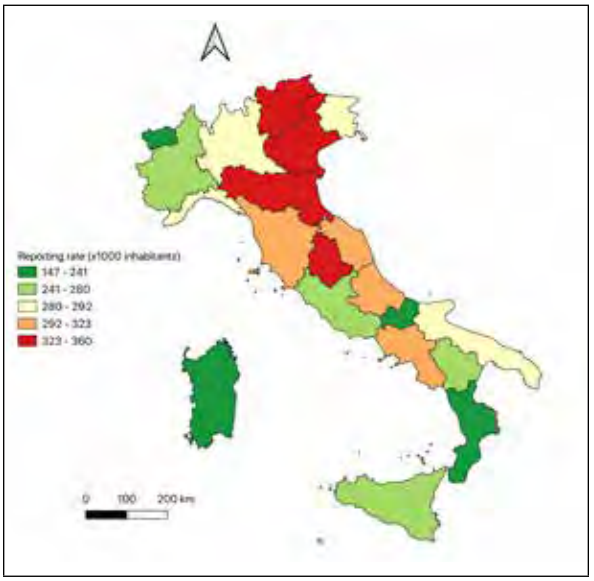

Figure 2
COVID-19 cumulative notification rate in Italy.
Choropleth map of the COVID-19 cumulative notification rate in Italy from 17 February 2020 to 31 May 2022.

ber of observed pathologies is 3.9 (median = 4, range 0-12) while in men (n = 5012) is 3.6 (median = 3, range 0-12).

By comparing the frequency of the main comorbidities, the main differences between women and men were observed for ischemic heart disease (23.66% in women and 31.30% in men, p <0.01), dementia (31.98% in women and 17.80% in men, p >0.01) and autoimmune diseases (6.45% in women and 3.51% in men, p >0.01).

In *Table 3*, the total number and the percentage of the different clinical outcomes in COVID-19 patients according to age and sex are reported.

Overall, a higher number of serious and critical cases occurred among men, while asymptomatic and mild cases were more among women. However, considering the age groups, among over 80 years of age the clinical severity was more frequent in women than in men (44.50% of the female severe cases *vs* 35.11% of the male ones; p <0.01). On the contrary, our results showed a higher percentage of male severe cases with respect to female ones, between 40-79 years (57.05% *vs* 43.95%; p <0.01). The reason beyond these two apparently contrasting claims is probably due to the hormonal protection that women have during their fertile period, which disappears after menopause, as treated in the discussion section.

We also observed that in people under 20 years of age the percentage of asymptomatic or mild cases was 99.60%, but this percentage decreased over the age groups, with the lowest value in males over 90 years of age *(Figure 3)*.

DISCUSSION

In this study, we used data retrieved from the Italian National Surveillance System of confirmed SARS-CoV-2 infections to elucidate features of COVID-19 infection that differ between male and female patients in terms of exposure and outcomes. Our data are consistent with previous reports clearly demonstrating a similar number of cases in women and men, but with more severe disease in men [19-21].

The overall number and proportion of cases of COVID-19 were slightly higher in women than in men, with greatest difference in the age groups from 20 to 60 years. This last result was quite unexpected because women were more likely to agree with the COVID-19 restriction measures and more compliant with such

Table 1
COVID-19 deaths, notification rates and case fatality rate by sex and age in Italy

Age groups	Cases			Deaths			Reporting rate (x1000)			Case fatality rate (%)		
	Female	Male	Total	Female	Male	Total	Female	Male	Total	Female	Male	Total
0-9	796,775	854,017	1,650,792	16	11	27	322.139	326.323*	324.290	0.002	0.001	0.002
10-19	1,133,915	1,140,688	2,274,603	14	16	30	406.673	382.704*	394.289	0.001	0.001	0.001
20-29	1,089,962	1,015,641	2,105,603	42	79	121	364.650	316.182*	339.544	0.004	0.008	0.006
30-39	1,302,050	1,090,096	2,392,146	158	259	417	370.420	306.280*	338.150	0.012	0.024	0.017
40-49	1,568,264	1,300,867	2,869,131	500	1,059	1,559	337.343	283.180*	310.423	0.032	0.081	0.054
50-59	1,412,128	1,242,534	2,654,662	1,769	4,236	6,005	295.819	271.378*	283.853	0.125	0.341	0.226
60-69	843,040	776,569	1,619,609	4,873	11,857	16,730	220.335	221.179*	220.739	0.578	1.527	1.033
70-79	563,582	531,503	1,095,085	13,538	26,926	40,464	174.185	194.904*	183.661	2.402	5.066	3.695
80-89	394,506	287,615	682,121	30,376	35,572	65,948	182.676	206.035*	191.847	7.700	12.368	9.668
90 and over	148,654	54,034	202,688	21,015	11,782	32,797	263.011	258.131*	261.692	14.137	21.805	16.181
Not known	99	105	204	15	17	32						
Total	9,252,975	8,293,669	17,546,644	72,316	91,814	164,130	298.726	282.244*	290.702	0.782	1.107	0.935

Distribution of the number of cases of COVID-19, deaths, infection rates (number of cases/ population), and case fatality rate by sex and age group from17 February 2020 to 31 May 2022 in Italy. Asterisk indicate statistically significant differences between female and male age groups (p>0.01).

Table 2
Comorbidities by sex in SARS-CoV-2 positive deceased patients in Italy

	Total cases		Women		Men	
Number of comorbidities per patient	**N**	**%**	**N**	**%**	**N**	**%**
No comorbidities	246	2.9	67	2.0	179	3.6
1 comorbidity	955	11.3	337	9.8	618	12.3
2 comorbidities	1,512	17.9	586	17.1	926	18.5
3 comorbidities and more	5,723	67.8	2,434	71.1	3,289	65.6
Comorbidities	**N**	**%**	**N**	**%**	**N**	**%**
Ischemic heart disease	2,379	28.2	810	23.7	1,569	31.3
Atrial Fibrillation	2,114	25.1	901	26.3	1,213	24.2
Heart failure	1,349	16.0	623	17.8	726	14.2
Stroke	950	11.3	419	12.2	531	10.6
Hypertension	5,550	65.8	2,327	68.0	3,223	64.3
Type 2-Diabetes	2,459	29.1	934	27.3	1,525	30.4
Dementia	1,987	23.6	1,095	32.0	892	17.8
COPD (Chronic Obstructive Pulmonary Disease)	1,476	17.5	487	14.2	989	19.7
Active cancer in the past 5 years	1,362	16.1	490	14.3	872	17.4
Chronic liver disease	427	5.1	145	4.2	282	5.6
Dialysis	198	2.3	66	1.9	132	2.6
HIV Infection	19	0.2	2	0.1	17	0.3
Autoimmune diseases	397	4.7	221	6.5	176	3.5
Obesity	981	11.6	391	11.4	590	11.8

Distribution by sex of the main comorbidities diagnosed before SARS-CoV-2 infection in a representative subset of SARS-CoV-2 positive deceased patients (n=8436) in Italy.

Table 3
Clinical severity of COVID-19 cases by sex and age in Italy

Clinical severity	**Age group (years)**										**TOTAL**
	0-9	**10-19**	**20-29**	**30-39**	**40-49**	**50-59**	**60-69**	**70-79**	**80-89**	**90 and over**	**Not known**	
Asymptomatic	9.72%	13.03%	11.24%	13.12%	14.86%	15.44%	10.17%	6.92%	4.24%	1.26%	0.00%	948,037
Female	8.82%	12.44%	11.11%	13.42%	15.33%	15.57%	10.16%	6.84%	4.63%	1.68%	0.00%	502,704
Male	10.74%	13.69%	11.39%	12.78%	14.32%	15.28%	10.20%	7.01%	3.80%	0.78%	0.01%	445,333
Mild	9.90%	12.70%	10.65%	12.78%	15.60%	15.82%	9.68%	6.90%	4.63%	1.34%	0.00%	334,800
Female	8.82%	11.96%	10.57%	13.30%	16.32%	16.10%	9.61%	6.76%	4.84%	1.72%	0.00%	183,198
Male	11.21%	13.60%	10.76%	12.16%	14.73%	15.47%	9.76%	7.06%	4.38%	0.88%	0.00%	151,602
Severe	2.61%	1.36%	1.99%	3.62%	5.08%	9.71%	14.05%	21.96%	29.59%	10.05%	0.00%	6,777
Female	2.29%	1.42%	2.87%	4.97%	4.48%	7.91%	11.64%	19.92%	31.90%	12.60%	0.00%	3,238
Male	2.91%	1.30%	1.19%	2.37%	5.62%	11.36%	16.25%	23.82%	27.47%	7.71%	0.00%	3,539
Critical	1.43%	1.43%	1.43%	3.17%	6.95%	16.04%	23.19%	25.33%	17.26%	3.27%	0.51%	979
Female	0.81%	1.89%	1.89%	3.50%	8.36%	13.75%	22.37%	22.37%	19.68%	4.58%	0.81%	371
Male	1.81%	1.15%	1.15%	2.96%	6.09%	17.43%	23.68%	27.14%	15.79%	2.47%	0.33%	608
Total	9.72%	13.03%	11.24%	13.12%	14.86%	15.44%	10.17%	6.92%	4.24%	1.26%	0.00%	2,581,186

Clinical severity of COVID-19 cases (in percentage) by sex and age group from 17 February 2020 to 31 May 2022 in Italy (details available for 2581186 cases).

measures than men, according to a recent international survey that included also Italy [22]. Behaviours, occupations, and societal and cultural norms may account for these differences in exposure to SARS-CoV-2 [23]. Indeed, women may have greater exposure then men, probably in relation to their social role of caregivers [19]: about 70% of health and social care workforce are women including frontline healthcare workers [24]. Moreover, women are more likely to care for children and/or other relatives in case of illness [25].

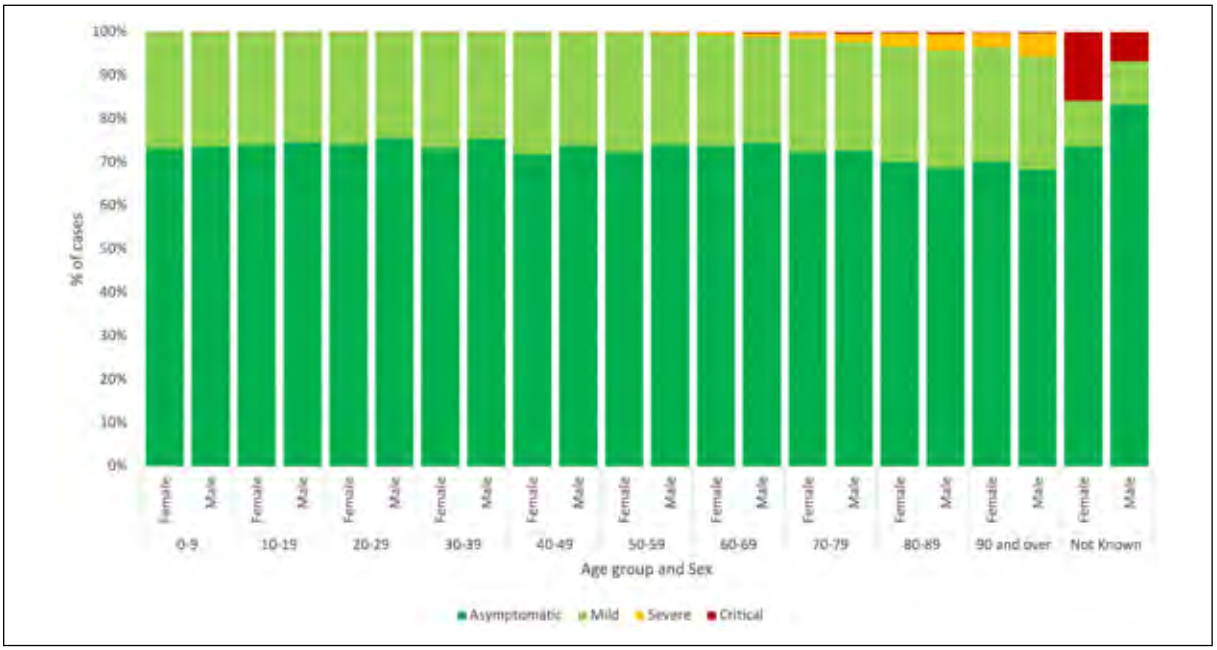

Figure 3
COVID-19 clinical cases by age and sex in Italy.
Percentage of COVID-19 cases by clinical severity, age group and sex in Italy from 17 February 2020 to 31 May 2022.

In the general population, we found that the infection rate was higher in women, but changed over 60 years of age, with higher proportion in men than in women. The different infection rate in the over 60 population could be due to both the lower perception of risk and the lower compliance with the restrictive measures of men compared to women. Furthermore, the health conditions of women in this age group are often worse, or perceived as worse than men, causing women to be more concerned about COVID-19 and consequently more compliant with the rules [22]. We also showed that the median age of diagnosed cases in Italy was different in male and female patients only during the first months of SARS-CoV-2 infection, when it was significantly higher in female. This was probably due to a number of outbreaks that occurred in Residential Care Facilities, where the people hosted were mainly elderly women, because of their longer life expectancy than men [26].

This different life expectancy among sexes may play thus a key role in the higher SARS-CoV-2 infections in Italy in women over 90 years of age, which is almost three times higher than in men.

According with previous reports, we found that, despite an equal distribution between men and women, the prevalence of severe symptoms and mortality rate are higher in male patients than in female ones [1, 27]. The Global Health 50/50 research initiative presented results of the Covid-19 sex-disaggregated data worldwide, clearly demonstrating an increased CFR in men in the majority of countries [4]. Our results confirmed that CFR in Italy was higher in men than in women, with significant difference over the 50 years of age. Moreover, a higher percentage of critically diseased men were reported in all the age groups studied, except in over 80 years group, where the greater number of older women affected the results.

Variations in disease severity and mortality rates were suggested to be associated with both gender (sociocultural) and sex (biological) differences [19]. Some social and behavioural habits more common in Italy among males, such as tobacco and alcohol consumption, are closely associated with COVID-19 comorbidities, including cardiovascular and lung diseases [6] and may account for some gender differences.

Sex-related genetic and hormonal factors and different immunological responses may also play a role in the sex bias in COVID-19 patients [28]. Unfortunately, we could not assess the level of sex hormones in the examined cohort because biological samples were not available. However, data from scientific reports strongly suggest that the poorer outcome in men can be explained by the intrinsic differences in innate and adaptive immunity as well as in sex hormones [29]. In particular, a lower testosterone concentration, that is typical of elderly men, has been considered among the risk factors for poor outcomes. The severity of COVID-19 illness, indeed, seems to coincide with the nadir of lifetime testosterone; furthermore, the comorbidities that predispose individuals to increased COVID-19 severity were associated with lower testosterone concentrations [30]. It was also demonstrated that increased estradiol to low testosterone ratio was associated with disease severity, inflammation and mortality in men with COVID-19 [31]. Moreover, a retrospective cohort study [32], showed that high estradiol and low testosterone levels were associated with critical illness in male but not in female COVID-19 patients, thus confirming that disturbance of sex hormone metabolism might represent a hallmark in critically ill men affected by COVID-19.

These results provide a possible explanation for the highest CFR in men over fifty years of age found in the present study.

Finally, our findings on children/adolescent COVID-19 patients confirmed recent results [33] showing that they have milder symptoms compared to adult (more than 99% of the cases under 19 years were asymptomatic or with mild symptoms). The reason for this finding is still unclear, but it could be related to a lesser development, at a younger age, of the angiotensin-converting enzyme (ACE) receptors, the recognised cellular receptor of the SARS-CoV-2 spike protein [34]. Moreover, since a cytokine storm has been involved in the pathogenesis of severe forms of the disease in adults [35], it has been hypothesized that children may have a weaker immune response to SARS-CoV-2 compared with adults [36].

In contrast with adults, in whom older age is an independent risk factor for severity and mortality, very young age seems to be a risk factor for severity in children [12]; however, sex/gender analyses in children are still very scarce.

Our analyses showed some limitations, mainly due to the data access constraint for privacy and data protection reasons. The level of detail in the data did not permit any additional inference about the role of sex and gender in the risk of severe illness and death. On the other hand, our analyses can provide insight into the risk of disease in the different age and sex groups, and speculate on some social and biological aspects potentially related to such risks.

Data collected from the Italian integrated COVID-19 surveillance system during the initial phase of the emergency presented some shortcomings, mainly related to lack of completeness. For this reason, the number of cases during the first pandemic are relatively low. In addition, not all regions reported the date of sampling at the beginning of the outbreak and when missing, we used date of diagnosis to construct epidemic curves. This has limitations because there is a lag between diagnostic sampling and confirmation of laboratory results. However, this interval is expected to be limited to 2-3 days and not to bias excessively the presentation of the time distribution of cases.

In conclusion, our data, retrieved from the Italian National Surveillance System of confirmed SARS-CoV-2 infections until 31 May 2022, further confirm the importance of integrating a sex/gender analysis into future studies, to better understand the complex interaction among sex/gender, age and disease exposure/outcomes. Preparedness and intervention plans for future pandemics should take into account these differences and seek to collect and evaluate data at individual-level by addressing sex/gender differences. These data contribute to provide the scientific basis to enable effective public health measures and specific gender-targeted solutions, also reducing both the social and the economic costs.

Authors' contributions

Conceptualization: LB, MD, PP and CC; methodology: LB, PP, MdM; data collection: extraction and analysis: AB, MdM, MS, SB, MB, DP, CS, MF, MFV, FR, PP; writing - original draft preparation: MD and CC; writing - review and editing: MD, CC, LB, PP and RM; funding acquisition: LB. All Authors have read and approved the final manuscript as submitted.

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Data availability statement

The data presented in this study are freely available on the www.epicentro.iss.it/coronavirus/sars-cov-2-sorveglianza-dati website (accessed on 18 October 2021).

Conflicts of interest statements

The Authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

Ethics approval

This study was not submitted for approval to an ethical committee because the scientific dissemination of COVID-19 surveillance data was authorized by the Italian Presidency of the Council of Ministers on 27 February 2020.

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Neurorehabilitation of severe acquired brain injury in the time of COVID-19: impact of the absence of caregivers

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Abstract

Introduction. During the COVID-19 pandemic, several restrictions were imposed to limit the circulation of the infection within communities. Hospitals denied access to the family and friends of inpatients, and thus to caregivers. This observational study evaluated the impact of the physical absence of caregivers during the lockdown period due to the COVID-19 emergency on the rehabilitation of inpatients with severe acquired brain injury (sABI).

Methods. The functional outcome at discharge was measured in 25 inpatients with sABI through the Disability Rating Scale (DRS), Glasgow Outcome Scale (GOS), and Levels of Cognitive Functioning scale (LCF) after neuropsychological rehabilitation in an Adult Inpatient Neurorehabilitation Unit for Patients with sABI. Fourteen patients were directly assisted by their informal caregivers physically present in the neurorehabilitation ward. Eleven patients were indirectly supported via remote connection because during the lockdown period (from March to July 2020) caregivers could not be admitted to the rehabilitation hospital. The Caregiving Impact on Neuro-Rehabilitation Scale (CINRS) was also used to evaluate both the change since the admission and the impact of the caregiver from the perspective of the cognitive therapist. Demographic characteristics, time since injury, injury severity (duration of impaired consciousness measured by the time to follow commands), level of functioning at the beginning of the rehabilitation, and duration of the rehabilitation treatment were comparable between the groups.

Results. Both groups improved after the treatment; however, the improvement was consistently greater in the group directly assisted by the caregivers. The results showed that although the caregivers ensured their virtual presence at distance, their physical absence played a role in hindering the functional outcome of the patients.

Conclusions. The role of the caregiver of patients with sABI is underlined in being not only a person handing out generic aid, cares, and affection, but also an integral part of the rehabilitation process.

Key words

- brain injury
- neurorehabilitation
- informal caregiver
- COVID-19 pandemic
- SARS-CoV-2
- lockdown

INTRODUCTION

A recent observational study [1] examined the role played by informal caregivers in the neurorehabilitation setting of patients with severe acquired brain injury (sABI), focusing on the relationships between the quality of caregiving and the psychological status of caregivers. On that occasion, the Authors developed the Caregiving Impact on Neuro-Rehabilitation Scale (CINRS), a scale based on a brief questionnaire completed by cognitive rehabilitation therapists to evaluate the *quality* and *amount* of informal caregiving.

The informal caregiver ("caregiver" from now on) is considered each person who, voluntarily and without receiving any payment, provides care and support to a loved one who is not self-sufficient in his/her family or social network [2].

In clinical practice, the importance of a global rehabilitation approach in many populations of patients (e.g., after sABI, spinal cord injury, neurodegenerative or oncologic diseases, etc.) is well known. Moreover, from a biopsychosocial perspective [3], it is necessary to implement a specific rehabilitation protocol with the support of the caregiver, who is a very relevant piece of the puzzle composed by the rehabilitation team as a whole.

However, the literature about the role of caregiving

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in rehabilitation settings is not ample and has produced contrasting results about the actual effectiveness of caregiving during the rehabilitation period or after discharge. For example, caregiver availability can be associated with a better outcome (e.g., a better motor improvement after treatment was found when caregivers were involved [4]), but alternatively it was hypothesized that either unavailability of caregivers can be associated with a better outcome (presumably because the awareness of the absence of any kind of help after discharge makes the motivation rise), or caregivers availability may hamper the outcome because their overprotection may reduce the patient's motivation to cooperate to the rehabilitation process [5]. Also, Ong and co-workers [6] explored how caregiving affects the rehabilitation outcome in sub-acute stroke and concluded that the primary caregiver identity (that is, whether he/she was a foreign domestic worker or an informal caregiver such as spouses), as well as their availability, seem to affect the rehabilitation outcome. In particular, there seemed to be a negative association between hired non-professional caregivers and the outcome at discharge.

Despite these examples of contrasting results, if one considers the increase in population ageing and the increased incidence of ABI, there is general agreement that there will be an increasing need for caregiving. In particular, caregiving is essential in the care of patients with sABI who, along with complex, multi-professional, and long-lasting rehabilitation programs, need constant assistance by a caregiver (e.g., [7]).

In many rehabilitation centres, before the COVID-19 pandemic, caregivers actively participated in the individual rehabilitation project (IRP) that is elaborated, as project manager, by the physician expert in physical and rehabilitation medicine (a physiatrist or other rehabilitation equipollent physician such as a neurologist, orthopaedic, rheumatologist, geriatrist, etc.), in coordination with the other professionals of the team. The caregiver cooperated with the team in many ways, for example, facilitating the communication of the patients' needs to the rehabilitation team, as well as engaging the patient in tasks and exercises in the intervals between formal rehabilitation sessions [8]. As COVID-19 became pandemic, several restrictions were imposed to limit the circulation of the infection within communities. In 2020, during the first wave of the COVID-19 pandemic, Italian hospitals denied access to the family and friends of inpatients, and thus to caregivers [9]. Our neurorehabilitation hospital (Santa Lucia Foundation, Rome) had to restrict any access of family members from 10 March to July. Consequently, during that lockdown period, newly admitted inpatients could not be directly assisted by any caregiver, while the caregivers of inpatients admitted before that date had to interrupt their assistance "in presence". Therefore, during the lockdown, the patients could be supported only indirectly by their caregivers, who were contacted by the patients' cognitive therapists (in the presence of the care recipient) on average two-three times per week, by a 15-minute lasting video call (via tablet).

The present study involved two groups of adult inpatients with sABI matched for demographic and clinical variables, admitted to a Neurorehabilitation Unit for Post-Coma patients. All patients were admitted with the diagnosis of sABI in the acute phase, that is, they were all suitable for an intensive rehabilitation program. Both groups underwent an IRP by a multi-professional rehabilitation team, according to the biopsychosocial approach [3], which emphasises the central figure of the patient and caregiver. The patients of one group were admitted before the COVID-19 outbreak and directly assisted by caregivers who were physically present in the neurorehabilitation ward for the whole length of stay. The patients of the other group were admitted during the COVID-19 outbreak and assisted during their stay by remotely connected caregivers. In particular, the caregivers who were physically present in the ward had daily contact and actively interacted with the cognitive therapists and the rehabilitation team. These caregivers directly assisted their care recipients, spending most of the day with them, thereby helping them in generalizing outside the rehabilitation setting the behaviours and daily activities focussed during the intervention. Conversely, the caregivers who were active during the lockdown could only participate through a remote modality and could not physically interact with their loved ones. Therefore, the peculiar though anguishing circumstances that occurred under the COVID-19 pandemic determined an exceptional forced condition, allowing us to evaluate what happens when caregivers cannot be physically present in the hospital. In fact, despite the cognitive therapists supplying both groups of caregivers with the same kind of indications along the IRP, the caregivers of the patients admitted during the lockdown had only a poor chance to implement them because their care recipients could only be contacted by video calls of short duration.

This observational study aims to examine the impact of the physical absence of the caregivers in the hospital on the outcome of inpatients with sABI. On one hand, the outcome at discharge was measured by standard instruments for evaluation of sABI (Disability Rating Scale: DRS; Levels of Cognitive Functioning scale: LCF; Glasgow Outcome Scale: GOS) and compared between the groups of inpatients. On the other hand, to evaluate the quality and amount of caregiving afforded by the physically present and the remote caregivers, the groups were compared using the Caregiving Impact on Neuro-Rehabilitation Scale (CINRS) [1].

METHODS

Participants

Forty-three inpatients with sABI consecutively admitted to the Neurorehabilitation Unit for Post-Coma of Santa Lucia Foundation in Rome (Italy) from February 2019 to May 2020 and their caregivers were enrolled on this observational study according to the inclusion criteria reported below. After having matched for gender, age, educational level, time since injury, injury severity (measured by time to follow commands, TFC), and level of disability at admission the groups of patients directly assisted and those not directly assisted by the caregivers, only twenty-five inpatients were included in the final sample. Fourteen patients were directly as-

sisted by their caregivers (who thereby were physically present, "Caregiver-IN") from February to December 2019, while 11 patients were only indirectly supported by their caregivers (group with a physically-out caregiver, from here on, "Caregiver-OUT") from March to July 2020.

The study was approved by the local Ethics Committee. All patients and their caregivers provided their written consent after being informed about the use of their data for the study.

Patients were selected according to the following inclusion criteria: 1) age ≥ 18 years; 2) diagnosis of severe ABI (Glasgow Coma Scale, GCS, score ≤ 8 in the acute phase); 3) presence of a primary caregiver who was involved by the cognitive therapist in the rehabilitation project of their loved one, whether he/she was physically present or not.

The inclusion criterion for both groups of caregivers was the absence of any current or previous severe neurological or psychiatric disorder.

The group of patients with Caregiver-IN consisted of 11 males and 3 females, with a mean age of 46.7 years (SD = 14.2), a mean educational level of 12.3 years (SD = 2.7), a mean time since the injury of 164.5 days (SD = 56.8), a mean TFC of 15.9 days (SD = 22.4), and a mean length of stay of 106.8 days (SD = 33.1). As for their aetiology, 6 suffered from TBI, 7 from vascular brain injury, and one from anoxic brain injury due to cardiac arrest. Caregivers-IN were 2 males (1 father and 1 husband) and 12 females (4 mothers, 6 wives/partners, 1 sister, and 1 granddaughter), with a mean age of 53.9 years (SD = 14.0), and a mean educational level of 12.2 years (median = 13.0; SD = 4.8). The group of patients with Caregiver-OUT consisted of 8 males and 3 females, with a mean age of 52.5 years (SD = 15.1), a mean educational level of 12.5 years (SD = 3.3), a mean time since the injury of 168.5 days (SD = 35.7), a mean TFC of 26.9 days (SD = 22.4), and a mean length of stay of 86.9 days (SD = 27.2). Three of them suffered from TBI, 4 from vascular brain injury, 1 from hypoxic coma due to a cardiac arrest, 1 from neurosurgical intervention of brain tumour removal, and 2 from meningo-encephalitis. Their caregivers were 1 male (a husband) and 10 females (1 mother, 5 wives/partners, 2 daughters, and 2 sisters), with a mean age of 46.8 years (SD = 9.0), and a mean educational level of 13.9 years (median = 13.0; SD = 3.0).

Measures

Patients' functional scores upon admission and discharge

Glasgow Outcome Scale (GOS). GOS [10] assesses the patients' functional recovery by 5 points, from 1 ("Death") to 5 ("Good Recovery", referring to light damage with minor neurological and psychological deficits).

Levels of Cognitive Functioning scale (LCF). LCF [11] assesses the cognitive and behavioural functioning levels of the patients. The score ranges from 1 (no response) to 8 (purposeful-appropriate).

Disability Rating Scale (DRS). DRS [12] assesses the level of disability in 8 areas of functioning: eye-opening, verbalization, motor response, levels of cognitive ability for feeding, toileting, and grooming, level of independence, and employability. The overall score can range from 0 to 29, with 0 representing intact functioning and 29 representing a vegetative state.

Caregiving evaluation

Caregiving impact on neurorehabilitation scale (CINRS)

The CINRS is an Italian questionnaire collecting information on the role of the caregiver in the neurorehabilitation process of adult patients with sABI [1]. The questions of Section A measure the *amount* of participation of the caregiver in the neurorehabilitation process and the *quality* of his/her caregiving. The final question (Section B) allows the cognitive therapist to subjectively evaluate the *general improvement* of the patient at the end of a period of rehabilitation. In detail, Section A measures the time spent in the hospital by the caregiver (item A1), the frequency of participation in the therapy sessions (A2), the level of participation/cooperation in the neurorehabilitation process (A3), and the availability of the caregiver when the therapist needs to communicate with him/her (A7). Moreover, it evaluates the possible presence of substituting attitude by the caregiver (A4), how much the patient cooperates when the caregiver is present (A5), and how much the caregiver trusts the neurorehabilitation process (A6). Finally, the therapist evaluates whether the global influence of the caregiver facilitated or hampered the whole neurorehabilitation process (A8). High scores in Section A indicate a high amount and better quality of caregiving. Section B is a 10-point scale, ranging from 0 ("no improvement") to 10 ("as much improved as possible") assessing the relative change from the beginning of the treatment. Further details about the response options for each item of the CINRS and the scores range are described in [1].

In the present study, the cognitive therapists responded to the CINRS to evaluate the caregiving of both the patients with Caregiver-IN and the patients with Caregiver-OUT. For this latter group, the cognitive therapists conveniently took into account the remote presence of the caregiver and responded to item A8 considering the influence globally played by the physical absence of the caregiver on the patient's rehabilitation.

Procedure

The observations for the comparisons between the groups were recorded at two time points: t0 and t1. The demographic and clinical baseline measures were taken at t0, immediately before the beginning of the rehabilitation period.

t1 was the time-point when the outcome was measured for both groups of patients at discharge (i.e., at the end of their rehabilitation). A neurologist administered the functional assessment (i.e., DRS, GOS, and LFC scales) to the patients at t0 and t1. A psychologist administered the CINRS at t1 to the cognitive therapist involved in the rehabilitation of the related patient.

Despite the pandemic and the lockdown period, standard rehabilitation protocols were maintained because the medical and rehabilitation staff did not undergo any change in the amount of personnel involved with respect to the pre-COVID-19 period, therefore both

groups of inpatients were treated in the same way, except for the absence of the caregivers in the ward during the lockdown in the case of the Caregiver-OUT group of patients.

Data analysis

Data analysis was carried out using SPSS software (version 27). Descriptive statistics were used to illustrate the demographic and clinical characteristics of the patients and caregivers.

Shapiro-Wilk normality test was used to determine if the variables (demographical and clinical data, standard scales scores, and CINRS scores) followed a normal distribution. Two-tailed t-tests for independent samples were run to compare the groups for normally distributed variables (age, time since injury, length of stay, and DRS at t0); Mann-Whitney tests were used for non-parametric analysis (educational level, TFC, GOS, LCF). For within-group comparisons between time points, t-tests and Wilcoxon tests for repeated measures were used for parametric and non-parametric analyses, respectively. As for DRS score, a one-way ANCOVA was used to compare the groups at t1 using the DRS at t0 as a covariate to control for a possible effect of the initial disability on the final score. As for the CINRS, differently from Bivona *et al.* [1], the total score did not include three items of Section A (A4, A5, and A6, concerning the trust of the caregiver in the rehabilitation process, his/her tendency to substitute for the patient, and the cooperation of the patients when the caregiver is remotely connected, respectively) because these were not fully applicable in the Caregiver-OUT group. Moreover, item A1 (time spent in the hospital by the caregiver) was excluded because it scored by default 1 for all the patients with Caregiver-OUT. Therefore, only the scores of the items A2, A3, A7, and A8 were summed up for both groups. This composite score as well as the score of Section B were submitted to parametric analysis for the group comparisons. Individual items of the CINRS Section A (except the items A4, A5 and A6 for the abovementioned reason) were singly compared between the groups with non-parametric tests.

RESULTS

Comparisons between Caregiver-IN and Caregiver-OUT groups

The groups of patients were comparable for gender ($X^2_{(1,\ N\ =\ 25)}$ = 0.115, p = 0.734), age ($t_{(23)}$ = 0.97, p = 0.343), educational level (U = 71.5, p = 0.767), time since injury ($t_{(23)}$ = 0.21, p = 0.839), TFC (U = 52.0, p = 0.183), and duration of rehabilitation ($t_{(23)}$ = 1.61, p = 0.121). The demographical features of the caregivers were comparable between the groups: there were no differences of gender $X^2_{(1,\ N\ =\ 25)}$ = 0.157, p = 0.692), age ($t_{(23)}$ = 1.46, p = 0.158), or educational level (U = 62.0, p = 0.434).

Standard scales at baseline (t0)

The groups of patients were comparable at t0 for all the standard scales assessing the disability level (*Table 1*). In particular, both the GOS and the LCF scores were comparable between the groups (Mann-Whitney U = 58.5, p = 0.317 and U = 65.0, p = 0.536, respectively) as well as the DRS score ($t_{(23)}$ = 1.08, p = 0.290). The data points in correspondence of t0 in *Figure 1* show the DRS scores at the baseline for the two groups.

According to the baseline scores (see *Table 1*), both groups of care recipients were characterized by a severe disability (median GOS equal to 3 for both groups and average DRS scores equal to 14.4 and 16.7, for the patients with Caregiver-IN and OUT, respectively) and by a confused-appropriate level of cognitive functioning needing moderate assistance for daily living activities (median LCF score equal to 6.0).

Standard scales after rehabilitation (t1)

Groups were comparable (see *Table 1*) for the GOS (U = 58.0, p = 0.317) and LCF outcome scores (U = 51.5, p = 0.166). In the case of the DRS score, the ANCOVA run controlling for the initial disability level showed a significant effect of group ($F_{(1,22)}$ = 4.95; p<0.05) with a large effect size (partial η^2 = 0.18), indicating that the patients with Caregiver-IN showed a better outcome than those with Caregiver-OUT (see in *Figure 1* the data points in correspondence of t1).

Baseline vs *outcome comparisons*

Comparisons between t0 and t1 were run for the standard scales score, separately for the patients with Caregiver-IN and Caregiver-OUT, to verify that there was an improvement at the end of the rehabilitation period. For all the scales, the comparisons showed that both groups significantly improved after treatment (see *Table 1*). In *Figure 1*, the slopes of the two lines connecting t0 with t1 show that both groups improved over time.

Synthesis of standard scales results

The level of disability severity at t0 was comparable between the groups; then both the Caregiver-IN and the Caregiver-OUT patients showed a statistically significant better performance at t1 with respect to t0 for all the standard scales. However, in terms of functional improvement after the neurorehabilitation treatment, the change in the field pictured by the GOS scale was only marginal and showed that patients did not reach a moderate level of disability (therefore both the groups still needed to be assisted by someone for daily life activities). The LCF scale at t1 showed that the Caregiver-IN group stepped towards level 7, meaning automatic/appropriate behaviour, which is characterized by minimal assistance for daily living skills, while the change for the Caregiver-OUT patients did not allow them to make a similar step towards. Finally, the DRS score improved significantly for both groups from t0 to t1, but while the patients with Caregiver-IN improved to a level of moderately severe disability (passing from 14.4 to 7.2), the patients with Caregiver-OUT, despite having passed from 16.7 to 12.6, remained at the initial severity category.

Overall, besides statistically significant changes, the Caregiver-OUT group did not change the level of disability severity, while the Caregiver-IN group passed to a level of moderately severe disability.

Finally, for the DRS, the direct comparison between the groups upon discharge, controlling for the possible

Table 1
Results for the standard scales scores (GOS, LCF, and DRS) measured at t0 (baseline) and t1 (outcome). Descriptive statistics are reported separately for the groups of patients with Caregiver-IN and with Caregiver-OUT. The results of the group comparisons performed separately at t0 and t1 are reported in the last two columns. The comparisons evaluating the difference between t0 and t1 are also reported separately for each group, in the time point columns. Significant comparisons are highlighted in bold

	Patients with Caregiver-IN				Patients with Caregiver-OUT				Group comparisons	
	Time point	**Mean**	**Median**	**SEM**	**Time point**	**Mean**	**Median**	**SEM**	**Test**	**p-value**
GOS	t0	3.1	3.0	0.07	t0	2.8	3.0	0.12	U = 58.5	0.317
	t1	3.6	3.0	0.20	t1	3.2	3.0	0.18	U = 58.0	0.317
Test	Z = 2.07				Z = 2.00					
p-value	**< 0.05**				**< 0.05**					
LCF	t0	5.4	6.0	0.39	t0	5.0	6.0	0.49	U = 65.0	0.536
	t1	6.7	7.0	0.34	t1	5.9	6.0	0.48	U = 51.5	0.166
Test	Z = 3.49				Z = 2.12					
p-value	**< 0.001**				**< 0.05**					
	Time point	**Mean**		**SD**	**Time point**	**Mean**		**SD**	**Test**	**p-value**
DRS	t0	14.4		5.7	t0	16.7		5.0	$t_{(23)} = 1.08$	0.290
	t1	7.2		5.3	t1	12.6		6.1	$F_{(1,22)} = 4.95$	**< 0.05**
Test	$t_{(13)} = 7.07$				$t_{(10)} = 3.12$					
p-value	**< 0.001**				**< 0.05**					

GOS: Glasgow Outcome Scale, LCF: Levels of Cognitive Functioning scale, DRS: Disability Rating Scale.

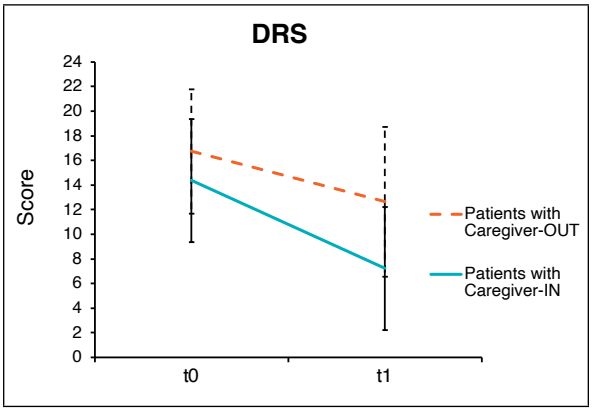

Figure 1
The Disability Rating Scale (DRS) score is reported for the baseline (t0) and for the outcome (t1) separately for the group of patients with Caregiver-OUT (dashed line) and with Caregiver-IN (continuous line). Error bars represent standard deviations.

effect of the baseline DRS, showed that the patients with Caregiver-IN had a significantly better outcome than those with Caregiver-OUT.

CINRS at the outcome

The group results are presented in *Table 2*. The difference between the groups for item A1 (which refers to the frequency of the caregiver in the rehabilitation ward) was statistically significant by default because the score reflected the absence of caregivers in the ward for all the patients with Caregiver-OUT. As for the other items, only A8 showed a significant difference between the groups, while A3 failed to reach significance, and A2, A7, and Section B did not differ between the groups. When the composite score was considered, the groups differed significantly, with the Caregiver-IN showing a better score than the Caregiver-OUT group. The Cohen's d was equal to 1.22, indicating a large effect size.

To synthesize, the contribution of the caregivers who participated in a remote modality was considered less determinant in the overall neurorehabilitation process than the contribution of the physically present caregivers. That is, even if availability and frequency of participation in the training sessions were considered comparable between the groups of caregivers, the cognitive therapists attributed an overall significant difference between them concerning their global influence on the IRP efficacy. However, the therapists judged the relative change from the beginning to the discharge with a similar score for the patients of both groups (5.9 and 5.4 points over a maximum score of 10, for the Caregiver-IN and -OUT patients, respectively).

DISCUSSION

The importance of the involvement of caregivers has been widely emphasized by the holistic and bio-psychosocial rehabilitation approach for patients with sABI [1, 3, 13]. Furthermore, in recent years, both international, as well as Italian, panels of experts and Italian legislators have also shown to be increasingly sensitive to this topic, as demonstrated by the publication of guidelines [14, 15] and the promulgation of law decrees.

From the perspective of the holistic approach, the present study followed up on a recent study [1], which examined the impact of caregiving in the rehabilitation setting on the outcome of patients with sABI. In that

study, it was concluded that the better the psychological status of the caregiver, the better the caregiving and the better the functional outcome of the patient.

Between March and July 2020, the exceptional restriction measures imposed to limit the COVID-19 pandemic determined the exclusion of all caregivers from the wards of the hospitals. Consequently, the absence of caregivers in the Post-Coma Unit of our neurorehabilitation hospital determined a peculiar condition that allowed evaluating the impact of the physical absence of the caregiver on the rehabilitation process. Therefore, we compared two groups of patients who were supported by their corresponding groups of caregivers: Caregivers-IN group and Caregivers-OUT group. In particular, the caregivers of the first group assisted their care recipients and participated in their rehabilitation process through daily contact with them, helping them to generalize across the whole day the intervention of the cognitive therapist. Differently, the caregivers of the Caregivers-OUT group could interact with their care recipients only poorly, because although the daily availability of remote connections was ensured, the communication between caregivers and patients lasted only fractions of hours instead of lasting the whole day.

Our results confirmed the importance of caregiving carried out under specific conditions, that is, in the presence of a person directly interacting and guiding the patient throughout the whole day before, during and after the official daily training sessions (see the comments about items A2 and A3 of the CINRS, below).

Like Caregivers-IN, also Caregivers-OUT were constantly informed and involved in the rehabilitation process; nevertheless, their physical absence in the rehabilitation setting seemed to have negatively impacted the functional outcome in the group of their care recipients. This was particularly evident if one considers the DRS score, which is the most sensitive among the standard scales used in the present study: the patients with Caregiver-OUT, despite the DRS score improved from admission to discharge, remained at the same disability category of the beginning ("severe disability"), while the group with Caregiver-IN reached a lower level of disability ("moderately severe disability"). The direct comparison between the groups, taken into account and controlled for possible group differences between the scores measured upon admission, showed that the outcomes of the groups significantly differed at discharge.

Of course, the small sample size and the lack of biomarkers for a more objective and mechanistic evaluation of the beneficial effects of caregiver physical presence can be considered as some limits of the present study. However, according to this specific result, we feel confident that the better outcome observed in the patients assisted by their Caregivers-IN could be closely related to the above-mentioned advantages determined by the physical presence of the caregivers in the rehabilitation ward. In saying this, we also lean on the fact that the medical and neurorehabilitation staff did not undergo any change in the amount of personnel in-

Table 2
Results for the CINRS measured at t1 are presented separately for each item of the questionnaire and as a composite score (sum of the items A2, A3, A7, and A8). Descriptive statistics are reported separately for the Caregiver-IN and the Caregiver-OUT groups. Group comparisons (tests and p-values) are also reported. Significant comparisons are highlighted in bold. Descriptive statistics of the items A4, A5, and A6 were not reported for the Caregiver-OUT group because of missing values for some participants, therefore the group comparisons were not run for these items

	Patients with Caregiver-IN			Patients with Caregiver-OUT			Group comparisons	
Items	**Mean**	**Median**	**SEM**	**Mean**	**Median**	**SEM**	**Test**	**p-value**
A1. Frequency of caregiver in the ward	3.8	4.0	0.24	1.0	1.0	0.00	U = 0.0	**<0.001**
A2. Frequency of participation of the caregiver in the neuro-rehabilitation setting	2.5	2.0	0.25	3.2	4.0	0.54	U = 60.0	0.373
A3. Amount of participation/cooperation by the caregiver	3.7	4.0	0.22	2.8	2.0	0.40	U = 43.0	= 0.066
(A4). (Caregiver tendency to substitute for the patient)	4.0	4.0	0.21	-	-	-	-	-
(A5). (Cooperation of the patient when the caregiver is present)	2.0	2.0	0.11	-	-	-	-	-
(A6). (Caregiver's trust in the rehabilitation process)	3.8	4.0	0.16	-	-	-	-	-
A7. Caregiver availability/easy to find	4.4	5.0	0.17	4.3	4.0	0.24	U = 69.5	0.687
A8. Caregiver's global influence on patient's rehabilitation	4.3	4.0	0.13	1.8	2.0	0.23	U = 0.0	**<0.001**
	Mean		**SD**	**Mean**		**SD**	**Test**	**p-value**
Part B (relative change since admission)	5.9		2.2	5.4		2.6	$t_{(23)} = 0.51$	0.614
Composite score (A2, A3, A7, A8)	14.9		1.9	12.1		1.7	$t_{(23)} = 3.04$	**<0.01**

CINRS: Caregiving impact on neurorehabilitation scale.

volved in the two periods under observation. In fact, standard neurorehabilitation protocols were applied to both groups of patients; the only change in the neurorehabilitation protocol and setting for the patients treated during the lockdown period was the extraordinary absence of caregivers.

As for the amount and quality of caregiving, on one hand, the CINRS Section B (which was based on the therapists' subjective appraisal of the relative change from admission to discharge) recorded a change in both groups. On the other hand, the CINRS composite score recorded a group difference which accounted for the actual lower amount (item A3) of participation and lower global influence played by the remote caregivers (item A8) in the overall neurorehabilitation process. This result highlights the fact that availability (item A7) and frequency (item A2) of (remote) participation in the training sessions (in other words, the sole presence during the therapy sessions) is not enough: effective cooperation and thus effective influence is possible only if a caregiver is present all day long, not only during the specific formal training session. In the light of our experience as an integrated group of clinicians cooperating in a team made by physicians, cognitive therapists, psychologists, and nurses, we would further suggest that the significant changes that occurred in the group of patients with Caregiver-OUT would not have been possible without an exceptional effort by the cognitive therapists who (as reported by all of them) tried to compensate for the absence of all-day caregivers. Of course, only a larger sample of patients would confirm these results and the related suggestions, although the hope is that similar exceptional conditions that allowed this study will not occur anymore in the future.

CONCLUSIONS

The role of caregiver participation in the assessment of responsiveness in patients with sABI and disorders of consciousness has been recently reported [16].

The previous study of Bivona *et al.* [1] demonstrated the relevant role of caregiving in rehabilitation but did not report any data on the absence of caregivers in the same neurorehabilitation milieu. The current pandemic COVID-19 made it possible to investigate the possible difference between the physical presence *vs* absence of caregivers in the neurorehabilitation ward in terms of the functional outcome of their care recipient.

The lockdown period has been challenging for the professionals making an effort to involve and specifically educate caregivers on the best practices, as well as psychologically sustain them in this dramatic phase of their life. However, it has undoubtedly also been challenging for the caregivers themselves, who had to contemporarily manage their psychological distress, their worry about being distant, and their anticipation of the future mental and physical effort related to the care recipient's demands.

We would here underline once again the importance of integrating at least one primary caregiver in the rehabilitation project of the care recipient, to address all the functional consequences of a severe ABI. We would also suggest that, on one hand, it is important that the therapists get the compliance and the participation of the caregivers in order to educate the family (even at distance) on how to functionally behave with the care recipient. On the other hand, as suggested by the study, it is crucial to guide the caregivers when they are *in presence* so that they can immediately guide and help the patients in generalizing outside the rehabilitation setting what the patients learned during the rehabilitation sessions.

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Authors' contributions

MDL and UB: conception and design. EDA, BO, FM, GF, MI, and SL: data acquisition. VB, MDL and UB: data analysis and interpretation of results. MDL and UB: original draft. RF: project supervision and manuscript revision. All Authors read and approved the final version of the manuscript.

Conflict of interest statement

The Authors declare that they have no conflicts of interest regarding the publication of this paper.

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ORIGINAL ARTICLES AND REVIEWS

Key performance indicators of breast cancer screening programmes in Italy, 2011-2019

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Abstract

Introduction. Performance indicators for organised breast cancer screening programmes in Italy, 2011-2019, were evaluated.

Materials and methods. Aggregated data were gathered by the National Centre for Screening Monitoring from over 150 regional or sub-regional screening programmes in Italy. Invitation and examination coverage, participation rate (PR), recall rate (RR), detection rate, positive predictive value (PPV) for the target population as a whole (women aged 50-69), by 5-year age-class, geographical macro-area (North, Centre, South-Islands with the exception of three Regions for missing/uncomplete data) and Region were estimated.

Results. Coverage showed an increasing positive trend, especially in the South-Islands, and PR was stable all over Italy. On the other hand, an increasing RR and decreasing PPV were recorded, especially at the first screening test and in some regions.

Discussion and conclusions. The positive increase in coverage is accompanied by a worsening of some performance indicators for which a better resource allocation and staff training are required. For this reason, further and continuous monitoring is mandatory.

Key words

- breast cancer
- cancer screening
- performance indicators
- early detection of cancer
- Italy

INTRODUCTION

Breast cancer (BC) is a leading cause of disease burden among women in Europe: an estimated 531,086 women were diagnosed with BC and 141,765 died of BC in 2020 [1]. As proved by many studies, mammographic screening (MS) can reduce BC mortality in women aged more than 50 years old. Estimates of mortality reduction range from 20% for women invited to screening to 48% for women who are screened [2, 3].

Many countries, including Italy, offer a population-based mammographic screening programme (breast cancer screening programme, BCSP), to give target women systematic and equal access to screening. In Italy, screening programmes are public health interventions prescribed by a 2001 national law, confirmed in 2017 (Essential Levels of Care) [4]. The quality assurance and data collection are performed in a centralized manner [5].

A cancer-screening programme is a complex process, which effectiveness depends on three main phases: the screening test execution, the referral for further diagnostic assessment, and the surgical/medical therapy [6]. The previous European guidelines for quality assurance in mammography screening underlined three fundamental steps in screening programmes: 1) the identification and information of the eligible population, the delivery of active invitation, the execution of the first level test with high-quality standards; 2) a timely referral of positive cases for further assessment and treatment procedures and the minimization of negative effects; 3) the management of information flows and the provision of constant quality assurance throughout the

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entire process [7]. More recently, the European Commission Initiative on Breast Cancer (ECIBC) recommended implementing organised BCSP for early detection of breast cancer and underlined the importance of comprehensive process monitoring as crucial element to BCSP programmes' success [8, 9]. Since 2004 the National Centre for Screening Monitoring (ONS), on behalf of the Italian Ministry of Health, monitors and supports Italian BCSP programmes. This effort is done together with the Italian group for mammography screening (GISMa), a scientific association whose main goal is to promote the quality of programmes through the development and application of indicators and benchmarks. To this end of primary importance, is the annually data collection of Italian breast screening activities. Data are collected in an aggregated way and gathered through a standardised form to calculate process and impact parameters which have been agreed on a national level [10]. Monitoring results has allowed not only to constantly compare outcomes with national and European standards but also to assess BCSP protocols and organisational features.

This work evaluates the temporal trend (2011-2019) of performance indicators (invitation coverage, examination coverage, participation rate, recall rate, cancer detection rate and positive predictive value) of Italian mammography screening programmes. This assessment is in continuity with a previous survey conducted between 2006-2011 [11]. The parameters assessed in this work were recently proposed as candidate breast cancer screening programmes performance indicators by the European Commission Initiative on Breast Cancer (ECIBC) and they well represent the different quality process domains in MS programmes [12].

METHODS

Setting

In Italy ONS and GISMa provide the common protocol for mammographic screening and each Region is responsible for the organisation and delivery of local BCSP activity. Data are annually gathered by ONS through a structured questionnaire filled by local programme referents and regional coordinators. Logical-formal and epidemiological checks are performed either at the regional or at the national level. In this paper screening programmes' data are analysed aggregated by region and geographical macro-area (North, Centre, South-Islands).

Data

This paper analysed data from the ONS archive, collected from over 150 local breast cancer screening programmes in Italy and collected and managed by the Institute for Cancer Research, Prevention and Clinical Network (Istituto per lo Studio, la Prevenzione e la Rete Oncologica, ISPRO, Florence) where ONS is set up. All data and parameters are referred to 50-69 years target population, and were analysed considering Italy as a whole, by the three Italian macro-areas. *Table 1* showed the Italian female 50-69-year-old target population from 2011 to 2019 (Istituto Nazionale di Statistica, ISTAT, Italian National Institute of Statistics data) the number of tests, recalled women, and screen-detected malignant cancers by the three Italian macro-areas for initial and subsequent screening tests. Target population, invitations and number of performed tests refer to all Italian regions. For South-Islands, the number of tests performed, the number of women with referrals to further assessments, and the number of women with screen-detected cancers by initial or subsequent test, were referred from the following regions from this macro-area: Abruzzo and Basilicata (from 2014), Campania, Sicily and Sardinia. Calabria, Puglia and Molise, were indeed excluded because of some incompleteness of data regarding the above-mentioned variables.

The following indicators were calculated:

- adjusted invitation coverage: percentage of women invited to screening during the analysed period, compared to the target population, excluding undelivered invitations and women with specific exclusion criteria. This parameter may exceed 100% if invitations are not evenly distributed over the years [13];
- examination coverage: percentage of women who performed the test compared to the target population, excluding women with specific exclusion criteria;
- adjusted participation in the screening programme (PR): percentage of invited women who performed the test within 6 months from the invitation, excluding undelivered invitations and women with recent mammography (<12 months);
- recall rate (RR): the number of women recalled for further assessments as a proportion of all women with a screening examination (specificity sentinel parameter);
- detection rate (DR): the number of all malignant cancers detected every 1,000 screened women (sensitivity sentinel parameter);
- positive predictive value (PPV): the ratio of lesions that are truly positive to those that test positive (programme performance sentinel parameter).

While invitation and examination coverages were examined for Italy as a whole, by region and by geographical macro-area (North, Centre, South-Islands), PR, RR, PPV and DR were also examined by 5-year age-classes (50-54; 55-59; 60-64; 65-69).

In calculating RR, DR and PPV by geographical area, Molise, Puglia and Calabria were excluded from South-Islands since data were missing or incomplete. Instead, data of Abruzzo and Basilicata were available from 2014 onwards; RR, PPV and DR were also stratified by initial and subsequent screening test.

Key performance indicators were annually estimated to analyse temporal trends; average annual percent changes (AAPCs) with their 95% confidence intervals (95% CI) were estimated using the Jointpoint Regression Programme (version 4.9.0). Moreover, indicators were combined in two graphs: one plotting invitation coverage versus participation rate or versus examination coverage, and another graph plotting RR *versus* PPV, where DR was shown as isobars, as proposed by Blanks *et al.* [14, 15] This visualization provides an overview of the main performance indicators.

Table 1
Italian National Institute of Statistics (ISTAT). Female 50-69 years old population, number of invited women, number of tests performed, number of women with referrals and with screen-detected malignant cancers in Italy and by geographical macro-areas. Period 2011-2019

			2011	2012	2013	2014	2015	2016	2017	2018	2019
	ISTAT target population		7,613,766	7,612,337	7,751,539	8,005,826	8,178,875	8,349,898	8,440,107	8,529,765	8,533,796
Italy*	**Invited women**		2,699,403	2,687,657	2,748,500	2,848,716	3,231,733	3,223,356	3,428,234	3,448,500	3,663,316
	Number of tests performed	First screening	260,115	286,029	285,632	302,864	360,624	347,663	338,164	329,148	356,252
		Subsequent	1,070,417	1,083,459	1,137,595	1,200,828	1,296,691	1,348,790	1,389,660	1,415,095	1,496,387
	Number of women with referrals to further assessments	First screening	22,533	27,615	28,223	31,365	34,378	38,157	37,485	39,329	43,173
		Subsequent	49,055	50,662	52,485	54,888	59,466	63,146	67,739	68,249	73,043
	Number of women with screen-detected cancers	First screening	1,237	1,427	1,437	1,644	1,756	1,811	1,750	1,610	1,815
		Subsequent	4,807	5,016	5,428	5,548	6,119	6,159	6,454	6,398	6,425
North	**ISTAT target population**		3,541,698	3,523,159	3,582,882	3,679,755	3,748,491	3,833,693	3,871,752	3,912,976	3,934,358
	Invited women		1,515,973	1,543,180	1,587,856	1,621,696	1,696,973	1,718,736	1,764,608	1,785,840	1,892,023
	Number of tests performed	First screening	160,055	161,957	162,442	150,358	147,160	149,535	156,975	157,949	158,084
		Subsequent	766,099	778,980	842,134	869,915	917,293	933,045	946,949	951,138	986,668
	Number of women with referrals to further assessments	First screening	14,311	14,964	14,889	15,436	14,411	16,154	16,633	15,829	16,526
		Subsequent	31,526	32,492	35,147	36,543	39,549	40,395	41,262	40,824	40,871
	Number of women with screen-detected cancers	First screening	879	838	923	940	944	906	889	872	895
		Subsequent	3,614	3,756	4,186	4,229	4,571	4,431	4,687	4,634	4,560
Centre	**ISTAT target population**		1,540,473	1,521,833	1,550,641	1,617,491	1,655,049	1,688,374	1,706,242	1,724,950	1,722,063
	Invited women		619,018	669,551	623,671	627,600	699,792	772,842	791,591	811,444	823,299
	Number of tests performed	First screening	80,266	79,760	77,914	79,694	97,083	94,434	99,595	92,750	96,502
		Subsequent	258,306	272,927	252,771	257,506	284,920	300,524	307,387	323,514	329,781
	Number of women with referrals to further assessments	First screening	6,606	9,178	10,111	9,963	10,054	12,799	13,733	15,039	15,276
		Subsequent	15,395	15,632	15,685	15,310	16,672	17,695	18,846	20,650	20,893
	Number of women with screen-detected cancers	First screening	262	404	353	387	374	542	559	457	447
		Subsequent	1,063	1,202	1,176	1,119	1,257	1,313	1,324	1,332	1,385
South-Islands*	**ISTAT target population**		2,531,595	2,567,345	2,618,016	2,708,580	2,775,335	2,827,831	2,862,113	2,891,839	2,877,375
	Invited women		564,412	474,926	536,973	599,420	834,968	731,778	872,035	851,216	947,994
	Number of tests performed	First screening	19,794	44,312	45,276	72,812	116,380	103,694	81,594	78,449	101,666
		Subsequent	46,012	31,552	42,690	73,407	94478,90837	115,221	135,324	140,443	179,938
	Number of women with referrals to further assessments	First screening	1,616	3,473	3,223	5,966	9,913	9,204	7,119	8,461	11,371
		Subsequent	2,134	2,538	1,653	3,035	3,245	5,056	7,631	6,775	11,279
	Number of women with screen-detected cancers	First screening	96	185	161	317	438	363	302	281	473
		Subsequent	130	58	66	200	291	415	443	432	480

*ISTAT target population and invited women covers all Italian regions; the number of tests performed, the number of women called for further investigation and the number of women with screen-detected cancers detected at screening are for the northern (Piedmont, Val d'Aosta, Liguria, Lombardy, Bolzano, Trentino, Veneto, Friuli-Venezia Giulia, Emilia Romagna) and central regions (Tuscany, Umbria, Marche, Lazio). For the South, data are available for the regions Abruzzo (since 2014), Campania, Basilicata (since 2014), Sicily, Sardinia. For Molise, Apulia and Calabria, data for some years are not available.

RESULTS

Invitation coverage, examination coverage, and participation rate

In Italy, the adjusted invitation coverage followed an increasing trend, from 73.5% in 2011 to 89.1% in 2019, with a significant annual increase of 2.7% (*Table 2*). This trend remained significant in all geographical macro-areas, especially in the South-Islands (AAPC from North: 0.8%; Centre: 2.2%; South-Islands: 6.8%). In the North, Piedmont Region significantly increased its invitation coverage as well as Marche and Lazio in the Centre. However, the most important increases were recorded in the South, especially in Campania and Sicily (*Table 1S* available online as Supplementary Material).

Examination coverage followed an increasing trend, from 40.4% in 2011 to 47.8% in 2019 (+2.0% annually) and this was particularly noticeable in the South-Islands (AAPC from North: 0.7%; Centre: 1.8%; South-Islands: 6.8%). When plotted against adjusted invitation coverage, a slight but evident increasing trend of both indicators was appreciated, with a more relevant increase in the South-Islands (*Figure 1A*). At the regional level, Piedmont, Marche, Lazio, Abruzzo, and Sicily recorded the most important increases (*Table 2S* available online as Supplementary Material).

In Italy, PR showed a slight, though significant, annual decrease of 0.7%: from 59.6% in 2011 to 57.9% in 2019 (*Table 2*). In the North, PR stalled around 68.0%-70.0%, while in the Centre and the South-Islands it was less stable and significantly lower (range in the Centre: 56.2%-60.0%; range in the South-Islands: 37.8%-46.9%), but with no significant trend (*Table 2*). Plotting adjusted PR against adjusted invitation coverage, a substantial stability of PR is observed in the whole period by macro-area, and a growing trend for invitation coverage in the South-Islands and partially in the Centre (*Figure 1B*).

At the regional level, Lombardy region showed a slight significant decrease, while Veneto and Friuli-Venezia Giulia showed significant PR increases. In the Centre Marche, and in the South Abruzzo and Basilicata showed PR increase (*Table 3S* available online as Supplementary Material).

Analyzing PR by age-class, it was higher among women aged over 55 years old across Italy (*Table 4S* available online as Supplementary Material).

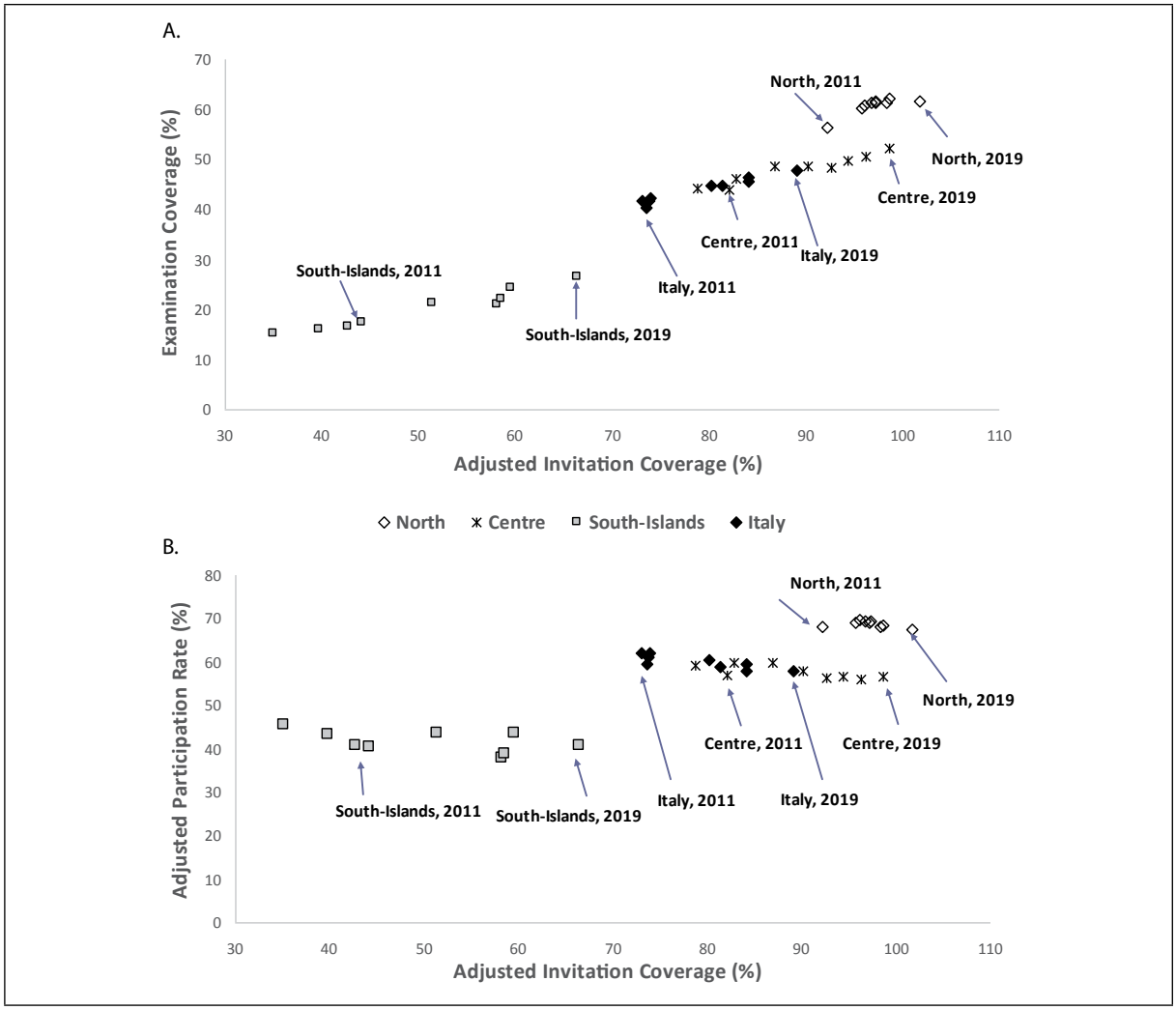

Figure 1
Adjusted invitation coverage *versus* examination coverage (A) and *versus* adjusted participation rate (B) by macro-area.

Main performance indicators: RR, DR, and PPV at the first screening test

Figures of PPV against RR with cancer DR as isobars, showed the relationship between RR, PPV and DR. From 2011 to 2019 for the first screening (*Figure 2A*), RR abscissa values increased, and PPV ordinate values non-proportionally decreased in Italy and in the three macro-areas.

At the same time, DR levels remain stable around the 5‰ DR curve for Italy and the Centre; between the 7‰

Table 2
Adjusted invitation coverage, examination coverage, adjusted participation rate, recall rate, detection rate, positive predictive value with average annual percent change (AAPC) and 95% Confidence Intervals (95% CI) by macro-area (North, Centre and South-Islands, Italy), 2011-2019

	2011	2012	2013	2014	2015	2016	2017	2018	2019	AAPC	95% CI
Adjusted invitation coverage (%)											
North	92.17	95.74	97.22	96.04	97.20	96.67	98.62	98.24	101.69	0.8	0.4; 1.2
Centre	82.08	90.15	82.78	78.74	86.82	92.63	94.32	96.18	98.55	2.2	1.2; 3.2
South-Islands	44.16	35.06	39.74	42.76	58.16	51.35	59.53	58.52	66.35	6.8	3.5; 10.2
Italy	73.52	73.06	73.94	73.77	81.37	80.23	84.07	84.06	89.05	2.7	1.9; 3.4
Examination coverage (%)											
North	56.58	60.20	61.76	60.87	61.53	61.39	62.26	61.49	61.65	0.7	0.0; 1.4
Centre	43.91	48.64	46.22	44.29	48.74	48.51	49.85	50.63	52.16	1.8	0.7; 2.9
South-Islands	17.32	15.17	15.92	16.54	21.14	21.36	24.38	22.04	26.55	6.8	3.8; 9.9
Italy	40.43	41.87	42.38	41.89	44.74	44.94	46.46	45.60	47.80	2.0	1.5; 2.5
Adjusted participation rate (%)											
North	68.22	69.25	69.51	69.75	69.06	69.45	68.50	68.23	67.44	-0.2	-0.5; 0.1
Centre	56.99	57.99	59.83	59.23	60.04	56.31	56.75	56.17	56.85	-0.5	-1.2; 0.3
South-Islands	40.49	45.57	43.20	40.81	37.80	43.55	43.67	38.83	40.85	-0.6	-2.5; 0.1
Italy	59.58	62.25	62.24	61.34	58.99	60.41	59.56	58.03	57.93	-0.7	-1.3; -0.1
Recall rate (%)											
First screening											
North	8.94	9.24	9.17	10.27	9.79	10.80	10.60	10.02	10.45	2.0	0.6; 3.4
Centre	8.23	11.51	12.98	12.50	10.36	13.55	13.79	16.21	15.83	6.2	2.6; 10.1
South-Islands*	8.16	7.84	7.12	8.19	8.52	8.88	8.72	10.79	11.18	5.7	3.3; 8.2
Italy*	8.66	9.65	9.88	10.36	9.53	10.98	11.08	11.95	12.12	3.9	2.5; 5.2
Subsequent screenings											
North	4.12	4.17	4.17	4.20	4.31	4.33	4.36	4.29	4.14	0.4	-0.3; 1.0
Centre	5.96	5.73	6.21	5.95	5.85	5.89	6.13	6.38	6.34	0.9	0.0; 1.9
South-Islands*	4.64	8.04	3.87	4.13	3.43	4.39	5.64	4.82	6.27	2.8	-4.7; 10.9
Italy*	4.58	4.68	4.61	4.57	4.59	4.68	4.87	4.82	4.88	0.8	0.3; 1.4
Detection rate (‰)											
First screening											
North	5.49	5.17	5.68	6.25	6.41	6.06	5.66	5.52	5.66	0.4	-1.8; 2.7
Centre	3.26	5.07	4.53	4.86	3.85	5.74	5.61	4.93	4.63	2.7	-2.4; 8.1
South-Islands**	4.85	4.17	3.56	4.35	3.76	3.50	3.70	3.58	4.65	0.2	-4.0; 4.6
Italy**	4.76	4.99	5.03	5.43	4.87	5.21	5.18	4.89	5.09	0.3	-1.0; 1.6
Subsequent screenings											
North	4.72	4.82	4.97	4.86	4.98	4.75	4.95	4.87	4.62	-0.2	-1.0; 0.7
Centre	4.12	4.40	4.65	4.35	4.41	4.37	4.31	4.12	4.20	-0.5	-1.7; 0.6
South-Islands**	2.83	1.84	1.55	2.72	3.08	3.60	3.27	3.08	2.67	1.8	-4.7; 8.8
Italy**	4.49	4.63	4.77	4.62	4.72	4.57	4.64	4.52	4.29	-0.6	-1.5; 0.3

Continues

Table 2
Continued

	2011	2012	2013	2014	2015	2016	2017	2018	2019	AAPC	95% CI
Positive predictive value (%)											
First screening											
North	6.14	5.60	6.20	6.09	6.55	5.61	5.34	5.51	5.42	-1.6	-3.4; 0.3
Centre	3.97	4.40	3.49	3.88	3.72	4.23	4.07	3.04	2.93	-3.3	-7.1; 0.7
South-Islands**	5.94	5.33	5.00	5.31	4.42	3.94	4.24	3.32	4.16	-5.0	-8.2; -1.6
Italy**	5.49	5.17	5.09	5.24	5.11	4.75	4.67	4.09	4.20	-3.4	-4.7; -2.1
Subsequent screenings											
North	11.46	11.56	11.91	11.57	11.56	10.97	11.36	11.35	11.16	-0.5	-1.2; 0.1
Centre	6.90	7.69	7.50	7.31	7.54	7.42	7.03	6.45	6.63	-1.4	-3.0; 0.1
South-Islands**	6.09	2.29	3.99	6.59	8.97	8.21	5.81	6.38	4.26	-2.8	-13.5; 9.2
Italy**	9.80	9.90	10.34	10.11	10.29	9.75	9.53	9.37	8.80	-1.4	-2.6; -0.3

*Recall Rates for South-Islands include data from Abruzzo (from 2014), Campania, Basilicata (from 2014), Sicilia, Sardegna. Data for Molise, Puglia, and Calabria regions are not available for every year. Recall rates for Italy include North, and Centre macro-areas plus the above-mentioned Southern regions.
**Detection rates and positive predictive values for South-Islands include data from Abruzzo (from 2014), Campania, Basilicata (from 2014), Sicilia, Sardegna. Data for Molise, Puglia, and Calabria regions are not available for every year. Detection rates, and positive predictive values for Italy include North, and Centre macro-areas plus the above- mentioned Southern regions.

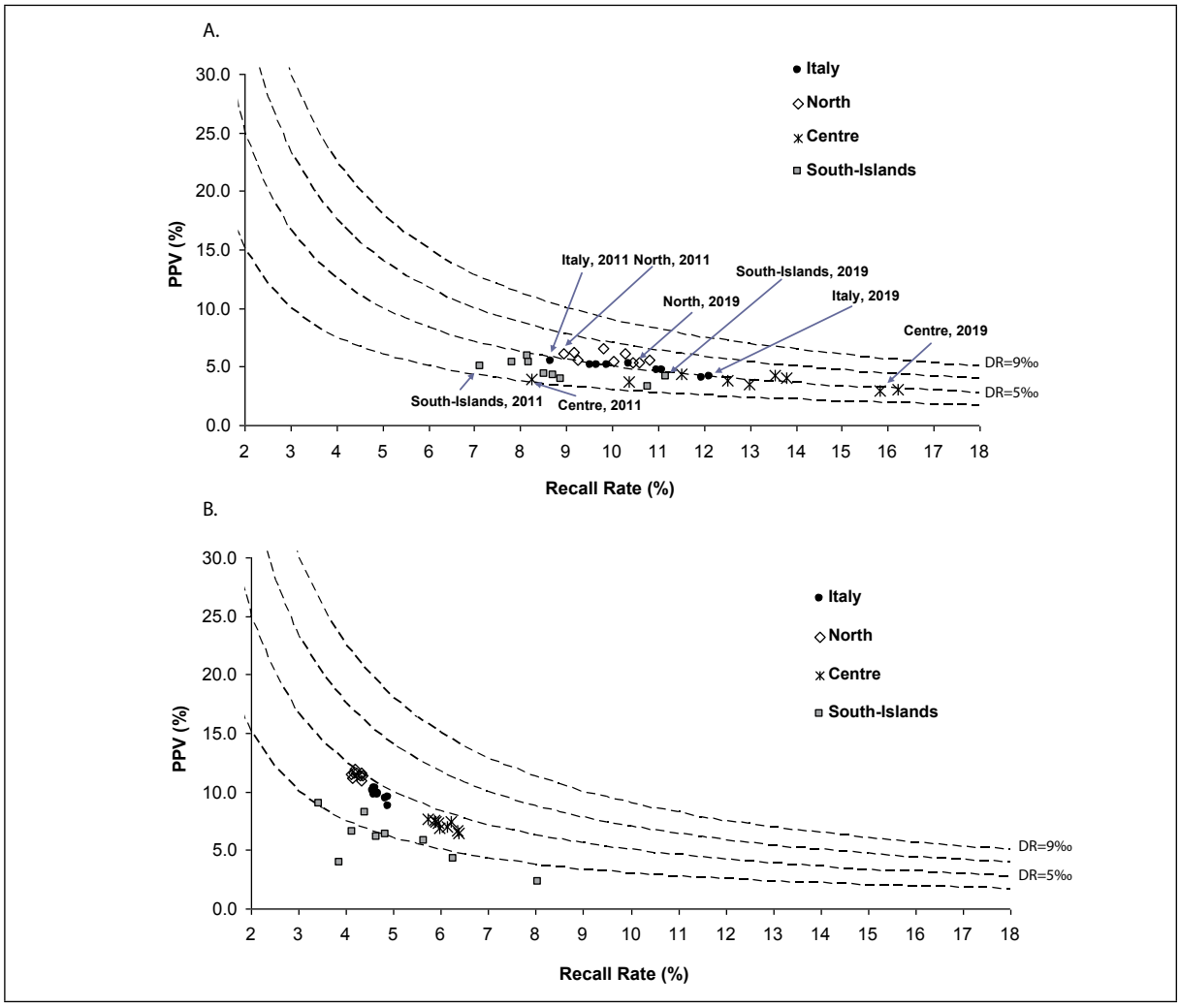

Figure 2
Recall rate (RR) *versus* positive predictive value (PPV) by macro-area; detection rate (DR) shown as isobars. First round (A), subsequent rounds (B).

and 5‰ DR curves for the North, and between the 5‰ and 3‰ DR curves for the South-Islands area. Indeed, RR at first screening showed an increasing trend of 3.9% per year in Italy (from 8.7% in 2011 to 12.1% in 2019); of 2.0% in the North; of 6.2% in the Centre; of 3.9% per year in the South-Islands (with no data from Basilicata, Molise, and Puglia) (*Table 2, Figure 2A*). The RR at the first screening increased substantially in Piedmont and Emilia-Romagna from the North (*Table 5S, Figure 1S* available online as Supplementary Material); for the Centre in Umbria, Marche, and Lazio (*Table 5S; Figure 2S* available online as Supplementary Material); for the South in Campania (*Table 5S; Figure 3S* available online as Supplementary Material). The RR values recorded in Marche since 2015 reached levels over 20%, with a significant increase also in DR (*Table 6S* available online as Supplementary Material). The RR increase was less marked, but still significant in Lombardy and Tuscany. In Autonomous Provinces (PA) of Bolzano and Trento an opposite trend was recorded: the first screening RR decreased significantly by 7.0% and 10.4%, respectively, especially from 2015 onwards.

In all age groups (*Table 4S*), the RR at first screening in Italy increased by 4%-6% per year. The 50-54 age class was the one with a constantly higher RR. In 2016-2018 RR increased considerably in all age groups and in particular for the 65-69 age-class (*Table 4S*).

Positive Predictive Value at the first test decreased by 3.4% per year in Italy as a whole (from 5.5% in 2011 to 4.2% in 2019), and especially in the South-Islands area (reduction of 5.0% per year; *Table 2*). At the regional level (*Table 7S* available online as Supplementary Material), PPV at first screening decreased in most Regions. On the opposite, Veneto showed an improvement in PPV at the first test. In age-stratified data for Italy as a whole (*Table 4S*), PPV increased with age. In women undergoing their first screening at 50-54 years of age, PPV decreased by 3.6% per year. PPV at first screening non-significantly decreased also in the other age groups.

Main performance indicators: RR, DR, and PPV at subsequent screening tests

For subsequent screening tests (*Figure 2B*), less variability in RR and PPV values was observed for all Italy, North and Centre; DR was around the 5‰ DR curve for the North, between the 3‰ and the 5‰ DR curves for Italy as a whole and the Centre, and around the 3‰ DR curve for the South. Even though RR at subsequent tests showed less variability than was observed at the first screening, there was a slight increase of 0.8% per year across Italy, particularly in central regions (0.9% per year; *Table 2*). Within the North area (*Table 8S; Figures 4S, 5S, 6S* available online as Supplementary Material), RR increased in Piedmont and Veneto, while in Autonomous Province of Trento and Liguria RR significantly decreased. In the Centre, RR decreased significantly in Marche, while in Lazio there was an opposite trend. There was also an important but non-significant increase in RR in Umbria, with a relevant and significant reduction in PPV and DR (*Tables 8S, 9S, 10S* available online as Supplementary Material). In the South-Islands, there were fewer variations, but a particularly high RR was observed in Campania in the last year (15.0%; *Table 8S, Figure 6S*).

By age-class, RRs ranged between 5.2%-5.7% across Italy for the 50-54 age group, while it ranged between 4.1%-4.8% in the older age groups (*Table 4S*).

The PPV was about twice as high for subsequent screening as for the first test. For Italy as a whole, there was a slight, but significant annual reduction of 1.4% in PPV for subsequent screenings (*Table 2*). It was higher in the North (above 11.0%); in the South it ranged from 6.1% in 2011 to 4.3% in 2019 and in the Centre from 6.9% in 2011 to 6.6% in 2019. Analyzing data by region (*Table 10S*), Piedmont, Emilia-Romagna and Umbria showed significant annual reductions. In the age group of women over 54, there was a significant annual reduction in PPV of 1%-2% (*Table 4S*).

The DR at first test was higher than that at subsequent screening tests. However, both DR remained substantially stable: DR at first screening ranged between 4.8‰-5.4‰, while DR at subsequent screenings ranged between 4.3‰-4.8‰ (*Table 2*). The lowest DR was observed in the South-Islands (range at first screening 3.5‰-4.7‰; at subsequent screening 1.6‰-3.6‰), while the highest DRs were observed in the North where values always exceeded the Italian average value (range at first screening 5.2‰-6.4‰; at subsequent screening: 4.6‰-5.0‰).

By age-class, the highest DR was observed in the 65-69 age group (first screening, range 7.1‰-11.0‰; subsequent screening, range: 5.8‰-6.5‰), while the lowest DR was recorded in the 50-54 age group (first screening, range: 4.0‰-4.5‰; subsequent screening, 3.0‰-3.1‰; *Table 4S*).

DISCUSSION

Between 2011 and 2019 in Italy, trends in indicators of organized mammography screening showed an increase in the invitation coverage and examination coverage, with a substantial stabilisation of the participation rate, in particular in those areas such as Lazio region and South-Islands macro-area, where screening programmes were not adequately implemented until 2011.

There is still a gap in screening coverage between North-Central Italy and South-Islands; almost all eligible women are reached in the North and the Centre, while slightly more than half of the target population is reached in the South. Nonetheless, the coverage appears to be improving over the years, especially in the South, in Lazio, but also in some areas of the North, as Piedmont and Liguria.

Participation rate is essential in order to record an impact on cancer-specific mortality. European standards for PR consider 70% and 75% an acceptable and desirable level of participation, respectively [7]. In Italy in 2011-2019 PR was constantly below the acceptable level. In the North macro-area PR was close to the acceptable standard in the whole period, while in the South-Islands it was below (40.9% in 2019), confirming a significant North-South gradient.

In particular, in Lazio, Molise, Campania, Sicily, Calabria and Sardinia participation was still below 50% in

2019, while in Val d'Aosta, Autonomous Province of Trento, Veneto, Friuli-Venezia Giulia, Emilia-Romagna, Tuscany, Umbria and Basilicata it was over 70% in 2019. The interpretation of these figures has to be cautious: there may be areas covered by opportunistic screening; participation may vary according to the socio-economic characteristics of the population and to citizens' trust in public health services [16, 17]. The PASSI (Progressi delle Aziende Sanitarie per la Salute in Italia) survey, one of the two National Health Interviews (NHIS) active in Italy, shows that opportunistic screening in the period 2017-2020 accounts on average for one fourth of the screening test coverage in the target population that reaches 75% for breast cancer screening, with differences between macro areas. Indeed, in 2019 it accounted for 14% in North (excluding Lombardy region), 20% for Centre and 23% for South [18, 19].

Comparison between PR recorded in 2011-2019 with those recorded in the previous survey conducted in 2006-2011 confirms the geographical gradient, even if a progressive improvement in invitation and examination coverages emerged in all regions. It is worth noting that a gradual increase in the programmes' coverage may initially lead to a relative decrease in the PR, especially at the first screening test, when invited women have never been invited before and therefore are still not committed to the programme. The higher PR may depict an organizational improvement along with a progressive increase of citizens knowledge and engagement to organized screening [11].

Considering other analyzed parameters, a significant increase of RR and a slight reduction of PPV were recorded, especially at the first screening in some regions of the North (Piedmont, Emilia-Romagna), of the Centre (Marche, Umbria, Lazio), and in Campania for the South.

The effectiveness of mammography screening is closely related to the reading performance of radiologists, the quality of images and the overall organizational quality of the BCSP [20]. If the aim of screening programmes is the early detection of malignant lesions (high sensitivity), this should ideally be accompanied by an acceptable RR and a low frequency of biopsies (high specificity), also to limit anxiety and stress in the involved women [21]. Thus, good RR, DR and PPV values indicate good quality of the programme and a positive impact on breast cancer mortality. Analyzing the RR (a screening specificity indicator), at the first screening, the acceptability threshold (<7%) is always exceeded, both at the national level and by macro-area. Moreover, RR constantly increased, highlighting performance worsening with risks of organizational unsustainability of the programmes [22]. The RR values were particularly high in Marche region (≥20% since 2015) in the Centre, and in Friuli-Venezia Giulia region, in the North, RR exceeded 15% in recent years.

The increase in RR could be explained by several reasons. First, lack of previous mammographic images could explain high RR, especially at first screening test, when women are also younger and with a more dense breast than older women. Second, the transition to digital mammography that occurred in recent years could have enhanced RR, as described in other experiences as well [23]. Third, the involvement in the BCSP of radiologists not mainly dedicated to screening, at least in some regions; fourth, the inadequate training of new health professionals involved in BCSPs. In fact, screening radiologists need dedicated training and should guarantee a minimum annual volume of readings (between 3,500 and 11,000 mammograms/year, as indicated by the European Commission Initiative on Breast Cancer, ECIBC) to reach and maintain high reading performances [8].

Results are better for RR at subsequent screening, as it was consistently below the threshold of acceptability (<5%) and had a constant trend over time. However, stratifying by macro-area, only in the North the RR was actually below this threshold. In particular, all the regions of the Centre and Campania region in the South-Islands area showed values above the acceptability threshold, especially after 2015. The DR of malignant tumours at first screening is higher than in subsequent screening and in older age groups, due to the higher prevalence of disease in this population. Analyzing PPV, as expected, at first screening the values were not only lower than at the subsequent ones, but also less stable. Indeed, a decreasing trend was observed since 2015, especially for women in the 50-54 and 55-59 age groups. While the PPV reached the highest values in the North area, it reached the lowest values in the South-Islands. Comparing the VPP trend in 2011-2019 with that recorded in 2006-2011, a decreasing trend is confirmed overall in both the first and subsequent examinations [11].

In Bolzano and Trento, a general improvement in performance was observed over the period, with good coverage and participation rates and improvements in RR and PPV. In the Province of Trento, this was especially noticeable since 2015; in 2014, Digital Breast Tomosynthesis (DBT) was introduced as the first level screening test, and this may have contributed to the improvement of the PPV [24]. In the Province of Bolzano, tomosynthesis is not used, but the good overall performance can be attributed also to the presence of highly qualified personnel who have been involved in BCSP for years as well as in DBT screening.

Tuscany, Lombardy, Veneto and Liguria showed good performance levels, with high coverage and stability of PPV overtime at first and subsequent screening tests, with slight increases in RR, except Liguria where there was a significant reduction in RR at subsequent screening.

In contrast, in other regions such as Umbria, performance appears to be declining, with an increase in RR and a decrease in PPV and DR.

In the South-Islands macro-area, the snapshot resulting from the present analysis is partial since data from some regions were missing. The fact that some screening programmes do not adequately collect data to estimate performance indicators is an issue that affects programmes monitoring. Regional commitment should be strengthened to address this issue, in accordance with Italian National Prevention Plan 2020-2025 that foresees an improvement of regional screening networks [25]. The complete and timely provision of data

is crucial to monitor the delivery of the LEAs and to ensure a high level of quality in healthcare. In several regions (i.e., Campania, Tuscany, Lombardy, Puglia) regional implementation projects of a unique screening software are being carried on. Those systems may be useful to improve the collection and transmission of data by screening managers in a more efficient and timely manner.

In this analysis, RR and PPV trends suggest an "erosion" of screening programmes performance in many Italian regions. This issue may arise from several causes. In recent years, resources for screening programmes have not been adequately allocated, and, at the same time, quality requirements are increasingly defined and stringent. Moreover, the lack of adequate recruitment, replacement and training policy for screening health professionals may create conditions that weaken the performance of BCSPs. The adequate training of staff dedicated to screening would become a priority to improve programme performances, patient safety and tackling defensive medicine, as well as ensuring equity. This issue has also recently been exacerbated by the deployment of screening staff to manage the pandemic emergency [26, 27].

Indeed, this paper analysed data up to 2019. As highly debated, the pandemic crisis had an impact on screening invitation coverages and tests' execution and also on invited people's propensity to participate to organized screening programmes in Italy (for mammography screening some estimates show 15% lower) [26, 27]. A careful analysis of pandemic and post-pandemic screening performances would become crucial in order to monitor recovery strategies and their effectiveness.

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Author's contribution

GG: conception and design, acquisition of the data, data analyses, critical revision of the article for important intellectual content, final approval of the article; PF: acquisition of the data, final approval of the article; LV: acquisition of the data, data analyses; FB: drafting of the article, critical revision of the article for important intellectual content, final approval of the article; PM, LG, SD, MZ, GS: critical revision of the article for important intellectual content, final approval of the article.

Conflict of interest statement

All Authors declare that they have no conflict of interest.

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A case of medicine in disguise: motion sickness patches sold as medical devices containing active pharmaceutical substances

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Abstract

Introduction. A case study is reported on anti-motion sickness transdermal patches sold in the Internet, claiming to contain only natural ingredients but, actually, containing undeclared medicinal active substances.
The visual inspection of the samples evidenced many inconsistencies in secondary and primary packaging, missing of various legal information and a non-compliant "CE" mark.
Methods. The qualitative analysis was performed by liquid chromatography - high resolution mass spectrometry and the quantitative by liquid chromatography with diode array detector.
Results. The analyses evidenced the presence of the antihistaminic drug Diphenhydramine and of other active substances (Capsaicin, a transdermal absorption enhancer, and Diclofenac in traces, probably a contaminant from other productions of the same plant). Moreover, the presence of several trace elements, including those potentially toxic to humans, was assessed by ICP-MS analysis.
Conclusions. The case discussed is a new case of "medicines in disguise" never reported in literature, and shows the presence of tangible risks for public health.

Key words

- transdermal patch
- falsified medicines
- diphenhydramine
- liquid chromatography
- mass spectrometry
- ICP-MS

INTRODUCTION

Motion sickness is a common disturbance occurring in healthy people when they travel by car, plane, boat or train. This syndrome is thought to be caused by discordant signals coming from the vestibular and the visual systems [1, 2]. Several antiemetic drugs have been studied since the early 1940s, and since 1976 anticholinergic drugs and antihistamines (mainly acting as histamine H1 receptor antagonists and, sometimes, muscarinic receptor antagonists) were identified as excellent antiemetics. Diphenhydramine is an example of antihistamine drug also effective to prevent and treat nausea, vomiting and dizziness caused by motion sickness. This drug has been marketed as antihistaminic since 1946 but its antiemetic properties, which made it useful in the treatment of motion sickness, were discovered three years later, in 1949 [3]. As a H1 receptor antagonist, it can cause somnolence and sedation as side effects. To avoid these side effects, Dimenhydrinate, a combination drug of Diphenhydramine and 8-Chlorotheophylline, a stimulant drug and derivative of Theophylline, was developed. In the EU market, Diphenhydramine is used for motion sickness only by oral administration (tablets, capsules, gum, oral solution, dosage from 12.5 to 100 mg) and it is not recommended in young children, in elderly or during breastfeeding [4].

For the same therapeutic indication, transdermal patches containing Scopolamine (dosage 1.5 mg per patch) are successfully used in the USA. Transdermal Drug Delivery Systems (TDDS), also known as "patches," are dosage forms designed to deliver a therapeutically effective amount of drug across the patient's skin. They were developed in the 1970s and in 1979 the Food and Drug Administration (FDA) approved a

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Scopolamine-containing patch. The therapeutic effect of the patch usually lasts from one to seven days, depending on the drug substance and the delivery system. The technology behind the Transdermal Drug Delivery System (TDDS) is critical to achieve good bioavailability, uniform blood drug levels, less side effects and a higher therapeutic effect with a lower dose compared with other delivery systems [5, 6].

Film forming solutions of Diphenhydramine for transdermal delivery have been studied [7], but in Europe no transdermal patches containing Diphenhydramine have been authorised by the competent authorities [8].

In the past years, the falsified medicine market has changed and expanded to other health products, such as food supplements, medical devices and cosmetics, where active pharmaceutical ingredients not declared on the label are fraudulently added [9-11]. In Europe the Official Medicines Control Laboratories (OMCLs) network coordinated by European Directorate for the Quality of Medicines & HealthCare (EDQM), name these products "medicines in disguise" [12] and invite the Member States to control these products on the national market with the aim of verifying the possible presence of undeclared active ingredients. The characteristic of these illegal products is that they do not claim to contain any active ingredients, but they generally claim to be "100% natural". Vegetal extracts and botanicals used for the preparation of natural health products such as herbal medicinal products, cosmetics or medical devices, can be naturally rich in minerals and trace elements (metallic and non-essentials) taken up by the plants during growth or as a result of environmental pollution from industrial and other anthropogenic activities [13, 14]. Inorganic impurities in medicinal products can originate from the manufacturing process, either added intentionally (e.g., reagents, ligands, catalyst) or resulting from contamination of raw materials or equipment employed during manufacturing. The presence of potentially toxic trace elements can be regarded as potential health concern for consumers' safety that should be warranted. Regulatory guidelines such as ICH Q3D [15] provides Permitted Daily Exposure (PDE) limits for those impurities considered having a higher potential safety risk (ICH Q3D).

In this study, we aimed to identify the nature and amount of any undeclared active pharmaceutical ingredients and toxic metal contamination of anti-motion sickness patches labelled as medical devices and claimed to be "herbal relief", marketed on e-commerce popular sites. The composition claim of these products includes *datura* plant, which also suggests the potential presence of Scopolamine as undeclared active drug substance with anti-sickness effect.

MATERIALS AND METHODS

Anti-motion sickness transdermal patches of four different brands were bought online on popular e-commerce web sites. Prior to instrumental analysis, samples were photographed and visually inspected for integrity of primary and secondary packaging, labelling (quality and coherence of information) and CE mark conformity. Sample information are summarised in *Table 1*. Batch numbers and expiry dates, where available, are also reported in *Table 1*.

Identification of active medicinal substances by liquid chromatography-mass spectrometry quadrapole time of flight (LC-MS Q-TOF)

All solvents and reagents used were of LC-MS grade by Sigma-Aldrich®. The presence of active medicinal substances contained in the patches was ascertained by liquid chromatography coupled to High Resolution Mass Spectrometry. Specifically, a screening analysis was carried out by a fast LC system, equipped with a diode array detector (Mod. 1290 Infinity) and a Dual ESI source MS Q-TOF detector, Mod. G6520B (all Agilent Technologies, Santa Clara, CA, USA). Data were processed with *MassHunter® Qualitative Analysis* version B.07.00. Identification of active pharmaceutical substances was obtained by MS and Auto MS/MS analysis in comparison with spectra contained in the MassHunter Forensic Toxicology Personal Compound Database and Library (ForTox PCDL B.07.01) and then confirmed in Target MS/MS against reference standard.

After removing the rear protective liner, each patch was divided in two halves for extraction. One-half was put in a small glass beaker containing 5 mL of methanol and the other one in 5 mL of water, both under magnetic stirring. After three hours, the extraction medium was analysed. The extraction was prolonged for further 6, 24 and 48 hours by adding 5 mL aliquots of fresh solvents each time. This procedure allowed checking solvent- and time-dependent differences in the extraction solutions. Sample extracts were diluted 1:10 with a solvent mixture of 0.1% formic acid in water/acetonitrile 50:50 v/v.

Diphenhydramine hydrochloride reference standard was purchased by Sigma-Aldrich®. Diphenhydramine standard solution for identification was prepared in methanol and then diluted in the same way as the sample extracts to obtain a final concentration of 0.01 mg/mL. All samples and standard solutions were filtered through polytetrafluoroethylene (PTFE) 0.2 µm filters before the analysis.

Chromatographic separation was achieved on a reversed-phase Zorbax Extend-C18 (2.1×50 mm, 1.8 µm) column by an in-house screening method consisting of a 15 minutes linear gradient elution from 100% of a mixture containing 0.1% formic acid in water/acetonitrile 95:5 v/v to 100% of a mixture containing 0.1% formic acid in water/acetonitrile 5:95 v/v. After the gradient, the system comes back to the initial condition in 1 minute and then remains in this condition for 4 minutes. Flow rate was 0.4 mL/min and the injection volume was 1 µL. Column temperature was set to 35 °C and the autosampler was thermostated at 15 °C.

MS analyses were carried out in both positive and negative ions mode; Auto MS/MS analysis was performed only in positive mode, since preliminary screening in MS mode did not show significant chromatographic peaks in negative mode. Finally, the presence of active medicinal substances was confirmed by Target MS/MS analysis by means of reference standards (purchased by Sigma-Aldrich®) in positive mode. MS parameters

Table 1
Results of the visual inspection on the primary and secondary packaging of patches

	Motion Sickness Patch 1	Motion Sickness Patch 2	Motion Sickness Patch 3	Motion Sickness Patch 4
Composition	*The abtract safflower, tall gastrodia tuber, sanchi, hairy datura flower, pinellia tuber, obtuseleaf cinnamon bark, frankincense, dahurian angelica root, borneol, etc.*	*The abstract of safflower, tall gastrodia tuber, hairy datura flower, pinellia tuber, obtuseleaf cinnamon bark, dahurian angelica root, frankincense, borneol, etc*	*Anti-sticking paper, matrix (the abstract of safflower, tall gastrodia tuber, sanchi, hairy datura flower, pinellia tuber, obtuseleaf cinnamon bark, frankincense, dahurian angelica root, borneol and medical pressure-sensitive adhesive), non-woven fabric*	*The abstract of safflower, tall gastrodia tuber, sanchi, hairy datura flower, pinellia tuber, obtuseleaf cinnamon bark, frankincense, dathurian angelican root, borneol, etc*
Notes on Batch number/expiry date	Inconsistency between the batch number and expiry date reported in primary and secondary packaging. Patches with different batch number/expiry date are in the same box	Batch number and expiry date are not reported	Batch number is reported as a date	Batch number is not reported (only two sequences of numbers are reported, probably related to the Manufacturing date and Expiry date)
Batch number/ expiry date (numbers are reported as in the samples)	*Lot. No.20181202/ Exp.: 20211001* and *Lot. No.20181002/Exp.:20211201* in the same packaging but on the secondary packaging is reported: *EXPIRY DATE: 01/AUG/2021*		*Lot No: 2018.12.16 Exp: 2021.12.15*	*20190702 20220701*
Presence of CE/ FDA Mark	"CE Certified by European Standard" and "FDA" marks are reported on the packaging. "CE" mark is counterfeit[1]			A "CE European Standards" mark is on primary packaging. "CE" mark is counterfeit[1]
Inconsistencies and claims	The number of patches reported on the secondary packaging is inconsistent with the real number "Long effect: 72 hours" "Safe and Effective"	Secondary packaging is in English, in the primary packaging pictograms and ideograms are reported Long effect: 72 hours Warnings include "not used by pregnant woman and kids under aged 4". "No side effects"	The packaging reports "100% herbal relief". Long effect: 72 hours Warning includes "one/two patches for time" and "not used by pregnant woman and kids under aged 4".	Absence of secondary packaging. Long effect (inconsistency: 48 reported in one face and 72 hours in the other one of the sachet)
Manufacturer/ Brand	The name of the Manufacturer is slightly different from the name reported in the logo. No information on the Country and address of the Manufacturer	The Brand reported in the secondary packaging is different from that reported in the primary packaging. No information on the Manufacturer name and address	No information on the address of the Manufacturer	No information on the Manufacturer name, address and Country of production. Only a logo is reported

[1]"CE" marking does not respect the distance between C and E of the original mark.

were: Fragmentor 100 V, Nitrogen temperature 300 °C, Drying gas 10 L/min, Nebulizer 40 psig, VCap 4000 V. Collision offset voltage (in Auto and Target MS/MS experiments) was 20 V. In Auto MS/MS experiments, the maximum precursors for cycle were 3. Mass range was 100-1200 Da in MS analysis and 50-1200 Da in MS/MS analysis.

Quantitative analysis of targeted active medicinal substances

All solvents and reagents were of high performance liquid chromatography (HPLC) grade. At least two patches of each sample were analysed. Samples extraction was optimised as follows: after removing the rear protective liner, each patch was cut in many parts (at least 5) and placed in a small glass beaker (closed with a petri disc) containing 10 mL of methanol. Two small magnetic stirring bars were used to prevent sticking of the patch on the bottom and the walls of the beaker, and to increase the solvent-patch surface contact. The solution was stirred for three hours, then the extraction medium was collected and analysed for the quantification of Diphenhydramine and Diclofenac (when detected). The same extraction procedure was repeated until the chromatographic signal of the analytes was negligible, i.e., at increasing times up to at least 72 hours (3, 6, 24, 48, 72 hours). For extracts containing higher quantity of Diphenhydramine (milligrams), the quantity of solvent added was increased up to 50 mL, to obtain the complete extraction from the patch.

The quantitative determination of Diphenhydramine and Diclofenac that had been previously identified in patches, was performed by an Agilent HPLC 1100 series equipped with a diode array detector (mod. 1260 Infinity). HPLC method for quantitative assay of Diphenhydramine was the one described in Euro-

pean Pharmacopoeia Diphenhydramine hydrochloride monograph for the determination of related substances [16] with slight modifications. Briefly, Diphenhydramine was eluted in isocratic conditions with a mobile phase containing 35/65 v/v acetonitrile/potassium dihydrogen phosphate buffer (5.4 g/L at pH = 3.0) (A) for 8 min as prescribed, then a gradient step, up to 90/10 v/v acetonitrile/mobile phase A, was added to elute potentially interfering molecules observed during LC-MS screening analysis. Chromatographic column was a Symmetry C8 250 x 4.6 mm, 5 µm particle size, the flow rate was 1.2 mL/min, detection wavelengths were at 220 and 254 nm, and the injection volume was 10 µL.

HPLC method for quantitative determination of Diclofenac was obtained from literature [17] Chromatographic separation was performed with an isocratic elution (methanol: phosphate buffer pH 2.5 70:30 v/v) and UV detection at 275 nm by using a Zorbax RX C8, 150 mm x 4,6 mm, 5 µm particle size column. Flow rate was 1 mL/min and the injection volume was 20 µL.

Trace elements analysis

Sample manipulations were carried out in clean room conditions under a laminar flow box (Spetec GmbH, Erding, Germany). Analytical grade HNO_3 67% w/w (Romil, Cambridge, UK), H_2O_2 30% w/w (Romil, Cambridge, UK) and HF 40% w/w (PanReac, Barcelona, Spain) were used for sample digestion. Ultrapure water obtained by a Milli-Q system (Zeener UP 900 Water Purification System, Human Corporation, Texas, United States) was employed for sample preparations and dilutions. Certified stock solutions of 1000 mg/L As, Co, Cr, Cd, Cu, Mo, Pb, Ni, Rh, Sb, Tl, Zn, and Rh (as internal standard) (High-Purity Standards, North Charleston, South Carolina, United States) were used to build the calibration curve for total elements' quantification by inductively coupled plasma mass spectrometry (ICP-MS). All standard solutions were daily prepared by diluting the stock solution in 1% v/v HNO_3. Complete sample dissolution was accomplished by mean of high temperatures and microwave irradiation system with mixtures of HNO_3, H_2O_2 and small amounts of HF, added in order to ensure complete sample decomposition. From 0.05 to 0.2 g of protective liner-free samples were digested by closed vessel microwave system (UltraWAVE, Milestone, FKV, Bergamo, Italy) with 1 mL H_2O + 3 mL HNO_3 + 1mL H_2O_2 +0 .5mL HF using the following temperature program: up to 85 °C (ramp 20 °C/min) and stabilization for 8 min; up to 145 °C (ramp 20 °C/min) and stabilization for 5 min; up to 200 °C (ramp 22 °C/min); hold at 200 °C for 20 min before cooling down. Each sample was digested in duplicate and digestion blanks were run in parallel.

Determination of total elements content was carried out by a NexION 350D ICP-MS (Perkin-Elmer, Shelton, CT, USA) equipped with a Meinhard micro nebulizer, a quartz cyclonic spray chamber and Pt cones. The instrument operated at 1600 W in standard mode with Argon as carrier gas and in collision mode (KED) with He (purity 4.9, Sapio, at 4.1 ml/min) filling the cell. Analytical masses were as follows: ^{75}As, ^{59}Co, ^{111}Cd, ^{112}Cd, ^{114}Cd, ^{63}Cu, ^{65}Cu, ^{95}Mo, ^{98}Mo, ^{206}Pb, ^{207}Pb, ^{208}Pb, ^{121}Sb, ^{123}Sb, ^{203}Tl, ^{205}Tl in standard mode and ^{52}Cr, ^{53}Cr, ^{60}Ni, ^{62}Ni, ^{64}Zn, ^{66}Zn in KED mode. The ICP-MS measurement conditions were optimized daily to provide the highest intensity using standard built-in software procedures (Syngistix for ICP-MS, Version 2.3). Quantitative measurements were carried out using the standard addition approach (calibration range 1-50 µg/L). Digestion blanks were analysed in parallel with samples belonging to the same analytical batch. The final concentration of the chemical elements was obtained by subtracting the blank signal to the sample signal for each analyte.

Due to the lack of suitable certified reference materials, the trueness of the measurements was evaluated by spiking samples with known amounts of analytes. The recovery rates turned out to be satisfactory, ranging from 91.6% to 116.9%.

Instrumental limits of detection (LDs) were calculated following the 3σ criteria, and were in the range 0.008-0.28 µg/g.

RESULTS

Visual inspection

All the samples consisted of round brown patches of variable diameters (20 mm Patches 1 and 3, 30 mm Patches 2, 4) contained in sachets as primary packaging. Sachets (10, 20 or 30) were contained in a card box (secondary packaging) except for sample "Patch 3" that was sold with no secondary packaging. All the sachets were intact. All the information were reported on the sachet and on the card box, when available. No leaflet was included for all samples. Descriptive information was reported in narrative form in English language, except for sachets of Patch 2 that reported only pictograms and ideograms. The composition reported on the label is given in *Table 1*, for each patch. The same ingredients were listed for all samples, with few differences in the description of Patch 3. All the samples reported the same indications: "relieve the vomiting, nausea, dizziness, anorexia, and other symptoms resulted from sickness of cars, ships, airplanes, trains and other means of transport". Instructions of use were the same for all the samples: site of application abdomen or behind one ear, ten minutes before the travel, long lasting 1-3 days. Patch 1 requires using one patch per time. Patch 3 one/two patch per time, "according to your body conditions". Warning sentences are quite different: Patch 2 and 3 reported the same peculiar indications: "Not used by pregnant women and kids under aged 4" and "Not recommended to use by poorly surgery body".

Visual inspection of the samples highlighted many anomalies in the labelling, suggesting an illegal production. Punctuation and grammatical/translation errors (e.g., "abstract" – instead of extract – "by poorly surgery body"); no botanic names were reported in the declared composition, so it was impossible to assess exactly the characteristics of the extracts used; in some patches (specifically, 1-3) the list of ingredients ended with "etc.".

The results of the visual inspection showed that many legal information, such as the name of the Manufacturer (absent in two cases) and the Manufacturer's ad-

dress (absent in all cases) were missing on the packaging. Inconsistencies concerning the number of patches contained in the box or between the batch number and expiry date reported in the primary and secondary packaging were observed, suggesting poor control during manufacturing or a potential risk of falsification. In one case (Patch 4) the secondary packaging (card box) was different from that reported in the primary one. Moreover, the "CE" mark, which means "European Conformity", was followed by the definition "Certified by European Standard" or "European standards" and in one case the mark was evidently false (the typographic font of C and E and the distance between them did not comply with the law requirements) [18]. *Figure 1* reports the photographic image of the patch with emphasis on inconsistencies.

Identification of active medicinal substances by LC-MS Q-TOF

MS qualitative analysis showed the presence of Diphenhydramine and its related impurity desmethyldiphenydramine (Eur. Ph. Impurity A) in all patches. Moreover, in three patches (Patch 1, 2 and 3) the presence of Diclofenac was also detected. Diphenhydramine and Diclofenac identification was confirmed by MS/MS in comparison with a commercial reference standard. *Figure 2* shows (for Patch 1) the extracted ion chromatographic peak, the mass spectrum and the Auto MS/MS spectrum (reporting the match in database for the identification of Diphenhydramine). Other undeclared constituents, such as Capsaicin and Dihydrocapsaicin were found in Patch 2 by Auto MS/MS analysis, with a high identification score with spectral database, suggesting cross-contamination problems in production. Ultimately, the presence of Scopolamine, that was suspected to be contained in the patch as an undeclared active drug substance with anti-sickness effect, was not confirmed by the results obtained.

Quantitative analysis of targeted active medicinal substances

Quantitative extraction was a critical point due to a very low patch-to-patch reproducibility, not only among patches of different batches, but also among patches of the same lot. Quantities lower than milligrams/patch of Diclofenac were found, probably due to contamination related to non-GMP compliant manufacture of different kind of products. On the other hand, a content of Diphenhydramine, ranging from 0.5 mg to 3 mg per patch was found. The results of the quali-quantitative analysis showed higher quantities of Diphenhydramine in Patch 3 and Patches 2 than in Patch 1 and Patch 4. It should be noted that for Patch 3 a 72-hour time-point was not sufficient to obtain negligible chromatographic signal of Diphenhydramine. Notwithstanding the extraction time was extended up to 210 hours, a steady state could not be reached and quantities in the order of milligrams were still recovered.

Determination of total elements content

Results obtained for total elements content are depicted in *Table 2*, where the mean value and the standard deviation (SD) associated with the instrumental measurements and digested samples (n = 4) is reported for each analyte.

Three groups of elements were considered accord-

Figure 1
Photographic image of a patch with emphasis on inconsistencies reported in the paper.

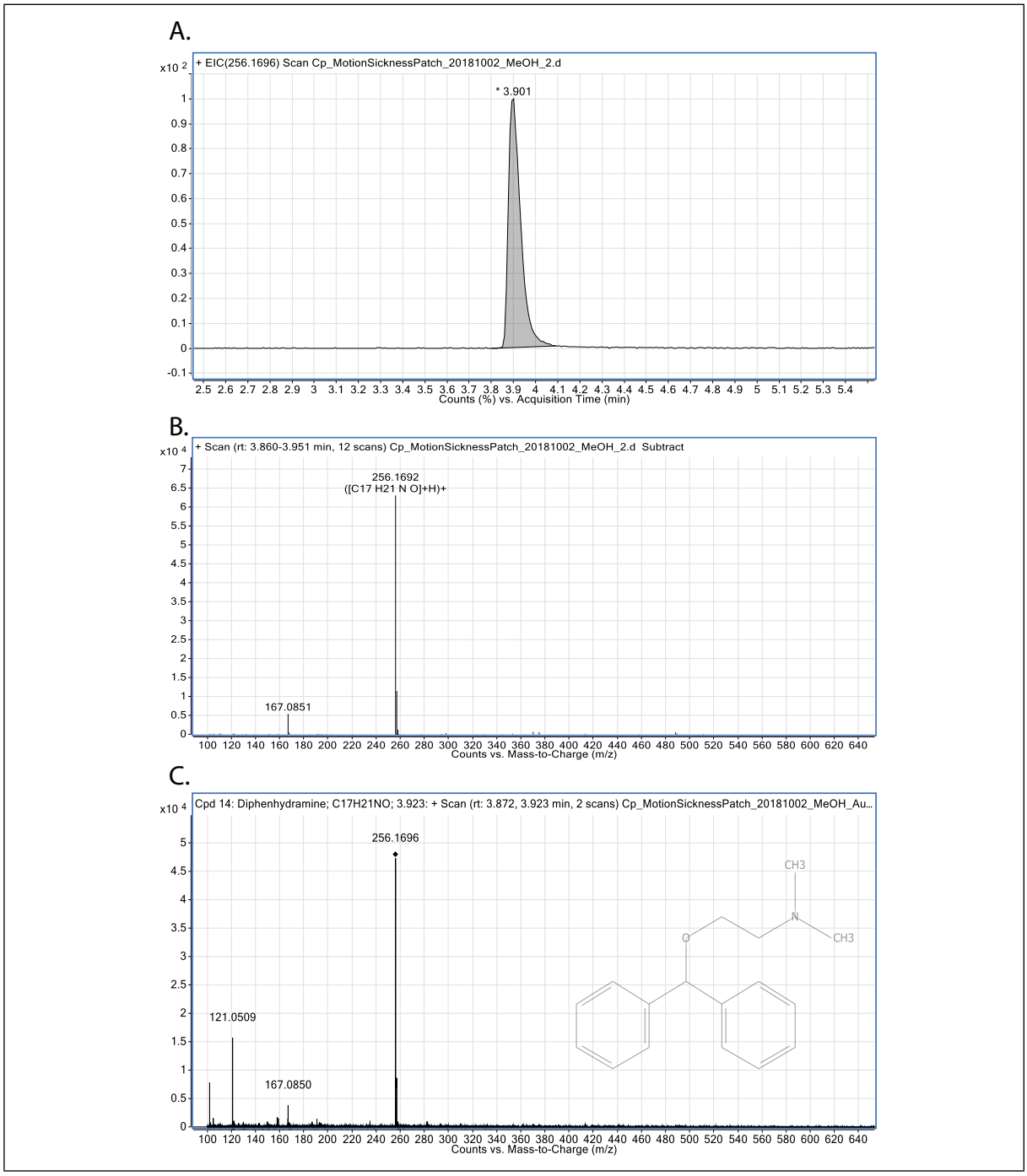

Figure 2
Extracted ion chromatographic peak of Diphenhydramine (panel A), mass spectrum of Diphenhydramine (panel B) and Auto MS/MS spectrum reporting the match in database for the identification of Diphenhydramine (panel C) of a sample of Patch 1.

ing to their ICH classification [15]: class 1 comprising known human toxicants such as As, Cd, Pb; class 2 including elements generally considered as route-dependent human toxicants such as Ni, Co, Tl and class 3 with all the other elements.

All samples showed low but detectable concentrations of As, Cr, Cu, Mo, Pb, Ni, Zn, Sb; on the other hand, Tl was systematically below the LD in all the analysed samples, Cd was below LD in two out of four samples and Co was below LD only in sample 2. The lowest detected amount of As (0.02 μg g^{-1}), Cr (0.66 μg g^{-1}), Cu (0.45 μg g^{-1}), Mo (0.05 μg g^{-1}) and Pb (0.13 μg g^{-1}), were found in sample 2, Ni (0.38 μg g^{-1}), Zn (4.96 μg g^{-1}) and Cd (0.037 μg g^{-1}) in sample 4, Sb (42.5 μg g^{-1}) in sample 1 and Co (0.09 μg g^{-1}) in sample 3, respectively. The overall elements content in samples followed the order 1~3 >4>2 for class 1, 1~4 >3~2 for class 2, and 2>4>3>1 for class 3, mainly due to the contribution of Sb (42.5-128.2 μg g^{-1}). The results highlight elemental concentration range in samples from different suppli-

Table 2
Distribution of trace elements and dermal exposures calculated according to ICH in transdermal systems selected for this study

	PDE	Sample Patch 1		Sample Patch 2		Sample Patch 3		Sample Patch 4	
	µg day^{-1}	µg g^{-1}	µg day^{-1}	µg g^{-1}	µg day^{-1}	µg g^{-1}	µg day^{-1}	µg g^{-1}	µg day^{-1}
As	15	0.208±0.012	0.019	0.021±0.001	0.002	0.187±0.019	0.012	0.103±0.003	0.017
Co	50	0.728±0.021	0.066	<LD	NA	0.089±0.006	0.006	1.298±0.024	0.214
Cr	11000	0.642±0.015	0.058	0.664±0.014	0.060	1.850±0.099	0.117	0.776±0.012	0.128
Cd	5	0.043±0.002	0.004	<LD	NA	<LD	NA	0.037±0.001	0.006
Cu	3000	0.808±0.049	0.073	0.450±0.029	0.040	0.520±0.023	0.033	0.801±0.056	0.132
Mo	3000	0.176±0.004	0.016	0.052±0.001	0.005	0.114±0.001	0.007	0.039±0.002	0.006
Pb	5	1.986±0.075	0.179	0.133±0.007	0.012	2.153±0.086	0.136	1.731±0.087	0.286
Ni	110	0.569±0.021	0.051	0.772±0.065	0.069	0.619±0.054	0.039	0.381±0.008	0.063
Sb	1200	53.40±3.03	4.81	128.2±9.12	11.54	78.47±2.28	4.94	96.92±2.68	15.99
Tl	8	<LD	NA	<LD	NA	<LD	NA	<LD	/
Zn	NA	8.68±0.52	NA	36.35±1.76	NA	8.03±0.42	NA	4.96±0.24	/

NA: not applicable; LD: limits of detection. ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.

ers (1-4) spanning a 10-30 fold variation range within elements of class 1, a 4-15 fold range for class 2, and a narrower 2-7 fold range for elements of class 3.

DISCUSSION

Undeclared active ingredients

Anti-motion sickness patches claiming only natural ingredients and freely marketed on e-commerce web sites, actually contain active drug substances undeclared on the label. Visual inspection showed many inconsistencies and errors in the labelling, indicating signs of a potential falsification or at least very poor quality in production. Appearance of all the patches was very similar, labels reported the same composition and often the same typing errors. All the analysed patches contained Diphenhydramine: after over 72 hours extraction Patch 3 still contained measurable quantities of Diphenhydramine suggesting a different matrix able of a longer lasting action; three patches showed low quantity of Diclofenac, suggesting a cross-contamination due to a non-GMP manufacture of different products; Capsaicin was identified in Patch 2.

Diphenhydramine is an antihistamine with anticholinergic and sedative effects. Commercial medicinal products containing Diphenhydramine are legally placed on the market as tablets, capsules, oral solutions, intramuscular or intravenous injections or pharmaceutical forms for topical use (creams) whereas there are not transdermal patches containing Diphenhydramine authorised in the EU. The authorised dosage of Diphenhydramine for oral use for motion sickness ranges from 12.5 to 100 mg in the EU. It is well known that transdermal patches require even lower dosages to achieve a therapeutic effect [5]. Medicines containing Diphenhydramine are contra-indicated in people with a specific hypersensitivity to Diphenhydramine and similar antihistamine molecules, in pregnancy and during breastfeeding, in patients with glaucoma and in people taking antidepressant drugs. Diphenhydramine has additive effects with alcohol that may jeopardise consumers health if they are not properly informed [19]. Capsaicin found in Patch 2 is an active medicinal substance generally used as topical analgesic and as patch in the treatment of neuropathic pain [20, 21]. Furthermore, its properties to promote skin permeability in transdermal drug delivery were reported [22]. The European Pharmacopoeia contains monographs for "Capsici fructus" and "Capsicum Oleoresin". The European Scientific Cooperation on Phytotherapy (ESCOP) has classified "Capsici fructus" as an herbal medicinal product. According to the outcome of the Manual of Borderline "a plaster with Capsaicin may not be qualified as a medical device" [23]. The undeclared presence of active pharmaceutical ingredients in patches claimed to contain only natural ingredients makes these products dangerous to health. Furthermore, transdermal patch is a sophisticated drug delivery system, which is difficult to formulate. It requires specialized manufacturing process/equipment to meet specific pharmacological and functional characteristics. The uncontrolled production of transdermal patches does not ensure these characteristics, leading to a device that could release the active substance too fast or, on the contrary, too slow, or leading to a rapid degradation of the active ingredient due to interaction with the patch matrix. Finally, in this formulation the choice of a non-toxic adhesive matrix that is suitable for dermal use should be carefully evaluated. In products freely marketed, these characteristics are not controlled and can cause allergic reactions and pose a health hazard.

Trace elements

Vegetal extracts and Botanicals used for the preparation of herbal medicinal products, cosmetics or medical devices can be rich in trace elements [24]. The distribution tendency of trace elements, specifically those of class 1 and 2, in the samples selected for this study cover a wide range of concentration notwithstanding a similar composition claimed on the product label. As pointed out in the visual assessment, the samples se-

lected for this study are characterized by inadequate or incomplete description of composition; therefore, exact taxonomic botany of components could not be ascertained. Possible explanations of the distribution tendency might be related to different plant origin, environmental factors [25] and production processes, including adulteration with active pharmaceutical ingredients. Trace elements and metals can in fact be regarded as impurities in pharmaceutical industry originating from elements intentionally added (e.g., reagents, ligands catalyst) or not intentionally added (e.g., contamination originating from the manufacturing equipment or raw materials) to the products [26, 27]. Over the last decades, trace elements have been studied in natural health products where undeclared or excessive active pharmaceutical ingredients were found [27, 29-31]. As (14.6 ppm), Pb (1.05-75 ppm), Cd (0.24-39 ppm), Ni (2.33-45 ppm), Cr (1.68-110 ppm), Cu (0.24-28 ppm), Mo (2.56-45.2 ppm) Tl (0.037-2.07 ppm), and Co (0.038-9.55 ppm) were found at higher levels than those found in the present study, but none of these investigations specifically focused on transdermal systems. On the other hand, Zn levels (13-80 ppm) were comparable whereas Sb concentrations (0.79-2.13 ppm) were considerably lower than those found in this study, likely due to the possible contribution of the non-woven substrate used for the production of the transdermal system [31, 32].

Provisional safety assessment

ICP-MS results were used to carry out a safety assessment for each sample calculating dermal exposure by assuming the use of one or two patches per time, as per indications on the label. Due to the presence of the active pharmaceutical ingredients Diphenhydramine and Diclofenac among others, the selected samples were regarded as medicinal products [33]. Therefore, the assessment was carried out following the principles of ICH Q3D guideline set out under the EU pharmaceutical legislation. Health based exposure limits are expressed as permitted daily exposure (PDE, mg/day) for all the studied elements. Element specific dermal PDEs were established by Bouvier et al. based on the oral PDEs set in ICH Q3D [34, 35]. Results are presented in *Table 2*. Dermal absorption of trace elements is typically low and dependent upon the properties of the skin, the anatomical site, the physical-chemical properties of the mixture and the characteristics of the application [13, 14, 36, 37]. The highest estimated daily exposures were found for Sb (Class 3) and Pb (Class 1), however for all samples the calculated cutaneous concentrations were below 10% of the estimated PDEs.

Among the studied elements, nickel, cobalt, and chromium are the most important contact human allergens, with nickel representing the leading contact allergen in most industrialized countries worldwide [38, 39]. Samples were evaluated for sensitization from Ni and Co, according to the approach developed by Lim *et al*. based on sensitization quantitative risk assessment [37]. For Chromium the sole PDE was considered appropriate (ICH). Therefore, transdermal systems were treated as leave-on cosmetic products and only single mineral exposure was considered. Dermal sensitization is a threshold-based phenomenon [40, 41], the % concentration of elements in a product type is acceptable if the Consumer Exposure Level (CEL) is lower than the Acceptable Exposure Level (AEL) [37]. The assessment reported in *Table 3* shows that AEL/CEL ratios were higher than 1, therefore the compounds were not indicative of a potential skin sensitizer. It is important to stress that this study only provides a snapshot of elemental levels in a limited number of samples that may not reflect the elemental content variability of transdermal systems. Actually, the assumptions made in this study for transdermal systems may represent a source of uncertainty to the proposed assessment. A more refined exposure assessment taking into account other sources of exposures (e.g., food) or the study of combined exposure to chemical sensitizers, is also recommended, specifically for children and other vulnerable groups.

CONCLUSIONS

This case study concerning falsified anti-motion sickness transdermal patches, proved for the first time that these products, claiming only natural ingredients and freely marketed on commercial web sites, actually contain active drug substances. These products are claimed as medical devices and some of them reported a falsified CE mark on the packaging. All of the analysed products reporting only natural ingredients and claiming to be "100% natural relief" in the composition contained some milligrams per patch of Diphenhydramine, an active medicinal substance. Transdermal patches containing Diphenhydramine are not authorised in the EU. Therefore, it is not possible to know whether the quantity of Diphenhydramine found in the patches can have a therapeutic effect, but Diphenhydramine was considered a candidate for non-invasive transdermal

Table 3
Sensitization assessment for Ni and Co

	Ni			*Co*		
	CEL (µg/cm²/day)	*AEL* (ug/cm²)*	*AEL/CEL*	*CEL (µg/cm²/day)*	*AEL* µg/cm²*	*AEL/CEL*
Sample Patch 1	4.1E-03	1.34	328	5.2E-03	1.04	199
Sample Patch 2	2.5E-03	1.34	545	2.0E-03**	1.04	530
Sample Patch 3	3.1E-03	1.34	432	4.5E-04	1.04	2329
Sample Patch 4	2.2E-03	1.34	602	7.6E-03	1.04	137

*Reported on Lim *et al*., 2018 [37]. **LD/2 was used for calculation. LD: limits of detection. CEL: Consumer Exposure Level; AEL: Acceptable Exposure Level.

delivery system [7]. Overall, patches sampled in this study can actually be considered "medicines in disguise" freely marketed on the internet and represent a potential health risk to end-users – including children over 4 – targeted with one or two patches per time for a long time (1-3 days) according to the label indications.

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Author's contribution

MCG: LC MS measurements and elaboration of results, drafting manuscript. LM: LC MS measurements and elaboration results. PB, EA: quantitative HPLC analysis. DDO: idea proposal, quantitative HPLC analysis. AR: statistical evaluation of results, revision of the manuscript. AS, FA: ICP-MS analysis and drafting manuscript. MB: coordination and critical revision of the study, revision of the manuscript.

Conflict of interest statement

None.

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Italians are still loyal to conventional cigarettes, despite novel tobacco products

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Abstract

Introduction. Over the last few decades in Italy, we observed a substantial reduction in conventional tobacco cigarette consumption, the introduction of electronic cigarettes (e-cigarette) in 2010, and the launch of heated tobacco products (HTP) in 2015.

Methods. We investigated novel products, i.e. e-cigarettes and HTP, use in Italy in 2018-2021 using data from the cross-sectional annual PASSI (Progressi delle Aziende Sanitarie per la Salute in Italia) survey conducted in representative samples of adults aged 18-69 (overall n = 101,458). We compared characteristics of conventional cigarette smokers with those of novel product users.

Results. A stall in e-cigarette use at around 2.4% and a three-fold increase in HTP use from 0.5% in 2018 to 2.5% in 2021 were recorded, with around 60% of e-cigarette users and 70% of HTP users who kept on smoking conventional cigarettes. Around 86% of smokers did not use novel products at all. Novel products use among former smokers was more likely in younger e-cigarette with no nicotine users, whereas older users of both novel products were less able to completely shift to an exclusive use.

Conclusions. After 10 years from the introduction of e-cigarettes and 5 years from that of HTP, the majority of smokers in Italy were still loyal to conventional tobacco cigarettes, and more than half of novel product users kept on smoking conventional cigarettes.

Key words

- smoking prevalence
- tobacco
- ENDS
- e-cigarette
- heated tobacco products
- heat-not-burn tobacco
- Italy

INTRODUCTION

Tobacco smoking was the second leading risk factor for premature death and disability worldwide in 2019 accounting for 8.71 million deaths [1]. However, the last decades have seen a substantial expansion and strengthening of tobacco control initiatives, following articles outlined in the World Health Organization Framework Convention on Tobacco Control (WHO-FCTC) and the 25×25 non-communicable disease (NCD) targets. As a result, a substantial reduction in tobacco use was recorded over the last few decades, at least in high-income countries [1]. Recently, novel products have been introduced into the market, including electronic cigarettes (e-cigarettes) and heated tobacco products (HTP). Their popularity and use grew rapidly worldwide [2], also thanks to their aggressive promotion, with claims that they were less harmful than conventional cigarettes [3].

Long-term health consequences of these novel products are still largely unknown [3]. Recently, an Australian report highlighted the lack of evidence to conclude that e-cigarettes are not dangerous [4]. Moreover, a recent article suggested that combining smoking with e-cigarette use did not reduce cardiovascular events [5]. However, there is still a huge debate in the scientific community as to whether e-cigarettes can be considered a technology to help smokers to quit and provide a safer alternative to cigarettes [3], or a tool that will allow the tobacco industry to subvert policies, renormalize smoking and new smokers [6, 7]. Notwithstanding that the debate is not over, Australia from October 2021 banned e-cigarettes because of the significant increase in young people.

Due to the alleged reduced harm, novel products obtained fiscal and regulatory benefits compared to

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conventional cigarettes in most high-income countries [6]. In 2014, however, the European Union introduced the Tobacco Products Directive, which included restrictions to advertising and mandatory warnings on e-cigarette products containing nicotine [8]. In addition, in 2018, the eighth session of Conference of the Parties stated that HTP meet the definition of tobacco products under FCTC, thus the full range of policy and regulatory measures contained in the WHO-FCTC apply to HTP [9].

E-cigarettes have been introduced into the Italian market in 2010 and HTP since the end of 2015. Data from a series of cross-sectional surveys conducted annually on representative samples of around 3,000 Italians aged >14 years showed that e-cigarette users increased form 1.2% in 2013 to 2.1% in 2017-2019, while HTP users were 1.1% in 2019 [10]. Moreover, data from the ongoing Italian behavioural risk factor surveillance system PASSI (Progressi delle Aziende Sanitarie per la Salute in Italia) showed the use of e-cigarettes as a quitting tool, with one out of ten smokers who attempted to quit in 2014-2015 using e-cigarettes [11].

The aim of this study is to use PASSI data to provide updated estimates of e-cigarette and HTP use in Italy in 2018-2021 and to compare characteristics of conventional cigarette smokers with those of novel product users.

METHODS

The PASSI surveillance system is a cross-sectional survey carried out annually on a sample of the Italian population aged 18-69 years. A random sample is extracted from the lists of residents in each Local Health Unit (LHU), stratified by sex and age group (18-34, 35-49, 50-69 years) based on the proportion of population in each stratum, obtaining annual estimates of the main variables at LHUs level with an acceptable precision. The survey collects information on a wide variety of health-related and behavioural topics along with demographic and socio-economic data. Informed consent was obtained from all participants. More details on methodological issues related to PASSI data collection have been described elsewhere [12].

For the present analysis we included data from the 2018-2021 PASSI surveys, comprising 139 Italian LHUs and 101,458 interviews (around 31,600 per year in 2018-2019, 16,361 in 2020 and 22,000 in 2021). We collected information on e-cigarettes, HTP and conventional tobacco cigarettes use, together with demographic and socio-economic characteristics.

We defined current e-cigarette users or current HTP users as respondents who declared to use nicotine or non-nicotine e-cigarettes or HTP on the date of the interview, respectively; current cigarette smokers as respondents who smoked at least 100 cigarettes in their lifetime and smoked in the last 30 days; former smokers as respondents who smoked at least 100 cigarettes in their lifetime but were not current smokers; never smokers as those who smoked less than 100 cigarettes in their lifetime; dual users as respondents who used e-cigarettes or HTP and kept on smoking conventional cigarettes. The present analysis included 24,508 current smokers, 17,779 former, and 59,092 never smokers.

Proportions were estimated by taking into account for the survey design using the Taylor series method for variance estimation and by assigning each record a probability weight equal to the inverse of the sampling fraction in each LHU stratum [12]. A Poisson regression model with robust variance was used for estimating prevalence ratios (PR) of e-cigarette or HTP use according to selected demographic, socio-economic and smoking characteristics. Interactions between age and economic status, smoking status and education were evaluated.

All the analyses were carried out using Stata 17 software.

RESULTS

In 2018-2021, e-cigarette users (with or without nicotine) stalled around 2.4% in the overall population and 4.0% among former smokers. Among current smokers, nicotine and non-nicotine e-cigarette users stalled respectively around 4.4% and 1.7%, with a slight increase from 2020 to 2021 in nicotine e-cigarette. On the other hand, among never smokers e-cigarette with nicotine increased from 0.1% in 2018 to 0.4% in 2021, and HTP users increased from 0.5% to 2.5% among total population, from 1.5% to 7.8% among current smokers, from 0.7% to 2.8% among former smokers, and from 0.0% to 0.3% among never smokers (*Figure 1*).

Most novel product users were dual users: in 2021 the proportion of dual users was 59.4% (=1.0% / [1.0% + 0.7%]) among nicotine e-cigarette users, 48.7% among non-nicotine users (= 0.4% / [0.4% + 0.4%]), and 73.4% among HTP users (= 1.8% / [1.8% + 0.7%]). Moreover, most smokers (in 2021 86.3% = 20.5% / [20.5% + 1.0% + 0.4% + 1.8%]) kept on exclusively smoking conventional cigarettes (*Figure 2*). Interestingly, e-cigarette (non-nicotine and nicotine) and HTP users among never smokers increased from 6.1% in 2018 to 12.0% in 2021.

Models stratified by age class for e-cigarette or HTP use were estimated due to a significant interaction between age and smoking status in both models (model for e-cigarette use: $p < 0.001$; HTP use: $p = 0.0193$). E-cigarette users aged 18-34 and 35-49 years were more likely to be males than females. Both e-cigarette and HTP users older than 35 years were more likely to report high education level. Moreover, both e-cigarette users aged 50-69 years and HTP users among respondents of all ages were less likely to be former smokers compared to current smokers. Users among never smokers were very few (*Table 1*). By analyzing separately e-cigarette use with or without nicotine (data not shown) former smokers aged 18-34 years were more frequently users without nicotine compared to current smokers, whereas among respondents aged 35-69 years users with nicotine were less likely to be former smokers.

DISCUSSION

Our findings on a slight decrease in prevalence of conventional cigarettes, a stall in prevalence of e-cigarette users, and an increase in HTP users were in broad agreement with data observed in a series of repeated representative surveys of Italian adults [10]. Moreover, the substantial increase in HTP use is consistent with sales data: the proportion of HTP sales on total tobac-

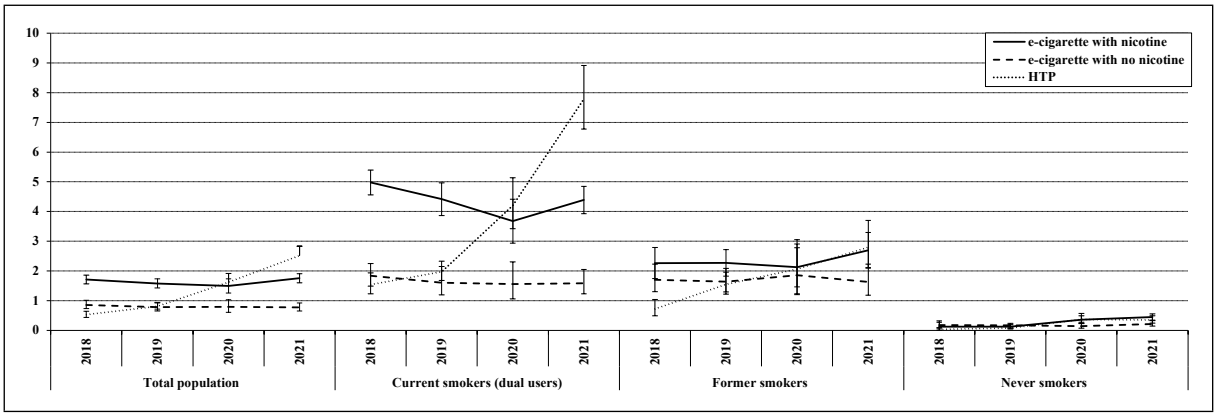

Figure 1
Prevalence of current electronic cigarette (e-cigarette) or heated tobacco products (HTP) use in the total population and by smoking status, 2018-2021.

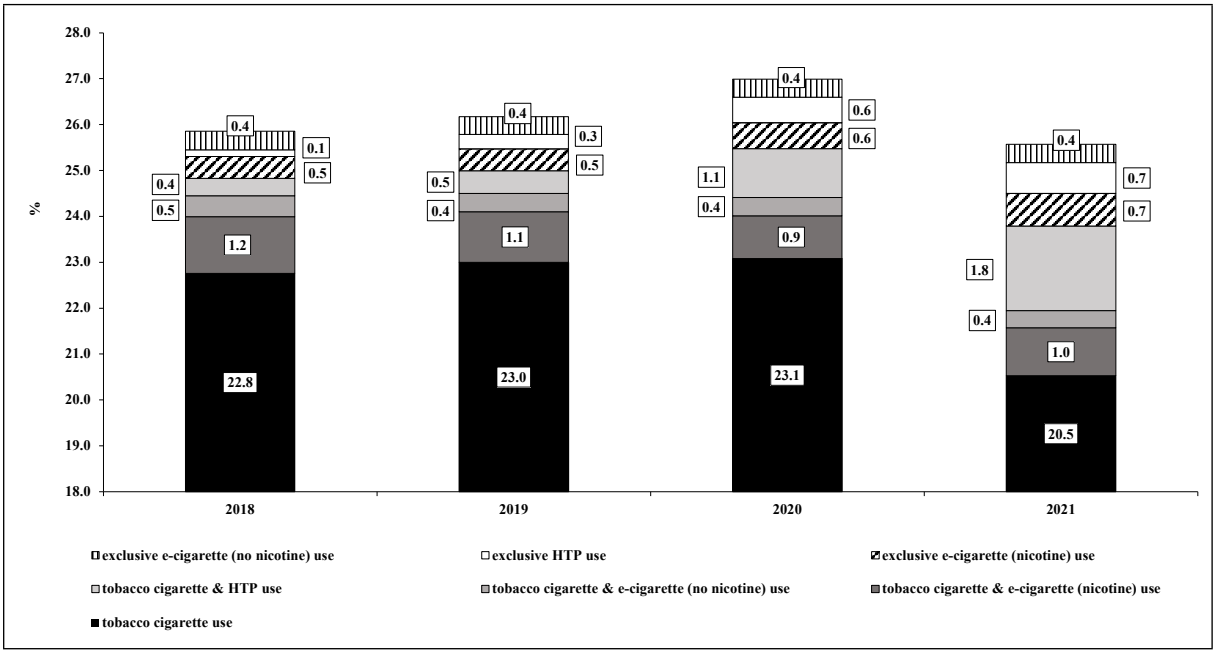

Figure 2
Prevalence of tobacco cigarette, electronic cigarette and heated tobacco products (HTP) use by years, PASSI 2018-2021.

co products grew from 2.0% in 2018 to 11.7% in 2021 [13]. Finally, in a representative survey conducted in Italy during the COVID-19 lockdown in 2020, a stall in smoking prevalence, albeit with an increase in smoking intensity, and an increase in both e-cigarette and HTP use were recorded [14].

The use of novel products was mainly characterized by a dual use, with 56% of e-cigarettes and 73% of HTP users continuing smoking conventional cigarettes. Moreover, 86% of smokers did not use novel tobacco products at all, suggesting that the vast majority of smokers were not attracted by novel products. A cross-sectional survey on e-cigarette use conducted in 2021 among English people found that 30.5% of e-cigarette users were dual users, the proportion of adult smokers who currently used e-cigarettes increased rapidly from 6.7% in 2012 to 17.6% in 2014, and then, up to 2021, it stalled at around 17%, as if no more than 1 out of 6 smokers were satisfied with vaping. As a consequence, among nicotine addicted subjects the proportion of exclusive tobacco smokers remained high also in the UK (83.1%) [15].

A possible benefit of the use of novel products is their use among former smokers, hypothesizing that these subjects made a complete shift from conventional cigarettes to novel products. In this paper, few users of e-cigarettes or HTP were able to make a complete shift. Only non-nicotine e-cigarette users aged 18-34 years were more likely to completely shift to e-cigarettes, i.e., were more likely to be former than current smokers, whereas users of both novel products aged 50-69 years were more likely to continue smoking, showing more difficulties in making a complete shift to novel products.

Table 1
Association between current electronic cigarette (e-cigarette) and heated tobacco product (HTP) use[a] and demographic, socio-economic characteristic, and smoking status, Italy 2018-2021. Total numbers of survey participants in each strata of the population and prevalence ratios with corresponding 95% confidence intervals

	Total	Current e-cigarette users				Current HTP users			
	N (%) 101,458 (100)	N (%) 2,427 (2.5)	PR (95% CI)			N (%)	PR (95% CI)		
			18-34 years	35-49 years	50-69 years	1198 (1.4)	18-34 years	35-49 years	50-69 years
Sex									
Women	52,109 (50.5)	975 (2.0)	1*	1*	1*	594 (1.3)	1*	1*	1*
Men	49,349 (49.5)	1452 (3.1)	1.45 (1.20-1.75)	1.3 (1.09-1.57)	0.9 (0.74-1.09)	604 (1.4)	0.82 (0.66-1.02)	0.88 (0.67-1.15)	0.78 (0.55-1.12)
Year									
2018	31,234 (27.2)	776 (2.6)	1*	1*	1*	149 (0.5)	1*	1*	1*
2019	31,934 (27.6)	760 (2.4)	1.03 (0.83-1.28)	0.88 (0.73-1.07)	0.83 (0.67-1.04)	266 (0.8)	1.66 (1.13-2.44)	1.48 (1.00-2.19)	1.34 (0.86-2.08)
2020	16,361 (20.7)	344 (2.3)	1.06 (0.80-1.41)	0.87 (0.65-1.17)	0.77 (0.56-1.04)	241 (1.7)	4.14 (2.77-6.17)	2.32 (1.51-3.55)	2.29 (1.36-3.84)
2021	21,929 (24.5)	547 (2.6)	1.39 (1.10-1.75)	1.07 (0.84-1.37)	0.77 (0.60-1.00)	542 (2.6)	5.86 (4.05-8.48)	4.67 (3.19-6.82)	3.49 (2.23-5.46)
Level of education**									
Low	31,638 (31.3)	650 (2.0)	1*	1*	1*	254 (0.9)	1*	1*	1*
High	69,686 (68.7)	1,775 (2.7)	1.12 (0.90-1.40)	1.74 (1.43-2.11)	1.48 (1.21-1.82)	944 (1.5)	1.03 (0.77-1.38)	1.57 (1.13-2.19)	1.66 (1.12-2.48)
Economic status***									
None economic difficulties	57,051 (54.4)	1,286 (2.4)	1*	1*	1*	724 (1.5)	1*	1*	1*
Some difficulties	35,035 (36.0)	880 (2.5)	1.02 (0.85-1.24)	1.11 (0.90-1.38)	1.01 (0.82-1.26)	373 (1.2)	0.8 (0.64-1.02)	0.79 (0.57-1.08)	1.14 (0.80-1.63)
Many difficulties	8,925 (9.6)	257 (2.9)	0.96 (0.69-1.34)	1.3 (0.98-1.72)	1.02 (0.73-1.42)	92 (1.1)	0.73 (0.44-1.20)	1 (0.65-1.52)	0.75 (0.38-1.48)
Geographic area									
Northern Italy	38,495 (34.8)	891 (2.5)	1.12 (0.90-1.40)	1.04 (0.83-1.31)	0.79 (0.63-1.00)	463 (1.5)	1.16 (0.89-1.50)	1.28 (0.90-1.82)	1.19 (0.75-1.90)
Central Italy	24,806 (22.0)	712 (3.1)	1.38 (1.12-1.70)	1.41 (1.13-1.76)	0.98 (0.78-1.24)	317 (1.5)	1.28 (1.00-1.65)	1.05 (0.72-1.53)	1.38 (0.87-2.20)
South Italy and Islands	38,157 (43.2)	824 (2.2)	1*	1*	1*	418 (1.1)	1*	1*	1*
Smoking status									
Current	24,508 (24.7)	1,489 (6.3)	1*	1*	1*	820 (3.9)	1*	1*	1*
Former	17,779 (17.2)	691 (4.1)	1.07 (0.85-1.36)	0.85 (0.70-1.04)	0.49 (0.4-0.61)	266 (1.8)	0.75 (0.57-0.99)	0.53 (0.38-0.74)	0.43 (0.29-0.63)
Never	59,092 (58.1)	246 (0.4)	0.11 (0.08-0.14)	0.07 (0.05-0.10)	0.03 (0.02-0.04)	112 (0.2)	0.06 (0.05-0.09)	0.03 (0.02-0.05)	0.03 (0.01-0.05)

[a]Respondents who declared to use both e-cigarette and HTP were defined as HTP users since many harmful substances are at higher concentration in HTP compared to e-cigarette (N=38).
Abbreviations: PR: prevalent ratio of current users *vs* non-current users. 95% CI: 95% confidence interval. PR and 95%CI were estimated using a Poisson regression model with robust variance after adjustment for sex, survey year, level of education, economic status, geographic area and smoking status.
*Reference category. **Level of education was assessed by asking: "What is your level of education?""none or elementary school or junior high school" = Low; "high school or university" = High. ***Economic status was assessed by asking: "With the available financial resources how do you get to the end of the month?""very easily or easily" = None economic difficulties; "with some difficulties" = Some economic difficulties; "with many difficulties" = Many economic difficulties.

In addition to the lack of a complete shift to novel products among current smokers, we observed that their use doubled among never smokers, suggesting that they are used for initiating nicotine dependence.

Public health implications of these results are that novel products cannot be considered a technology to help smokers to quit, especially HTP and nicotine e-cigarettes, and that their use is increasing among never smokers and youths.

Limitations of this study were those inherent to the cross-sectional design, including the impossibility to infer causality in the observed associations. Our results

should be confirmed by prospective cohort studies. Furthermore, sales data on e-cigarettes are not yet available for Italy, so we were not able to verify whether the plateau of e-cigarette use we recorded was consistent with official sales data.

In conclusion, after 10 years from the introduction of e-cigarettes and 5 years from that of HTP in Italy, although novel products enjoyed huge fiscal and regulatory benefits compared with conventional cigarettes, the vast majority of nicotine addicted people were still loyal to conventional cigarettes, and almost two out of three novel tobacco product users kept on smoking conventional cigarettes.

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Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki, and is part of the Italian surveillance system PASSI (Progressi delle Aziende Sanitarie per la Salute in Italia). The Ethics Committee of the Italian National Institute of Health (ISS - Istituto Superiore di Sanità) has issued a favourable ethical opinion on the Italian behavioural surveillance system PASSI. The protocol number of the final opinion is CE-ISS 06/158 - 8th of March 2007. PASSI complies with General Data Protection Regulation and informed consent was obtained from all subjects involved in the study.

Conflict of interest statement

All Authors must declare any conflicts of interest.

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Knowledge, attitude and barriers of the Italian National Guidelines System for the development of clinical practice guidelines: a cross-sectional survey of registered scientific-technical societies

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Abstract

Background. To explore knowledge, attitude, and barriers of the Italian National Guidelines System (SNLG) for the development of clinical practice guidelines (CPG) among scientific-technical societies (STS) of health care professional.

Methods. A cross-sectional survey was distributed to the STS registered in the Italian Ministry of Health (n = 336). The questionnaire consisted of three sections: Respondent characteristics; Perception, knowledge, attitude, and use of CPGs; Knowledge of the SNLG.

Results. The survey sample was 194 (57.7%) STS: 69% STS members stated they "often consulted CPGs". Two out of three STS perceived scientific activities as extremely important. Additionally, 20.6% STS had submitted at least one CPG to the SNLG platform after the Gelli-Bianco Law went into effect (median 1 CPG; interquartile range, IQR, 1-4). The most often cited barrier (62.7%) to CPG submission was limited economic resources.

Conclusions. STS members hold a positive attitude towards CPGs despite barriers to CPG development.

Key words

- evidence-based practice
- cross-sectional studies
- clinical practice guidelines
- surveys and questionnaires

INTRODUCTION

Clinical practice guidelines (CPGs) provide support for evidence-based clinical decisions. The World Health Organization (WHO) defines evidence-informed CPGs as "a set of recommendations to support informed decision-making on the desirability of carrying out specific interventions at clinical or public health level, since these guidelines provide a basis for selecting and prioritizing, among a set of possible interventions, the most appropriate" [1]. The purpose of CPGs is to support practitioners in their evidence-based clinical decision making and to maximize the effectiveness of treatment allocation for specific outcomes [2]. CPGs thus encourage standardised health care practices across a country, reducing inconsistency and disparities, increase accessibility to the best evidence, and create a shared understanding of a topic for researchers and for clinicians in particular [3].

Criticism has been raised that CPGs are an oversimplified "cook book" approach to complex clinical questions [4]: CPGs may restrict clinician autonomy in personalizing interventions to individual patients, local resources, or cultural values [5]. Nonetheless, CPGs have gained increasing acceptance for reducing "postcode" variations in clinical practice: CPGs are defined as "a reasonable body of opinion" in cases of litigation in some countries [6, 7].

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In Italy, the quality and number of national CPGs has been unsatisfactory so far, indeed only a small number of guidelines were made by Italian scientific-technical societies (STS).

The Gelli-Bianco Law (no. 24/2017) concerning professional responsibility has assigned a pivotal role to CPGs in clinical decision making and liability [8]. By law, CPGs are to be developed by public or private institutions or STS of health care professionals registered within the List of STS of the Italian Ministry of Health, in implementation of article 5 of Law no. 24/2017 and Ministerial Decree of 2 August 2017 [8, 9].

The Italian National Institute of Health (Istituto Superiore di Sanità, ISS), through the National Centre for Clinical Excellence, Quality and Safety of Care (Centro Nazionale per l'Eccellenza Clinica, la Qualità e la Sicurezza delle Cure, CNEC), drives CPGs governance by its methodological authority and provides access to CPG development through the National Guidelines System (Sistema Nazionale Linee Guida, SNLG) [10, 11]. The CNEC applies national and international quality standards [12] outlined in its methodological manual [13] to screen and assess the quality of CPGs submitted by public and private institutions or a STS. Submitted CPGs that meet the high quality criteria are then posted on the SNLG website [11].

With the present study we wanted to explore the perception, knowledge, attitude, use, and barriers of CPGs development in clinical practice. We also wanted to determine how well STS members were acquainted with the Italian SNLG. The overarching aim was to gain insight into how to improve national governance of the CPG process.

METHODS

Design

For this cross-sectional study involving a structured online survey to ensure high quality standards for reporting, we followed the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) [14]. Details are given in the protocol, shared publicly via the Open Science Framework, at https://osf.io/4m6kf/. No major protocol amendments were made.

Survey questionnaire

There existed no questionnaires to appropriately address the aim of this study, which was to investigate a specific local system (i.e., SNLG). Drawing on similar questionnaires published in the literature [15-20], we built our theoretical framework *(Supplementary material A available online)* and piloted the survey with CNEC members to assess content validity of survey development. Ten STS members provided additional comments to refine the face validity of the final questionnaire version. The final questionnaire version consisted of 32 items divided into three sections: 1) Respondent characteristics (items 1 to 9); 2) Perception, knowledge, attitude, and use of CPGs (items 10-18); 3) Knowledge of the Italian National Guidelines System (SNLG) (items 19-32). Response to all items was mandatory. Questionnaire details are provided in the *Supplementary material B available online*.

Survey invitation and sample

A web-based closed questionnaire posted on the SurveyMonkey platform [21] was launched on 23 June 2021 by email sent to STS registered within the List of the Italian Ministry of Health updated to 18 December 2019, and therefore authorized to generate CPGs [9] *(Supplementary material C available online)*. The survey invitation identified the target respondents (i.e., representative STS member involved in CGP development) and explained the aim, the contents, and the time needed to complete it. Data collection terminated on 30 September 2021. Informed consent was obtained from survey respondents before they completed and submitted their survey responses.

Sample size calculation

We used the SurveyMonkey sample size calculator [22] to calculate the number of responders with completed responses that we expected to receive as sample size. Based on a population size of 336, which is the total number of STS registered within the List of the Italian Ministry of Health, a margin of error of 5% (how many survey results reflect the views of the overall population), and a sampling confidence level of 95% (how confident we can be that the population would select an answer within a certain range), the calculated sample size of completed responses was 180 completed answers.

Statistical analyses

Descriptive statistics are presented as median and interquartile range (IQR) or absolute frequency and related percentage, when appropriate. The questionnaire responses are presented in tabular and graphic formats (Microsoft Excel or Power Point 2016). An automated count of the response rate was acquired for each of the four sections in order to account for the sample size and to determine whether the questionnaires were terminated early (i.e., users did not go through all four questionnaire sections). Questionnaires which were terminated early (where users did not go through all four sections) were not included in the analyses. We used intention-to-treat analysis in cases of dropouts (failure to complete later questionnaire sections, e.g., Section 3). Data were exported from SurveyMonkey and analysed with STATA software [23].

RESULTS

Response rate

Overall, 194/336 STS responded to the survey, yielding a response/participation rate of 57.7%. The sample for each section is presented in the flow diagram *(Figure 1)*. Two respondents dropped out before completing Section 3, question 27.

Section 1. Respondent characteristics

Table 1 presents the general characteristics of the overall cohort of respondents. The median year of STS foundation was 1989 (1970-1999 IQR, min 1879, max 2017) and the majority of STS (41.2%) had from 51 to 500 registered members. More than half (56.7%) had registered members from different health care catego-

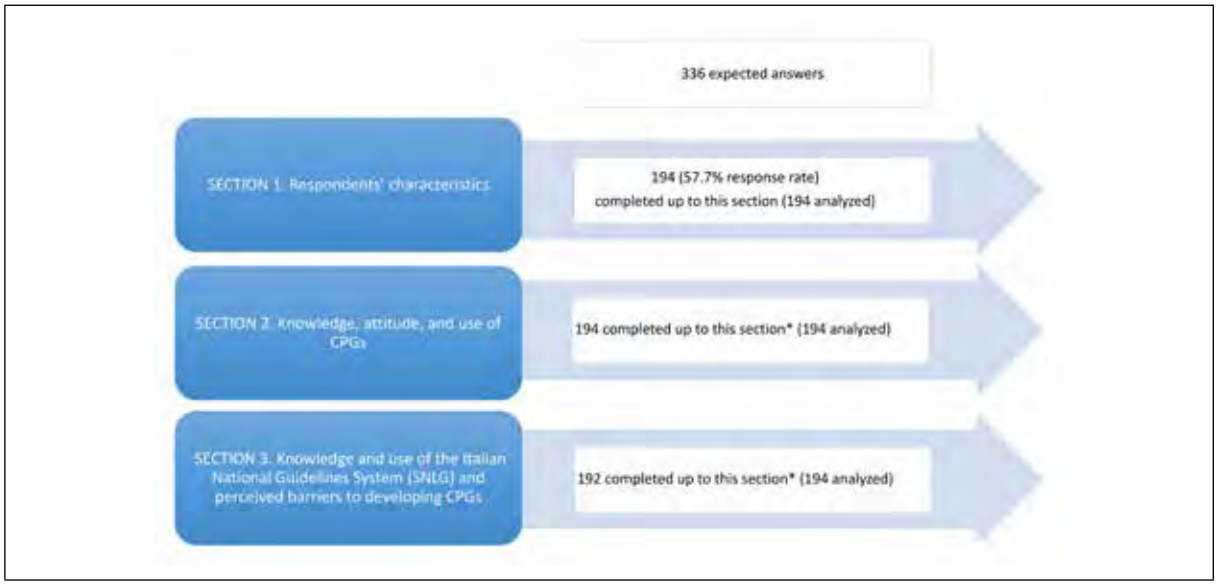

Figure 1
Flow diagram of respondents.
*Indicates the presence of conditional items.

Table 1
General characteristics of the scientific-technical societies

Number of registered members	Frequency (percentage of 194)
0-50	1 (0.52)
51-500	80 (41.24)
501-1000	47 (24.23)
1001-5000	55 (28.35)
>5000	11 (5.67)
Members from different health care worker categories	**Frequency (percentage of 194)**
No	84 (43.30)
Yes	110 (56.70)
Registration date*	**Frequency (percentage of 194)**
18/03/19	21 (10.82)
18/12/19	13 (6.70)
19/12/18	21 (10.82)
07/11/18	139 (71.65)

*Registration date in the Italian Ministry of Health List of scientific-technical societies (in implementation of article 5 of Law no. 24/2017 and Ministerial Decree of 2 August 2017).

ries (e.g., physicians, nurses, physiotherapists). November 7, 2018 was the most frequent registration date with the Italian Ministry of Health (71.7%). Before the Gelli-Bianco Law went into effect, a median of 1 (0-5 IQR, min 0, max 45) CPG was produced by the STS (*Supplementary material D available online*, *Figure 1*).

Section 2. Use and perceived effectiveness of clinical practice guidelines

Training courses (73.1%), scientific production and development of CPGs (67%), and communication, information, and dissemination (76.3%) were perceived as extremely important scientific activities by the majority of the STS. The STS seemed well (42.3%) or very well acquainted (54.1%) with the purposes of CPGs but less (39.7%) and much less (51.5%) about CPGs development. STS members reported that they often used and referred to CPGs (68.6%), which were stored in a repository in 52% of the STS. Nearly half of the respondents (48.4%) stated that their STS had never had a stakeholder role *(Table 2)*.

Section 3. Knowledge of the Italian National Guidelines System

Overall, 92.3% (n = 179) of STS members stated they were acquainted with the SNLG and 91.1% stated they had consulted its website at least once in the past. Overall, 73.2% consulted the methodological manual for CPGs development and the operative manual (54.6%) at least once in the past. Among those who responded "never consulted" (26.8%), the most frequent reason given was "no need" (48.1%). Overall, 20.6% had submitted at least one CPG to the SNLG platform (median 1 CPG; IQR 1-4), while 39.7% responded that they are working on or planning CPGs. Among those who had never submitted a CPG (38.7%), the most frequent reason was difficulty in management and development (42.7%) *(Table 3)*.

Perceived barriers to implementing CPGs in clinical practice are presented in *Figure 2*. The most often cited barrier was limited economic resources (62.7%) followed by overly complex CPG development (50.8%), and inadequate internal methodological competence (33.9%). Around 5% of the respondents (n = 11) added comments about barriers to CPG development, such as unclear role of funding source, not enough time, unclear operative procedures, and some topics were not applicable.

Table 2
Use and perceived effectiveness of CPGs

How important do you rate the following scientific activities of your STS (scale 1-9)?			
	Training in the clinical field of interest	**Scientific production, CPG development**	**Comunication/information/ dissemination**
	Frequency (%)	**Frequency (%)**	**Frequency (%)**
1 (not important)	0 (0)	1 (0.52)	0 (0)
2	1 (0.52)	0 (0)	0 (0)
3	0 (0)	3 (1.55)	0 (0)
4	0 (0)	1 (0.52)	0 (0)
5	3 (1.55)	4 (2.06)	2 (1.03)
6	5 (2.58)	4 (2.06)	1 (0.52)
7	12 (6.19)	14 (7.22)	8 (4.12)
8	30 (15.46)	37 (19.07)	35 (18.04)
9 (extremely important)	143 (73.71)	130 (67.01)	148 (76.29)
How well do you think that your registered STS members (scale 1-5)			
	Knows about the purpose of CPGs	**Knows about how CPGs are developed**	**Uses/consults CPGs?**
	Frequency (%)	**Frequency (%)**	**Frequency (%)**
Not at all	0 (0)	3 (1.55)	0 (0)
Little	7 (3.61)	77 (39.69)	29 (14.95)
Much	82 (42.27)	100 (51.55)	133 (68.56)
Very much	105 (54.12)	12 (6.19)	28 (14.43)
Don't know	0 (0)	2 (1.03)	4 (2.06)

CPG: Clinical Practice Guideline; STS: Scientific-technical society.

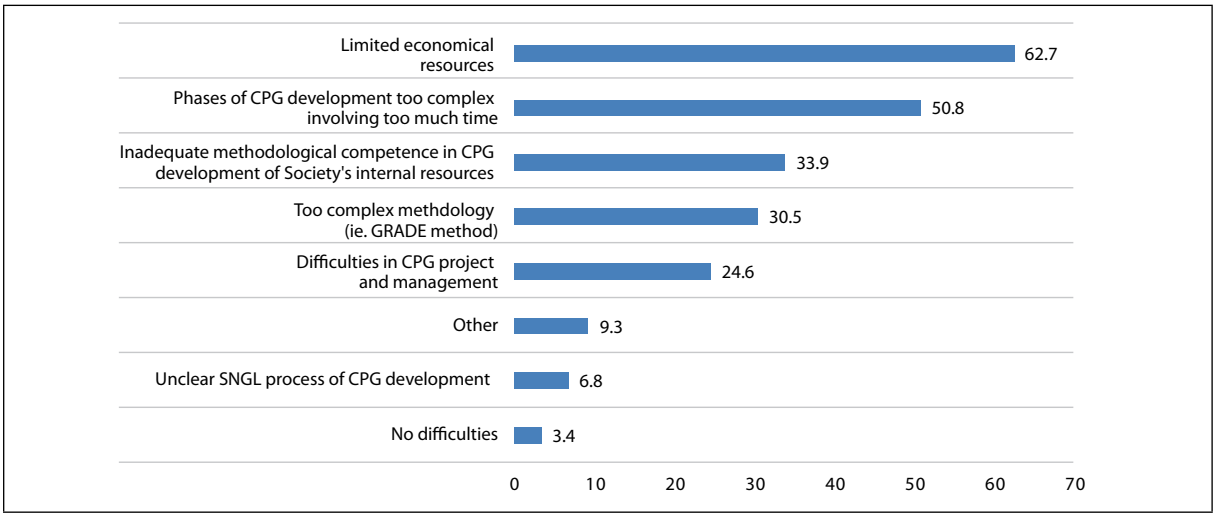

Figure 2
Barriers to implementing CPGs in clinical practice.
CPG: Clinical Practice Guideline; SNLG: Italian National Guidelines System (Sistema Nazionale Linee Guida); GRADE: Grading of Recommendations Assessment, Development and Evaluation.

DISCUSSION

Main findings

Our findings are based on a moderate response rate (about 60%) of Italian STS authorized to generate CPGs. Overall, 41.2% of the STS contacted have more than 500 registered members, half of which belonging to different health care categories. Three out of four STS held a very positive opinion of perception, knowledge, attitude, and use of CPG in clinical practice (e.g., CPG education, development, dissemination). STS members often use and refer to CPGs in their clinical work, but only one out of two STS provide CPGs access through a repository or have played a stakeholder role.

Nearly all respondents stated they knew the SNLG

Table 3
Knowledge of the Italian National Guidelines System (SNLG)

Are you acquainted with the Italian SNLG? (n = 194)	**Frequency (% out of 194)**
Yes	179 (92.27)
No	15 (7.73)
If yes, have you ever consulted the SNLG website?§ (n = 179)	**Frequency (% out of 179)**
Yes	163 (91.06)
No	16 (8.94)
Which sections of the website do you consult often? (more than one answer possible)§ (n = 179)	**Frequency (% out of 179)**
News	61 (34.08)
Communication CNEC	24 (13.41)
CPG SNLG - consultation	108 (60.34)
CPG SNLG - assessments and publications	63 (35.2)
CPG SNLG - production	63 (35.2)
Good practice	90 (50.28)
International guidelines	87 (48.6)
FAQ	20 (11.17)
Have you ever had difficulty consulting the Italian SNLG website? (more than one answer possible)§	**Frequency (% out of 179)**
Not difficult	90 (50.28)
Not user-friendly for browsing	32 (17.88)
Unattractive graphic interface	31 (17.32)
Unclear information	12 (6.7)
Redundant information	3 (1.68)
Incomprehensible information (e.g., technical terms)	8 (4.47)
Difficulty in searching for guidelines of interest (e.g., "search" tab faulty)	39 (21.79)
Other (specify)*	6 (3.35)
Has your STS ever submitted a proposal for an ongoing CPG or a complete CPG to the SNLG?	**Frequency (% out of 194^)**
Yes	40 (20.62)
No	75 (38.66)
Not yet (ongoing/planned)	77 (39.69)
If you have submitted CPGs, has your STS had difficulty submitting a CPG proposal or a complete CPG to the Italian SNLG? (more than one answer possible)§	**Frequency (% out of 40)**
No difficulties	15 (37.5)
Yes, unclear submission procedure	15 (37.5)
Yes, long and complex Document A	7 (17.5)
Yes, difficulty uploading the final document	8 (20)
Other (specify)**	5 (12.5)

CPG: Clinical Practice Guideline; SNLG: Italian National Guidelines System (Sistema Nazionale Linee Guida); STS: scientific-technical society.
^192/194 respondents (intention-to-treat analysis); *most STS reported other difficulties to find their field of interest in the website; **mainly difficulties with saving data in the system; §conditional questions.

and had accessed its website at least once in the past. More than half had consulted the operative and methodological manual for CPG development. This positive attitude is dampened by the gap between theory and practice, however [24]. Despite legislative efforts toward promoting civil responsibility and care safety [25], CPGs production is still limited: a median of only one CPG submitted (or ongoing) after the Gelli-Bianco Law went into effect in 2017 and subsequent legislation in 2018 [8].

While investment in the "CPG industry" seems socially and economically viable for improving quality of care and patient outcomes and reducing costs [26], social and organizational factors remain critical in CPG development, implementation, and use. The three barriers most often cited were limited economic resources, overly complex CPG development, and inadequate methodological competence of STS members.

Comparison to previous studies

Previous surveys investigating CPG knowledge, perception, use, and barriers to development [17-20] includ-

ed health care workers from a specific health care field or STS. Differently, our survey addressed the perspective of many STS (represented by one member of an STS mainly involved in CPG development) in various health care fields. Our response rate is similar to that of previous surveys. In addition, similar studies [17-20] investigated barriers to the implementation of CPGs, whereas none investigated obstacles to CPGs development.

Strengths and limitations

This is the first web-based survey to investigate the perception of knowledge, attitude, use, and perceived barriers to developing CPGs among STS in Italy after the Gelli-Bianco Law went into effect in 2017. The present study has several limitations. We were able to reach a sample size sufficient to achieve high statistical precision at a 95% confidence level with a type I error of 5%; nonetheless, this does not mean that selection bias was absent. For example, non responders may hold views that differ from responders: less compliance with the SNLG, less motivation or lack of interest in endorsing CPGs development and implementation. In addition, we cannot be certain that the survey was delivered as intended due to missing certified email addresses.

We did not collect STS characteristics (i.e., Section 1) of non responders since most characteristics were unavailable or irrelevant (e.g., number of registered members or year of foundation).

Finally, the data accuracy for perceived knowledge and importance is uncertain as the data were collected via a self-reported survey from representative members of the STS involved in CPG development. While we cannot be sure that the perceptions and the beliefs of the representative STS member are shared by its other members, we can use it as a proxy for feasibility purposes. A future area of focus is to identify knowledge, attitudes, and barriers to CPGs from the perspective of STS members.

Implications for practice

Developing CPGs is challenging: it involves making changes within the STS and the Italian health care system [27]. A closer relationship between the STS and the ISS is necessary to achieve this. To overcome operative and methodological barriers (i.e., overly complex CPGs development and inadequate methodological competence among STS members), we identified key interventions at all levels. For instance, there is a need for greater involvement of STS at all stages of CPG development (production, dissemination, implementation, auditing) as promoters of CPG submission or as stakeholders. Taking a more active role could boost their engagement in CPG development by identifying barriers to development, linking interventions to barriers, and planning and implementing the change process [28].

Our findings reflect scarce collaboration among STS, as highlighted in a retrospective Italian study (published prior to enactment of the Gelli-Bianco Law) where a lack of cooperation "to bring about necessary changes in the healthcare process and to define the benefits expected from adopting the guidelines" emerged [29]. STS should promote change and foster the formation of multidisciplinary work teams with other STS to optimize resources. Indeed, a criterion for publication in the SNLG is that CPGs are developed in a multidisciplinary and multi-professional approach.

Poor participation in CPG development and lack of collaboration between STS may be explained by the differences in health care education programs. EBM is not widely taught, though a better understanding of the knowledge, skills, and expertise in guideline development is urgently needed [27, 30]. STS should invest in education and training in EBM (e.g., training courses) for their health care providers to gain an understanding of the advantages of evidence-based CPGs [27]. As mentioned by David Sackett in 1996, any external guideline must be integrated with individual clinical expertise in deciding whether and how it matches the patient's clinical state, predicament, and preferences, and thus whether it should be applied [31]. Greater awareness could fill the void created by the perceived inadequate methodological competence within STS. Gaining more methodological competence could promote collaboration with recognized methodological centers in the synthesis of evidence, such as the Lazio Region-ASL Rome GRADE Center [32] and clinical epidemiology departments in Italy.

The ISS, through the CNEC, can increase its efforts to encourage and boost CPGs production by enhancing participation in CPG guideline development groups, which is key to guideline success. The goal is to orient and train STS member who have no experience with CPGs. An operative manual [33] guiding CPG submission, assessment, and publication is available, however, contribution and participation by STS have become more demanding. As in other international CPG organizations (e.g., World Health Organization, European Commission), STS need to be oriented to the tasks and the processes for developing tools, such as the Guideline Participant Tool (GPT) so that the STS can be informed about their role (e.g., conducting guideline group meetings) [34]. For instance, supporting checklist, frequently asked questions (FAQs) via videos or websites could be effective strategies to support STS and communicate with them. In this context, we advocate the ongoing efforts by the Guidelines International Network (GIN) and McMaster University to overcome methodological issues and to create a guideline development certification and credentialing program (INGUIDE.org). The GIN prepares methodologist courses for promoting standardization of skills. The ISS, through the CNEC, should establish an expert referral system that meets certified criteria (e.g., recognized methodological centers for the synthesis of evidence), as reported in other experience [35].

The main barrier of limited economic resources refers to the substantial cost of full CPG production, which depends on "the availability of monetary and non-monetary resources, credibility, maximization of uptake, the benefits of sharing information widely, and the avoidance of duplication of efforts". Professional societies cannot support such costs independently; they need to decide on the best approach to optimize their resources and define strategies and capabilities [36].

Trade-offs in internal financial sources must be settled: an STS needs to define where to invest its mon-

etary and non-monetary resources, while sacrificing something to obtain something else ("opportunity cost"). For instance, an STS that wants to invest more in residential clinical courses will have fewer or no resources to invest in CPGs production. Economical alternatives in the organisational CPG budget can be devised. For example, virtual meetings may allow expert panels to meet at lower cost, thus releasing resources toward methodological support, such as recognized centers for the synthesis the evidence [37]. This is the need for trade-offs as "guns versus butter" expressed in introductory economic courses [38].

STS might look for external financial sources (e.g., biomedical companies) as demonstrated in 63% of published CPGs on the National Guideline Clearinghouse website in Campsall *et al*., in 2016 [39], however, effective policies for transparently managing direct and indirect conflicts of interest need to be put into practice [39, 40]. The GIN has published principles for the management of financial conflicts of interest of CPG committee members [41].

CONCLUSION

CPGs development is a resource-intensive undertaking. STS hold a positive attitude towards CPGs principles. Barriers (i.e., financial, managerial, knowledge-based) might be more appropriately assessed as a stimulus than as an obstacle. Clinical guidelines risk remaining limited to a juridical role, with a weak impact on professional practice. Coordinated efforts between STS and the SNLG System are necessary to develop national CPGs of high quality that can be beneficial for all health care providers working in the public or the private sector, health care payers, health sector regulators, patients, and all other stakeholders.

Availability of data and materials

The dataset supporting the conclusions of this article is available in the OSF repository at https://osf.io/4m6kf/.

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Authors' contributions

GC and SG conceived the original idea for the study, designed the study, and planned the methods. GC and SG developed the first version of the questionnaire. DD, AN, DC, AF, OP, PI revised, piloted, and approved the questionnaire final version and provided input for the study protocol. GC, SG, and SB collected the data. GC, SG, and SB wrote the first draft of the manuscript. All Authors provided important intellectual content of the manuscript, its revision, and approved the final version. All Authors approved submission of the manuscript, the accuracy/integrity of the work.

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Conflict of interest statement

The Authors declare no competing interests.

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Urban mobility and health: a multicentric survey conducted in some Italian cities

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Abstract

Introduction. Urban and transport planning, environmental exposures, physical activity and human health are strictly linked. The aim of this study was to analyze the determinants of sustainable and active mobility in 4 Italian provinces.

Materials and methods. An online multiple-choice survey was administered via Google Form between October 2019 and February 2020.

Results. 605 people answered the questionnaire, reporting their mobility practices. The home location did not seem to influence mobility behaviours, with the exception of the greater use of public transport for those who did not live in the province capital. Working or studying in central areas was associated with less use of the car, while not working or studying in the province capital was associated with less use of the motorbike. Women use cars more, and motorcycles/bicycles less. Age and educational level did not seem to influence mobility practices, while being a student compared to a worker was related to greater use of public transport and tendency to walk to the work/study place as well as to lesser car use.

Discussion. It is essential that all cities adopt solutions to encourage healthy mobility. The positive relationship between BMI and car use, between good food score and bike use and between frequent light physical activity and healthy mobility indicators confirmed that risk factors are often interconnected and that improving even one single habit could have a positive effect on the others as well.

Conclusion. An urgent paradigm shift is needed to transform urban areas from agglomerations oriented on motorized transport to ones that rely on active and sustainable mobility, in order to turn cities into places generating wellness and health.

Key words

- urban mobility
- urban health
- active mobility
- sustainable mobility
- motorized transport
- urban policy

INTRODUCTION

Nowadays city mobility is undoubtedly a driver of urban development and a key contributor to economic returns, as it facilitates economic competitiveness and social progress [1-3].

As a matter of fact, urban transport networks allow people to reach workplaces and public services, to satisfy citizen's needs, opportunities and social contacts as well as to take part in urban and social life. However, especially in metropolitan areas, mobility also has direct impacts on population's health, especially with regards to the use (and non-use) of motorized vehicles [1, 4, 5].

High-income countries have been economically and culturally dependent on motor vehicles as the primary means of urban mobility and this factor has heavily dominated urban planning and policy. Nevertheless,

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also in low-income countries, despite mass motorization started later, motorized transport represents a major risk for city's livability and Public Health [1, 5-7].

Air pollution, noise, greenhouse gases, green space impairment and urban heat islands together constitute traffic-related exposures, resulting in stressors both on population's health and on the environment [8, 9].

Cities are the largest producers of carbon emissions and energy consumption; in fact, they produce about 75% of CO2 emissions. In Italy in 2018, 87 out of 95 cities did not reach the annual target of 10 micrograms per cubic meter. In 2021, the latest WHO air quality guidelines strongly indicate halving the recommended level of exposure to ultra-fine PM2.5 particulate emissions related to combustion processes, from 10 micrograms per cubic meter to 5 micrograms per cubic meter [10-12].

In addition, mass motorization and the consequent associated lack of active movement reduce physical activity increasing sedentary behaviors [1, 13-15].

Moreover, current urban patterns, planning and policies are furthermore reinforcing the use of motorized transport for short-distance trips, exacerbating the effects described above [16, 17].

All these factors related to motorized transport are in turn associated with a significant burden of disease and increased premature mortality: for example, air pollution and sedentary lifestyle are associated with an annual 7 million and 2.1 million global deaths, respectively [1, 18].

Health impacts are significant in many cities, for example in Barcelona, Spain, where traffic related exposures and the lack of physical activity are responsible for nearly 3,000 premature deaths, 5,000 disease cases, and 50,000 disability-adjusted life-years (DALYS) [19, 20].

Transport planning and policy can affect human health through different pathways. Motor vehicles collisions have been associated with premature mortality, injuries, traumas and post-traumatic stress. Traffic related air pollution has been associated with premature mortality, cardiovascular and respiratory disease, lung cancer, diabetes, obesity, reduced lung and cognitive function in children, low birth weight, and premature birth. Noise has been associated with cardiovascular mortality and morbidity, annoyance and sleep disturbance, type 2 diabetes, high blood pressure in children, and reduced cognitive function in children. Heat islands have been associated with premature mortality, cardiorespiratory morbidity, hospital admissions, children's mortality, and hospitalization. The lack of green space has been associated with premature mortality, cardiovascular disease, poor mental health, poorer cognitive function, and behavioral problems in children. Sedentarism has been associated with premature mortality, cardiovascular disease, dementia, breast cancer, diabetes, and colon cancer. Climate change has been associated with extreme weather events, adverse effects on the ecosystem and species, sea level rise, thermal stress, premature deaths, illness and injury from floods, food poisoning, unsafe drinking water, changes in vector-pathogen host relations and in infectious disease geography/seasonality, impaired nutrition, adverse mental and physical health. Social exclusion and community severance have been associated with poorer mental health and well-being, premature mortality, lack of physical activity, and stress [1, 21].

So, investments in car facilities have led many cities and urban areas to a car-friendly development, encouraging the building of infrastructures such as roads networks and parking areas. These factors resulted in higher levels of air pollution, noise, heat island effects, less active travel and physical activity, and, in consequence, reduction of public spaces that can be used for other purposes such as green areas and public services for people's well-being [1, 22, 23].

In summary, urban and transport planning, environment exposures, physical activity, and human health are strictly linked.

The aim of this study was to analyze the relationship between citizens' characteristics and sustainable and active mobility behaviours through an online survey in 4 different Italian provinces.

MATERIALS AND METHODS

Study population

This study was conducted between October 2019 and February 2020 in the Provinces of Rome, Genoa, Milan and Palermo by the Working Group on Mobility and Health, National Advisory Body of Medical Residents in Public Health, Italian Society of Hygiene, Preventive Medicine and Public Health (SItI). The data collected anonymously was only accessible to the study researchers.

The questionnaire

An online multiple choice questionnaire was administered to the study population using Google Form. The survey took approximately 20 minutes to complete and investigated several aspects of mobility behaviours and respondents' characteristics (items shown in *Table 1* and *Figure 1*).

The link to the self-administered questionnaire was shared via social media (WhatsApp, Telegram, Facebook etc.) with a "snowball" effect (cascade effect that makes the participants themselves administrators). Questionnaires were completed anonymously after obtaining consent to process sensitive data for the study.

In order to allocate citizens in shared homogeneous groups with regard to living and working/studying places in cities, it was used the OMI (Italian Observatory of the Real Estate Market) classification.

The Italian Revenue Agency, in fact, has divided province capitals maps into bands which are indirect proxies of the socio-economic status of the citizens who live there.

The groups are "central", "semi-central", "peripheral", "suburban" and, for those who lived or studied/worked in the other municipalities of the province, "not in PC".

In order to analyze the relationship between food behaviors and sustainable and active mobility, it was used a synthetic numerical food score according to the model of the Mediterranean Food Alliance (https://oldwayspt.org/system/files/atoms/files/RateYourMedDietScore.pdf) in which higher values are proxies of healthy eating habits and high dietary variability.

Table 1
Characteristics reported by survey respondents

Number of respondents = 605	n (%) or Median (IQR)
Province	
Rome	154 (25.5%)
Genoa	168 (27.8%)
Milan	162 (26.8%)
Palermo	121 (20.0%)
Home location in PC	
Central	75 (12.4%)
Semi-central	234 (38.7%)
Peripheral	180 (29.8%)
Suburban	31 (5.1%)
Not in PC	85 (14.0%)
Work/study place location in PC	
Central	125 (20.7%)
Semi-central	307 (50.7%)
Peripheral	97 (16.0%)
Suburban	36 (6.0%)
Not in PC	40 (6.6%)
Educational level	
None or primary	1 (0.2%)
Lower secondary	5 (0.8%)
Upper secondary	143 (23.6%)
University degree	315 (52.1%)
Post-graduate degree	141 (23.3%)
Occupation	
Tradesman	8 (1.3%)
Public manager	43 (7.1%)
Policemen/firefighter etc.	7 (1.2%)
Employee/technical-administrative	198 (32.7%)
Freelance	105 (17.4%)
Workman/artisan	12 (2.0%)
Student	232 (38.3%)
Male gender	240 (39.7%)
Age (years)	29.0 (16.0)
BMI (kg/m²)	22.5 (4.1)
Food score	8.0 (3.0)
Smoking (past and/or present)	245 (40.5%)
LPA > 2 DPW	315 (52.1%)

PC: province capital; BMI: Body Mass Index; LPA: light physical activity; DPW: days per week.

Light physical activity indicates how often the respondent practices physical activity in his/her free time (walking for at least 1 km, soft gymnastics, etc.).

The five indicators of healthy (sustainable and active) mobility behaviours referred to the usual means of transport used to reach studying or working place. Public transport included bus, train, tram and metro.

Statistical analysis

Statistical analysis was performed using R 4.0.2 (released on 2020-06-22). Statistical significance α was fixed to 0.05.

Categorical variables were reported as absolute (n) and relative (%) frequencies. In order to account for non-normality, evaluated through the Shapiro Wilk test, numerical variables were reported as median and interquartile range (IQR).

In order to analyze the association between citizens' characteristics and healthy mobility indicators, 5 multiple binary logistic regression models were fitted with estimation of the odds ratios (OR) and 95% confidence intervals (CI).

The goodness of fit of the models was evaluated through the Hosmer-Lemeshow test.

RESULTS

Characteristics and healthy mobility indicators of the 605 respondents to the questionnaire were reported in *Table 1* and in *Figure 1*.

The majority of respondents were from Northern Italy (54.5%), lived in province capitals (86.0%), in particular in semi-central areas (38.7%), worked or studied in province capitals (93.4%), in particular in semi-central areas (50.7%), had a university or post-graduate degree (75.4%), were a worker (61.7%), were female (60.3%), weren't smokers at the time of the survey nor in the past (59.5%) and used to have light physical activities more than 2 days per week (52.1%).

Median (IQR) age was 29.0 (16.0) years, BMI (body mass index) 22.5 (4.1) kg/m² and food score 8.0 (3.0).

As far as healthy mobility indicators are concerned, 65.1% of respondents used the car less than 3 days per week, 83.3% used the motorbike less than 3 days per week, 43.8% used the public transport more than 2 days per week, 44.5% used to walk more than 2 days per week and 9.9% used the bike more than 2 days per week.

Results of multiple logistic regression models were reported in *Table 2*.

All models passed the Hosmer-Lemeshow goodness of fit test ($p>0.05$).

The variables positively associated with a frequency of car use lesser than 3 days per week were living, compared to Rome Province, in Milan Province (OR 2.16, 95% CI 1.20-3.95), being a student (OR 3.02, 95% CI 1.80-5.16), male gender (OR 1.69, 95% CI 1.10-2.60) and having light physical activity more than 2 days per week (OR 1.50, 95% CI 1.02-2.19).

The variables negatively associated with a frequency of car use lesser than 3 days per week were living, compared to Rome Province, in Palermo Province (OR 0.43, 95% CI 0.24-0.77), working/studying, compared to central area, in semi-central area (OR 0.52, 95% CI 0.29-0.91), suburban area (OR 0.19, 95% CI 0.07-0.50) and not in the province capital (OR 0.22, 95% CI 0.09-0.53), and BMI (OR 0.94, 95% CI 0.89-0.99).

The variables positively associated with a frequency of motorcycle use lesser than 3 days per week were

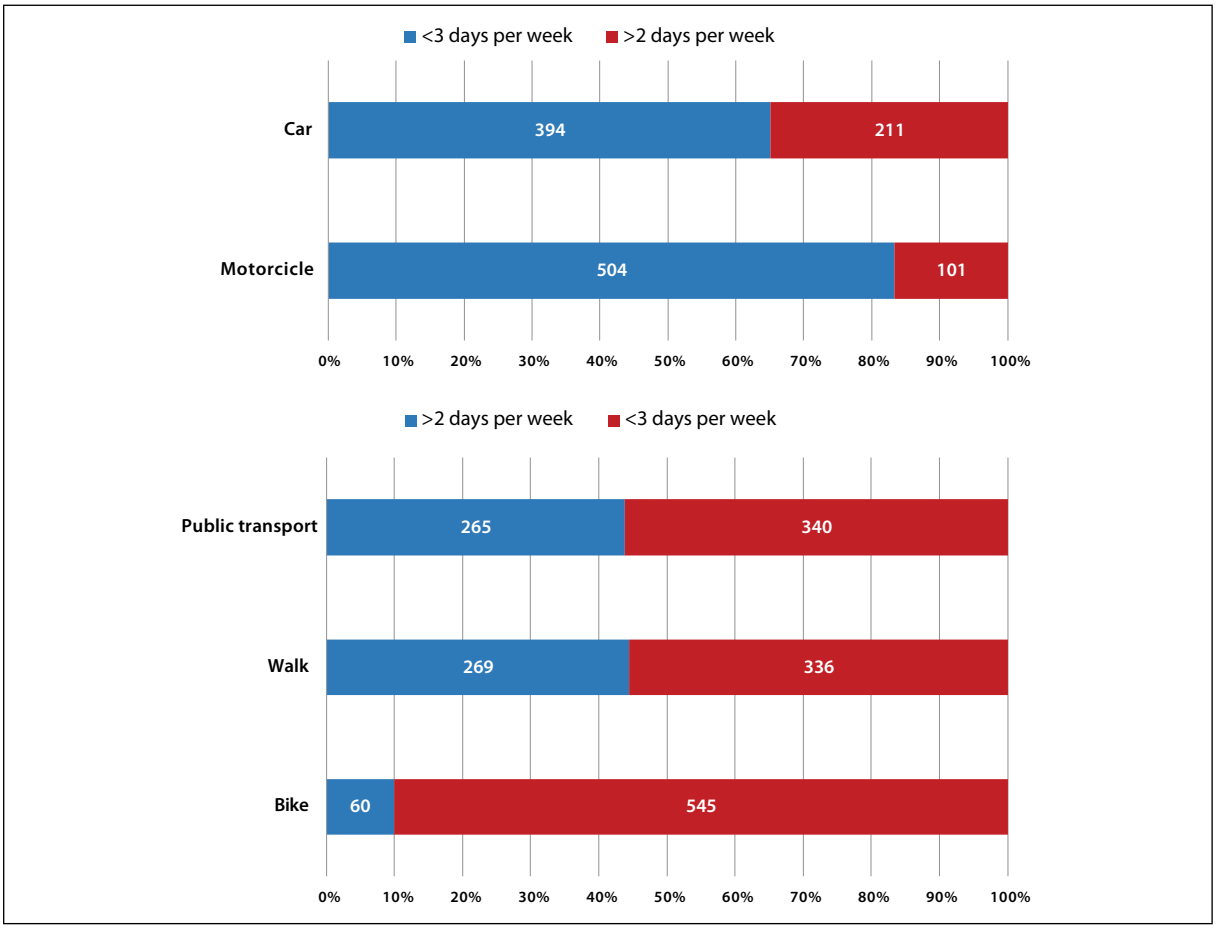

Figure 1
Healthy mobility indicators reported by survey respondents.

working/studying, compared to central area, not in the province capital (OR 7.25, 95% CI 1.33-135.60) and having light physical activity more than 2 days per week (OR 1.90, 95% CI 1.18-3.07).

The variables negatively associated with a frequency of motorcycle use lesser than 3 days per week were living, compared to Rome Province, in Genoa Province (OR 0.32, 95% CI 0.15-0.65) and male gender (OR 0.36, 95% CI 0.22-0.58).

The variables positively associated with a frequency of public transport use greater than 2 days per week were living, compared to central area, not in the province capital (OR 2.30, 95% CI 1.13-4.75), being a student (OR 2.13, 95% CI 1.36-3.36) and having light physical activity more than 2 days per week (OR 1.83, 95% CI 1.28-2.62).

The variable negatively associated with a frequency of public transport use greater than 2 days per week was living, compared to Rome Province, in Palermo Province (OR 0.29, 95% CI 0.16-0.53).

The variables positively associated with a frequency of walking greater than 2 days per week were being a student (OR 2.03, 95% CI 1.30-3.18) and having light physical activity more than 2 days per week (OR 2.25, 95% CI 1.58-3.22).

The variables positively associated with a frequency of bike use greater than 2 days per week were living, compared to Rome Province, in Milan Province (OR 10.19, 95% CI 4.00-29.18), male gender (OR 1.97, 95% CI 1.03-3.78), food score (OR 1.16, 95% CI 1.02-1.32) and smoking habits at the time of survey or in the past (OR 2.34, 95% CI 1.26-4.40).

DISCUSSION

The first interesting finding consists in the difference found among the scrutinized provinces in terms of sustainable and active mobility indicators, and the consequential effects on human health. In particular, living in the Province of Milan was associated with less car use and more bike use, while in Palermo there was a greater use of the car and a lesser use of public transport. It is therefore essential that all cities adopt solutions to encourage sustainable and active mobility, for example by increasing urban green spaces and implementing bikeways.

The home location did not seem to influence significantly mobility behaviours, with the exception of the greater use of public transport for those who did not live in the provincial capital. This could be linked to economic factors related to the lower cost of using public transport on extra-urban routes compared to the car.

Otherwise, working or studying in a central area was associated with less use of the car, while not working or studying in the province capital was associated with less

Table 2
Results of multiple binary logistic regression models for the five healthy mobility indicators (Hosmer-Lemeshow tests' p >0.05)

Number of respondents = 605	OR (95% CI)				
	Car <3 DPW	MC <3 DPW	PT >2 DPW	Walk >2 DPW	Bike >2 DPW
Province					
Rome	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Genoa	1.46 (0.81-2.62)	**0.32 (0.15-0.65)**	1.28 (0.76-2.17)	1.55 (0.92-2.64)	0.83 (0.26-2.72)
Milan	**2.16 (1.20-3.95)**	0.74 (0.34-1.58)	1.43 (0.85-2.41)	1.01 (0.60-1.72)	**10.19 (4.00-29.18)**
Palermo	**0.43 (0.24-0.77)**	0.70 (0.32-1.53)	**0.29 (0.16-0.53)**	0.66 (0.37-1.17)	0.57 (0.14-2.03)
Home location in PC					
Central	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Semi-central	1.37 (0.71-2.60)	0.82 (0.36-1.78)	1.74 (0.96-3.22)	1.04 (0.58-1.85)	2.40 (0.94-6.65)
Peripheral	1.00 (0.51-1.93)	0.90 (0.39-2.00)	1.57 (0.86-2.93)	0.88 (0.48-1.61)	1.23 (0.46-3.51)
Suburban	0.45 (0.16-1.24)	0.86 (0.23-3.70)	1.95 (0.74-5.19)	0.66 (0.25-1.71)	0.97 (0.05-6.74)
Not in PC	0.66 (0.31-1.39)	1.35 (0.49-3.82)	**2.30 (1.13-4.75)**	1.43 (0.71-2.87)	1.03 (0.28-3.61)
Work/study place location in PC					
Central	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Semi-central	**0.52 (0.29-0.91)**	0.93 (0.48-1.74)	0.75 (0.46-1.23)	0.72 (0.44-1.18)	1.76 (0.75-4.32)
Peripheral	0.57 (0.28-1.14)	0.87 (0.40-1.92)	0.87 (0.48-1.55)	0.93 (0.52-1.66)	0.83 (0.33-2.01)
Suburban	**0.19 (0.07-0.50)**	0.54 (0.19-1.57)	0.62 (0.25-1.50)	0.55 (0.22-1.32)	2.37 (0.45-10.28)
Not in PC	**0.22 (0.09-0.53)**	**7.25 (1.33-135.60**)	0.65 (0.29-1.47)	0.64 (0.28-1.45)	0.63 (0.16-2.14)
University or post-graduate degree	1.34 (0.85-2.12)	0.77 (0.43-1.33)	0.88 (0.57-1.37)	0.74 (0.48-1.14)	0.70 (0.32-1.61)
Student	**3.02 (1.80-5.16)**	0.90 (0.49-1.65)	**2.13 (1.36-3.36)**	**2.03 (1.30-3.18)**	0.73 (0.34-1.57)
Male gender	**1.69 (1.10-2.60)**	**0.36 (0.22-0.58)**	0.69 (0.46-1.02)	0.73 (0.49-1.07)	**1.97 (1.03-3.78)**
Age (years)	1.00 (0.98-1.02)	1.01 (0.98-1.04)	0.99 (0.97-1.01)	0.99 (0.97-1.01)	1.03 (1.00-1.06)
BMI (kg/m²)	**0.94 (0.89-0.99)**	0.94 (0.88-1.00)	1.04 (0.98-1.09)	0.96 (0.91-1.01)	0.90 (0.80-1.00)
Food score	1.07 (0.98-1.16)	1.03 (0.93-1.15)	1.00 (0.93-1.08)	1.01 (0.94-1.09)	**1.16 (1.02-1.32)**
Smoking (past and/or present)	0.90 (0.60-1.34)	0.78 (0.48-1.26)	0.70 (0.48-1.01)	0.80 (0.55-1.15)	**2.34 (1.26-4.40)**
LPA > 2 DPW	**1.50 (1.02-2.19)**	**1.90 (1.18-3.07)**	**1.83 (1.28-2.62)**	**2.25 (1.58-3.22)**	0.98 (0.53-1.82)

DPW: days per week; MC: motorcycle; PT: public transport; PC: province capital; BMI: Body Mass Index; LPA: light physical activity.

use of the motorbike. The first association is probably linked to zone-specific urban policy and city-planning factors, such as to the greater tendency of central areas of cities to be oriented towards sustainable and active mobility due to limited traffic areas and limited presence of parking lots. The second association is probably linked to the difficulty of traveling daily extra-urban routes by motorcycle.

For these reasons, the improvement, from a sustainable perspective, of our living, work, study and social life spaces in a sustainable perspective is an essential objective.

In Italy, many research works published by several experts related to the Italian Society of Hygiene and Preventive Medicine (SItI) and to European Public Health Association (EUPHA) contributed to the body of knowledge on the topic, confirming that good urban planning, improvement of road traffic, redevelopment of degraded and disadvantaged areas, and creation of green spaces, pedestrian and cycle paths appeared to be crucial elements in the development of resilient cities [24-26].

In particular, in the context of the research project titled "Urban Health: good practices for health impact assessment of urban and environmental redevelopment and regeneration interventions" and awarded by the Italian National Center for Disease prevention and Control (CCM) in 2017, the working group developed a multi-criteria, quali-quantitative assessment framework, capable of providing an effective and flexible support to the Local Health Agencies for evaluating the Urban Health strategies' integrations into urban plans. Specifically, the tool is composed by 20 criteria divided into 7 macro-areas: general criteria; environment; soil and subsoil; sustainability and hygiene of the built environment; urban and social development; mobility and transport; outdoor spaces [24, 26].

Another noteworthy finding of this survey is the fact that women reported greater use of cars and lesser use of motorcycles and bicycles. These gender differences could be linked to women's poor perception of safety in an open vehicle (motorbike or bicycle) compared to a closed private vehicle (car). This data highlights how the problem of sustainable mobility must be tackled in

a complex and articulated multidisciplinary perspective that also includes considerations of a social and cultural nature.

In the present work, age and educational level did not seem to be linked to the type of mobility, while being a student compared to a worker was related to lesser use of the car, a greater use of public transport and a greater tendency to walk to the work/study place. This data could be linked both to cultural and economic factors. An interesting fact, difficult to explain, was the association between smoking habits and use of the bike.

The positive relationships between BMI and car use, between food score and bike use, between frequent light physical activity and all healthy mobility indicators (except for the use of the bike) confirmed that risk factors are often interconnected and that improving even one single habit could have a positive effect on the others as well. Tackling these issues through Public Health measures, both with policy and health promotion interventions, could lead to great benefits in terms of human health.

In this sense, a winning strategy is certainly to promote a life-course health-oriented approach involving all possible stakeholders: e.g. the Italian National Prevention Plan for 2020-2025, like the previous one, has adopted an intersectoral approach which promotes multidisciplinary actions to change the determinants of health through health promotion and prevention policies [27].

Another key issue is to effectively deal with the problem of contemporary physical inactivity, which is a major Public Health problem. To this regard, transport planning has an important role in providing opportunities for active mobility physical activity: infact, encouraging people to use public transport, to walk and to cycle to study/workplace would make them physically more active and thus healthier as well as it would have positive environmental effects such as reducing their carbon footprint, local air pollution and noise levels [1, 23, 28].

Current transport practices produce unwanted side effects and adverse environmental exposures, while a more holistic approach to our cities could promote sustainable and active mobility and physical activity through Public Health oriented urban and transport planning and policies (mixed land use, greater street connectivity, street furniture, safe urban environments, pedestrian-friendly and cyclist-friendly amenities, free up public space) [1, 21, 29-31].

This study has some strengths and limitations. Firstly, given that it was used a self-administered questionnaire, there is a possibility of response bias in the participants' answers. Moreover, the questionnaire was administered to inhabitants of large Italian cities where journeys mostly take place by car to travel great distances, especially to go to work. On the other hand, a strong point was the ability to quickly send the questionnaire to many people via different platforms in different cities that are representative of different regions of the Country. To this regard, in the future it could be useful to extend this study to additional Italian cities and also to re-administer the questionnaire to the cities of this study to monitor the results over time, analyzing the impact of the COVID-19 upon urban mobility as well.

In fact, COVID-19 has brought to light a different approach to urban health, forcing the scientific community to analyze the impact of urban transport on human health in terms of both communicable and non-communicable diseases [32].

According to the UN, the environment around us can drastically affect our lifestyle habits. For this reason, the improvement, from a sustainable perspective, of our living, work and social life spaces is an essential goal. Urban Health strategies must be considered from the early stages of urban planning as a powerful tool for the prevention and promotion of human health [32, 33].

CONCLUSION

These results strongly confirmed the need to develop and implement urban policies in order to shift investments from car facilities to infrastructure for public and active transport, such as cycling infrastructures. These interventions can lead to an increased use of public and/or active transport, reducing air pollution, noise, heat island effects and stress. Moreover, public and/or active transport would increase physical activity, with a reduction in morbidity and premature mortality [22, 23].

As a matter of fact, cities represent the fulcrum for the implementation of policies oriented to sustainability and to effective responses to the challenges of climate change, urbanization and social inclusion. Good governance requires cooperation, sharing of knowledge and perspectives, and the creation of common agendas. Decision making can strongly influence citizens' choices, affecting both health and environment. Public health plays a big role in this process, as it can really make the difference through the development of effective health programs [34].

In conclusion, an urgent paradigm shift is needed to transform urban areas from agglomerations oriented on motorized transport to ones that rely on active and sustainable mobility, in order to turn cities into places generating wellness and health.

Conflict of interest statement

None.

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Health Belief Model efficacy in explaining and predicting intention or uptake influenza vaccination during pregnancy

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Abstract

Introduction. The influenza vaccination is a priority during pregnancy due to infection-related-outcomes. The study aim is to assess the acceptance by women of influenza vaccination during pregnancy based on Health Belief Model (HBM).

Methods. A multicentre observational study was carried out with a convenience sample of 300 respondents.

Results. Most women (53.7%) declared that they worried to contract influenza during pregnancy and 80.7% of them agreed that there is a risk of contracting influenza during the first months of life. Vaccine benefits (adjOR 4.3 CI 95% 1.7-10.9 p <0.01), information on vaccination (adjOR 2.6 CI 95% 1.2-5.5 p <0.01) and trust in guidelines (adjOR 3.5 CI 95% 1.6-7.3 p <0.01) are some factors associated with intent/vaccination during pregnancy.

Conclusions. HBM confirms its effectiveness in explaining/predicting health behaviours. It is necessary to create trust in the vaccinations through an integrated work of health professionals to set up training programs and to provide effective health communication.

Key words

- Health Belief Model
- vaccination
- pregnancy
- health promotion

INTRODUCTION

Seasonal influenza is an acute respiratory illness that can appear with different signs and symptoms and with variable severity [1]. It is typically caused by a group of RNA viruses (A, B, C and D) and the symptoms develop after an incubation period of approximately 1-4 days (average of two days) [1]. Although chronic diseases significantly affect the European healthcare systems [2], COVID-19 pandemic has reminded us that the burden of infectious diseases can be equally severe. Influenza is an important global public health issue in terms of direct and indirect costs for the implementation of control measures and the management of cases and complications of the disease. One billion cases, 3-5 million severe cases, and 290,000-650,000 influenza-related respiratory deaths are estimated worldwide [3]. According to the Centres for Disease Control and Prevention (CDC), influenza was associated with 35 million illnesses, 16 million visits to healthcare providers, 380,000 hospitalizations and 20,000 deaths in the United States during the 2019-2020 influenza seasons [4]. The last report of ECDC showed that in the Europe, the circulation of viruses is comparable to previous seasons [5], with an influenza virus positivity in sentinel specimens below the epidemic threshold (10%) [6]. In Italy, in the 44th week of 2021, the estimated cases were about 207,000, for a total of about 573,000 cases since the start of surveillance. In this period the incidence was 0,8 cases per thousand cared with a level of incidence of influenza syndromes like illness which has been stably maintained at below the basal threshold throughout the season [7].

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The clinical manifestations of influenza in pregnancy are similar to those in the general population, ranging from fever, headaches to myalgia and malaise and often are accompanied by cough, sore throat and a runny nose [8]. Nevertheless, pregnant women have a higher risk of acute respiratory disease and of admission in intensive care unit than general population [9, 10]. This risk, in addition of risk of complications from influenza, is increased in case of chronic diseases such as cardiac and pulmonary disease, diabetes mellitus, renal disease, immunological disorder [11]. Moreover, the influenza in pregnant women may result in several adverse neonatal outcomes. A recent systematic review and meta-analysis on the effect of influenza virus infection on pregnancy outcomes showed that there was an increased risk of stillbirth, with no significant effect on preterm birth, foetal death, small for gestational age, and low birth weight [12]. Previous studies, focusing on one of different types of influenza viruses, showed, instead, that pregnant women were likely to adverse pregnancy outcomes, including preterm birth, small for gestational age, stillbirth, low birth weight and others [13-15].

Due to pregnancy and neonatal outcomes, the influenza vaccination is a priority among pregnant women. According to the position paper of the World Health Organization, pregnant women are a priority group for seasonal influenza vaccination [16]. The Global Influenza Initiative recommends the inactivated influenza vaccination to all pregnant women, regardless of trimester, in order to prevent seasonal influenza morbidity and mortality [17]. The Italian Ministry of Health in the "National Vaccination Prevention Plan" (2017) recommends the vaccine against influenza for all women who, during influenza season, are in second or third trimester [18]. This recommendation represents an indicator of the new National Prevention Plan [19]. Pregnant women should not receive a live-attenuate vaccine because some concerns about safety emerged [20]. A systematic review showed the effectiveness of influenza vaccine in pregnant women in reducing the influenza like illness and the neonatal influenza in vaccinated women, without serious adverse events [21]. Furthermore, in another systematic review and meta-analysis, pregnant women who were vaccinated for influenza had a lower risk of premature/preterm birth (<37 weeks) and of very preterm birth (<32 weeks) as compared to those women who were not vaccinated and there was no increased risk for infants [22].

An estimated 50% of pregnant women in the US protected themselves and their babies from influenza by getting an influenza vaccine [23]. In Italy, the national surveillance system on vaccination coverage regards other population groups and it is still not available for pregnant women [24]. More often, pregnant women receive the information on vaccination from healthcare professionals, who play a key role in informing the women on risk and benefits of vaccination. If there is not a good and effective health communication, the women are unaware of the benefits and may believe that influenza vaccination is contraindicated during pregnancy [25], impacting on the choice to get vaccinated. In this context, Health Belief Model (HBM) is useful to predict health choices and behaviours, based on different factors that influence the health choices and behaviours of an individual and the access to healthcare services [26]. Its effectiveness has been demonstrated in different areas [27, 28] also during pregnancy and in assessing the seasonal influenza vaccination degree of acceptance of this population [29-31].

To our knowledge, there is no Italian study on HBM effectiveness investigating the factors that influence the choice to vaccinate against influenza during pregnancy. Therefore, the aim of this study is to assess the factors that influence the acceptance by Italian pregnant women of influenza vaccination based on HBM constructs and the associated characteristics.

METHODS

Design

A multicentre observational study was carried out.

Participants and setting

All women in the 2nd and 3rd trimester of pregnancy, met at the maternal clinic of two Italian hospitals, were asked to participate in the study. The exclusion criteria were not being able to read and understand the Italian language. From October 2019 to January 2020, the convenience sample included 300 respondents and none refused to answer the questionnaire. One hundred and fifty women came from an accredited Italian private facility and another 150 from a public one. After explanation of study's purpose and methods, the women accepted to participate to the study and gave their oral informed consent. The women of the two different centres completed an anonymous self-administered questionnaire. All had the opportunity to have any further clarifications during the compilation.

Study instrument

The questionnaire, including validated items on the effectiveness of the HBM in predicting the levels of acceptance of influenza vaccination during pregnancy [29], was divided into two sections. The first included 6 socio-demographic items and 2 related to the intention to vaccinate. The second section included 8 items related to HBM constructs (*risk susceptibility, risk severity, benefits, barriers*) on influenza vaccination using a 5-point Likert scale, ranging from "1-Completely agree" to "5-Completely disagree" (Cronbach's alpha = 0.77). Other 6 items were in common with the section related to pertussis vaccination.

Authorization and privacy

The Heads of the Health Department of both hospitals authorized the administration of the anonymous questionnaire. The responders were informed and agreed to the use of anonymous data in accordance with Italian and European data protection legislation.

Data analysis

Categorical variables of greater interest were reported as frequency and percentage. The bivariate analysis allowed to assess the presence of significant asso-

ciations, leading the definition of the logistic regression model. In this way it was possible to identify predictors of vaccination or the intention to be vaccinated against influenza. Odds ratio (OR) and 95% confidence intervals (CI) were calculated. Statistical analyses were conducted using STATA v16. Significance was set at a p-value <0.05.

RESULTS

Demographic characteristics

As for the previous study on pertussis vaccination [32], the average age of the sample was 33.3 years (SD ± 6), 83.3% were Italian and 53.3% were married. About parity, 50% of women were nulliparous, the other 50% said they had 1 (37%) or 2 or more children (13%) *(Table 1)*. Of 300 women, 30% were vaccinated or planned to get vaccinated against influenza during the current pregnancy.

Table 1
Women's socio-demographic characteristics and frequencies of influenza vaccination or intention to get vaccinated

Data of participants'	N (%)
Mean age in years	33.3 (SD ± 6)
Nationality	
Italian	250 (83.3%)
Foreigner	50 (16.7)
Marital status	
Married	160 (53.3)
Unmarried	133 (44.3)
Separate/Divorced	7 (2.4)
Educational level	
University degree	143 (47,7)
Secondary school	132 (44)
Lower secondary	20 (6.7)
Primary school	5 (1.6)
Occupation situation	
Employed	201 (67)
Housewife	35 (11.7)
Unemployed	33 (11)
Student	4 (1.3)
Other	27 (9)
Parity	
Nulliparous	250 (50)
1 or ≥2	250 (50)
Influenza vaccination or intention to get vaccinated	
No	210 (70)
Yes	90 (30)

HBM and influenza vaccine

Figure 1 shows the frequency of the HBM dimensions. With regard to *risk susceptibility,* 53.7% of women declared that they worried to contract influenza during pregnancy and 80.7% of them agreed that there is a risk of contracting influenza during the first months of life. About the foetal complication following the influenza during pregnancy, 14% disagreed and 40% were unsure. Even the perception of complications and severity during the first months of life had 56% of women agree. On the other hand, 68.7% agreed that vaccination during pregnancy could reduce the risk for mother to contract influenza and 47.7% agreed that vaccine during pregnancy protects the child before and after birth. Moreover, only 15% of women have had the perception that the vaccine against influenza could transmit the disease to themselves and 12.7% that the vaccine is unsafe during pregnancy for the baby's health.

Compared to pertussis vaccination [32], women seem less worried that their baby may get the influenza during the first few months of life (7.3% *vs* 18.3%). With regard to *risk severity*, 14% of women disagreed that the influenza contracted during pregnancy could lead to complications for the baby, while the 40% were unsure. Related to the possibility of contracting the influenza in the first months of life, 56% of women agreed that the influenza increases the risk of severe illness and complications. Compared to pertussis, more women disagreed that the influenza vaccine during pregnancy reduces the mother's risk of contracting the influenza (8% *vs* 2%).

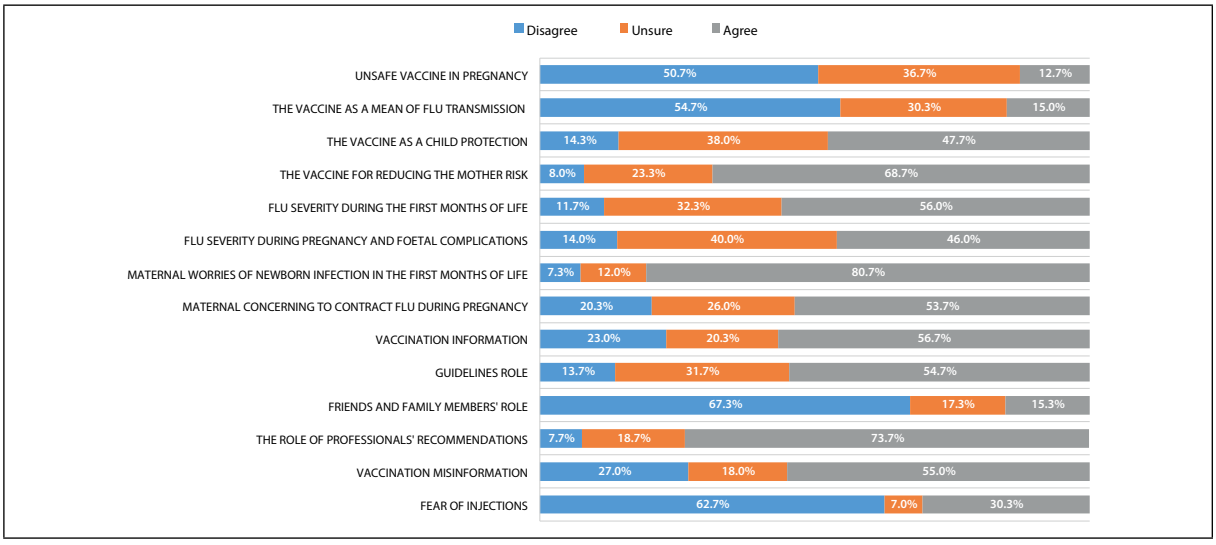

Figure 1
Frequency of the HBM model dimensions (n = 300).

Nonetheless, perceived benefits remained high. Even for the protection of the baby before and after birth through vaccination, women showed a greater degree of agreement on influenza vaccination than vaccination against pertussis (14.3% *vs* 5.3%). The barriers are almost overlapping in the two types of vaccine.

HBM confirmed its effectiveness in explaining or predicting health behaviours and choices also for flu vaccination *(Figure 2)*.

As for the common section, the associations found in the previous study are confirmed [32]: the Italian nationality showed a significant association also with not being afraid of injections (adjOR 3 CI 95% 1.6-5.8 p <0.01), with not being discouraged by friends and family to vaccinate during pregnancy (adjOR 2.9 CI 95% 1.6-5.5 p <0.01) and with the perception of not having received all information needed to decide whether to get vaccinated or not (adjOR 0.4 CI 95% 0.2-0.8 p <0.01). Moreover, being employed was associated with the fact that injections do not represent an obstacle to vaccination (adjOR 2.3 CI 95% 1.3-3.9 p <0.01), with not being worried to lack of knowledge on vaccinations during pregnancy (adjOR 1.9 CI 95% 1-3.8 p <0.05) and with not having been discouraged by friends and family to get the vaccination (adjOR 2.1 CI 95% 1.2-3.6 p <0.01). Fear of injections represented a barrier in women aged less than or equal to 31 years (adjOR 0.4 CI 95% 0.3-0.7 p <0.01) *(Table 2)*.

Having one or more children was associated with the idea that the influenza in the first months of life of baby can increase the risk of severe illness and complications (adjOR 1.7 CI 95% 1.08-2.7 p <0.05). The Italian nationality was negatively associated with the concern of contracting influenza during pregnancy (adjOR 0.5 CI 95% 0.2-0.9 p <0.05) and of related complications for the baby (adjOR 0.4 CI 95% 0.2-0.7 p <0.01) *(Table 2)*.

The logistic regression model *(Table 3)* showed that the perception of vaccine benefits (adjOR 4.3 CI 95% 1.7-10.9 p <0.01), of having received all the information needed (adjOR 2.6 CI 95% 1.2-5.5 p <0.01), the trust in guidelines (adjOR 3.5 CI 95% 1.6-7.3 p <0.01), the fear of contracting the disease (adjOR 5.1 CI 95% 2.6-10.3 p <0.01) and not being worried to lack of knowledge on vaccinations during pregnancy (adjOR 3.1 CI 95% 1.5-6.4 p <0.01) are factors associated with intent or vaccination against influenza during pregnancy.

DISCUSSION

Our study aimed to assess the factors that influence the acceptance of influenza vaccination during pregnancy and confirmed the effectiveness of HBM in explaining and predicting health behaviour already demonstrated in a previous study [32].

In our study 30% of women declared to be vaccinated/intention to get vaccinated during pregnancy against influenza. Rodrigues-Blanco *et al.* [33] reported 66% of intention to be vaccinated in postpartum women.

Our results show that perceived benefits remained high, despite 40% of women were unsure about complications of influenza on the baby. The doubts on vaccine safety are the main reason for rejecting the vaccine [34-36]. Other reasons are: the belief that the vaccine is not necessary or effective, the distrust towards the vaccine, having a cold, the possibility of becoming sick, not believing in vaccines and not knowing the recommendations [33]. The so-called construct of the "good mother", described in the literature on the use of medications during breastfeeding [37, 38], is polarized between two profiles of pregnant women: on one hand, the women who are unsure of the flu vaccine safety and therefore avoid exposing the foetus to this perceived risk and, on the other hand, those who intend to get vaccinated in order not to expose the foetus to risks and complications in case of flu contracted during pregnancy.

Most of our women agreed that influenza increases the risk of severe illness and complications and this may have been a motivation for vaccination, perceiving the risk of disease higher than vaccine. In fact, the erroneous belief that the vaccine itself can cause influenza in case of cold like symptoms and clinical manifestations without fever could represent a barrier to vaccination [34]. In a historical period in which a pandemic is afflicting the world and in which various organism and institutions [39, 40] recommend anti-COVID-19 vac-

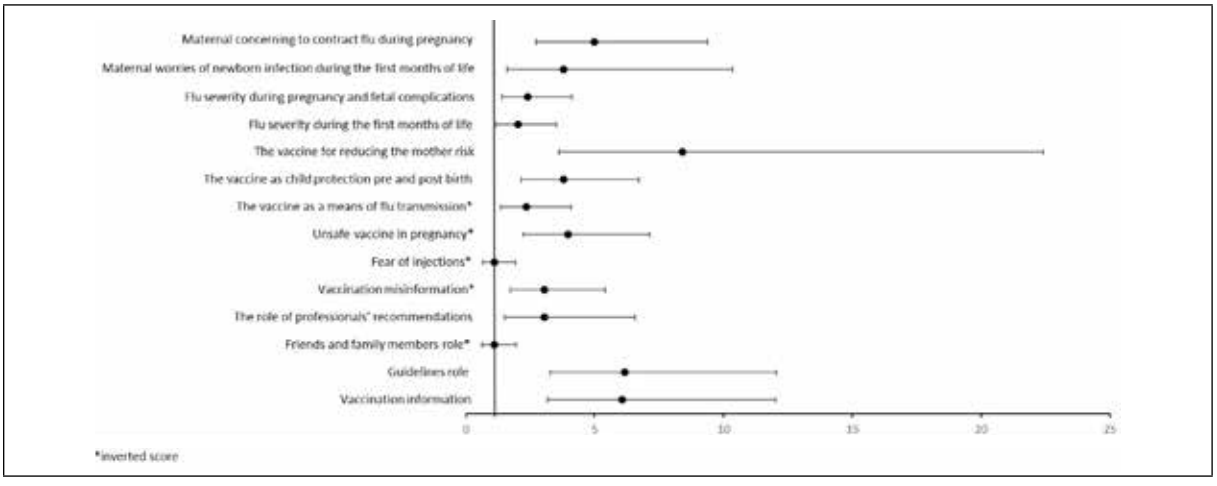

Figure 2
HBM and intention or uptake of influenza vaccination during pregnancy.

Table 2
HBM and social-demographic characteristics

	I'm worried about getting the flu during pregnancy (risk susceptibility)	If a pregnant woman contracts the flu, complications for her baby can develop (risk severity)	If a child contracts the flu in the first few months of life, the risk of severe illness and complications increases (risk severity)	I'm afraid of injections (barriers to action)*	I'm worried there may be things I don't know about vaccinations in pregnancy (barriers to action)*	Friends or family members have discouraged me from getting vaccinated during pregnancy (cues to action)*	I believe I have received all the information needed to decide whether to get vaccinated (self-efficacy)
Educational level High Low	-	-	-	-	-	-	54.9% 76%
Occupation situation Employed Unemployed	-	-	-	67.5% 47.2%	29.8% 18%	71.5% 80.7%	-
Parity 1 or ≥2 Nulliparous	-	-	62.7% 49.3%	-	-	-	-
Nationality Italian Foreigner	50.8% 68%	76.1% 66%	-	67.2% 40%	-	71.6% 46%	53.6% 72%
Age ≤31 >31	-	-	-	51.3% 69.9%	-	-	-

*Inverted score.

cination even in pregnant women, after a careful assessment of the risks and benefits, it is essential to avoid any form of misunderstanding.

In our study, the Italian nationality is a facilitator of vaccination. A previous study conducted in France [41] showed that during pandemic H1N1 influenza virus, the foreign nationality in pregnant women was a risk factor for not vaccination. There is a general perception that, while in Western Countries, pregnancy is considered as a potential risk condition, migrant women deem it as a physiological process [42].

Table 3
Logistic regression model

	Intention or uptake of influenza vaccination during pregnancy (Yes *vs* No)
	adjOR (CI 95%)
The vaccine for reducing the mother risk Disagree Agree	 1 4.3 (1.7-10.9)
Vaccination information Disagree Agree	 1 2.6 (1.2-5.5)
The trust in guidelines Disagree Agree	 1 3.5 (1.6 - 7.3)
Maternal concerning to contract flu during pregnancy Disagree Agree	 1 5.1 (2.6-10.3)
Vaccination misinformation* Disagree Agree	 1 3.1 (1.5-6.4)

*Inverted score.

Our previous study on HBM on pertussis [32] and this study on influenza show a higher *risk severity* perception for pertussis compared to influenza (80.3% *vs* 56%), and a related vaccination behaviour (being vaccinated or intention to vaccinate 48.3% *vs* 30%). The same phenomenon has been described by other authors [43, 44], showing that risk perception is increased for infancy vaccine-preventable diseases, compared to seasonal influenza, and is associated with lower influenza vaccination uptake. Pertussis, as other infancy vaccine-preventable diseases, is of greater concern compared to influenza, whose social representation could be of lower gravity due to its "seasonal" occurrence. Another reason for the higher gravity perception of pertussis and consequent vaccination behaviour in pregnancy could be the historical memory of its morbidity and mortality in early childhood in the last century. The perception of lower severity of influenza during pregnancy could be addressed by specific communication strategies.

Our logistic regression reconfirms the key role of healthcare professionals in providing information and recommendations on vaccinations. This is a factor positively associated to be vaccinated or to intention to get vaccinated. These results are confirmed for vaccination against pertussis [32] and for others health behaviours

on women's health [45]. In previous studies the recommendations on vaccination against influenza were provided by midwives, who represented the most helpful sources [35, 46]. Healthcare professionals' knowledge, attitudes and practices impact on infant health protection and promotion in many clinical settings [47], but their role is pivotal even before the birth, providing complete and exhaustive information to the expectant parents. The specific training for midwives for increasing the probability to receive the vaccination against influenza during pregnancy is needed [48]. The e-learning, proved effective in different areas of maternal-child fields such as breastfeeding [49, 50], could be a solution for improving knowledge and skills of healthcare professionals on vaccinations. In addition, the trust relationship established by midwife for mother and child health promotion is integral part of her/his habitual activities [51-53].

This study has some limitations: the use of a convenient sample of women and a questionnaire that includes items from validated questionnaires, but overall it has not undergone a validation process; the impossibility to assess the HBM effectiveness in the two groups of intentioned and vaccinated women, due to aggregated collection of data through questionnaire; the possible selection bias due to exclusion of women who could neither read nor understand Italian.

CONCLUSIONS

The vaccination is a public health priority. Through vaccination, it is possible to prevent several diseases and complications in the general population and in pregnant women, without high risks due to vaccination itself. Thus, it is necessary to create trust in the vaccinations through an integrated work of midwives, gynaecologists, paediatricians and others health professionals in order to set up training programs and to provide correct and effective health communication, as risk perception can constitute a predictor of decision making in health behaviours.

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Author contribution

All Authors participated in the interpretation of the study results and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conflict of interest statement

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Searching for an alliance with journalism: a survey to investigate health literacy in Italy

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Abstract

Objectives. This study (GLASS) aimed to explore low health literacy (HL) prevalence among journalists and general population and factors associated with low HL.

Methods. GLASS was an Italian online cross-sectional study. Questionnaires included instruments for different HL dimensions: single item literacy screener (SILS), medical term recognition test (METER), medical data interpretation test (MDIT). For each instrument, multiple regressions were performed.

Results. Participants were 665. A total of 24.6%, 85.0%, and 58.9% journalists and 19.5%, 77.8%, and 62.6% general population reported low HL (SILS, METER, MDIT, respectively). Regressions showed that journalists who had never written about health and journalists who had personally written about health without being health journalists had a higher likelihood of low HL compared with health journalists.

Conclusion. Since journalists are key players in public health, our findings are relevant; especially considering the context of the current pandemic. It would be advisable to bolster a stronger collaboration between professionals in the media world and the scientific community.

Key words

- health literacy
- journalism
- health communication

INTRODUCTION

Health literacy (HL) is defined by the World Health Organization (WHO) as a combination of skills every human being needs to "access, understand, appraise and apply health information, to make judgements and take decisions in everyday life" for protecting and maintaining health [1]. Despite being the result of multiple social and individual factors [2], HL can be described using (at least) three progressively higher levels of individual autonomy and personal empowerment: functional, interactive and critical HL [3].

Quantification of HL [4] has been crucial to determine its effect on health-related outcomes. Since its first debut in 1974 [5], it is now clear that a low HL level is associated with more hospitalizations, greater use of emergency care, low receipt of health prevention initiatives such as screenings (i.e., mammography) and influenza vaccine, and also poorer ability in taking medications correctly or to interpret labels and health messages [6], possibly undermining efforts in developing patient empowerment.

Low HL level has been recognized to play an essential role in the context of health information seeking and quality assessment using both classic and new media [7]. In this regard, the quality of information is crucial, and in 2006 health journalism accepted the challenge with Health News Review organization developing a set of 10 rigorous criteria that "all health care news stories and all health care news (press) releases about interventions should include" [8, 9]. It was found that the stories considered during 2005-2010 successfully met just less than half of the criteria, particularly in terms of "spinning" research results (magnification of findings and picturing a new treatment a major breakthrough) and failing to discuss costs and quality of evidence of drugs or health [10, 11].

Although a direct effect of media coverage on HL is unclear [12], evidence that an inaccurate coverage could influence health choices is well [13, 14], and possibly exacerbated during critical times such as a pandemic, with the development of the so-called infodemic, defined as "too much information including false or misleading information in digital and physical environments during a disease outbreak" [15].

Focusing on the Italian context, the legislation does not provide a defined path to become a health journalist. Moreover, registered journalists do not need to specialize in a certain field, although it naturally occurs among

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editorial staff of the most widely circulating newspaper and TV newsrooms. The same does not always apply to small magazines and newspaper staff or among relatively new online journal realities, where medical and health-related news can be covered by journalists with a broad range of backgrounds [16].

Therefore, given the role of a low HL in conditioning health outcomes and the importance of quality in health journalism to provide an accurate coverage of health information, our primary aim was to assess the prevalence of low HL among Italian general population and, especially, among journalists to explore if journalists operating in the health field had the proper skills to correctly interpret health communication and adequately convey it to the reader. Additionally, we aimed to investigate factors potentially associated with low HL both in general population and journalists.

METHODS

Study design

The GLASS (Livello di Alfabetizzazione su Salute e Sanità nei Giornalisti, i.e., health literacy level among journalists) study was a cross-sectional survey conducted in Italy amongst a convenience sample of adults. The study was approved by the Internal Review Board of the Department of Public Health Sciences of the University of Turin. Criteria for the inclusion in the study were: age ≥18 years old; being resident in Italy and being able to give informed consent.

The research was conducted using the computer-assisted web interview (CAWI) method. The survey was developed using the Uniquest (Limesurvey) platform. The survey consisted of a questionnaire distributed mainly on Facebook through a web link shared by institutional social media pages and personal accounts of researchers. The survey was spread from June to September 2019. Before starting the survey, a brief explanation of the study was shown to each participant. Then, by confirming the enrolment to the study, each participant declared their informed consent. Participation was voluntary and anonymous, and participants received no compensation.

Instruments

For each participant, the first section of the questionnaire consisted of ten questions investigating the socio-demographic and health-related characteristics, e.g., age, gender, education, perceived economic status and presence of a personal chronic disease/disability. Participants were asked if their work/study background was in healthcare, journalism or other. Journalists were asked four additional questions to frame their professional activity.

The next section was dedicated to HL: as recommended for robust research methods in HL measurements [17], we included multiple measures. We used: the single item literacy screener (SILS) [18], the medical term recognition test (METER) [19] and the medical data interpretation test (MDIT) [20].

The SILS is a single question which has shown high reliability and validity [18]. It asks "How often do you need to have someone help you when you read instructions, pamphlets, or other written material from your doctor or pharmacy?" and 4 answers are possible, with a score of 2 set as cut-off [18]. It was used in its validated Italian version [21]. Scores greater than 2 help identifying individuals at higher risk of limited reading and understanding ability regarding health information [18, 21]. It is considered a self-reported comprehension tool to investigate HL [22].

The METER is another measurement with high reliability and validity [19], which was used in its Italian validated version [23]. It consists of a list of 70 terms that are both real medical terms (40 items) and words that sound alike but are not real words (30 items). The participants are asked to check off those words they recognize as actual medical terms. The score is defined as the sum of correct words recognized and the cut-off points have been set as 0-20 for low, 21-34 for marginal and 35-40 for functional HL levels [19]. It is considered a word recognition tool to assess HL [22].

The MDIT is a reading/numeracy comprehension tool, which is focused on skills to understand and compare medical statistics about disease risk and about risk reduction and can be an assessment of abilities for making sense of ordinary health information [20]. It was used the Italian short version, which consists of 10 items [24]. The percentage of correct answers represents the final score: a 0-100 scale with higher scores indicating greater abilities in interpreting information [20]. A score ≥75 can be considered as "passing" HL [25].

Statistical analysis

This paper had three outcomes: having a "low HL" according to the above-mentioned tools (SILS: score >2 [18]; METER: score <35 [19]; MDIT: score <75 [25]).

In this paper, we were primarily interested in studying the general population, specifically focusing on journalists. The target groups were: "health journalists" (journalists whose primary area of specialization is medicine/health); journalists who had personally written about medicine/health/public health in their career but whose primary area is not medicine/health (i.e., non-health journalists who have personally written about medicine); journalists who had never written about medicine/health/public health in their career; general population (excluding journalists). Additionally, we collected data on people working/studying in the healthcare field. We considered the whole sample for descriptive analyses and different subsamples in the regression analyses as explained below.

Descriptive analyses were performed. Continuous variables were expressed as median and interquartile range (IQR) since the Shapiro-Wilk test showed non-normal distributions. Chi-squared tests (Kruskal-Wallis or Mann-Whitney U tests for continuous variables) were computed to assess differences between: groups defined by the work/study background; groups defined by the outcomes. Relationships between outcomes were explored by chi-squared statistics and Cohen's kappa coefficient.

For each outcome, simple logistic regressions were conducted with the target groups as covariate. The effects of the independent variables on the outcomes

were analyzed with multiple logistic regressions adjusted for age and gender. Final models were achieved with a backward stepwise method (results expressed as odds ratios OR, 95% CI). Specifically, the default option of the SPSS software for backward elimination was used (likelihood-ratio statistic greater than 0.10 as removal criterion). In the *Supplementary material*, a list of the variables that were entered at the first step is shown *(Supplementary Methods M1 available online)*. For each outcome, the models were executed in different subsamples: general population (including journalists); journalists (also entering the variables specifically collected for this subgroup); participants with a healthcare background. We decided to keep "healthcare people" separated from the others as they may report different variables influencing HL due to their background.

SPSS software (version 26) was used, and a two-tailed p-value <0.05 was considered to be statistically significant. Missing values were excluded.

RESULTS

Characteristics of the sample

The sample consisted of 665 participants. Females accounted for 66.5%. The median age was 37 years (IQR = 30-49). The majority had an educational level higher than the high school diploma (68.1%). A total of 82.6% were workers.

Stratifying the sample by work/study background, some significant differences were revealed. For instance, participants with journalism background were less likely to have a Bachelor or Master's degree (p <0.001), be a student or non-worker (p <0.001), and have a good/excellent perceived economic status (p = 0.025). Details are in *Table 1*.

Additional information was collected for participants with a journalism background. The majority consisted of journalists working for a daily newspaper (38.7%), followed by freelance journalists (20.4%), journalists working for periodical (19.7%) and for online magazine (19.7%) (chance to select more than one option). The most frequent primary areas of specialization were: politics (35.9%), news report (32.4%), education (28.2%), and medicine/health (25.4%) (chance to select more than one option). A total of 64.8% declared to have personally written about medicine/health and 31.7% stated to have studied health communication or scientific dissemination through a course or other means. Thus, 25.4% reported medicine/health as the primary area (n = 36), 39.4% reported to have written about medicine/health but medicine/health was not their primary area (n = 56), and 35.2% neither reported medicine/health as the primary area nor declared to have written about medicine/health (n = 50). Details are presented in *Table S1 (Supplementary material available online)*.

Description of the outcomes

A total of 115 participants (17.3%) reported an inadequate HL according to the SILS (median score 2, IQR = 1-2). According to the METER, 438 participants (68.4%) reported low (n = 69) or marginal (n = 369) levels of HL, while 202 reported functional levels of HL (31.6%) (median score 32, IQR = 27-35). Based on the MDIT, 322 individuals (59.2%) reported a non-passing HL against 222 individuals (40.8%) with a passing HL (median score 70%, IQR = 60-80%). The categories of low HL defined by the different outcomes were associated each other *(Table 2)*. However, the Cohen's kappa coefficient indicated poor concordance (METER *vs* SILS: 0.106; MDIT *vs* SILS: 0.100; METER *vs* MDIT: 0.125).

The prevalence of low HL was different between the categories of work/study background (SILS: p <0.001, METER: p <0.001, MDIT: p = 0.096). A total of 24.6% (SILS), 85.0% (METER), and 58.9% (MDIT) journalists reported low HL. Among participants neither with journalism nor with healthcare background, the prevalence of low HL was 19.5% (SILS), 77.8% (METER), and 62.6% (MDIT). Participants with healthcare background had reduced frequencies of low HL *(Table 2)*. It must be noted that for the METER the above-mentioned results for "low HL" refer to low and marginal levels. Considering only actual low HL, such percentages are: 21.4% for journalists, 9.7% for general population, 3.4% for healthcare participants.

Both considering METER and MDIT, the prevalence of low HL showed a significant decreasing frequency with the increase of education level. The distribution of age was not different across the categories defined by the outcomes (SILS p = 0.651, METER p = 0.531, MDIT p = 0.082). The prevalence of poor HL was lower among those with a perceived good/excellent economic status (SILS, MDIT), among those with a chronic disease/disability (METER), and among those with a family member working in the healthcare field (METER). Participants with a family member working in the healthcare field showed a higher prevalence of inadequate HL according to SILS. Other details are in *Table 2*.

Considering additional journalists' information, there was no significant differences according to the SILS. Both for METER and MDIT, health journalists were less likely to report low HL (METER: 69.4%, MDIT: 26.7%), while non-health journalists who had personally written about medicine/health (METER: 87.5%, MDIT: 68.6%) and journalists who had never written about medicine/health (METER: 93.8%, MDIT: 69.8%) showed a greater prevalence of low HL (METER: p <0.007, MDIT: p <0.001). It must be noted that for the METER the above-mentioned results for "low HL" refer to low and marginal levels. Considering only actual low HL, such percentages are: 0% for health journalists, 19.6% for non-health journalists who had personally written about medicine/health, 39.6% for other journalists.

Moreover, journalists writing for online magazine (METER: p = 0.018), journalists writing for daily newspapers (MDIT: p = 0.012), and journalists whose primary area was technology and computer science (MDIT: p = 0.017) reported lower frequencies of poor HL. Journalists whose primary area was sports/motor sports (MDIT: p <0.001) or entertainment (MDIT: p = 0.024) reported higher prevalence of low HL. Having studied health communication or scientific dissemination through a course or other means showed no significant association with HL. Details are in *Table S1 (Supplementary material available online)*.

Table 1
Characteristics of the sample: overall descriptive analyses and stratified by work/study background

Characteristic	Overall sample (n = 665) N (%)	Journalism background (n = 142) N (%)	Healthcare background (n =158) N (%)	Neither journalism nor healthcare background (n = 365) N (%)	p-value
Age*	37 (30-49)	40 (33-52)	34 (28-45)	38 (30-48)	**0.001**
Gender					
Male	222 (33.5)	80 (56.7)	43 (27.2)	99 (27.3)	**<0.001**
Female	440 (66.5)	61 (43.3)	115 (72.8)	264 (72.7)	
Nationality					
Italian	659 (99.1)	142 (100)	158 (100)	359 (98.4)	0.083
Other	6 (0.9)	0 (0)	0 (0)	6 (1.6)	
Area					
Northern Italy	544 (81.8)	88 (62)	131 (82.9)	325 (89)	**<0.001**
Central Italy	60 (9)	27 (19)	15 (9.5)	18 (4.9)	
Southern Italy	61 (9.2)	27 (19)	12 (7.6)	22 (6)	
Education level					
High school or lower	212 (31.9)	46 (32.4)	29 (18.4)	137 (37.5)	**<0.001**
Bachelor or Master's degree	327 (49.2)	59 (41.5)	82 (51.9)	186 (51)	
Postgraduates degree	126 (18.9)	37 (26.1)	47 (29.7)	42 (11.5)	
Household					
1 person	111 (16.7)	30 (21.1)	21 (13.3)	60 (16.4)	0.329
2 persons	169 (25.4)	39 (27.5)	39 (24.7)	91 (24.9)	
More than 2 persons	385 (57.9)	73 (51.4)	98 (62)	214 (58.6)	
Occupation					
Worker	537 (82.6)	135 (95.7)	119 (78.3)	283 (79.3)	**<0.001**
Non-worker (homemaker, retiree, unemployed)	52 (8)	3 (2.1)	7 (4.6)	42 (11.8)	
Student	61 (9.4)	3 (2.1)	26 (17.1)	32 (9)	
Perceived economic status					
Good/excellent	433 (65.1)	80 (56.3)	101 (63.9)	252 (69)	**0.025**
Insufficient/poor	232 (34.9)	62 (43.7)	57 (36.1)	113 (31)	
Personal chronic disease or disability					
No	548 (82.5)	125 (88.7)	126 (79.7)	297 (81.4)	0.088
Yes	116 (17.5)	16 (11.3)	32 (20.3)	68 (18.6)	
Family member with a chronic disease or disability					
No	393 (59.2)	93 (66)	83 (52.5)	217 (59.5)	0.061
Yes	271 (40.8)	48 (34)	75 (47.5)	148 (40.5)	
Family member working in the healthcare field					
No	440 (66.3)	100 (70.9)	81 (51.3)	259 (71)	**<0.001**
Yes	224 (33.7)	41 (29.1)	77 (48.7)	106 (29)	

n = sample size. Figures are expressed as number (N) and column percentages (%). P-value obtained via chi-squared tests. *Figures expressed as median (interquartile range).

Regression models

Table S2 shows simple regressions for each outcome with the target groups as independent variable *(Supplementary material available online)*. No group reported a significant association with low HL defined by the SILS. Concerning both the METER and the MDIT, non-health journalists who had personally written about medicine/health and journalists who had never written

Table 2
Descriptive analyses stratified by the health literacy outcomes

	SILS: inadequate HL			METER: low/marginal HL			MDIT: non-passing HL		
	No (n = 550) N %	Yes (n = 115) N %	p	No (n = 202) N %	Yes (n = 438) N %	p	No (n = 222) N %	Yes (n = 322) N %	p
METER: low/marginal HL									
No	187 (92.6)	15 (7.4)	**<0.001**	-			-		
Yes	339 (77.4)	99 (22.6)							
MDIT: non-passing HL									
No	201 (90.5)	21 (9.5)	**<0.001**	84 (37.8)	138 (62.2)	**0.003**	-		
Yes	254 (78.9)	68 (21.1)		83 (25.8)	239 (74.2)				
Work/study background									
Journalism	107 (75.4)	35 (24.6)	**<0.001**	21 (15)	119 (85)	**<0.001**	51 (41.1)	73 (58.9)	0.096
Healthcare	149 (94.3)	9 (5.7)		103 (69.6)	45 (30.4)		60 (48.8)	63 (51.2)	
Neither journalism nor healthcare	294 (80.5)	71 (19.5)		78 (22.2)	274 (77.8)		111 (37.4)	186 (62.6)	
Gender									
Male	186 (83.8)	36 (16.2)	0.627	65 (30)	152 (70)	0.532	87 (47)	98 (53)	**0.035**
Female	362 (82.3)	78 (17.7)		136 (32.4)	284 (67.6)		134 (37.6)	222 (62.4)	
Nationality									
Italian	546 (82.9)	113 (17.1)	0.297	202 (31.9)	432 (68.1)	0.095	220 (40.7)	320 (59.3)	0.707
Other	4 (66.7)	2 (33.3)		0 (0)	6 (100)		2 (50)	2 (50)	
Area									
Northern Italy	456 (83.8)	88 (16.2)	0.060	173 (33)	351 (67)	0.092	187 (42.5)	253 (57.5)	0.214
Central Italy	43 (71.7)	17 (28.3)		18 (31)	40 (69)		19 (36.5)	33 (63.5)	
Southern Italy	51 (83.6)	10 (16.4)		11 (19)	47 (81)		16 (30.8)	36 (69.2)	
Education level									
High school or lower	167 (78.8)	45 (21.2)	0.147	46 (22.7)	157 (77.3)	**0.004**	47 (27)	127 (73)	**<0.001**
Bachelor or Master's degree	274 (83.8)	53 (16.2)		111 (35.1)	205 (64.9)		123 (46.4)	142 (53.6)	
Postgraduates degree	109 (86.5)	17 (13.5)		45 (37.2)	76 (62.8)		52 (49.5)	53 (50.5)	
Household									
1 person	94 (84.7)	17 (15.3)	0.833	25 (23.8)	80 (76.2)	0.124	41 (47.7)	45 (52.3)	0.214
2 persons	139 (82.2)	30 (17.8)		59 (35.5)	107 (64.5)		62 (43.1)	82 (56.9)	
More than 2 persons	317 (82.3)	68 (17.7)		118 (32)	251 (68)		119 (37.9)	195 (62.1)	
Occupation									
Worker	448 (83.4)	89 (16.6)	0.930	157 (30.1)	364 (69.9)	0.081	189 (41.6)	265 (58.4)	0.057
Non-worker (homemaker, retiree, unemployed)	44 (84.6)	8 (15.4)		20 (40.8)	29 (59.2)		9 (23.7)	29 (76.3)	
Student	50 (82)	11 (18)		23 (41.8)	32 (58.2)		19 (48.7)	20 (51.3)	
Perceived economic status									
Good/excellent	369 (85.2)	64 (14.8)	**0.019**	141 (34.1)	273 (65.9)	0.066	156 (44.1)	198 (55.9)	**0.035**
Insufficient/poor	181 (78)	51 (22)		61 (27)	165 (73)		66 (34.7)	124 (65.3)	
Personal chronic disease or disability									
No	450 (82.1)	98 (17.9)	0.289	154 (29.3)	372 (70.7)	**0.008**	187 (42.1)	257 (57.9)	0.191
Yes	100 (86.2)	16 (13.8)		48 (42.1)	66 (57.9)		35 (35)	65 (65)	
Family member with a chronic disease or disability									
No	324 (82.4)	69 (17.6)	0.749	110 (29.2)	267 (70.8)	0.120	137 (42.4)	186 (57.6)	0.357
Yes	226 (83.4)	45 (16.6)		92 (35)	171 (65)		85 (38.5)	136 (61.5)	
Family member working in the healthcare field									
No	374 (85)	66 (15)	**0.038**	119 (28.3)	302 (71.7)	**0.013**	145 (40.2)	216 (59.8)	0.668
Yes	176 (78.6)	48 (21.4)		83 (37.9)	136 (62.1)		77 (42.1)	106 (57.9)	

n = sample size. Figures are expressed as number (N) and row percentages (%). P-value obtained via chi-squared tests y.
HL: health literacy (HL). MDIT: medical data interpretation test; METER: medical term recognition test; SILS: single item literacy screener.

about medicine/health were more likely to have low HL. General population had a higher likelihood of reporting a low HL defined by the MDIT.

The multiple regression model confirmed no significant differences in HL defined by the SILS between the target groups. Participants from Central Italy and people with a family member working in the healthcare field were more likely to report a low SILS HL. Increasing age was associated with a lower likelihood of poor HL. The model considering only the journalists' subsample confirmed the relationship with age *(Table 3)*.

The METER multiple regression model revealed that, in addition to the relationships highlighted in the simple regression *(Supplementary material, Table S2, available online)*, also general population had a higher likelihood of reporting low HL compared with health journalists. Specifically, general population seemed to have a risk lower than the one of non-health journalists who had personally written about medicine/health and journalists who had never written about medicine/health; however, the 95% CIs were overlapped. Participants with a high school diploma or lower education level showed a higher likelihood too. Non-workers had a lower probability of reporting low HL compared with workers. The model considering only the journalists showed that an increasing age was associated with a higher likelihood of low HL and journalists whose primary area was politics or science and medicine had a lower probability of poor HL *(Table 3)*.

The MDIT multiple regression model confirmed non-health journalists who had personally written about medicine/health and journalists who had never written about medicine/health were more likely to have low HL, while this relationship was not confirmed for general population. Participants with a high school diploma or lower education level and females also showed a higher likelihood of low HL. Increasing age seemed to slightly reduce the odds of low HL. Additionally, the model considering only the journalists' subsample showed journalists working for daily newspaper were less likely to report poor HL *(Table 3)*.

Lastly, multiple regression models were performed in the healthcare subsample. Both for the SILS and the METER models, increasing age reduced the odds of poor HL (SILS: OR 0.92, 95% CI 0.87-0.97, p = 0.004; METER: OR 0.96, 95% CI 0.94-0.98, p <0.001). Students were less likely to report low HL defined by the METER (OR 0.19; 95% CI 0.04-0.88, p = 0.034). Concerning the MDIT, participants with an insufficient/poor perceived economic situation had a greater likelihood of low HL (OR 2.75, 95% CI 1.16-6.56, p = 0.022) *(Supplementary material, Table S3, available online)*.

DISCUSSION

This study aimed to estimate the prevalence of low HL among journalists and general population and to explore the factors potentially associated with low HL.

Concerning self-reported comprehension (i.e., SILS), a meta-analysis found a prevalence of low HL of 42% (95% CI 36-48%) in Europe and 42% (95% CI 33-51%) in Italy [22]. Compared with such pooled prevalence, in our sample the low HL defined by the SILS was found to be less frequent, especially among healthcare professionals (5.7%), health journalists (13.9%) and general population (19.5%). Interestingly, both journalists who have never written about medicine/health and non-health journalists who have personally written about medicine/health reported the greatest levels of "self-reported" low HL (28% and 28.6%, respectively).

About word recognition items, the prevalence in Europe was found to be 27% (95% CI: 18-38%) and in Italy 38% (95% CI: 35-41%) [22]. In our sample there were lower percentages of people with low HL in word recognitions items, except for journalists who have never written about medicine/health (39.6%) and non-health journalists who have personally written about medicine/health (19.6%). Adding participants with marginal HL, the percentages of people with non-functional HL are remarkably high, from 30.4% of "healthcare" participants to 69.4% of health journalists, 77.8% of general population, 87.5% of non-health journalists who have personally written about medicine/health and 93.8% of journalists who have never written about medicine/health.

Last, regarding reading/numeracy comprehension items, our results are in line with the dramatically high levels of low HL found in Italy by Baccolini, *et al*. [22]. Indeed, in Europe this kind of low HL was found to be 42% (95% CI: 33-53%), while in Italy 72% (95% CI: 32-93%). We found percentages between 62% and 70% for general population and non-health journalists (also those who have personally written about medicine/health). Interestingly, in this case the lowest percentages were reported by health journalists (26.7%) and not by the "healthcare" participants (51.2%). This could be partially due to the fact that the category "healthcare" can include a wide range of professionals and their knowledge may vary especially when considering reading/numeracy comprehension. Indeed, we found significant associations between higher levels of HL and "healthcare" participants both for SILS and METER, while we did not find any significant association for MDIT.

Therefore, in our study, the greatest levels of low HL in all the studied dimensions were reported by journalists who have never written about medicine/health and journalists who have personally written about medicine/health without being health journalists. These findings are confirmed in the multiple regression models, where the above-mentioned subgroups had a significantly higher likelihood of reporting low HL both for METER and for MDIT. Since also journalists that have no specific expertise in medicine may write about it, these findings are alarming as journalists are widely recognized to be a potential key player in public health and health-related initiatives [26-29]. Although it is difficult to find evidence about HL of journalists in scientific literature, some findings are in line with the low HL we found. Shah and colleagues outlined that the low HL rate of journalists was a major obstacle to accurate and comprehensive polio vaccine coverage in Pakistan [26]. Wilson *et al*. reported that most magazines with "health" in the tile showed poor quality and unreliable health advice [30]. Interestingly, Hinnant and col-

Table 3
Multiple regression models with poor health literacy as outcome (according to SILS, METER, and MDIT)

	SILS						METER						MDIT					
	Journalists and general population			Journalists			Journalists and general population			Journalists			Journalists and general population			Journalists		
	adjOR	95% CI	p	adjOR	95% CI	p	adjOR	95% CI	p	adjOR	95% CI	p	adjOR	95% CI	p	adjOR	95% CI	p
Age	0.97	0.95-0.98	<0.001	0.95	0.92-0.98	<0.001	0.99	0.98-1.01	0.434	1.07	1.03-1.11	0.002	0.98	0.96-0.99	0.018	1.02	0.99-1.04	0.260
Female	1.17	0.71-1.9	0.541	0.86	0.37-2.01	0.734	1.08	0.67-1.74	0.754	1.05	0.34-3.21	0.930	1.56	1.01-2.42	0.047	0.34	0.14-0.83	0.018
Health journalists	Ref.						Ref.						Ref.					
Non-health journalists who had personally written about medicine/health	1.00	0.41-2.42	0.994				5.37	1.99-14.5	0.001				2.81	1.15-6.91	0.024			
Journalists who had never written about medicine/health	1.11	0.44-2.81	0.831				14.20	3.02-66.86	0.001				2.64	1.04-6.71	0.041			
General population	0.55	0.28-1.06	0.074				3.54	1.87-6.71	<0.001				1.89	0.96-3.73	0.066			
Nationality other than Italian	2.83	0.49-16.21	0.244										0.51	0.07-3.87	0.515			
Northern Italy	Ref.						Ref.			Ref.			Ref.					
Central Italy	2.11	1.05-4.26	0.036				1.81	0.71-4.67	0.217	4.56	0.88-23.54	0.070	1.27	0.6-2.7	0.536			
Southern Italy	0.52	0.22-1.27	0.153				*			*			1.43	0.63-3.21	0.392			
Bachelor or Master's degree	Ref.			Ref.			Ref.			Ref.			Ref.			Ref.		
High school or lower	0.93	0.56-1.55	0.786	1.74	0.62-4.88	0.291	1.76	1.02-3.02	0.043	0.25	0.05-1.3	0.100	2.29	1.4-3.76	0.001	2.24	0.71-7.08	0.170
Postgraduate degree	0.55	0.27-1.12	0.099	0.59	0.18-1.93	0.380	1.44	0.74-2.81	0.287	0.46	0.12-1.78	0.260	0.72	0.39-1.29	0.268	0.61	0.17-2.26	0.460
Insufficient/ poor economic situation	1.39	0.89-2.18	0.148				1.25	0.77-2.03	0.361							2.06	0.85-5	0.110
Family member with a chronic disease or disability	0.87	0.55-1.39	0.560							0.57	0.20-1.64	0.296				2.52	0.97-6.5	0.057
Family member working in the healthcare field	2.10	1.31-3.37	0.002				0.84	0.51-1.37	0.478									
Household: 1 person				Ref.									Ref.					
Household: 2 persons				2.41	0.67-8.64	0.177							0.92	0.49-1.72	0.784			
Household: More than 2 persons				3.14	0.96-10.3	0.059							1.11	0.63-1.96	0.728			
Worker							Ref.						Ref.					
Non-worker							0.35	0.16-0.75	0.007				2.13	0.83-5.42	0.114			
Student							2.08	0.59-7.33	0.255				0.64	0.24-1.71	0.371			
Personal chronic disease or disability							0.72	0.39-1.31	0.282	0.27	0.05-1.37	0.114	1.16	0.64-2.11	0.625	3.77	0.7-20.24	0.122
Primary area of specialization: education				2.12	0.86-5.25	0.104												

Continues

Table 3
Continued

	SILS						METER						MDIT					
	Journalists and general population			Journalists			Journalists and general population			Journalists			Journalists and general population			Journalists		
	adjOR	95% CI	p	adjOR	95% CI	p	adjOR	95% CI	p	adjOR	95% CI	p	adjOR	95% CI	p	adjOR	95% CI	p
Primary area of specialization: science & medicine				0.30	0.08-1.12	0.073				0.25	0.06-0.99	0.049				0.22	0.06-0.87	0.030
Primary area of specialization: politics										0.19	0.05-0.75	0.018						
Primary area of specialization: news report										4.14	0.88-19.51	0.073						
Having personally written about medicine				0.86	0.35-2.14	0.745				1.36	0.36-5.08	0.651				0.93	0.33-2.61	0.896
Having studied health communication or scientific dissemination through a course or other means				2.31	0.73-7.3	0.155				1.29	0.32-5.32	0.721				2.71	0.7-10.48	0.149
Daily newspaper																0.32	0.12-0.86	0.024
Periodical																0.33	0.09-1.19	0.091

Figures are expressed as adjusted Odds Ratios (adjOR) and 95% Confidence Interval. *Southern Italy was omitted because of the small size (CI).
HL: health literacy (HL); MDIT: medical data interpretation test; METER: medical term recognition test; SILS: single item literacy screener.

leagues showed that health journalists view their primary responsibility to their audience as individuals and not as a public service to the society, thus highlighting that the way how journalists perceive their role may be an important field of additional studies [27]. Beyond HL and skills of journalists, it must be noted that, to achieve an improved health communication, it is also essential to promote a substantive public engagement of scientists [31] as stronger collaborations between scientists and journalists might help in improving public health outcomes [28].

Additionally, our findings seem even more alarming in the light of the COVID-19 pandemic. Indeed, it is possible that journalists that have never written about medicine and health-related topics have to write about pandemic-related information during the so-called infodemic [15]. False information is not necessarily designed with bad intentions and misinformation caused by a poor HL of journalists can be harmful: the coverage of health in the mass media and its quality is critical since it is the key source for information for the general population [32]. It also should be noted that, during the pandemic, trust towards journalists may be reduced [33], thus suggesting that increasing reliability for instance through the improvement of journalists' HL could be essential to reach the population with correct information.

Moreover, beyond the journalists' area of specialization, other factors were associated with low HL. Both for METER and MDIT, low education increased the likelihood of low HL consistently with other relevant works [34, 35]. Such relationship was not found for the SILS probably due to the nature of the instrument: even if a very short self-reported comprehension tool can be useful to quickly assess the HL status, subjective estimates of HL may have higher misclassification rates [36]. Similarly, the fact that participants with a family member working in the healthcare field had a higher likelihood of low HL according to the SILS could be due to the self-reported nature: those participants probably ask more for help since they have the chance to easily receive a professional answer. Concerning age, our results conflict with most of HL literature that shows older age is linked to low HL [22, 34, 35]. However, this could be partially explained by the quite young median age of our sample. Furthermore, according to the MDIT model, women had a higher likelihood of low HL in the general population sample while they had a lower likelihood in the journalists' subsample. Thus, also considering that other relevant works are conflicting about this issue [34, 35], the relationship with gender should be further explored to understand if some gender-related determinants can influence HL. Lastly, considering only the journalists' subsample, it is interesting that also journalists whose primary area of specialization was politics had a lower likelihood of low HL: this could be explained by the fact that politics journalists must comprehend health policies. More-

over, the possible reasons for the higher HL reported by journalists working in daily newspapers should be further investigated. It is worth noting that having studied health communication/scientific dissemination was not significant for any outcomes, perhaps because the experience gained working in the medicine-related field might be more important than attending courses.

Regarding the models for the healthcare subsample, observations like in the general population model can be done about age. Interestingly, students had a lower likelihood of low HL and this could be partially explained by the fact that, perhaps, students present a higher internet use, which has been found linked to high HL [34]. Last, participants with an insufficient/poor perceived economic situation had a greater likelihood of low HL consistently with findings about HL [35] (it must be noted that the healthcare subsample did not include only medical doctors but all possible workers/students within the healthcare field).

This work had some strengths and limitations. To our knowledge, it was one of the first studies examining the HL among different kind of journalists and it used only validated tools to measure HL [21, 23, 24]. It should be noted that the categories defined by the instruments were significantly associated, although with a poor concordance. This could be partially due to the fact that these tools do measure different dimensions of HL. Specifically, the use of multiple measures of HL, as we did, is recommended for robust research methods in HL [17]. The small sample represented the main limitation, along with the cross-sectional design and the convenience sampling. Besides, the generalizability of the results is also limited to the Italian context. However, this study offers a glimpse of the pre-COVID-19 situation among Italian mass media operators and it can be a starting point to investigate the HL among the journalists' category, which should be a public health priority due to the infodemic that is characterizing the current scenario.

In conclusion, health journalists and general population showed good levels of HL compared with non-health journalists, even though they have written about medicine/health during their career. These findings are remarkable, especially in the light of the current infodemic that is following the pandemic. The role of journalists in improving health communication and public health outcomes must be further investigated and it would be advisable to bolster a stronger collaboration between journalism and science.

Ethical approval

The study was approved by the Internal Review Board of the Department of Public Health Sciences of the University of Turin, Italy.

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Author's contribution

Conception and design: GLM, DC, GV, MRG, RC, FB, RS; data acquisition: GLM, DC, RC; analysis and interpretation of data: GLM, DC, GV, MRG, AS, RC; writing publication: GLM, DC, GV, AS; critical revision: GLM, DC, GV, MRG, FB, RS; supervision and final approval: MRG, FB, RS.

Conflict of interest statement

The Authors of this paper declare no conflict of interest.

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Book Reviews, Notes and Comments

Edited by
Federica Napolitani Cheyne

WILD ROME
La vita selvatica della città eterna
Photos by Roberto Isotti, Alberto Cambone
Text by Micòle Ricci, Roberto Isotti
Paintings by Fulco Pratesi
HA Editore; 2021. 176 p.
ISBN 978-88-946261-0-0
€ 29,00.
[*Wild Rome. The wildlife of the eternal city*]

BESTIARIO INVISIBILE
guida agli animali delle nostre città
Marco Granata
Milano: Il Saggiatore; 2022.
317 p.
ISBN 978-88-428-3003-0
€ 22,00
[*Invisible bestiary: field guide to the animals of our cities*]

Introduced by Roberto Isotti, zoologist and conservation photographer, forwarded by scientific journalist Marco Cattaneo, with textual inserts by zoologist Bruno Cignini (for decades in charge of the animal communities of the Rome metropolitan area, chief officer at the Municipality of Rome) this artistic book provides a collection of lovely photos, depicting most of the commonest animal species observed in the Rome metropolitan areas, ranging from birds to snakes, insects, crabs, porcupines, dormice, hedgehogs, foxes, squirrels, spiders, bats, toads, turtles, salamanders and so on.

Photographs, one or two for each species, are provided by a condensed, short legend: which contains, in admirable few lines, the most relevant information regarding urban zoo-anthropological and zoo-geographical characteristics of the species, with some notes on their biology.

The book therefore provides a delightful picture of animal species having colonized metropolitan areas, while providing basic information on their ethology and conservation status. To readers of the biomedical field, this information may result crucial, given the recognized problems caused by zoonotic risk by (reciprocal) transmission between wild species inhabiting inner central zones of cities and the crowded human population. The recently emerged concept of One Health [1, 2], according to which terrestrial ecosystems represent an *unicum* and therefore the correct and efficacious safeguarding of human health, has to take into account any contact with nonhuman species.

Signed by biologist Granata, the second volume *Invisible bestiary: field guide to the animals of our cities* provides a much higher amount of information concerning urban-living species, with particular focus on insects (the first hundred pages are completely devoted to them) and deal with home-inhabiting species, including spiders. Also, birds and reptiles are considered vivaciously, and some amphibians and mammalian species as well. It is worth noticing that rarely considered free-living nonhuman beings, as wild rabbits, dormice, slow worms, green lizards, tenches, badgers, etc. are briefly mentioned. This latter represents an original and positive element of this volume, since most books on urban communities do not enclose animals difficult to be encountered, yet the possibility that any species may become a vector of disease is often unpredictable.

Overall, this volume follows a fluid narrative style, a kind of personal exploration by the author that accompany the reader throughout the animal communities inhabiting urban areas. Its weakness, possibly for officers of public health, may be some lack of systematicity in the way the various species are illustrated. In other words, this book does not represent an urban-life encyclopedia, nor a classical textbook for studying urban fauna. Nevertheless, its readability and the well-defined draws, allow to easily recognize wild urban species. The fact that it includes, as already mentioned, quite rare animals, makes this book a recommended reading for veterinarians, zoo-anthropologists, animal behaviour experts and urban planners as well. In a mature perspective of One Health, it represents a good cultural and operational framework for monitoring the likelihood of physical (or close) contact between *Homo sapiens* and the wide variety of animal species living in cities, large metropolitan areas but also towns, villages and very small settlement centers [3].

Links, already promising, between zoo-anthropology and preventive medicine should be further stabilized and strengthened.

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Publications from International Organizations on Public Health

Edited by
Annarita Barbaro

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS (FAO)

Thinking about the future of food safety - A foresight report. Rome: Food and Agriculture Organization of the United Nations 2022; 158 p. ISBN 978-92-5-135783-5. In this publication, the FAO food safety foresight programme provides an overview of the major global drivers and trends by describing their food safety implications including, among others, climate change, changing consumer behaviour and preferences, new food sources and food production systems, technological advances, microbiome, circular economy, and food fraud. The methodology applied is described in the introductory chapter, while the remainder of the publication consists of a compilation of short briefs describing emerging areas by providing a concise overview of the topics of interest in terms of what they are, why they are important from a food safety perspective, and how to take stock of the issues moving forward. Thinking about the future of food safety – A foresight report is targeted at a broad audience – from policymakers, researchers, food business operators, private sector to all of us, consumers as food safety is everyone's business.

The State of the World's Forests 2022. Forest pathways for green recovery and building inclusive, resilient and sustainable economies. Rome: Food and Agriculture Organization of the United Nations 2022; 166 p. ISBN 978-92-5-135984-6. Against the backdrop of the Glasgow Leaders' Declaration on Forests and Land Use and the pledge of 140 countries to eliminate forest loss by 2030 and to support restoration and sustainable forestry, the 2022 edition of The State of the World's Forests (SOFO) explores the potential of three forest pathways for achieving green recovery and tackling multidimensional planetary crises, including climate change and biodiversity loss. The three interrelated pathways are halting deforestation and maintaining forests; restoring degraded lands and expanding agroforestry; and sustainably using forests and building green value chains. The balanced, simultaneous pursuit of these pathways can generate sustainable economic and social benefits for countries and their rural communities, help sustainably meet increasing global demand for materials, and address environmental challenges. The State of the World's Forests 2022 presents evidence on the feasibility and value of these pathways and outlines initial steps that could be taken to further pursue them.

Assessment of agricultural plastics and their sustainability: a call for action. Rome: Food and Agriculture Organization of the United Nations 2021; 160 p. ISBN 978-92-5-135402-5. Most agricultural plastic products are single use and can persist in the environment long after their intended use. Degrading into microplastics, they can transfer and accumulate in food chains, threatening food security, food safety and potentially human health. This report presents the results of a study on agricultural plastic products used globally in a range of different value chains. The investigation covered all sectors under FAO's mandate: crop production, livestock, aquaculture, fisheries and forestry, including subsequent processing and distribution. The study assessed the types and quantities of plastic products, their benefits and trade-offs. Sustainable alternative products or practices were identified for products assessed as having high potential to cause harm to human and ecosystem health or having poor end-of-life management. The report is based on data derived from peer-reviewed scientific papers, governmental and non-governmental organization's research reports, as well as from industry experts, including relevant trade bodies. The report's recommendations were verified during extensive consultation and review with FAO and external experts.

INTERNATIONAL SCIENCE COUNCIL (ISC)

Unprecedented and unfinished: COVID-19 and implications for national and global policy. Paris: International Science Council 2022; 110 p. The object of this report is, firstly, to inform policy-makers and the public about the wide-ranging, long-term impacts on the entire global community from COVID-19, and to help elucidate the key decisions and actions that could shift the evolution of the pandemic towards more positive and equitable outcomes across societies. Secondly, it should inform planning and responses to other existential crises, whether pandemics, natural disasters, or the impacts of climate change. This report therefore provides an entry point to addressing the wide-ranging impacts of COVID-19 in two parts: part 1 sets the scene by outlining three plausible scenarios over a five-year time horizon that could conceivably emerge from the pandemic's cascading impacts, taking into account policy interactions and uncertainties that may affect outcomes. These scenarios are intended as simply as illustrations to help the global community plan for the future, by seeking to assess the broader impact of decisions taken today and the costs of inaction; part 2 then provides recommendations on how the global community can prepare for the future to mitigate the impacts of COVID-19 and address other existential crises that

we will inevitably face. The hope is that this should improve outcomes and provide many lessons for other global emergencies.

UNITED NATIONS ENVIRONMENTAL PROGRAMME (UNEP)

Frontiers report: noise, blazes and mismatches? - Emerging issues of environmental concern. Nairobi: United Nations Environmental Programme 2022; 59 p. ISBN 978-92-807-3917-6. Since 2016, UNEP's Frontiers Reports have cast a spotlight on emerging environmental issues and solutions for effective and timely responses. This year's edition, Noise, Blazes and Mismatches, looks at three concerns: noise pollution in cities, the growing threat of wildfires and shifts in seasonal events – such as flowering, migration and hibernation, an area of study known as phenology.

Harnessing nature to build climate resilience: scaling up the use of ecosystem-based adaptation. Nairobi: United Nations Environment Programme 2022; 142 p. ISBN 978-92-807-3952-7. The aim of this report is to highlight the opportunities for scaling up the use of EbA (Ecosystem-based Adaptation) to help put the world on a more climate-resilient and nature-positive pathway. This report is based on a detailed review of over 750 documents (including scientific papers, technical publications, policy briefs and project reports) as well as input from 59 global EbA experts from 30 organizations. It begins by examining the role of EbA in helping society adapt to climate change, while also contributing to biodiversity conservation, climate mitigation and sustainable development efforts. Then, it assesses the current state and trends in EbA implementation. Next, it explores the barriers that are currently slowing the widespread application of EbA in policy and practice. Finally, it provides a set of recommendations on how to enhance the scale and pace of EbA implementation to more fully harness the potential of ecosystems to deliver adaptation benefits.

EUROPEAN FOOD SAFETY AUTHORITY (EFSA)

European Food Safety Authority (EFSA), Luis Carrasco Cabrera and Paula Medina Pastor. **The 2020 European Union report on pesticide residues in food.** EFSA Journal 2022; 20(3): 7215, 57 p. The 2020 EU report on pesticide residues in food provides an overview of the official control activities on pesticide residues carried out in the EU Member States, Iceland and Norway. It summarises the results of both the EU-coordinated control programme (EU MACP) and the national control programmes (MANCP and is intended to provide information to the general and informed public and stakeholders with an interest and responsibilities in the food chain, in particular food supply chain operators. Its aim is to present a comprehensive overview of residue findings in food placed on the EU market, including possible non-compliances with legal limits, and to assess the potential exposure of consumers to pesticide residues. Furthermore, it gives recommendations on various possible risk management options where appropriate. The report's findings are systematically used by the Commission and the Member States to establish priorities for controls on food on the market, including the most relevant substance/commodity combinations to be included in the EU MACP regulation or in the national control programmes of Member States.

WORLD HEALTH ORGANIZATION (WHO)

Report of the technical consultation on measuring healthy diets: concepts, methods and metrics. Geneva: World Health Organization 2021; 73 p. ISBN 978-92-4-004027-4 (electronic version) ISBN 978-92-4-004028-1 (print version). This Report is the result of a consultation held from 18-20 May 2021 in order to promote increased communication, coordination, and collaboration to accelerate progress toward identifying or developing a parsimonious set of metrics for global monitoring of healthy diets. This technical consultation was organized by the WHO-UNICEF Technical Expert Advisory Group on Nutrition Monitoring (TEAM) and the Food and Agriculture Organization of the United Nations (FAO), with technical and logistical support from USAID Advancing Nutrition. This report provides a summary of the consultation presentations, working group contributions, discussions and recommendations. The report highlights three overarching topics addressed during the consultation: overview of global diet monitoring and prioritization of metric criteria and characteristics; methods, tools and metrics to measure diets; and definition and prioritization of next steps for identifying a global metric for monitoring of healthy diets.

Imagining the future of pandemics and epidemics: a 2022 perspective. Geneva: World Health Organization 2022; 65 p. ISBN 978-92-4-005209-3 (electronic version) ISBN 978-92-4-005210-9 (print version). This World Health Organization's 1st foresight report attempts to explore what the future of infectious threats might look like, using a short time horizon (3-5 years) to encourage immediate action. Inspired by the COVID-19 pandemic, the report sets out possible scenarios which are not predictions of the future, but instead invite us to imagine the different directions that the current and future pandemics might take and to expand the range of plausible futures. The scenarios are an opportunity to identify possible risks and solutions, discuss implications and propose actions aimed at preventing the occurrence or mitigating the impact of the current and future infectious threats.

World report on the health of refugees and migrants. Geneva: World Health Organization 2022;

344 p. ISBN 978-92-4-005446-2 (electronic version) ISBN 978-92-4-005447-9 (print version). This report is the first to offer a global review of health and migration and calls for urgent and concerted action to support refugees and migrants across the world to access health care services that are sensitive to their needs. It illustrates the pressing need to study and mitigate the root causes of migration and to radically reorient health systems to respond to a world increasingly in motion. Two of the key findings of the report are the virtual absence of comparable data across countries and over time on refugee and migrant health and the lack of disaggregation according to migratory status within global health data sets. The report shows critical gaps globally in data quality and knowledge and calls for investment in fit-for-purpose data, surveillance and monitoring to support robust evidence-informed policies and plans for implementation. If this vital data gap remains, refugees and migrants will continue to be left behind, and achieving the Sustainable Development Goals (SDGs) will be impossible. This publication outlines current and future opportunities and challenges and provides several strategies to improve the health and well-being of refugees and migrants. It is an advocacy tool for national and international policy-makers involved in health and migration.

Optimizing brain health across the life course: WHO position paper. Geneva: World Health Organization 2022; 106 p. ISBN N 978-92-4-005456-1 (electronic version) ISBN 978-92-4-005457-8 (print version). Many determinants are known to affect brain health at different stages of life. The World Health Organization (WHO) worked with a group of international experts, including people with lived experience of neurological disorders, to develop a position paper on optimizing brain health across the life course through an iterative process of desk reviews, consultations and peer review. The position paper provides a conceptual framework of brain health and brain health optimization describing the impact that optimizing brain health would have for the individual as well as for society, and offering practical policy solutions and future directions for the field. The position paper discusses how brain health can be optimized throughout life with actions across the following clusters of determinants: physical health, healthy environments, safety and security, learning and social connection, and access to quality services. Optimizing brain health can not only reduces the prevalence and burden of neurological disorders, but also improve mental and physical health overall and create positive social and economic impacts, all of which contribute to greater well-being and help advance society, irrespective of the presence or absence of disorders.

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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.

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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.

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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.

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