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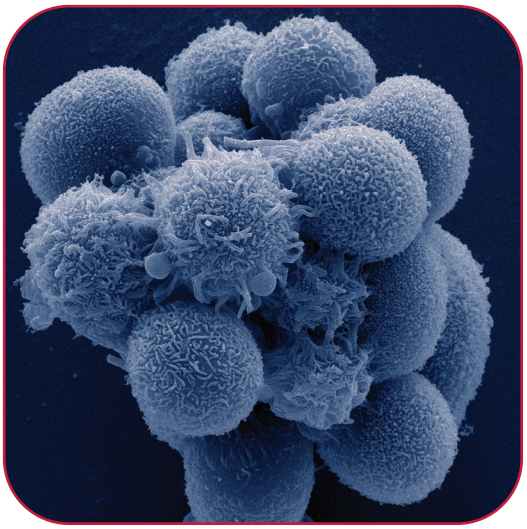
The cover image shows the different cell types in an in vitro lung cancer organoid visualized by scanning electron microscopy. The image is provided by the Microscopy Area, Core Facilities, in collaboration with the Department of Oncology and Molecular Medicine, Istituto Superiore di Sanità, Rome, Italy.



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COVID-19 in meat plants: a survey framed within a Target Prevention Plan, in Italy

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Abstract

Background. During the COVID-19 pandemic, several outbreaks have been recorded worldwide in industrial slaughterhouses and meat-processing plants. Competent Italian health authorities at regional and provincial levels agreed on a risk-oriented control plan.

Methods. Advocacy actions were activated, targeting meat plant managers and related food business operators. A questionnaire focused on the inventoried risk factors from literature was developed and administered voluntarily to interested stakeholders. In addition, an outbreak questionnaire was proposed to the prevention department of local health units.

Results. From 2021 to 2022, 333 advocacy and 24 outbreak questionnaires on 4,765 inventoried plants were collected. The lack of awareness in updating the Risk Assessment Document for COVID-19, non-instrumental body temperature checks at the entrance, working force from different subcontractors, poor hygiene in shared places, and insufficient ventilation were the main critical points recorded.

Conclusions. Results provide a *post hoc* review with an eye toward future zoonotic pandemics.

Key words

- COVID 19
- meat plants
- target prevention plan
- survey

INTRODUCTION

During the COVID-19 pandemic, it has become increasingly clear that some occupational non-healthcare settings could be vulnerable to outbreaks, such as meat plants (slaughterhouses, meat processing, and cutting plants), where the combination of environmental, social, and working condition factors represent a driver for contagiousness among workers [1] and extend in some cases to relatives in residential settings [2]. Since 2020, rapid and large-scale COVID-19 outbreaks in high-throughput industrial meat plants with a working force of up to 20,000 workers have been reported in the United States, Canada, and the European Union [3-5]. Epidemiological investigations have increasingly elucidated the risk factors that facilitate entry and persistence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the workspace and its spread among workers, such as: a) workforce recruitment and turnover, collective transport systems to/from the workplace, and housing [6-8]; b) workplaces with poor ventilation and insufficient fresh air exchange; c) presence of aerosol/vapours able to transport the virus well above the 1-2 m distance prescribed among workers; and d) cool surfaces where virus particles could condense and persist for days [9]. As industrial slaughterhouses are critical in ensuring the meat supply chain from farm to fork, COVID-19 and other disease outbreaks in such essential settings for the food chain represent a food insecurity factor. Postponing the slaughtering of poultry and pigs for only a few days can compromise animal

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welfare and meat quality, making meat production less cost-effective and causing food waste. In addition, the presence of the SARS-CoV-2 genome on the surface of packaged meat [10, 11] has been a matter of international import/export dispute within the World Trade Organization [12], thus causing food chain disruption.

In this study, we aim to describe the results of a targeted COVID-19 prevention plan in meat plants in Italy, set up at the end of 2020. Such a target prevention plan designed based on the first epidemiological evidence in Italy and abroad has been proposed to regional and provincial health authorities for adoption and implementation despite the urgent priorities in the healthcare territory setting determined by the evolution of the pandemic in Italy.

In Italy, preventive medicine in occupational settings has been assigned to Regions and Provinces under the coordination of the Italian Regions Conference, technically supported by the Working Group (WG) on "Health and Safety at Working Places". This WG has the mandate to propose the activation of the so-called "Target Prevention Plans" to the Regions and Provinces; these plans consist of an advocacy action with the stakeholders to reach priority and risk-oriented targets of health prevention in the working places.

Figure 1 illustrates the activation steps of this plan in the context of the recorded pandemic curve in healthcare and non-healthcare workers in Italy from official data (https://www.epicentro.iss.it/coronavirus/sars-cov-2-dashboard).

MATERIALS AND METHODS

Set up of questionnaires for COVID-19 occupational health in meat plants and study design

Within this framework, in April 2020, the Istituto Superiore di Sanità (ISS, Italian National Institute of Health), a technical scientific institution of the Italian Health System, contacted the local health unit of the Bari-Apulian region, which reported the first COVID-19 outbreak in a meat plant [13]. Based on the evidence from the field and those reported in the scientific literature, an advocacy webinar was organised in September 2020, with the involvement of meat plant associations and national, regional, and provincial authorities, to share evidence and experiences. The outcome was the proposition of three different tools to support a targeted COVID-19 prevention plan in meat plants: 1) a questionnaire addressing the critical control points to be considered for the prevention and risk assessment of COVID-19; 2) a second questionnaire addressed to local health authorities for the reporting of COVID-19 outbreaks; and 3) a harmonised checklist for official inspection by competent local authorities at meat plants. After the first on-field validation, the first two questionnaires were published with Italian and English versions in the COVID-19 Reports edited by Istituto Superiore di Sanità [14] (see *Supplementary Material available online*). A descriptive and observational study design based on voluntary participation to the initiative by private meat plants owners was then set up. Italian Meat Plant Associations were asked to inform their members of the opportunity to participate in such surveys voluntarily. Online questionnaires were made freely available to stakeholders via the Google Modules platform under the national General Data Protection Regulation (GDPR). The responses to the advocacy and outbreak questionnaires were collected from the end of December 2020 to the end of December 2022. The distribution of responses (frequency analyses) were reported as results in this study. In *Figure S1 available online as Supplementary Material* the flow diagram illustrates the network between the main health-related stakeholders and COVID-19 prevention activities in workplaces in Italy.

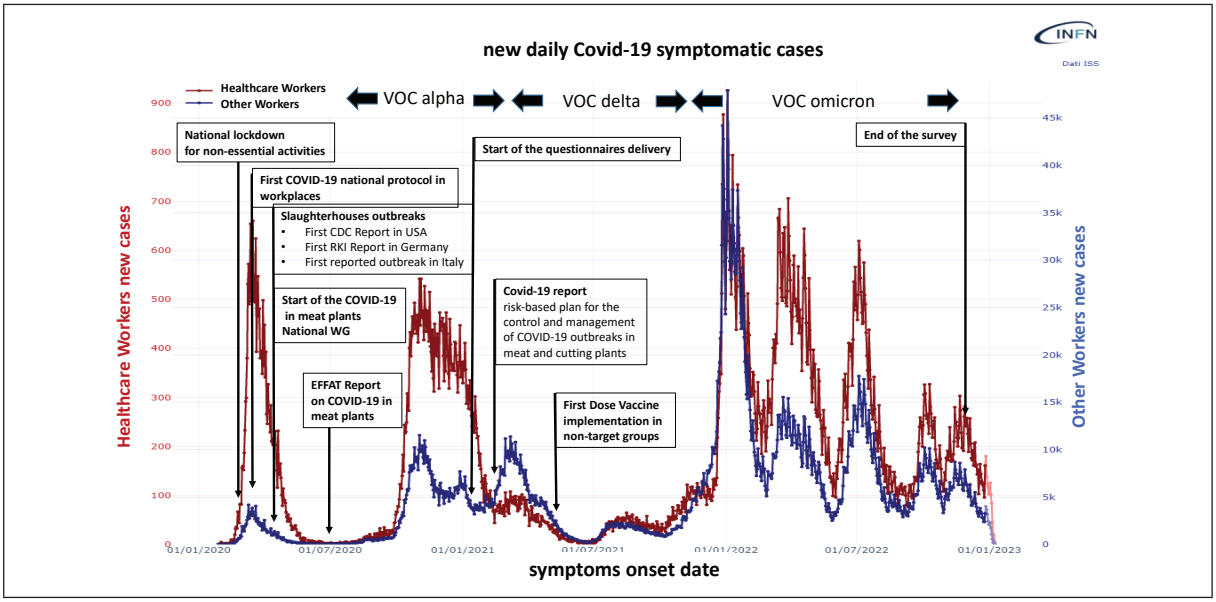

Figure 1
COVID-19 pandemic curve in Italian workers, along with the events leading to the activation of a target prevention plan in meat plants, in Italy.

RESULTS

Critical control points to be considered by meat plant management

Meat plant profiling and workforce

During the two-year timeframe (2020-2022), we recorded 333 completed and validated COVID-19 awareness questionnaires from 4,675 slaughterhouses and meat cutting and processing plants inventoried at the central level by the competent authorities (https://www.dati.salute.gov.it/dati/dettaglioDataset.jsp?menu=dati&idPag=8). The platform recorded submitted modules, only: no information about access number and time spent on the platform were available. The geographical provenance of such modules largely acknowledges the Italian Regions/Autonomous Provinces that have explicitly declared their interest in such a Targeted Prevention Plan. Lombardy (N=140); Veneto (N=95); Trentino (N=37); Calabria (N=29); Apulian (N=11); Piedmont (N=9); Emilia-Romagna (N=6); Sardinia (N=3); Lazio, Sicily, and Umbria each (N=1). We report different plant settings that, in some cases, acknowledge the presence of a cutting plant associated with the slaughterhouse and activities addressed to different animal species in the Supplementary materials (*Table S1 available online as Supplementary Material*).

Most of the responding plants indicated that their operations were not extended on all 6-7 working days. This implies that the workforce was mostly unshifted on the same working day (N=302; 91%). Two and three working shifts/d were recorded for 5% and 2% of the plants, respectively. Missed answers =2%. The details are presented in *Table 1*. Non-permanent staff (cooperatives, third parties, and autonomous workers) were present in 42% of the companies (N=139). Cooperatives are regularly present in 125 plants. Of these, 52, 36, 18, 10, and 9 plant managers engaged 1, 2, 3, 4-5, and ≥6 cooperatives, respectively. Non-permanent staff are generally spread across different activities, from livestock handling to cleaning and packaging. The overall number of workers (permanent and non-permanent) in the responding plants is reported in *Table 1*.

Table 1
Working days per week (left) and number of workers in those plants participating to the survey (right)

Working days	S	PC	S+PC	Total	Workers	Plants
1	54	8	4	66	**N**	**N**
2	61	7	4	72	**1-5**	105
3	15	8	2	25	**6-10**	52
4	14	7	3	24	**11-25**	55
5	45	60	7	112	**26-50**	31
6	13	13	7	33	**51-100**	15
7	1	-	-	1	**>100**	42
Total	203	103	27	333	**missed**	33

S: slaughterhouse; PC: processing/cutting plant; S+PC: slaughterhouse and processing/cutting plant; N: number; missed: data not available.

Preventive measures at the workplace and personnel management

All responding plant managers declare that workers have been properly informed about the preventive measures in case of suspicion of COVID-19 (such as staying at home if symptomatic, calling the appointed physician of the healthcare system, alerting the plant staff if symptomatic at the workplace and avoiding close contact, and following rules to prevent contagiousness at the workplace). A regular instrumental check of the body temperature at the entrance of the plant was reported in 73% of the answers (243/333). Fifty-six (17%) required self-declaration, while one omitted this procedure. A total of 10% had missed or inconsistent answers. Separate and time-shifted entry and exit for workers and visitors were present in 92% of the cases (305/333), whereas dedicated toilets were present in only 37% (123/333).

Visitors were not informed about preventive measures in 19/333 cases (9%), and checks on the appropriate and regular application of preventive measures were not fully implemented in 123/333 plants (37%). Regular cleaning and sanitisation of shared places, changing rooms, and canteens were in place in 95% of the plants, with daily frequencies in 59% of cases, three/four times a week in 15%, and once/twice a week in 15%. The remaining 1% reported cleaning and sanitisation intervals of >7 days.

Accessible and easy-to-find handwashing dispensers were declared in 99% of the prevention questionnaires. Personal Protective Equipments (PPEs) were declared always available in 83% (278/333) of the cases when inter-personnel distances were less than 1 meter, according to the national guidelines issued by the Italian Government on March 20 (Decreto del Presidente del Consiglio dei Ministri 11 marzo 2020), and the technical updated on April 2020 by the National Institute for Insurance against Accidents at Work (Istituto Nazionale per l'Assicurazione contro gli Infortuni sul Lavoro INAIL), a public, non-profit entity safeguarding workers against physical injuries and occupational diseases (see *Supplementary Material available online*) (https://www.inail.it/cs/internet/docs/alg-pubbl-rimodulazione-contenimento-covid19-sicurezza-lavoro.pdf). In 16 cases (5%), because the worker's distance was greater than 1 m, the answer was negative. Missed or incorrect answers accounted for 10% of all answers. PPEs were reported to be changed daily in 99% of the cases, and information and instructions about its proper use/wearing were present in 95% (315/333). Details about the PPE used in the plants according to the workforce are present in 293 questionnaires are shown in the *Table S2 available online as Supplementary Material*.

Appropriate workplace organisation to maintain the prescribed minimum distance of 1 m between workers was implemented in 53% (173/333), whereas in 41% (135/333), the implementation of such measures was reported to be not necessary. The remaining 6% of the plants provided either negative or missing answers.

The presence of physical barriers between workers was present in 116 answers (35%), while in 50% of the cases, the absence of a specific need was declared.

The time zones at the entrance and exits were designed to meet the 1 m distance requirement in 50% of the plants (168), while in 143, this was not the case. Negative answers accounted for 7% of the responses (23). Staggered shifts to the canteen and shared places were present in 87% of the cases (290).

Smart working was implemented in 63 plants (19%) for non-essential activities; a personnel turnover plan to reduce contact was implemented in 71 plants (21%), and not in the remaining 263. Social valves in case of absence from work due to COVID-19 were present in 86 plants (26%). In 164 cases (49%), workers were asked to take holidays, with negative or missing answers for the remaining 25%.

The activation of a committee (with occupational health responsibilities and trade union representatives) (*Figure S1 available online as Supplementary Material*) in charge of verifying the application of COVID-19 preventive measures was noticed in 171 plants (51%), and the COVID-19 update of the mandatory document on risk assessment was noted in 83% of the answers.

Ventilation and vapour/aerosol formation

In *Table 2*, we report the recorder answers to the questions related to ventilation according to the different plant premises.

Regular maintenance of heating, ventilation, and air conditioning (HVAC) filters is declared in 90% of the plants, whereas records of ventilation maintenance are reported in only 50%.

In 287 plants (86%), high-pressure water jets were used for cleaning workspaces. Among these, 65 plants (20%) reported performing such operations in the presence of workers. In pig slaughterhouses, scraping was performed using hot water baths (N=94), steam and water (N=7), singeing (N=52), brushing and showering (N=43), and infrared beams (N=7). The missing responses accounted for 33. In scraping activities where water was used, 80 answers reported such procedures in the presence of workers. The distance from the vapour/aerosol source was <1 m in seven plants, >1<2 m in 38, and >2 m in 35. Aspiration systems were used in place of the 59/89 plants. In poultry slaughterhouses, the use of water as a proxy for vapour generation for animal electric stunning is reported in 23/32 plants. Nebuliser systems to improve animal welfare in the pre-slaughter area and lairage were present in 42/230 slaughterhouses and in nine cases in the presence of workers.

Table 2

Number of natural ventilation *vs* mechanical heating, ventilation, air conditioning (HVAC) in the premises of 333 meat plants: between (brackets), the number of premises with HVAC air recycling >30%

Premise	Ventilation		
	Natural	HVAC	HVAC Not reported
Working area	234	91 (26)	8
Offices	306	8 (2)	19
Changing room	288	25 (7)	20
Canteen	156	17 (6)	160
Shared places	245	24 (7)	64

Results from outbreak questionnaires

Within the 2021-2022 time frame, 24 validated outbreak reports were voluntarily received from the officers of the preventive departments of local health units. *Table 3* reports the descriptors of the outbreaks; the corrective measures taken are shown in *Table S3 available online as Supplementary Material*.

DISCUSSION

The main objectives of the questionnaires were: a) to provide a technical guidance document to harmonise and risk-orient the activities of the local Health Prevention Departments on the national territory; b) to increase the awareness of meat plant managers and related food business operators to prevent COVID-19 in meat plants in an evidence based way; and c) to cover the knowledge gaps about the main risk factors in meat plants at national level. Despite meat plant companies reporting the implementation of measures to address COVID-19 in accordance with national guidelines, such as promoting physical distancing in communal areas, installing barriers, and mandating the use of masks, epidemiological evidence indicates that the risk of COVID-19 transmission to workers in large meat plants is significantly higher than that for the general population of the district/state/region [15].

Consequently, as a first step towards the initiation of a targeted prevention plan at the regional/provincial level in Italy, it seemed worthwhile to propose an advocacy questionnaire to stakeholders in meat plants and to provide feedback on the information gathered. Although not generalizable to all on-field situations, the results from advocacy questionnaires offer insights into the occupational health risk faced by meat and poultry workers during the COVID-19 pandemic. These findings are consistent with those from identified studies and other research-based sources on various topics relevant to our paper. The main feature of Italian slaughterhouses and processing/cutting plants is their large numbers (N=4,675 officially registered). Among them, approximately 20 plants have a working force from 500 up to 2,000, and in the poultry sector, six industrial plants account for 90% of the national production. Within this framework, the reduced workforce in most of the plants, along with activities not conducted throughout the week (*Table 1*), represent mitigating factors with respect to COVID-19 spread and related outbreaks reported in large industrial plants as higher worker density coupled with longer stay in the workplace because of overtime, as already noted by Dyal *et al*. and Waltenburg *et al*. [3, 4]. However, the widespread presence of plants in Italy hampers the capillary monitoring activity of the preventive COVID-19 procedures in place. It is worth noting that during the pandemic (*Figure 1*), the professional resources of the prevention departments of the local health unit in charge of health prevention in the workplace were preoccupied with other health priorities such as contact tracing, testing, and vaccination. Therefore, advocacy activities based on a targeted

Table 3
Descriptors of the COVID-19 outbreaks recorded in Italian meat plants, on voluntary basis

Province	Species	Workers (N)			Outbreak dd/mm/yy			Tested workers and results				Report dd/mm/yy
		Permanent	S_C	T_W	Start	End	Days	Tested	Positives	%	Agencies (N)	
Trento	S (S)	210	2	40	09/09/20	02/10/20	22	169	33	20	3	04/12/20
Napoli	S (P)	195	2	0	28/08/20	10/10/20	41	195	87	45	2	15/12/20
Trento	S (S)	206	3	71	08/09/20	23/09/20	15	140	33	24	4	05/01/21
Trento	CP (S)	119	4	71	01/09/20	23/09/20	22	122	81	66	5	05/01/21
Trento	S (S)	36	2	42	16/09/20	05/10/20	19	36	25	69	3	05/01/21
Trento	CP (na)	35	5	71	04/09/20	23/09/20	19	35	13	37	3	05/01/21
Bari	S (C, S, SR, H)	13	0	0	03/11/20	30/11/20	27	15	4	27	1	14/01/21
Bari	S (C, S, SR, H)	50	0	0	13/11/20	20/12/20	37	50	6	12	1	03/02/21
Treviso	S (C, H)	19	5	26	20/11/20	27/11/20	17	18	0	0	1	12/02/21
Bari	S (C, S, SR)	438	7	71	23/04/20	19/05/20	26	487	112	23	7	26/03/21
Treviso	S (C)	180	5	50	17/11/20	10/12/20	23	43	20	47	1	27/04/21
Venezia	S (P)	122	2	6	28/10/20	10/01/21	12	180	49	27	2	19/07/21
Ragusa	S (P)	205	2	na	05/11/20	02/12/20	27	205	12	6	1	15/09/21
Ragusa	S (P)	250	2	na	30/03/21	30/06/21	90	57	8	14	1	16/09/21
Mantova	S (S)	350	4	65	29/06/20	15/07/20	16	350	50	14	5	04/10/20
Mantova	S (S)	184	5	56	10/07/21	30/07/21	20	184	10	5	3	19/01/21
Mantova	S, CP (S)	350	2	60	10/06/21	25/06/21	15	123	38	31	2	30/09/21
Mantova	CP (na)	15	1	17	30/06/20	13/08/20	44	15	7	47	2	04/11/21
Mantova	S, CP (C, S)	150	1	6	22/02/21	05/04/21	44	152	5	3	1	29/09/21
Mantova	S (S)	270	3	40	16/08/21	24/08/21	8	8	1	13	3	20/10/21
Mantova	CP (na)	400	2	5	26/07/21	16/08/21	20	30	6	20	1	27/09/21
Mantova	S (C)	270	6	70	04/04/20	29/10/20	25	267	47	18	4	05/11/21
Padova	S (P)	45	2	20	22/10/20	09/11/20	18	27	9	33	1	10/08/21
Reggio C.	S (C, S, SR, H)	7	0	0	01/01/21	30/06/21	180	7	7	100	1	26/09/22

S_C: subcontractors; T_W: temporary workers; na: not available; S: slaughterhouse; CP: processing and cutting plant; C: cattle; S: swine; P: poultry; SR: small ruminants; H: horses; agencies: N of companies recruiting temporary workers; N: number.

prevention plan seem more appropriate and practicable. The results presented in this paper do not cover all the initiatives taken to prevent and manage COVID-19 outbreaks in meat plants in the national territory. For instance, the Emilia Romagna Region independently activated cultural mediators to inform and form non-Italian workers about procedures to be adopted to lower the risk (such as quarantine period back from holidays in the country of origin, priority in the diagnostic tests, and then, support for vaccination), as reported in a Canadian-Ontario case [8]. The shared knowledge of such preventive measures and actions in a webinar organised in September 2020 by Istituto Superiore di Sanità, with the participation of representatives of meat plant associations and health stakeholders, contributed to the questionnaire setup.

The participants (N=333) in the advocacy questionnaire represented 7% of the registered plants in Italy and were mostly located in those districts whose regional/province health authorities agreed to activate targeted prevention (Lombardy, N=140; Veneto, N=95), according to the flow diagram reported in *Figure S1 available online as Supplementary Material*. Support at the local level has also been determined by the high social and economic benefits of processed meat products (such as ham and salami) from such geographical areas. The reduced dimensions of meat plants in Italy may have contributed to a reduced perception of the relevance of the initiative, thus limiting voluntary participation in the survey. In the United States, a survey on COVID-19 in slaughterhouses reported the active participation of 28 out of 50 states (56%), accounting for an average of 3,500 meat plants with an overall workforce of 525,000 workers [4].

Despite only 7% adherence to the Italian initiative, the answers recorded from the advocacy questionnaire

reflected the presence of structural, environmental, and management risk factors, as reported in the literature [16-18].

Workforce management, with non-permanent staff (cooperatives, third parties, and autonomous workers) present in 42% of the companies (N=139), indicates the risk of the formation of non-homogeneous teams as a factor that could facilitate contagiousness within the same work shift. This critical factor found feedback in 24 reported outbreaks, where, on average, three cooperatives (min/max=0-6) were present (*Table 3*). In personnel management, a combined risk indicator for the entrance and spread of COVID-19 among workers includes the number of animals slaughtered/processed daily, the number of time shifts per day, and data on the external workforce. Within this framework, the answers about the instrumental check of body temperature at the entrance recorded in only 27% of the plants represent another weak point of the preventive action, especially in the presence of a pandemic R_t well >1 in the general population. The mitigation of risk in the workplace also relies on appropriate information and formation of the workers, along with the verification of whether the preventive measures are correctly put in place, and last but not least, the activation of COVID-19 illness social valves (in our survey, present in 26% of plants only). Again, the relevance of such factors has been highlighted by the evidence from outbreak management (*Table S3 available online as Supplementary Material*), where the plant responsibilities had to reinforce the checks, redraft the entrance and exit paths of workers and external personnel, improve information and formation (42% of the reported outbreaks), and provide devices for better personal hygiene (38% of the cases).

The overall need for advocacy activity towards the real adoption of COVID-19 preventive measures and the check of their correct application by meat plant management is highlighted by the recorded delay in the establishment of the meat plant committee formed by occupational safety responsibilities and trade union representatives in charge of this task (51% of positive answers), despite the COVID-19 update of the mandatory document on the risk assessment recorded in 83% of the answers (*Figure S1 available online as Supplementary Material*). In this respect, the recorded generation of vapour and aerosols in some working areas according to each plant structure should not be overlooked in the updated plant document on risk assessment. This is because it has been demonstrated that SARS-CoV-2 can reach distances well over the minimum prescribed by workers (1-2 m) in the presence of vapours and aerosols, as reported in industrial slaughterhouses in Germany [19]. This represents a risk factor, especially if vapour/aerosol-exposed workers do not wear adequate PPEs (*Table 2*).

Ventilation with adequate natural air exchange represents another preventive measure stressed in the advocacy questionnaire, as it has been demonstrated that the relative percentage of CO_2 can be used as a proxy for insufficient indoor air exchange [16, 20]. When air is recycled, a recycling percentage >30% may be inadequate for prevention, particularly when adequate filtering systems are not in place. A high percentage of recycled air may acknowledge seasonal trends as a matter of energy savings policies to keep the room temperature adequate for the specific activities of the working area (e.g., chilling or air warming during summer or winter). For this purpose, structural modifications of ventilation were considered in six out of 24 cases in the management of outbreaks (*Table S1 available online as Supplementary Material*). Such a measure has been associated with increased interworker distance in 17% of the cases. Finally, in the presence of an HVAC system, the air flux in the working area must be addressed correctly.

Considering the reported outbreak dates, it is worthwhile to fix July 20 as a discriminant for the COVID-19 vaccination campaign extended to the Italian general population (including meat plant workers). Before this date, vaccines were administered to fragile persons and the most exposed worker categories, such as those working in healthcare settings, schools, and police forces. We registered 14 outbreaks before and 10 outbreaks after the start of the COVID-19 vaccination campaign extended to the Italian general population. This means that vaccination alone could not represent effective prevention in such settings, but it should accompany all the supporting preventive measures, especially when the workforce is largely non-autochthonous [8].

The outbreaks lasted on average 26 days (one outlier data of 180 days excluded) (*Table 3*), with an overall 26% positivity rate among workers, in line with the prevalence reported in other studies: 3-24% from Waltenbur *et al*. [4], 18% from Di Leone *et al*. [13], 26% from Steinberg *et al*. [21], 30-40% from Vanderwaal *et al*. [22], 12-16% from Pokora *et al*. [9], 33% from Walshe *et al*. [16], and 36% from Finci *et al*. [17]. Of interest are the five outbreaks reported in the Trentino-Alto Adige Province, where almost the same cooperatives were turned over among the plants involved (Dario Huber, personal communication).

Among the reported outbreaks, the description of the widest Italian outbreak that occurred in a poultry slaughterhouse and cutting plant (August to September 20) was missing. From publicly available information, as reported on the website of the Veterinary Trade Union of the Veneto Region, positivities included 200/675 workers belonging to 12 different nationalities, and the massive and intensified screening with rapid tests allowed a 50% reduction in the activities, instead of their full withdrawal (https://www.sivempveneto.it/covid-19-focolai-in-impianti-di-macellazione-il-sivempveneto-massima-attenzione-alla-sicurezza-dei-veterinari-ufficiali-protezioni-e-screening-costanti/).

This evidence underscores the necessity of establishing standardized actions, akin to those implemented for healthcare workers, to enhance the protection of worker health in meat plants, thereby minimizing associated social and economic consequences. *Figure 2* shows the cross-cutting aspects of the prevention activity at meat plant level for COVID-19 with Sustainable Development Goals Nos. 1, 2, 3, 8, 9, 10, 12, and 17 proposed by the United Nations. Consequently, as a first step towards the initiation of a targeted prevention plan at the regional/provincial level in Italy, it seemed worthwhile to propose an advocacy questionnaire to stakeholders

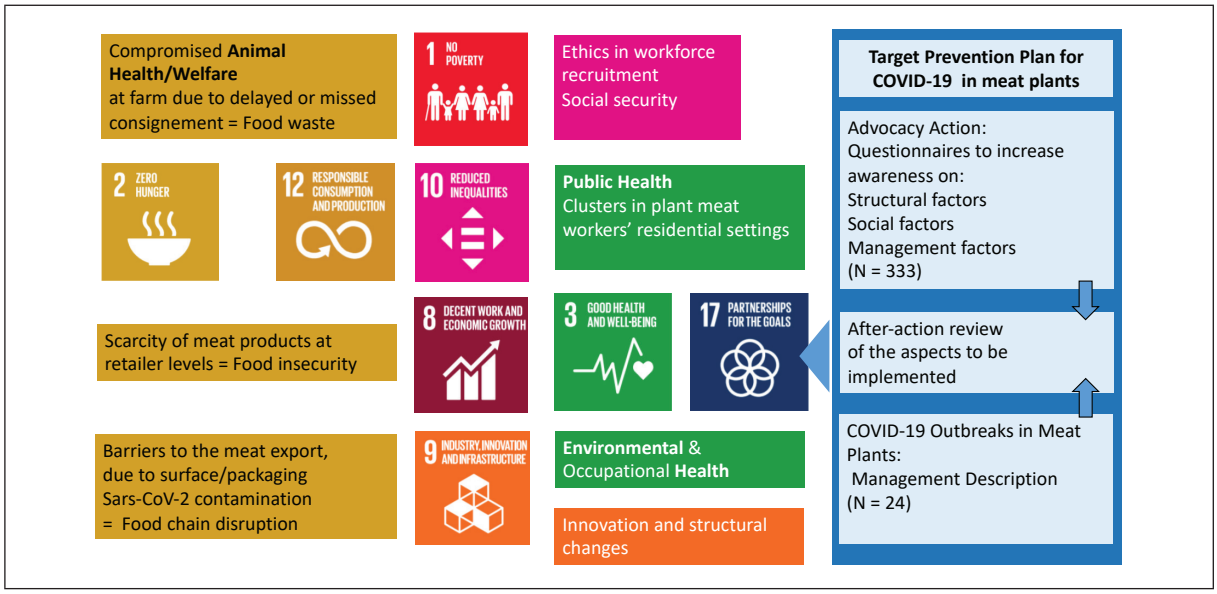

Figure 2
Impact of the activation of a target prevention plan in meat plants on the Sustainable Development Goals Nos. 1, 2, 3, 8, 9, 10, 12, and 17 proposed by the United Nations.

in meat plants and to provide feedback on the information gathered. Although not generalizable to all on-field situations, the results from advocacy questionnaires offer insights into the infectious challenges faced by meat and poultry workers during the COVID-19 pandemic. These findings are consistent with those from identified studies and other research-based sources on various topics relevant to our paper [23]. Key lessons learned from this initiative can be summarized as follows:

- *regional and provincial prioritization*: the proposal for the activation of a COVID-19 prevention plan in meat plants in Italy was not uniformly selected as a priority by all Regional and Provincial Health Authorities. This decision appears to be influenced by the fluctuating COVID-19 pandemic curve in different territories. Consequently, the responses received from the advocacy questionnaire may not reflect the outcomes following the full activation of targeted prevention plans at the local level;
- *voluntary participation limitation*: the voluntary nature of meat plant owners' participation in the initiative posed limitations on the representativeness of the results at the national level. Additionally, this voluntary approach hindered the ability to test a priori hypotheses or draw inferences from the data, as the questionnaire was completed on a voluntary basis;
- *complexity of advocacy questionnaire*: the complexity of the advocacy questionnaire, designed to consider a combination of various environmental, social, and working condition risk factors specific to meat plants, may have restricted participation to the most motivated stakeholders. The absence of specific guidelines for the meat plant sector might have contributed to this limitation.

These observations highlight the importance of addressing regional variations in priorities, considering strategies to enhance participation, and refining questionnaire design for a more comprehensive understanding of the challenges associated with COVID-19 prevention in meat plants

CONCLUSIONS

In conclusion, the proposal for a Target Prevention Plan on COVID-19 in meat plants, supported by specific guidelines and advocacy questionnaires, stands as a valuable tool to standardize and risk-align the activities of health prevention departments across the national territory. The integration of results from both advocacy and outbreak questionnaires facilitates a comprehensive assessment, providing stakeholders with insights into critical points for implementation in terms of preparedness. This process contributes to an effective after-action review for essential work settings in the food chain, beyond those directly associated with healthcare services.

Recognizing COVID-19 as an "emerging infectious disease of probable animal origin", meat plants and related settings emerge as multifaceted environments encompassing health, culture, society, economy, and food safety/security. Within this context, the adoption of "One Health" preventive and cost-effective approaches is not only feasible but also essential, as underlined from recent recorded cases of highly pathogenic avian influenza in dairy cattle farms, in the USA (https://www.fda.gov/food/alerts-advisories-safety-information/updates-highly-pathogenic-avian-influenza-hpai). These strategies can enhance overall resilience and responsiveness to emerging infectious diseases, reinforcing the interconnectedness of human, animal, and environmental health.

Conflict of interest statement

The Authors declare no conflict of interest.

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Children's diet assessed with the Mediterranean Diet Index: the finding of new eating habits and their impact on a cohort of Italian children

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Abstract

Objectives. Mediterranean Diet (MD) has been inversely associated with many diseases: it reduces total mortality and lowers cardiovascular risk. Despite the known benefits of MD, variations of dietary habits have occurred in recent years especially in young people. The aim of our study is to evaluate MD adherence in a cohort of Italian children and adolescents living in Southern Italy.

Methods and results. Adherence to MD was evaluated with the Mediterranean Diet Index (KIDMED). Sex, age, and anthropometric measures were recorded on a population of 132 children; of those 71.2% showed poor adherence to MD, 26.5% average adherence and only 2.3% good adherence. Higher prevalence of poor adherence was recorded in obese children and there was statistically significant inverse correlation between age and adherence score.

Conclusions. Our results highlight low adherence to MD in a cohort of Italian children. These findings support the importance of monitoring dietary habits, especially in adolescents.

Key words

- mediterranean diet
- dietary modifications
- child nutrition
- adolescent nutrition

INTRODUCTION

The term "Mediterranean Diet" (MD) is inspired to all the traditional eating habits of people living around the Mediterranean Basin. It is characterized by high consumption of fresh fruit, vegetables, cereals, legumes, moderate quantity of fish, eggs, cheese, dried fruit, nuts and low amounts of red meat and processed food. The main source of fat is supplied by the extra virgin olive oil. This dietary pattern contains a low dose of saturated fatty acids and high dose of monounsaturated fatty acids, a balanced ratio of polyunsaturated fatty acids, omega-6 and omega-3, high content of complex carbohydrates, fibres and antioxidants [1]. Previous studies have demonstrated an inverse correlation between MD and many diseases, including type 2 diabetes, obesity and metabolic syndrome, cardiovascular and cerebrovascular diseases, neurodegenerative diseases, and certain cancers [2, 3]. For its beneficial effects, in November 2010 MD has been recognized by United Nations Educational, Scientific and Cultural Organization (UNESCO) as "Intangible Cultural Heritage of Humanity". In the last years, with the urbanization phenomenon, dietary patterns different from the MD have increased, especially in adolescents. The "Western diet", a dietary pattern rich in saturated fat, refined grains, simple carbohydrates, and processed foods has replaced healthy food choices in the last years. This phenomenon is closely connected with the high prevalence of pediatric overweight and obesity worldwide [4]. In 2004, Serra-Majem *et al.* developed the KIDMED score (Mediterranean Diet Quality Index for children and adolescents), a nutritional index validated in several languages that evaluates the adherence to MD and the quality of diet in children and adolescents [1]. Several studies have explored adherence to MD in pediatric populations living in Mediterranean countries, but few papers concern Italian children [5, 6].

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The aim of this study is to assess the correlations existing between adherence to MD and anthropometric measures on a cohort of children living in Southern Italy.

MATERIALS AND METHODS

Recruitment

This study was conducted between April and September 2023 in the Pediatric Department of "Casa Sollievo della Sofferenza", in San Giovanni Rotondo (FG), Southern Italy. The analysed population included 132 children and young people (52.3% females and 47.7% males). The population age ranged from 2 to 17.9 years, mean age 11±3.4 years. The total cohort included healthy children, without important comorbidity. Informed consent was obtained from a parent or caregiver before participating to the study.

Anthropometric examinations

We collected anthropometric measures of all children in the same condition, as they were wearing underwear and T-shirt. Body weight was measured to the nearest 0.1 kilogram (kg) using an electronic scale. Height was measured with a standard stadiometer to the nearest 0.5 centimetre (cm) during maximal expiration. Body Mass Index (BMI) was used to evaluate nutritional status. Children were stratified according to sex and age-specific BMI using the World Health Organization (WHO) growth charts in: underweight (less than the 5th percentile), normal weight (5th percentile-85th percentile), overweight (85th percentile-97th percentile) and obese (97th percentile or greater) [7].

Waist circumference was measured on the horizontal plane midway between the lowest border of rib cage and the upper border of iliac crest, at the end of normal expiration, with the adolescents standing erect and relaxed with arms at the sides and feet close together [8]. Waist to height ratio (WHtR) was obtained by dividing waist size by height in centimetres and deemed as an indicator of the distribution of body fat. Values of WHtR higher than 0.5 is considered as abdominal obesity [9].

Adherence to MD

We evaluated children's adherence to MD with the KIDMED score proposed by Serra-Majem *et al*. This questionnaire is composed of 16 dichotomous items related to different aspects of MD, each item can be assigned a value of +1 or -1, obtaining a maximum final score of +12. The items considered are: 1. takes a fruit or fruit juice every day (+1); 2. has a second fruit every day (+1); 3. has fresh or cooked vegetables regularly once a day (+1); 4. has fresh or cooked vegetables more than once a day (+1); 5. consumes fish regularly, at least 2-3/week (+1); 6. goes >1/week to a fast-food restaurant (-1); 7. likes pulses and eats them >1/week (+1); 8. consumes pasta or rice 5 times or more per week (+1); 9. has cereals or grains (bread, etc.) for breakfast (+1); 10. consumes nuts at least 2-3 times/week (+1); 11. uses olive oil at home (+1), 12. skips breakfast (-1); 13. has a dairy product for breakfast (+1); 14. has commercially baked goods or pastries for breakfast (-1); 15. takes two yoghurts and/or some cheese (40 g) daily (+1); 16. takes sweets and candy several times every day (-1) [10].

These items concern the daily consumption of fruits, vegetables, virgin olive oil, pasta/rice, milk and its derivatives; the weekly consumption of fish, legumes, nuts, cereals, and whole food; low consumption of red meat, commercial and processed foods, eggs, butter, sausages, fried and sweet food; the tendency to skip breakfast or eat fast food. Scores ≤3 reflect poor adherence to MD, indicating very low diet quality; scores 4-7 demonstrate an average adherence, suggesting that diet quality could be improved to meet the recommended MD intakes. Scores ≥8 indicate good adherence, reflecting optimal diet quality. We translated all the 16 items in Italian and provided clear explanations of the content to the child's parent or caregiver. The questionnaire was administered by a paediatrician.

Statistical analysis

Results are expressed as mean ± Standard Deviation (SD) with 95% confidence interval for continuous variables, as percentages for categorical and discrete variables. The Kolmogorov-Smirnov goodness of fit test was used for assessing the hypothesis of normality of the data, all data were normally distributed. Data were analyzed by t-Student test and χ^2 test. Bonferroni test and pairwise comparison according to Dunn-Bonferroni *post hoc* method were applied for multiple simultaneous comparisons. The calculation of Spearman's rho and Pearson's coefficients, as appropriated, were used to evaluate the degree of association between variables. Values of $p<0.05$ were considered statistically significant. Statistical analysis was performed with Statistical Package for Social Science (SPSS), Version 22 statistic software package.

RESULTS

Our cohort was composed by 132 children (63 males and 69 females), mean age 11±3.4 years (range 2-17.9 years). According to nutritional status 5.5% of the children were considered underweight, 53.9% normal weight, 18.8% overweight and 21.9% obese. Median BMI z-score was 0.7 (z-score interval: -0.23-1.5). In our analysis, 71.2% of the global population showed poor adherence to MD, 26.5% average adherence and only 2.3% good adherence.

There was no statistically significant association between BMI and adherence scores (rho=-0.074, p=0.407), but the prevalence of poor adherence was slightly higher (75%) in obese children compared to underweight (57.1%), normal weight (72.5%) and overweight (66.7%). The nutritional status of the study population and the degree of adherence to MD are described in *Figure 1*.

No difference was recorded in adherence to MD between males and females (score 2.33±2.5 for males, 1.94±2.8 for females, p=0.406). In particular, no adherence was found in 66.7% of males *vs* 75.4% of females, intermediate adherence wad found in 33.3% of males *vs* 20.3% of females, good adherence was found in 0% of males and 2.3% of females.

No association was detected between WHtR and adherence scores (rho=0.003, p=0.975), even after adjustment for age and sex (r=-0.008, p=0.948).

In our cohort, only 3.8% consumed more than one portion of vegetables per day, 87.9% consumed commercial food daily and 76.5% consumed cured meat more than twice a week. Regarding fast-food consumption, our data showed that 73.5% of our sample routinely consumed fast food or had hamburger at least once a week, the prevalence was higher in males (79.4%) compared to females (68.1%).

We documented a statistically significant inverse correlation between age and adherence scores (rho=-0.226, p=0.009). We divided our sample into quartiles of age: I quartile: <8.3 years, II quartile; 8.3-11.3 years; III quartile: 11.3-13.8 years; IV quartile: 13.8-17.94 years; mean adherence score was 3.15±2.8 in first quartile of age, 2.12±2.4 in second quartile, 2.41±2.7 in third and 0.85±2.3 in fourth (p=0.005). These results were also confirmed by the trend test (p=0.006). In linear regression analysis MD adherence score was significantly predicted by age (adjusted R2 6.4%, beta =-0.255, p=0.03).

DISCUSSION

Mediterranean Diet has traditionally been given a great value in both children and adults for its beneficial effects. In our study, we investigated the diet quality of a cohort of Italian children and adolescents living in Southern Italy by using the KIDMED Index and we found an overall low adherence to MD, more evident in adolescents. This is in agreement with recent literature which suggests that adherence to traditional MD is decreasing in children and adolescents living in the Mediterranean countries [11, 5]. Data from a recent systematic review showed how different adherence scores can be among different Mediterranean countries, i.e., poor adherence varied from 1.6% in Spanish children to 62.8% in Greek adolescents while good adherence varied from 4.3% in Greek adolescents to 53.9% in Spanish children [12]. In Italy Roccaldo *et al*. studied for the first time, in the ZOOM8 study, adherence to MD in a representative sample of 1,740 Italian children, aged 8-9 years, from Northern, Central and Southern Italy. They reported an optimal KIDMED score in only 5% of the sample, while 62% and 32% of the sample had intermediate and low score, respectively [5]. In this study, low adherence to MD was explained in most cases by low consumption of fruits and vegetables and higher consumption of commercial food. This is in line with our study as we found that the consumption of more than one portion per day of vegetables is rare (only 3.8% of our cohort) in contrast with the large daily consumption of commercial food (recorded in 87.9% of children). This could be explained with the increasing use of commercial products and the growing spread of fast-food restaurants. This "Westernization" of the diet is the result of the globalization phenomenon. The Western diet phenomenon is particularly common among adolescents: as adolescents grow older, they tend to eat outside, abandoning the familial model of MD. This is confirmed in our study, in fact we revealed an inverse correlation between age and MD adherence. This is also consistent with other studies conducted on Greek adolescents. One of those verified the correlation between adolescent increasing buyer power and MD adherence, reporting an increased fast-food consumption and breakfast skipping in adolescents who received larger sums of money [12].

Moreover, it was observed in several Mediterranean countries that inhabitants of urban areas are less likely to be adherent to traditional dietary patterns than those living in rural areas [13].

High intakes of fast-food and processed products along with low consumption of vegetables are related to the increasing prevalence of overweight and obesity in infancy, childhood, and adolescence in all countries. In 2013 WHO estimated that about 42 million children were overweight or obese and over 70 million will be overweight or obese by 2025 [14]. Overweight and obesity are strongly associated with the develop-

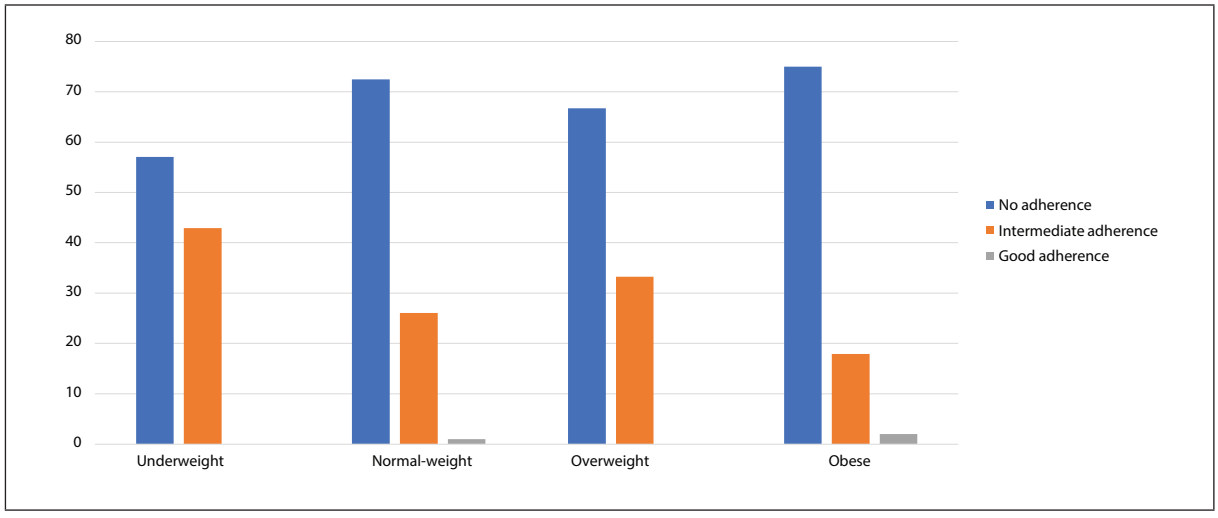

Figure 1
Adherence to Mediterranean Diet in underweight, normal-weight, overweight and obese subset.

ment of multiple cardiovascular risk factors [15]. In our study we didn't find any association between KIDMED scores and BMI, but a slightly higher prevalence of poor adherence was recorded in the obese subset. Nevertheless, the positive correlation between low adherence to MD and overweight/obesity in children has been widely proved in previous studies [16-19]. Ojeda-Rodriguez *et al*. studied the effect of a lifestyle intervention on a population of children and adolescents with abdominal obesity by using the KIDMED score. Participants were able to reduce their BMI and improve their MD adherence, reaching an average final KIDMED score corresponding to optimal diet quality [20].

Waist-to-height ratio is a strong anthropometric predictor of obesity and indicator of cardiometabolic risk in children and it has been previously proved that adherence to MD decreases waist circumference [8]. In the IDEFICS study by Tognon *et al*., high adherence to MD was inversely associated with overweight and obesity in the cross-sectional analysis and with waist circumference or WHtR in the prospective analysis [21]. In our analysis, we didn't observe any correlation between MD adherence and WtHR, since all of the patients' subsets showed a high frequency of poor MD adherence.

According to previous evidence [18, 6, 19], in our study sex was not associated with MD adherence, although other studies suggested that in western societies women tend to have better dietary habits than men [22]. A cohort study by Field *et al*. also reported that parents' concerns about body weight has a strong influence on adolescents' diets [23].

Our study presents both strengths and limitations. We described two important trends, in accordance with recent literature. The first consideration is the overall low adherence to MD in our cohort of children living in Southern Italy, regardless of sex or current nutritional status. This underlines an important variation from the traditional healthy dietary habits of this Mediterranean area. The second finding is the strong inverse correlation between age and MD adherence.

A limitation of our study was the sample size, as it was a pilot study, and the fact that children were enrolled in a single Hospital.

CONCLUSIONS

Our Center experience shows an overall low adherence to MD in underweight, normal-weight, overweight and obese children living in Southern Italy, regardless of nutritional status; this could easily lead to the spread of obesity as predicted by the WHO. With the "Western Diet" phenomenon, children are slowly abandoning the MD. It is thus important to monitor eating habits, especially in adolescents, and provide lifestyle interventions and dietary education in Southern Italy, disregarding the fact that MD is a cultural inheritance of this area. Those strategies should lead to the prevention of childhood obesity and overweight to avoid the future development of metabolic syndrome, atherosclerosis, and cardiovascular diseases. In order to gain an understanding of the dietary habits of the Italian pediatric population, future research should be conducted on a larger population and children living in different areas should be enrolled.

Authors' contributions

IR developed the idea of the study and collected data from the study population, participated in analysis and interpretation of the results and gave final approval to the draft. RC participated in data collection and drafting of the Manuscript. RG participated in data collection and drafting of the Manuscript. MLM participated in interpreting data and in review and revision of the draft. MS participated in critical review and revision of the article and MRP conducted the final draft revision and gave approval to the article submitted.

Conflict of interest statement

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Changes in the use of nicotine-containing products during and after the COVID-19 pandemic in a representative sample of the Italian adult population

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Abstract

Introduction. To assess nicotine-containing products (NCPs; heated tobacco products and/or electronic cigarettes) use in relation to conventional smoking.

Methods. "LOST IN ITALY" ("LOckdown and Lifestyles IN ITALY") and "LOST IN TOSCANA" cross-sectional surveys estimated lifestyles changes before, during, and after the lockdown in a representative sample of the Italian population. A Poisson regression model was used to estimate prevalence ratios of NCP use according to socio-demographic, mental distress, and smoking variables.

Results. The prevalence of conventional cigarette smokers did not decrease, remaining stable at 23%. Exclusive conventional cigarette smokers decreased from 21% before the lockdown in 2020 to 15% in 2023 but dual users, representing the large majority of NCP users, increased by 4 times, and exclusive NCP users decreased from 7% in 2020 to 5% in 2023.

Conclusions. NCPs are mostly accompanying instead of replacing conventional cigarettes. A targeted campaign should be developed in Italy to raise awareness on that.

Key words
- smoke
- tobacco control
- e-cigarettes
- heated tobacco products
- COVID-19

INTRODUCTION

COVID-19 pandemic and Italians' lifestyles

SARS-COV2 (COVID-19) up to the end of 2023 caused more than 770 million cases and almost 7 million deaths worldwide. In Italy, it caused 26 million cases and about 192,000 deaths (https://data.who.int/dashboards/covid19/cases?n=c). As known, the first outbreak of COVID-19 in Italy dates back to 21 January 2020 and since then the virus spread rapidly throughout the country. In order to contrast the epidemic, a lockdown restrictive measure was adopted as of 8 March 2020. It consisted in prohibiting all Italian citizens from leaving their homes, except for reasons of basic necessity or health needs, and in closing most workplaces and public places (with the exception of tobacco retailers, since smoking was considered a basic necessity) [1]. As the epidemic declined, the restrictive measures were gradually relaxed; until 31 March 2022,

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when the COVID-19 state of emergency was declared over, various containment measures and vaccination campaigns alternated according to the severity of the epidemic. The lives of millions of Italians were profoundly changed by the restrictions. Although the containment measures had a positive effect in reducing the number of COVID-19 cases, these measures changed the habits of millions of people, leading to an increase in psychological discomfort and significant changes in diet, physical activity, alcohol and drug consumption and smoking habits [2-6].

Nicotine-containing products ahead of the pandemic

Tobacco use is the modifiable risk factor causing the largest number of deaths in the world with around 8 million estimated premature deaths per year [7]. Furthermore, tobacco epidemic has become complex with the emergence of alternative products such as electronic cigarettes (e-cigs) and Heated Tobacco Products (HTPs) [8]. In Italy, the use of e-cigs increased since 2010, while the use of HTPs became widespread since 2016 [9]. Their use grew rapidly worldwide, partly due to the tobacco industry's promotion of these products as a safer alternative to conventional tobacco cigarettes [10]. However, although their long-term health consequences are still unknown, there is growing evidence that these products are not harmless [11] (http://data.europa.eu/88u/dataset/S2146_87_1_458_ENG). Through the multi-purpose survey "Aspects of Daily Life", the Italian National Institute of Statistics (Istituto nazionale di statistica, Istat) started to assess e-cig use since 2014 and HTP use since 2021 in the Italian population aged 14 years and over. In 2021, the survey sample included over 45,000 individuals, and e-cig and HTP users were 2.8%, and 2.1%, respectively (https://www.istat.it/it/files//2023/01/TODAY-Sigaretta-elettronica-tabaccoriscaldato.pdf). Similar percentages of users were recorded through the cross-sectional "Progressi delle Aziende Sanitarie per la Salute in Italia" (PASSI) Italian behavioural risk factor surveillance system, a survey on a representative sample of the Italian population aged 18-69 years, including 22,000 subjects: e-cig users in 2021 were 2.4%, HTP users 2.5% [12].

Changes in smoking habits during the pandemic

As with all behaviours, smoking habits changed during the pandemic. The effect of COVID-19 lockdown on smokers is equivocal and appears to lead to either an improvement or worsening of smoking habits [3, 13]. In Italy, on the whole during the pandemic, an increased use was reported for conventional cigarettes, e-cigs and HTPs [13-16], and the number of people who started or resumed smoking was higher than the number of people who quit smoking during the pandemic [13]. In detail, smoking prevalence decreased among young people, occasional smokers and unemployed people, and increased if psychological distress symptoms were present [3]. New e-cig users during lockdown were more frequently men and young adults; new HTP users were with higher education level [6]. Moreover, in Italy quit attempts were more frequent among exclusive smokers of conventional cigarettes than exclusive e-cig users [17].

Despite these data, there are only few studies to date regarding the simultaneous use of several tobacco products during the lockdown in Italy. Furthermore, no data have been published on the change in smoking habits after the lockdown, once all work activities and social habits have resumed. It is therefore crucial to understand how behavioural changes caused by the epidemic changed again when pre-epidemic conditions were restored.

Aim

This study aims to assess the prevalence of HTP and/or e-cig users in relation to conventional cigarette smoking habit during and after the COVID-19 pandemic, using two cross-sectional surveys carried out on a representative sample of the Italian adult population. Secondarily, the study outlines the characteristics of conventional cigarettes and nicotine-containing products (NCPs) users in 2023 in order to adopt targeted tobacco control strategies.

MATERIALS AND METHODS

Setting, study design and study population

The paper is based on data from the studies "LOckdown and LifeSTyles IN ITALY" (LOST IN ITALY) and "LOckdown and LifeSTyles IN TOSCANA" (LOST IN TOSCANA), which were focused on behavioural changes in lifestyle and mental health during and after COVID-19 lockdown. The former project was coordinated by the Mario Negri Institute in Milan, the latter by the Institute for cancer research, prevention and clinical network (Istituto per lo Studio, la Prevenzione e la Rete Oncologica, ISPRO) in Florence, in collaboration with the Italian National Institute of Health (Istituto Superiore di Sanità, ISS), and other Italian universities and research institutes. The two study protocols were approved by the Ethics Committee of the coordinating centres (Istituto Besta, file number: 71-73, April 2020, and Comitato Etico Regionale per la Sperimentazione Clinica della Toscana, Sezione Area Vasta Centro, file number: CEAVC 19834, April 2021, respectively). All the enrolled participants provided informed consent to participate in the study [18].

The "LOST IN ITALY" project included 6,003 people, with an oversampling of Lombardy, the Italian region initially most affected by the COVID-19 epidemic. The sample, representative of the Italian population, was drawn from the DOXA online panel. The latter is based on a sample of the Italian population aged 18-74, including approximately 40,000 active subjects, i.e., people who have participated in at least one survey in the last 12 months (average update: 25%), for a total of over 120,000 subjects [19]. Participants reported their habits via a self-administered online questionnaire before the start of the lockdown and at the time of the interview, which took place between 27 April and 3 May 2020.

The "LOST IN TOSCANA" Study collected data comparable to the national data previously collected by the "LOST IN ITALY" project, through two further

surveys carried out between 24 February and 21 March 2022 and between 1 April and 30 April 2023, respectively, thus maintaining the representativeness of the Italian adult population, with an oversampling for Lombardy and Tuscany regions. The total sample recruited in March 2022 consisted of 6,600 people, of whom 4,831 also participated in the baseline survey of "LOST IN ITALY"; the sample recruited in April 2023 consisted of 6,600 people, of whom 4,445 also participated in "LOST IN ITALY". Subjects were re-interviewed using a 20-minute self-administered online questionnaire that included questions about their lifestyles, mental health, quality of life and other aspects related to the pandemic (vaccinations, use of social networks, changes in interpersonal relationships). For new recruits, information on socio-demographic characteristics was also collected.

Variables of interest

In addition to socio-demographic information, the questionnaire included detailed sections on psychological characteristics (symptoms of anxiety and depression, quality and quantity of sleep, quality of life, use of psychoactive drugs), lifestyle habits (smoking habits, use of HTPs and e-cigs).

With regard to conventional cigarette use, participants were asked to indicate whether, at the time of completing the questionnaire, they were current smokers (i.e., they smoked at least 100 cigarettes in their lifetime and were currently smoking), former smokers (i.e., they smoked at least 100 cigarettes in their lifetime but were not currently smoking) or never smoked 100 cigarettes in their lifetime (never smokers). With regard to e-cig or HTP use, current users were those who reported having used e-cigs or HTPs in the last 30 days, former users who had used e-cigs/HTPs in the past but not in the last 30 days, and non-users who had never used e-cigs or HTPs. Dual users were defined as respondents who used e-cigs or HTPs and were also smokers of conventional cigarettes.

"Other smokers" were defined as dual users (smokers of conventional cigarettes that also used at least one NCP) plus exclusive users of NCPs.

To quantify the risk of smoking in association to psychological distress, we focused on anxiety and depression symptoms using validated scales. Anxiety symptoms were assessed using the 2-item generalised anxiety disorder (GAD-2), a short version of the 7-item scale (GAD-7) [20]. A score of GAD-2≥3 indicated the presence of anxiety symptoms. The presence of depressive symptoms was established using the 2-item Patient Health Questionnaire (PHQ-2), based on the 9-item validated scale (PHQ-9) and a score of PHQ-2≥3 indicated the presence of depressive symptoms [21].

Statistical analysis

Statistical weights were used to ensure that the samples, for each survey, were representative of the total Italian adult population aged 18-74 years in terms of age, gender and geographical area. A Poisson regression multivariate model with robust variance was used for estimating adjusted prevalence ratios (PR) of conventional cigarette, e-cig or HTP use according to selected demographic, socio-economic characteristics and symptoms of anxiety and depression of the survey conducted in 2023. All the analyses were performed using STATA 17.0 software.

RESULTS

Out of a total of 6,003 subjects recruited at baseline, almost 50% were males (*Table 1*). The most common age group was 35-54 years (about 41% of the sample), about half of participants were from Northern Italy (20% Center and 34% South and Islands) and about 34% of participants reported having a high education level (university degree). More than half of the sample was employed at baseline.

Almost a quarter of participants (23.4%) reported smoking conventional cigarettes before the lockdown (*Table 2*). The prevalence decreased to 21.9% during the lockdown, and then increased again in March 2022 and April 2023, when 24.5% and 23.4% of participants reported smoking conventional cigarettes, respectively, returning to the pre-lockdown prevalence. Regarding e-cig use, there was an increasing trend with 8.1% of respondents used e-cigs before lockdown, and 10.4% in 2023. Similarly, the number of HTP users increased steadily across all surveys: from 4.0% before lockdown to 7.3% in 2023.

A steady decrease in the proportion of exclusive conventional cigarette smokers occurred, from 21.3% in

Table 1
Description of the total sample by sex, age, geographical area, education level and working status (Italy, 2020)

	Raw N (% weighed)
Total	6,003 (100.0)
Sex	
Male	3,026 (49.3)
Female	2,977 (50.7)
Age	
18-34 years	1,456 (25.9)
35-54 years	2,760 (40.9)
55-74 years	1,787 (33.2)
Geographical area	
North	3,386 (46.0)
Center	1,026 (20.0)
South & Islands	1,592 (33.9)
Education level	
High[a]	2,283 (34.3)
Medium[b]	2,895 (50.5)
Low[c]	825 (15.2)
Working status	
Employed	4,166 (62.4)
Inactive	1,301 (24.8)
Retired	536 (12.8)

[a]Participants with a degree; [b]participants with a diploma; [c]participants with a secondary school qualification or lower.

Table 2
Prevalence (weighted %) of smokers of conventional cigarettes, users of e-cig and HTP before, during and after the lockdown (Italy 2020-2023)

	Pre-lockdown February 2020 %	During lockdown April-May 2020 %	March 2022 %	April 2023 %
Conventional cigarette smokers	23.3	21.9	24.4	23.3
E-cig users	8.1	9.1	9.0	10.4
HTP users	4.0	4.5	6.7	7.3
Exclusive conventional cigarette smokers	21.3	19.9	16.5	14.9
Conventional cigarette smokers & e-cig users	1.0	1.1	2.9	3.4
Conventional cigarette smokers & HTP users	0.1	0.0	1.8	2.1
Conventional cigarette smokers & e-cig & HTP users	1.0	0.9	3.3	3.0
Exclusive e-cig users	3.9	4.3	2.2	3.1
Exclusive HTP users	0.8	0.8	0.9	1.3
Exclusive e-cig and HTP users	2.2	2.9	0.7	1.0

E-cig: electronic cigarettes; HTP: heated tobacco products.

pre-lockdown 2020 to 14.9% in 2023 (*Figure 1*; *Table 2*). In contrast, the dual use of conventional cigarettes with HTPs and/or e-cigs recorded a 4-time increase: from 2.1% during the 2020 pre-lockdown to 8.5% in 2023. Interestingly, the exclusive use of NCPs decreased from 6.9% in the 2020 pre-lockdown, to 5.4% in 2023.

Among conventional cigarette smokers, the proportion of those using only conventional cigarettes decreased over time, from 91.0% (=21.3%/23.3%; *Table 2*) before the lockdown to 63.9% (=14.9%/23.3%) in 2023. Most NCP users were dual users: by 2023, 61.5% (=(3.4%+3.0% [dual users])/10.4%) of vapers were using e-cigs and concurrently smoking conventional cigarettes, compared with only 24.7% (=(1.0%+1.0%)/8.1%) before the lockdown. Similarly, the proportion of HTP users who concurrently smoked conventional cigarettes more than doubled, from 27.5% (=(0.1+1.0)/4.0) who also smoked conventional cigarettes before the lockdown to 69.9% in 2023 (=(2.1+3.0)/7.3). For both NCP, the proportion of NCP users who concurrently smoked conventional cigarettes increased from 22.9% before the 2020 lockdown to 61.0% in 2023.

In 2023, when all work activities and social habits have resumed, exclusive conventional smokers were 14.9%, exclusive NCP users or dual users 13.9%, never and former smokers 33.4% and 37.9%, respectively (*Table 3*). Results from the multivariate model highlight that males smoked significantly more than females both conventional cigarettes only and new products (PR=1.17, 95% confidence intervals [95% CI]: 1.03-1.34; PR=1.28,

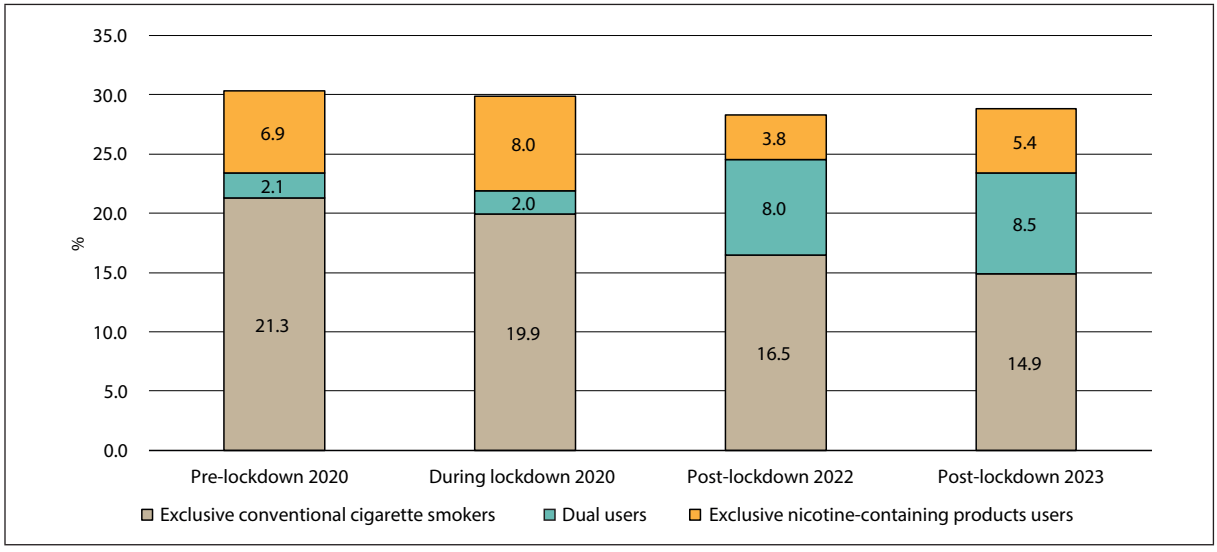

Figure 1
Prevalence (weighted %) of exclusive conventional cigarette smokers, dual users of conventional cigarettes and nicotine-containing products (heated tobacco products and/or electronic cigarettes), and exclusive users of nicotine-containing products before, during and after the lockdown, Italy.

Table 3
Distribution of exclusive smokers of conventional cigarettes, other smokers (i.e., all smokers not considering the exclusive smokers of conventional cigarettes) and never smokers of conventional cigarettes after the lockdown according to sex, age, geographical area, education level, working status, anxiety and depression symptoms. Total numbers of survey participants in each strata of the population, prevalence (weighted %) and aPR with corresponding 95% CI (Italy, 2023)

	Exclusive smokers of conventional cigarettes	Other smokers	Never smokers of conventional cigarettes	Exclusive smokers *vs* Never smokers	Other smokers *vs* Never smokers
	N (%)	N (%)	N (%)	aPR (95% CI)	aPR (95%CI)
Total	984 (14.9)	916 (13.9)	2,282 (33.4)		
Sex					
Male	491 (49.7)	474 (53.9)	1,032 (44.8)	**1.17 (1.03-1.34)**	**1.28 (1.12-1.46)**
Female	493 (50.3)	442 (46.1)	1,250 (55.2)	1*	1*
Age					
18-34 years	216 (22.0)	272 (33.6)	486 (22.2)	**0.80 (0.65-0.98)**	1.11 (0.91-1.35)
35-54 years	459 (38.4)	437 (40.1)	1,193 (45.4)	**0.72 (0.62-0.84)**	**0.82 (0.69-0.98)**
55-74 years	309 (39.6)	207 (26.3)	603 (32.4)	1*	1*
Geographical area					
North	493 (46.9)	425 (44.1)	425 (46.4)	1*	1*
Center	248 (25.9)	211 (23.2)	211 (23.2)	**1.22 (1.04-1.44)**	1.14 (0.96-1.37)
South & Islands	243 (27.3)	280 (32.8)	280 (32.8)	1.16 (0.99-1.35)	**1.33 (1.15-1.55)**
Education level					
High[a]	318 (30.5)	360 (34.2)	926 (36.7)	1*	1*
Medium[b]	504 (51.9)	462 (53.5)	1,087 (49.3)	1.17 (1.00-1.37)	1.13 (0.98-1.29)
Low[c]	162 (17.6)	94 (12.3)	269 (14.0)	**1.30 (1.06-1.59)**	1.00 (0.80-1.25)
Working status					
Employed	689 (64.5)	728 (72.0)	1,684 (66.7)	1*	1*
Inactive	168 (16.5)	130 (19.6)	319 (15.2)	1.04 (0.88-1.24)	1.06 (0.87-1.29)
Retired	127 (19.0)	58 (8.4)	279 (18.1)	0.88 (0.71-1.09)	**0.53 (0.39-0.72)**
Anxiety					
Low	709 (73.4)	637 (69.1)	1,761 (78.3)	1*	1*
High	275 (26.6)	279 (30.9)	521 (21.7)	1.18 (1.00-1.38)	**1.21 (1.03-1.43)**
Depression					
Low	785 (82.0)	709 (77.4)	1,952 (85.5)	1*	1*
High	199 (18.0)	207 (22.6)	330 (14.5)	1.12 (0.94-1.34)	**1.21 (1.02-1.45)**

Bold indicates statistically significant results. *Reference category; [a]participants with a degree; [b]participants with a diploma; [c]participants with a secondary school qualification or lower; aPR: adjusted prevalence ratios; CI: confidence intervals.

95% CI: 1.12-1.46 for conventional cigarettes and other products, respectively). Exclusive conventional smokers were less likely to be aged <35 years (PR=0.80, 95% CI: 0.65-0.98), while young adults were more likely to use NCPs. Respondents from Central Italy used conventional cigarettes more than those from Northern Italy (PR=1.22, 95% CI: 1.04-1.44), whereas respondents from Southern Italy and Islands used more frequently NCPs (PR=1.33, 95% CI: 1.15-1.55). Those with lower education levels used conventional cigarettes more than those with a university degree (PR=1.30, 95% CI: 1.06-1.59). Retired respondents were less likely to be NCP users in comparison to employed ones (PR=0.53, 95% CI: 0.39-0.72). Respondents manifesting anxiety and depression symptoms were more frequently smokers of both conventional cigarettes and other tobacco products (anxiety: PR=1.18, 95% CI: 1.00-1.38, and PR=1.21, 95% CI: 1.03-1.43 for conventional cigarettes and other products, respectively; depression: PR=1.12, 95% CI: 0.94-1.34 and PR=1.21, 95% CI: 1.02-1.45 for conventional cigarettes and other products, respectively).

DISCUSSION

In summary, in our study the prevalence of conventional cigarette smokers did not decrease, remaining stable at 23%. Exclusive conventional cigarette smokers decreased from 21% before the lockdown in 2020 to 15% in 2023 but dual users, representing the large majority of NCP users, increased by 4 times, and exclusive NCP users remained from 2020 to 2023 decreased from 7% in 2020 to 5% in 2023.

Although the use of conventional cigarettes decreased during the lockdown (before the lockdown: 23.4% of the total sample; during the lockdown: 21.9%), at the end of the pandemic with the resumption of works and social activities it increased again (2022: 24.5%; 2023: 23.4%), confirming the plateau in smoking prevalence observed since 2014 in Europe (Special Eurobarometer 458: Attitudes of Europeans towards tobacco and electronic cigarettes - Data Europa EU). In any case, Italians are no more so loyal to conventional cigarettes: the exclusive use of them decreased steadily, from 91.0% in 2020 to 63.9% in 2023, and dual use of conventional cigarettes with e-cigs or HTPs, recorded a 4-time increase in 2023 [12]. These trends, with also an increase of vapers and HTP users, being most of them dual smokers, was reported also in previous studies [9, 12, 14].

Our study confirmed that males smoked significantly more than females both conventional cigarettes and NCPs (https://www.istat.it/it/files//2023/01/TODAY-Sigaretta-elettronica-tabaccoriscaldato.pdf; Istat-Audizione-Commissione-Affari-Sociali-3-ottobre-2023.pdf). Moreover, older people and those with lower education levels tend to be more loyal to exclusive conventional cigarette smoking, whereas NCP users are more likely to be young people with a diploma or a university degree, highlighting the progressive cultural change of the new generations regarding smoking habits. Regarding the geographical distribution, respondents from Central Italy used conventional cigarettes more than those from Northern Italy, whereas those from Southern Italy and Islands were more frequently NCPs users. Both conventional cigarettes smokers and other tobacco products users were more likely to manifest anxiety and depression symptoms than those who never smoked, reconfirming the close relationship between smoking and stress already found in the literature and underlining a similar association of NCPs (https://www.istat.it/it/files//2023/01/TODAY-Sigaretta-elettronica-tabaccoriscaldato.pdf) [9, 22]. Furthermore, it should be taken into account that during COVID-19 lockdown in Italy overall prevalence of depressive and anxiety symptoms doubled and these the psychological distress worsened addictive behaviours, including tobacco smoking [6].

Main findings of this paper could be interpreted in the light of the spread of NCPs which much more often accompany instead of replace conventional cigarettes, as evidenced by the increase in dual use after the pandemic and by the plateau or a slight decrease recorded in the prevalence of exclusive use of e-cigs or HTPs, which has not changed significantly over time.

It is noteworthy to highlight that in Italy disposable e-cigs have been on the market since 2021, with a high uptake and consumption rates especially among adolescents. Disposable e-cigs could be partially responsible of the increase in e-cig use in the study period.

New products obtained fiscal and regulatory benefits compared to conventional cigarettes and tobacco industries are selling new products using new marketing tactics [12, 23, 24]. Therefore, instead of accelerating the process towards a tobacco endgame, the availability of NCP provided negative feedback on tobacco control [9]. In addition, the use of more than one product at the same time may lead individuals to smoke more frequently (most conventional cigarette smokers use e-cigs where smoking conventional cigarettes is prohibited) and increase the negative health effects, considering also that combining smoking with e-cigs did not seem to reduce cardiovascular events [25, 26]. In practical terms, our data confirm that in real life NCPs are not effective as smoking cessation tools [27-29].

Limitations of this study were represented by the cross-sectional design, including the impossibility to infer causality in the observed associations. Our results should be confirmed by prospective cohort studies and extended to other European countries.

CONCLUSIONS

In conclusion, after the pandemic there was a reduction in the exclusive consumption of conventional cigarettes, with an increased use of NCPs, mostly used in combination with conventional cigarettes. Preventing young people from smoking is crucial in order to stop the tobacco epidemic. The establishment of an effective and targeted tobacco control programme in Italy would need to take into account the increasing use of nicotine-containing products, mainly among young people, in order to increase smokers' awareness of the risks associated with new products, especially when used in combination with conventional cigarettes.

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No conflict of interest is declared by all the Authors regarding this paper.

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Regulation of gene transcription in *Escherichia coli* O157:H7 in response to a natural derivate peptide of esculentin-1a used in combination with essential oils from plants of the *Cymbopogon* genus

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Abstract

Introduction. We analyzed the expression of several genes implicated in the pathogenicity of *Escherichia coli* O157:H7, treating bacteria with Esc(1-21), a derivative of peptide esculentin-1 in combination with three essential oils obtained from plants from the *Cympopogon* genus.

Methods. We used the checkerboard assay to determine the antimicrobial activity of the combinations. We analyzed the expression of some genes implicated in the pathogenicity and quorum sensing system of *E. coli* O157:H7 by real-time RT-PCR technique.

Results. Treatment of the bacteria with the peptide combined with oils had an efficacious antimicrobial activity. The analysis of gene expression showed that all used combinations regulate positively the *esp*AD and *ler* genes, located in the pathogenicity island, named the locus of enterocyte effacement. None of the combinations affects the quorum sensing genes: *lsr*ABCFKR and *qse*BC.

Conclusions. This study demonstrates that the use of essential oil/peptide combinations can be effective in fighting microbial infections.

Key words

- *Escherichia coli* O157:H7
- essential oils
- esculentin-1a
- *Cymbopogon spp*
- real time RT-PCR

INTRODUCTION

The development and spread of antibiotic resistance is currently one of the main causes of death worldwide. This has induced considerable efforts in the research for new antimicrobial agents, finding, in the use of essential oils (EOs) and natural peptides, a new weapon in the fight against drug resistance and in the synergistic interactions of drugs a novel strategy.

The human enterohemorrhagic *Escherichia coli* (EHEC) O157:H7 is a pathogen that causes foodborne infections and the absence of an effective therapy, to counteract its pathogenicity, makes it an interesting target in the search for new antimicrobial compounds. It is the causative agent of several outbreaks of bloody diarrhea and hemolytic-uremic syndrome throughout the world, as it colonizes the large intestine, causing attaching and effacing (AE) lesions [1]. The genes involved in the formation of the AE lesions are encoded within a chromosomal pathogenicity island named the locus of enterocyte effacement (LEE) [2]. LEE encodes a type III secretion system, an outer membrane protein called intimin, a translocated intimin receptor called Tir, and the proteins EspA, EspD, and EspB secreted by the type III secretion apparatus. EspA forms a filament-like structure, which is essential for early bacterial attachment to epithelial cells. This filament connects the needle of the secretion system to a translocation pore within the plasma membrane of the host cell, which is composed of EspD and EspB; EspB and Tir are translocated into host cells, where

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Tir serves as a receptor for intimin [3]. Nucleotide sequence analysis of the LEE region of *E. coli* O157:H7 EDL933 strain revealed the presence of 41 open reading frames, most of which are organized into five polycistronic operons named *LEE1* through *LEE4* and *tir*. The Ler protein, encoded by the gene *ler* of the *LEE1* operon, is essential for transcriptional activation of the *LEE2*, *LEE3*, and *tir* operons, which encode many of the protein factors required to produce the attaching and effacing phenotype by EHEC strains on host cells. It has been demonstrated in *E. coli* O157:H7 that Ler acts as a positive regulator of *esp* genes expression and that the quorum sensing (QS) system regulates LEE genes [4, 5].

QS is a complex mechanism of cell-to-cell signaling involving the production of hormone-like compounds called autoinducers. Through the accumulation of these autoinducers, the bacteria "sense" their population as well as the population of other bacteria in a given environment. When a concentration threshold is reached the autoinducers will bind to a transcriptional activator, which in turn will activate or repress a series of genes. Gram-negative bacteria usually produce acyl-homoserine lactones as autoinducers: autoinducer-1 and autoinducer-2 (AI-1 and AI-2); AI-2 is found in both gram-positive and-negative bacteria [5]. Two genes participate in the synthesis of AI-2, the *lux*S and *pfs* genes [6]. *lux*S positively controls the expression of *lsr*ACDBEFG operon and the flanking genes *lsr*R and *lsr*K, implicated in the AI-2 uptake and modification system [7]. Furthermore, the AI-2 regulates the expression and motility of flagella by the two-component regulatory system QseBC, where QseB is the response regulator and QseC is the sensor kinase [8].

LEE locus and QS signaling systems are considered attractive targets for new antimicrobials because they play an essential role in the pathogenesis of *E. coli* O157:H7. In this study, we used a combination of Esc(1-21), corresponding to the first 20 amino acids of frog skin-derived peptide esculentin-1a [9], with three EOs of the genus *Cymbopogon: Cymbopogon flexuosus* (Nees ex Steud.) Will.Watson, *Cymbopogon citratus* (DC.) Stapf and *Cymbopogon martinii* (Roxb.) Wats var. motia Burk. In our latest study, we observed that the three combinations, working synergistically, were able to enhance their antimicrobial effect on *E. coli* O157:H7 [10]. The aim of this work was to extend the study on the effect of these EO/peptide combinations on the expression of some LEE and QS regulated genes. Using RT-PCR technology, we analyzed the expression regulation of *ler*, *esp*A, and *esp*D genes (locus LEE) and *lux*S, *pfs*, *lsr*ABCFKR, and *qse*BC genes (QS system) in bacteria treated with EO/peptide mixtures.

MATERIALS AND METHODS

Bacteria and growth conditions

In this study, we used the enteropathogen *E. coli* O157:H7 reference strain EDL933, belonging to our laboratory collection. Bacteria were grown in modified M9 minimal medium (modM9) [11] at a standardized inoculum of $1x10^6$ CFU/ml.

Peptide

The peptide Esc(1-21) used in this study was synthesized and purified as described in Scotti *et al*. [9], but a different batch was employed.

Essential oils chemical composition

The commercial EOs *C. citratus*, *C. flexuosus* and *C. martinii*, utilized in this study were purchased from Naissance Trading (Swansea, Dyfed UK). The EOs were stored at 4 °C in the dark and the stock solutions at 10% (v/v) were prepared dissolving 50 µl of EO in 450 µl of dilution buffer (10% DMSO, 0.5% Tween 80 in PBS) before use.

Gas chromatography-mass spectrometry (GC-MS) analysis

The chemical composition of the EOs was analyzed by gas chromatography-mass spectrometry (GC-MS), using an Agilent 8890 N chromatograph (GC), equipped with a single quadrupole 5977B mass spectrometer (Santa Clara, California, USA) and an autosampler PAL RTC120 (CTC Analytics AG, Zwingen, Switzerland). The mobile phase was helium (99.999%) whereas the stationary phase was an HP-5MS (30 m x 0.25 mm, 0.1 µm i.d.) capillary column from Agilent. The analytical conditions, including injection, split mode, temperature programme, scan mode, as well as the identification and quantification of components, were the same reported by Scotti R. *et al*. [11].

Determination of MIC and FIC Index

We determined the minimum inhibitory concentration (MIC) of the peptide Esc(1-21) and the three EOs (*C. citratus, C. flexuosus* and *C. martinii*) by the broth microdilution method [11], using a two-fold dilutions of each product. An overnight inoculum was diluted in modM9 at the final concentration of $1x10^6$ CFU/ml in a total volume of 200 µl, in the absence or presence of increasing concentrations of drugs. The concentration of EOs ranged from 0.1 to 6.4% (v/v) and the concentration of the peptide ranged from 1 to 32 µM. Samples were inoculated in triplicate in a 96-well polystyrene plate and incubated at 28 °C with constant agitation for 24 h. The MIC was determined as the lowest concentration of each compound at which no visible growth was observed.

We used the checkerboard technique and the fractional inhibitory concentration (FIC) index to assess the synergy between the peptide and the three EOs. The FIC index of two compounds, A and B, is calculated using the following formula: $\Sigma FIC=FIC_A+FIC_B$ where FIC_A is obtained by the ratio between the value of MIC of compound A alone and in combination; FIC_B is obtained correspondingly [10, 12]. We inoculated a 96-well microplate with an overnight culture, in a total volume of 200 µl of modM9 per well, to obtain a final concentration of $1x10^6$ CFU/ml. Each row (x-axis) in the plate contains the same diluted concentration of the antimicrobial compound A, while the concentration in each subsequent row is half this value. Similarly, each column (y-axis) in the plate contains the same diluted concentration of the antimicrobial compound B, while the concentration in each subsequent column is half

this value. We incubated the microplate at 28 °C for 24 h. The lowest concentration of compounds in wells with no visible growth was used to calculate the FIC index. Two compounds are defined as synergistic when the FIC index value is less than 0.5 [12].

RNA isolation and quantification of gene expression

We obtained mRNA by bacteria grown in the presence or absence of Esc(1-21) combined with the three EOs as described in an our previous work [9]. Bacteria were inoculated in 8 ml of modM9, at the initial concentration of $1x10^6$ CFU/ml in the presence or absence of a concentration of ¼ FIC for the three EO/peptide mixtures. Cultures were incubated at 28 °C for 24 h with 250 rpm agitation and stabilized with RNA Protect Bacteria Reagent (Qiagen). RNA extraction was performed using Presto mini RNA bacteria kit (Geneaid), DNA contamination was eliminated using DNase I (Epicentre) for 20 min at 37 °C, and RNA was precipitated with 0.7% isopropanol and 0.3 M sodium acetate. RT-PCR was used for quantification of mRNA expression of some genes involved in pathogenesis and QS system. Data were normalized using a 16*s* rRNA gene as an internal control. The primers used for analyzing genes are listed in *Table 1*.

Statistics

The assays were performed in triplicate for at least three independent experiments. Data represented average values ± the standard deviations. The significant level was set at *P* value of 0.05.

RESULTS AND DISCUSSION

In recent years, the rapid emergence of antibiotic resistance in bacteria has induced the development of alternatives to antibiotics. One of these alternatives has been the use of combination therapies, with the employment of drugs that proved to have synergistic potential. In our previous works, we studied the antibacterial activity of EOs extracted by *Cymbopogon* spp. [11] and the frog derived peptide Esc(1-21) [9].

The components of EOs were determined by gas chromatography-mass spectrometry analysis. The main compounds of the EOs from *C. citratus* and *C. flexuo-*

Table 1
Primers used in this study for reverse transcription-quantitative polymerase chain reaction

Oligo name	Sequence 5′-3′	
	For	Rev
16*s*	CATCCACAGAACTTTCCAGAG	CCAACATTTCACAACACGAG
	For	Rev
*esp*A	CGGCACAAAAGATGGCTAAT	ATAGCCGCCTTCACTGTTTG
	For	Rev
*esp*D	AATTGTTGGCCAGGTCTTTG	GCTTGCGGCCATAGATATTC
	For	Rev
ler	TCATTGCGGTAGTAAACACCT	CAAATTGCAGTTCTACAGCAG
	For	Rev
*lsr*A	AACATCCTGTTTGGGCTGGCAA	AAACAAGCGTTCGGTTTCCGCA
	For	Rev
*lsr*B	AGCATCCTGGCTGGGAAATTGT	AAATTCTTTCACCGTGCCGCG
	For	Rev
*lsr*C	GCGGGTAACCCTTCAATCCA	TCGCGACTTTACTGCTTGGT
	For	Rev
*lsr*F	CCGGTACCCATTGTTATTGC	AGTTCATATGCCCGATCAGC
	For	Rev
*lsr*K	ACCATCCGTGACTGGAAACC	CACCTTCAGACCGCAGAGTT
	For	Rev
*lsr*R	ATTGGTTTTGGCGAGGCAAC	TATAAGAACCGACGCCACCG
	For	Rev
luxS	GGCATCACTTCTTTGTTCGG	GCTTCACAGTCGATCATACC
	For	Rev
pfs	TTGAAATTGTGGCAGACATGG	GCATTTGGTTATGAATACGGTC
	For	Rev
*qse*B	GGTTTACACAAGGTCGTCAG	ACAGATAATCGTCAGCTCCC
	For	Rev
*qse*C	GTGGGCGATAAAGATCAATGG	GTTCACGACCCAGTAGTACC

sus were the monoterpene aldehydes neral (33.84 and 33.22%, respectively) and geranial (42.83 and 42.4%, respectively); the main components of EO from *C. martinii* were the monoterpene alcohol geraniol (81.4%) and its ester geranyl acetate (11.74%). These percentages were slightly different from those previously reported [11] since different batches of EOs were employed.

The MIC values for the single component and FIC indexes for the three EO/peptide combinations were reported in *Table 2*.

MIC of Esc(1-21) was 8 µM and MIC of EOs ranged from 0.2 to 0.8%. The quantities corresponding to the MICs of the individual components EOs and the peptide were greater than those reported in previous works [9, 11] since different batches of EOs were employed. Furthermore, all FIC values obtained were less than 0.5 indicating their synergistic effect against bacteria, as already demonstrated in our latest work [10]. This translates into a greater effectiveness of the mixtures compared to the individual components, with a reduction in the dosages of the used compounds and their possible toxic effects. In the same work [10] we highlighted how the EOs and the peptide used in combination differently affected the expression of the genes analyzed, indicating that the underlying mechanism of antibacterial activity of the combinations was different compared to when the compounds were used individually. Therefore, this study focused on the analysis of gene expression due to the combined use of EO/peptide, able to produce substantial reductions in MIC values, minimizing negative side effects. However, gene expression due to the use of individual components was not taken into consideration, since it is the combined use of multiple antibacterial agents that represents one of the promising alternatives for the treatment of serious infections.

QS is a cellular mechanism, mediated by autoinducers, that allows bacteria to organize their behavior depending on their density [8]. QS system regulates different pathogenic processes like secretion of virulence factors, biofilm formation and antibiotic sensitivity [13] by producing autoinducers AI. In *E. coli* the Lsr system is responsible for the detection, uptake and signal transduction of the autoinducer AI-2. The genes *lux*S and *pfs* contribute to the AI-2 synthesis and the proteins encoded by genes of *lsr* operon (*lsr*ACDB) are involved in the transport of AI-2 inside the cell. After AI-2 is phosphorylated by LsrK kinase, it represses the activity of LsrR repressor, with the consequent activation of *lsr* operon [14]. Creating agents that interfere with the microbial QS signaling systems is considered a novel strategy to develop new antimicrobials because it does not give rise to the emergence of resistance [15]. Since the LEE locus plays an essential role in the pathogenesis of *E. coli* O157:H7 and is regulated by the QS system, we decided to study the effect of the three EO/peptide combinations on the expression of some LEE and QS regulated genes. For this purpose, we examined the expression profile of some genes implicated in the production and uptake of AI-2 (*lux*S, *pfs*, *lsr*ACBF, *lsr*K, and *lsr*R), the attaching and effacing phenotype (*ler*, *esp*A, and *esp*D) and the regulatory system *qse*BC. *Figure 1* showed that *lux*S was not affected by the treat-

Table 2

A) Minimal inhibitory concentrations (MIC); B) Fractional inhibitory concentration (FIC) index. The values are expressed in µM for peptide and in percentage (v/v) for oils

A	***C. citratus***		***C. flexuosus***		***C. martinii***		**Esc(1-21)**		
	0.40%		0.20%		0.80%		8 µM		
B	**Esc(1-21)+**	***C. citratus***	**FICI**	**Esc(1-21)+**	***C. flexuosus***	**FICI**	**Esc(1-21)+**	***C. martinii***	**FICI**
	0.5 µM	0.10%	0.312	1 µM	0.05%	0.375	0.5 µM	0.10%	0.187

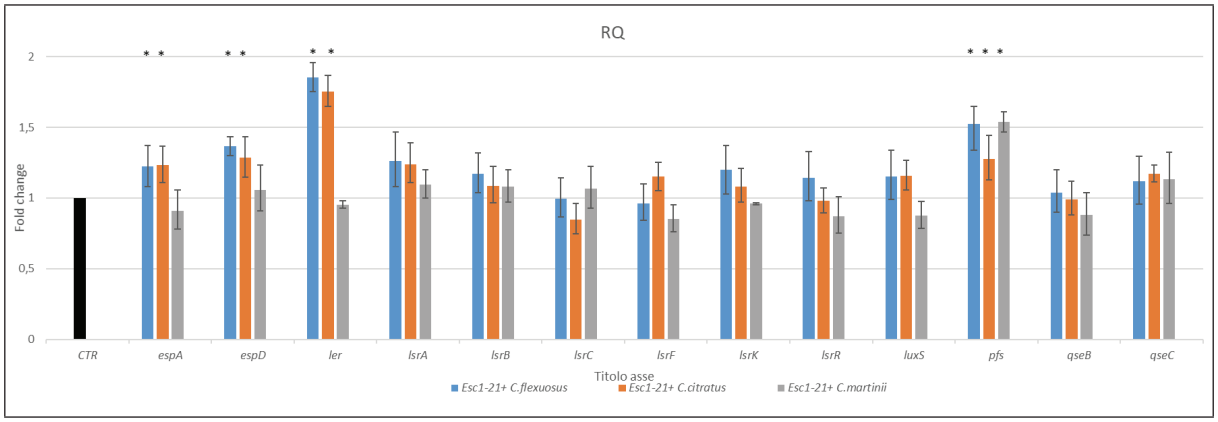

Figure 1

RT-PCR analysis of expression changes of genes related to production and uptake of AI-2, attaching and effacing phenotype and regulatory system. Relative gene expressions (RQ) represent transcriptional levels after exposure of *Escherichia coli* O157:H7 EDL933 to mixtures versus untreated control (CTR). The gene transcription level was normalized to that of the reference gene 16*s* rRNA. Data represent means ± SD of three experiments conducted in triplicate. *$P \leq 0.05$.

ment with the three EO/peptide combinations, unlike the *pfs* gene showed a significant increase.

It was also evident that the *lsr* operon genes, in the presence of the mixtures, were expressed at a similar level to the control, represented by bacteria grown in media modM9. The QS regulator genes *qse*B and *qse*C had similar behavior to the *lsr* operon, with no substantial difference from the control. These results suggested that the QS system was not involved in the response to the treatment with the three combinations and that the induction of the only *pfs* gene was not enough for the upregulation of this system.

The first gene in the LEE1 operon is *ler* and, as shown in *Figure 1*, it was significantly upregulated, 1.8-fold and 1.7-fold, by *C. flexuosus* EO/Esc(1-21) and *C. citratus* EO/Esc(1-21), respectively, but it was not by *C. martinii* EO/Esc(1-21) mixtures. We found that the *esp*A and *esp*D genes (LEE4), involved in bacterial attachment to epithelial cells, were induced by the same two mixtures, following a similar transcription profile of *ler*. This was in line with what is known from the literature, namely that Ler upregulates *esp* genes expression [4].

In summary, the three combinations did not induce the QS system. The examined LEE genes had an opposite behavior, showing to be induced by the peptide in combination with EOs from *C. flexuosus* or *C. citratus* but not in combination with that from *C. martinii* that was capable of inducing, in combination with the peptide, only the *pfs* gene. The observed different effect of the three combinations on LEE genes could be due to the composition of the EOs, which are similar in *C. flexuosus* and *C. citratus*, but different in *C. martinii*. In fact, *C. flexuosus* and *C. citratus* have as main components neral and geranial, while geraniol was the main component of *C. martinii*. However, it is also possible that other minor molecules present in the oils [16] modulate the activity of the major phytocompounds as between factors determining the activity of essential oils there are synergistic interaction of their components. In this regard, to elucidate how the different composition of oils is able to influence their activity, a new study will be carried out to better understand the action of the individual phytocompounds present in the complex mixtures of essential oils.

In conclusion, our results indicated that all EO/Esc(1-21) combinations had an efficacious antimicrobial activity with a synergistic effect on *E. coli* O157:H7 and suggested a probable mechanism of action of the compounds. Furthermore, these results should be taken into consideration when looking for new treatments capable of inhibiting the QS system and pathogenic processes, to obtain effective antimicrobial and antibiofilm activity. Understanding the mechanisms underlying the antibacterial effect of a synergistic drug combination is therefore critical to finding new and suitable therapy.

Conflict of interest statement

The Authors declare no conflict of interest.

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Clinical medical practice and stigma towards patients with substance use disorder in an Italian sample of healthcare workers

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Abstract

Introduction. People with substance use disorder (SUD) face challenges like stigma and discrimination, impacting their healthcare experiences.

Aim. This study aims to: (i) assess physicians' clinical practices and stigma toward SUD patients among healthcare personnel and (ii) explore the relationship among stigma, psychological well-being, and burnout.

Methods. A survey covering sociodemographic data, physicians' clinical practices, stigmatizing attitudes, psychological well-being, and burnout was completed by 1,796 employees of the Veneto's Local Health Units (Italy).

Results. Healthcare professionals reported increased stigma towards SUDs (*p*-values<0.05). Stigma consistently correlated with variables such as sex, profession, department, and levels of burnout (*p*-values<0.05). Notably, high burnout levels were associated with increased stigma. Staff in addiction departments displayed lower stigma levels compared to other departments. No significant differences were found in physicians' clinical practices.

Conclusions. Targeted training for healthcare professionals is crucial to reduce stigma, enhance attitudes toward SUDs, and broaden overall knowledge of the condition.

Key words

- substance-related disorders
- social stigma
- health personnel
- practice patterns
- physicians'

INTRODUCTION

People with substance use disorder (SUD) commonly face several negative consequences ranging from health problems to economic and social issues such as stigma and discrimination. According to the American Psychological Association [1], stigma is defined as "the negative social attitude attached to a characteristic of an individual that may be regarded as a mental, physical, or social deficiency. A stigma implies social disapproval and can lead unfairly to discrimination against and exclusion of the individual". Stigma typically occurs in relation to personal characteristics and social constructs, such as ethnicity and sexual orientation, but can also occur in relation to dimensions concerning the individual's health status, particularly mental status [2]. In this perspective, substance use disorders are severely stigmatized compared to other mental conditions [3, 4].

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Health professionals play a key role in the diagnosis and treatment of SUDs. Consequently, the presence of stigma in the healthcare context can have detrimental effects on SUD patients [5]. Previous literature has found that stigmatizing attitudes among healthcare professional toward SUD patients can lead to several treatment complications such as inadequate staff connection, unsatisfactory therapeutic alliance, premature treatment interruption, difficulty in accessing therapies, up to treatment avoidance [5-7]. Another frequent complication is the so-called "diagnostic overshadowing" which refers to the tendency of clinicians to attribute signs and symptoms of physical illness to the mental illness or addiction disorder [8]. This type of discrimination can lead to underdiagnosing and not properly treating physical conditions [9]. According to a recent systematic review [5], healthcare providers generally have a negative attitude toward SUD patients, and in particular, perceive these patients as more violent, manipulative, and with low motivation to treatment. These negative attitudes toward SUD patients can have a huge impact on treatment outcomes, such as receiving suboptimal care with respect to other patients [10].

Given the substantial negative effects that a stigmatizing attitude of healthcare providers can have on SUD patients, it is of the utmost importance to measure the presence and the level of stigma among health professionals towards SUD patients. Previous literature on this phenomenon has been mainly conducted in English-speaking countries [5], with only limited studies being conducted in Europe and including Italian healthcare workers. Gilchrist and colleagues [11] conducted a multi-centre study investigating the availability of different healthcare professionals among eight European countries (n=866; Italy n=70) to work with different patient groups, including SUD patients. According to the results, the willingness to work with either alcohol or drug users was significantly lower compared to patients with other physical or mental conditions across all countries [11]. Nevertheless, this study did not investigate other dimensions of stigma and included a limited number of Italian health professionals. Another study [12] examined the perception of stigma towards drug users in a sample of Italian (n=200) and Belgian students and health workers, highlighting higher levels of perceived stigma among the Italian participants compared to the Belgian ones. Still, this study was not precisely focusing on a population of healthcare professionals and did not analyse other possible stigmatizing attitudes, such as clinical medical practice.

Research in this field is still in its infancy, especially when considering the Italian context, which makes it essential to expand the knowledge about the presence of stigma in healthcare settings and the possible factors that can be related to this construct. Accordingly, the present study aims to evaluate medical doctors' clinical practice patterns and the stigma levels towards SUD patients of healthcare personnel of the Local Health Units of the Veneto Region, Italy. Furthermore, the study aims at individuating factors related to stigma levels by exploring the relationship between stigma, psychological well-being, and burnout.

MATERIALS AND METHODS

Procedure and material

For the present study, an ad hoc online and anonymous survey was developed and distributed through a link to the employees of the Local Health Units (*Unità Locale Socio Sanitaria, ULSS*) of the Veneto Region, Italy. No personal data was collected via the questionnaire.

The survey is composed of demographic questions (i.e., age, sex, marital status), questions concerning employment characteristics (i.e., profession, specialisation, department/service, setting), questions concerning daily clinical practice administered only to medical doctors, and specific questions concerning the willingness to work with people with SUDs and beliefs about treatment in people with SUDs. In addition, within the survey, there are questions taken from four standardised questionnaires adapted to the present context [13]: Depression Stigma Scale subscale of personal stigma [14], Social Distance Scale [15], World Health Organisation-Five Well-Being Index (WHO-5) [16], and Maslach Burnout Inventory (MBI) [17]. Questions regarding clinical practice (block 1) refer to 4 different situations: people with alcohol use disorder (i.e., AUD), people without AUD, people with cocaine, amphetamine, or opioid use disorder (i.e., DUD) and people without DUD. Questions regarding the willingness to work and beliefs about treatment (block 2) refer to people with AUD, people with DUD, people with other psychiatric disorders, and people with internal diseases (i.e., diseases that pertain to the internal medicine area). The personal stigma scale and the social distance scale refer to people with AUD and people with DUD. *Table 1* describes in detail the scales and the ad hoc questions.

Participants

Answers to the questionnaire were collected from 1,832 health workers of the ULSS of the Veneto Region. Of these, 36 participants were excluded due to missing data (>80%). The final sample, on which the analyses were conducted, consisted of 1,796 subjects.

Statistical analysis

The sample was first inspected and missing data were imputed using the predictive mean matching method [18, 19].

Subsequently, descriptive analyses were performed, reporting the frequency for categorical variables and the mean and standard deviation for continuous variables. Paired-sample t-tests were conducted to assess how medical doctors scored on questions about medical practice toward those SUDs (i.e., AUD and DUD) compared to those without these disorders. We also tested if there were differences in how willing participants were to work with patients with SUDs and their beliefs about treatment for patients compared to people with other disorders like psychiatric conditions or internal diseases. Paired-sample t-tests were, also, conducted to assess whether there were differences in total scores on the personal stigma and social distance scales towards persons with AUD and persons with DUD. We used linear regression models to predict total scores on the stigma and social distance scales towards both per-

Table 1
Description of the questions and scales of the online survey administered to health personnel

Questionnaires	Description
Clinical medical practice (block 1)	32 questions addressed to medical personnel only. *"How often would you prescribe the following exams or interventions in persons (**with** or **without**) an **alcohol use disorder**?"* *"How often would you prescribe the following exams or interventions in persons (**with** or **without**) a **cocaine, amphetamine, or opioid use disorder**?"* • *faced with acute onset chest pain of 7/10 intensity an echocardiogram or cardiac ultrasound or troponin or D-Dimer;* • *for abdominal pain of 7/10 intensity of acute onset, a blood count, ultrasound or X-ray;* • *for a headache of 7/10 intensity of acute onset, a brain scan;* • *in the case of type II diabetes mellitus, request HbA1c or prescribe metformin;* • *in the case of type II diabetes mellitus or hypercholesterolaemia, physical activity;* • *in the case of type II diabetes mellitus or hypercholesterolaemia, diet;* • *in women, when indicated by age, a screening mammography for breast cancer;* • *when indicated by age, a screening PAP test for cervical cancer in women or PSA in men.* Answers range from 1 ("never") to 7 ("always").
Willingness to work and beliefs about treatment in people with substance use disorders and other pathologies (block 2)	13 questions: • *"I would work with people with (**alcohol use disorder** / **cocaine, amphetamine, or opioid use disorder** / **psychiatric disorders**)" (3 questions)*; • *"I would work in an (**addiction** / **mental health**) service or community" (2 questions)*; • *"People with (**alcohol use disorder** / **cocaine, amphetamines, or opioids use disorder** / **psychiatric disorders** / **internal diseases**) are adherent to treatment" (4 questions)*; • *"Motivation to treatment may change after motivational intervention in people with (**alcohol use disorder** / **cocaine, amphetamines, or opioids use disorder** / **psychiatric disorders** / **internal diseases**)" (4 questions).* Responses ranged from 5 ("completely disagree") to 1 ("completely agree"). Higher scores represent a higher stigma with respect to working with people with a certain problem and with respect to the belief that people with a certain problem adhere to treatment and that it works. 2 questions: • *"Do you think that intervention with the territorial social network can help in the treatment of (**alcohol use disorder** / **cocaine, amphetamines, or opioids use disorder**)?"* Answers range from 1 ("not at all") to 5 (" fundamental").
Depression Stigma Scale subscale personal stigma (DSS) [14]	The DSS is an 18-item scale to measure stigma. It consists of two subscales of 9 items each: personal stigma (i.e., reflects the participant's personal attitudes towards depression) and perceived stigma (i.e., reflects the participant's beliefs about the attitudes of others). For the present study, only the personal stigma subscale consisting of 9 items was used, adapting it to the specific context [13scales have not been developed and validated for assessing substance-use stigma. Given its importance for targeting interventions, the aim of the present study was to validate a Chinese substance-use stigma measure including three dimensions of substance-* use-disorder-related stigma (personal stigma, perceived stigma and social distance]. The subjects were asked to imagine two situations: • *"Anthony is a person with **alcohol use disorder**. The next questions will be about your personal predisposition towards Anthony"*; • *"Jack is a person with a **cocaine, amphetamine, or opioid use disorder**. The next questions will be about your personal predisposition towards Jack".* And to answer the following questions for each of the two situations: *1. people with this problem could get out of it if they wanted to;* *2. this kind of problem is a sign of personal weakness;* *3. this kind of problem is not a real medical illness;* *4. people with this kind of problem are dangerous;* *5. it is better to avoid people with this kind of problem so as not to develop the same problem;* *6. a problem like this makes people unpredictable;* *7. if I had this kind of problem I would not tell anyone;* *8. I would not hire anyone that I know has this kind of problem;* *9. I would not vote for a politician I know has this kind of problem.* For each question the subject must indicate the degree of agreement from 1 ("completely disagree") to 5 ("completely agree"). Total scores range from 9 to 45. Higher scores represent a higher personal stigma.
Social Distance Scale (SDS) [15]	The SDS is a 7-item scale that measures the social distance the respondent wants to maintain in relation to people with a particular condition. For the present study, the questionnaire was adapted for the specific context [13scales have not been developed and validated for assessing substance-use stigma. Given its importance for targeting interventions, the aim of the present study was to validate a Chinese substance-use stigma measure including three dimensions of substance-* use-disorder-related stigma (personal stigma, perceived stigma and social distance], including 5 items investigating the subject's willingness to be involved in 5 social situations with regard to ***alcohol use disorder*** and ***cocaine, amphetamine, or opioid use disorder***: *1) having a person with this problem as a neighbour, 2) spending an evening socialising 3) having a person with this type of problem as a friend, 4) working closely with a person with this problem 5) having some family member marry a person with this type of problem.* For each question, the subject indicates the degree of availability from 4 ("definitely not available"') to 1 ("definitely available"). Total scores range from 5 to 20. Higher scores represent a higher social distance.

Continues

Table 1
Continued

Questionnaires	Description
The World Health Organisation- Five Well-Being Index (WHO-5) [16]	WHO questionnaire measuring the level of psychological well-being. It consists of five items that refer to positive mood (feeling good, relaxed), vitality (feeling active, awake, and rested) and general interests (being interested in new things). The subject must respond to each item by choosing from six options on a Likert scale ranging from 0 ("never") to 5 ("always"). The raw total score ranges from 0 to 25, where 0 represents the worst possible quality of life and 25 represents the best possible quality of life. Higher scores correspond to a better level of well-being.
Maslach Burnout Inventory (MBI) [17]	The MBI is designed to assess the severity of the burnout syndrome. It consists of 22 items, which form 3 subscales and identifies a burnout condition with • high total scores on the subscales of emotional exhaustion (EE - 9 items) and depersonalisation (DP - 5 items); • and with low total scores on the subscale of personal accomplishment (PA - 8 items). The items are written in the form of statements about personal feelings or attitudes and subjects must respond according to the frequency with which they experience them following a 7-point Likert scale from 0 ("never") to 6 ("every day").

sons with AUD and persons with DUD. Results with p-values<0.05 are considered significant. All analyses were performed using the statistical software R [20] and Jamovi [21].

RESULTS

Sample characteristics

The average age of the sample is 47.3 years with a standard deviation of 10.4 years, the age range goes from a minimum of 19 years to a maximum of 68. The sample is mainly composed of female subjects (n=1,418; 79%) and married subjects (n=1,086; 60.5%). Most of the sample comprises nurses/health professionals (n=950; 52.9%) and health care assistants (n=275; 15.3%), whereas medical doctors account for 10.2% of the sample (n=183). Around 13% of the subjects (n=233) works in emergency departments, 11.1% (n=200) in addiction departments, and 9.6% (n=172) in mental health departments. Finally, the majority of the sample works in the hospital setting (n=1,082; 60.2%) followed by the territorial/ ambulatory setting (n=694; 38.6%). *Table S1* (*available online as Supplementary Material*) shows in detail all the socio-demographic characteristics of the sample.

Subjects from all the ULSS of the Veneto Region participated in the survey. Specifically, ULSS2 and ULSS3 exhibited the highest response rates with 7.74% and 5.88% of their employees participating in the survey, respectively. Together, ULSS2 and ULSS3 comprised the 41% (n=736) and 25.3% (n=455) of the total survey participants. However, despite comprehensive ULSS participation, the response rates for individual units remained relatively low. *Table S2* (*available online as Supplementary Material*) provides a breakdown of participants per ULSS, along with their response rates, adjusted for the total number of employees within each ULSS.

Clinical medical practice (block 1)

Regarding the questions concerning clinical medical practice, medical personnel does not show a significant difference in prescribing examinations or visits to persons with AUD compared to persons without the disorder. On the other hand, there is a significant difference in prescribing a diet for DUD patients with diabetes or high cholesterol compared to non-DUD patients (p=0.014); specifically, doctors tend to prescribe the diet more often in persons without DUD compared to persons with the disorder. Clinical practice differs significantly when it comes to AUD patients compared to DUD patients. Physicians tend to prescribe exams for headache (p<0.001) more often to DUD patients, whereas they tend to prescribe more often interventions (i.e., physical activity: p<0.001, diet: p=0.013) to contrast diabetes and high cholesterol, and screening examinations (i.e., mammography: p<0.001, PAP/PSA test: p=0.005) for cancer prevention to people with AUD.

Willingness to work and beliefs about treatment (block 2)

Considering the questions of the second block of the survey there is a significant difference (p-values<0.001) in the healthcare personnel' willingness to work with SUD patients compared to psychiatric patients. Specifically, healthcare professionals are less willing to work with DUD patients than with other patients (i.e., with AUD or with psychiatric disorders). Health personnel also show greater reluctance (p<0.001) in working in an addiction service or community compared to working in a mental health service.

Regarding participants' beliefs about patients treatment adherence, there are significant differences (p-values<0.001) relating to the type of disorder. In more detail, health personnel believe that DUD patients are the least adherent to treatment, followed by AUD, and psychiatric patients.

About the statement that motivation can change as a result of motivational intervention, significant differences can be found when comparing people with different disorders (i.e., AUD *vs* DUD: p<0.001, AUD *vs* psychiatric disorders: p<0.001, internal diseases *vs* psychiatric disorders: p<0.001). This difference is not significant when comparing DUD and psychiatric patients. Specifically, health personnel believe that motivation is less likely to change after interventions in DUD or psychiatric patients, followed by AUD patients.

Finally, about the belief in the usefulness of the motivational intervention, healthcare professionals believe that this is more useful when it is directed at AUD patients than at DUD patients ($p<0.001$).

Personal stigma and social distance

Personal stigma refers to the personal attitudes towards people with a certain condition, whereas social distance represents the distance the respondent wants to maintain in relation to people with a certain condition. There are significant differences in scores on the personal stigma ($p<0.001$) and social distance ($p<0.001$) scales for AUD patients compared to DUD patients. In more detail, healthcare personnel report higher scores on the personal stigma and social distance scales when these are referred to people with DUD. *Table 2* presents the results of comparative analyses.

Regression analyses

We used linear regression models to identify which of the investigated variables were related to stigma scores (i.e., personal stigma and social distance scales) towards AUD and DUD patients.

Significant variables that are predictive of the scores on the personal stigma scale towards people with AUD are: the age of the healthcare personnel ($p=0.047$), psychological well-being as measured by WHO-5 ($p<0.001$), emotional exhaustion as measured by the MBI ($p=0.005$), sex ($p=0.049$), marital status ($p=0.032$), profession ($p<0.001$), and department ($p<0.001$). Considering the social distance scale, personal accomplishment as measured by the MBI ($p<0.001$), sex ($p=0.019$), profession ($p=0.003$), and department ($p=0.002$) were significant.

For the same analysis referring to personal stigma toward persons with DUD, we found that age ($p=0.008$), psychological well-being ($p<0.001$), emotional exhaustion ($p=0.004$), profession ($p<0.001$), and department ($p<0.001$) were significantly related to the scores on the personal stigma scale. For the social distance scale, personal accomplishment ($p=0.017$), sex ($p=0.049$), profession ($p<0.001$), and department ($p<0.001$) were significant.

In more detail, the personal stigma scores towards people with AUD are higher for health personnel of older age, with high levels of psychological well-being, and of emotional exhaustion. The personal stigma score is higher on average when considering the male sex, separated or divorced status, nurses or health professionals, health care workers, and administrative/ technical staff. Instead, professionals working in addiction departments are significantly associated to lower personal stigma scores on average. Personal stigma scores towards people with DUD are influenced in the same way as personal stigma scores towards persons with AUD except for the sex and marital status variables.

Social distance scores towards AUD and DUD patients are higher when burnout levels are high (i.e., low personal accomplishment). Social distance scores towards persons with AUD are higher on average in the female sex, nurses or health professionals, physicians, health care workers, and administrative/ technical staff. When these scores are referred to persons with DUD, there is not a significant association with administrative staff but with psychologists. Social distance scores are lower on average for professionals working in addiction departments. *Table 3* shows the four linear regression models in detail.

DISCUSSION

The present study aimed at analysing the habitual clinical practice of medical doctors of the Local Health Units of the Veneto Region in Italy, when confronted with people with SUD or with other diseases to highlight possible stigmatizing conducts that can have detrimental effects on patients and their treatment courses. In addition, this study aimed at evaluating stigma levels among all healthcare professionals and identifying the possible factors that can be related to stigma.

The first goal of the present study was to investigate prescription practice among medical doctors in order to spot possible clinical misconducts referrable to the "diagnostic overshadowing" which typically occurs in the context of mental illnesses [8, 22]. According to our results, medical doctors did not exhibit significantly different clinical conducts in prescribing examinations or visits to people with SUDs and people without these disorders; however, there is a significant tendency for the physicians to prescribe exams with a different frequency to people with AUD compared to people with DUD. People with DUD are prescribed more brain scans and blood exams, whereas people with AUD are prescribed more physical activity and diet interventions together with cancer screenings.

The second goal of the present study was to assess stigmatizing attitudes among healthcare providers. The results showed that healthcare professionals are less prone to work with people with DUD, compared to people with AUD or psychiatric disorders; they also prefer working in mental health services rather than in addiction services. This is in line with previous studies reporting the lower availability and willingness of healthcare providers to work with SUD patients compared to patients with other mental and physical disorders [5, 11]. In addition, healthcare professionals think that SUD patients are less adherent to treatment compared to psychiatric patients or patients with other pathologies. Furthermore, healthcare professionals think that motivation for treatment cannot change after a motivational intervention in people with SUD or psychiatric disorders, while this belief is less strong for AUD patients. Alongside, the personnel thinks that motivational interventions can be more useful when delivered to AUD patients rather than DUD patients. According to the literature, health professionals typically hold negative beliefs about treatment attitudes and outcomes among SUD patients [23]. When it comes to analysing the levels of personal stigma, reflecting the participant's attitudes towards SUDs, and the levels of social distance, referring to the distance the respondent wants to maintain in relation to people with SUDs, healthcare professionals reported significantly higher levels of both personal stigma and social distance towards DUD patients compared to AUD patients.

Table 2
Comparative analysis of clinical medical practice and stigma questions

	Mean	Mean	Student's t	*p*-value
Prescription frequency (n=183)	**DUD**	**Without DUD**		
Diet for type II diabetes/ hypercholesterolaemia	6.03	6.17	-2.474	0.014
	AUD	**DUD**		
Headache exams	5.35	5.62	-4.094	<0.001
Type II diabetes examinations	5.51	5.66	-1.931	0.055
Physical activity for type II diabetes/ hypercholesterolaemia	6.33	6.1	3.535	<0.001
Diet for type II diabetes/ hypercholesterolaemia	6.18	6.03	2.511	0.013
Mammography	6.36	6.21	3.445	<0.001
PAP/PSA test	6.34	6.22	2.821	0.005
Disagreement level (n=1,796)	**Addiction**	**Mental health**		
Working in service/ community	3.14	2.89	8.75	<0.001
Disagreement level (n=1,796)	**AUD**	**DUD**		
Working with people with	3.25	3.45	-12.5	<0.001
Adherence to treatment	3.39	3.59	-12.7	<0.001
Motivational intervention	2.22	2.55	-18.54	<0.001
	AUD	**Psychiatric disorders**		
Working with people with	3.25	2.96	10.4	<0.001
Adherence to treatment	3.39	3.04	15.3	<0.001
Motivational intervention	2.22	2.55	-14.79	<0.001
	DUD	**Psychiatric disorders**		
Working with people with	3.45	2.96	17.2	<0.001
Adherence to treatment	3.59	3.04	23.8	<0.001
Motivational intervention	2.55	2.55	0.00	1.000
	AUD	**Internal diseases**		
Adherence to treatment	3.39	2.51	30.8	<0.001
Motivational intervention	2.22	2.09	6.3	<0.001
	DUD	**Internal diseases**		
Adherence to treatment	3.59	2.51	35.9	<0.001
Motivational intervention	2.55	2.09	18.23	<0.001
	Psychiatric disorders	**Internal diseases**		
Adherence to treatment	3.04	2.51	21.5	<0.001
Motivational intervention	2.55	2.09	20.45	<0.001
Usefulness level (n=1,796)	**AUD**	**DUD**		
Usefulness of territorial social network intervention	3.52	3.43	9.66	<0.001
Scale scores (n=1,796)	**AUD**	**DUD**		
Personal stigma	24.7	26.2	-16.6	<0.001
Social distance	12.6	13.8	-24.4	<0.001

AUD: alcohol use disorder; DUD: drug use disorder (cocaine, amphetamine, or opioid); PSA: prostate specific antigen; n: number.

Overall, these results highlight more stigmatizing attitudes towards people with SUDs compared to people with other diseases, and in particular towards people that make use of drugs. Other authors reported similar results in different contexts [4, 24, 25], suggesting that individuals diagnosed with SUDs are among the mostly stigmatized patients both from the general public and the healthcare community.

The last goal of our study was to identify possible variables associated with stigma (i.e., personal stigma and social distance). According to the regression analyses, the variables more consistently associated with personal stigma towards SUDs were the age, the profession, the department, the levels of psychological well-being, and the levels of burnout dimension of emotional exhaustion. More specifically, personnel with older ages, with

Table 3
Linear regression models for personal stigma and social distance scales

	Estimate	SE	Student's *t*	*p*-value
Personal stigma – AUD				
Intercept	15.34078	2.4480	6.2666	<0.001
Age	0.02774	0.0139	1.9905	0.047
Psychological well-being (WHO-5)	0.13284	0.0303	4.3879	<0.001
Emotional exhaustion (MBI_EE)	0.05160	0.0182	2.8288	0.005
Depersonalization (MBI_D)	0.02768	0.0303	0.9126	0.362
Personal accomplishment (MBI_PA)	-0.00462	0.0204	-0.2257	0.821
Sex:				
Male – Female	0.64144	0.3252	1.9726	0.049
Marital status:				
Single – Married	-0.06987	0.3158	-0.2212	0.825
Separated, divorced – Married	0.89417	0.4178	2.1401	0.032
Profession:				
Social worker – Educator/ professional educator	0.28918	0.8126	0.3559	0.722
Nurse or health professional – Educator/ professional educator	2.11550	0.5936	3.5637	<0.001
Medical doctor – Educator/ professional educator	0.21510	0.6890	0.3122	0.755
Health care assistant – Educator/ professional educator	3.44254	0.6612	5.2065	<0.001
Psychologist – Educator/ professional educator	0.45474	0.7816	0.5818	0.561
Administrative/ technical staff – Educator/ professional educator	3.21586	0.7484	4.2969	<0.001
Department:				
Emergency – Addiction	2.84020	0.6056	4.6901	<0.001
Mental health – Addiction	1.53427	0.5719	2.6830	0.007
Other – Addiction	2.83585	0.4781	5.9313	<0.001
Setting:				
Missing – Nursing home	0.27649	2.6283	0.1052	0.916
Hospital – Nursing home	0.78073	2.2020	0.3546	0.723
Territorial/ ambulatory – Nursing home	0.14565	2.2147	0.0658	0.948
Social distance - AUD				
Intercept	11.24347	1.39955	8.0337	<0.001
Age	0.01552	0.00797	1.9471	0.052
Psychological well-being (WHO-5)	0.00230	0.01731	0.1330	0.894
Emotional exhaustion (MBI_EE)	0.01910	0.01043	1.8314	0.067
Depersonalization (MBI_D)	0.01647	0.01734	0.9496	0.342
Personal accomplishment (MBI_PA)	-0.04973	0.01169	-4.2543	<0.001
Sex:				
Male – Female	-0.43471	0.18591	-2.3383	0.019
Marital status:				
Single – Married	0.08087	0.18056	0.4479	0.654
Separated, divorced – Married	0.21575	0.23887	0.9032	0.367
Profession:				
Social worker – Educator/ professional educator	0.76802	0.46455	1.6532	0.098
Nurse or health professional – Educator/ professional educator	1.01749	0.33938	2.9981	0.003
Medical doctor – Educator/ professional educator	1.11762	0.39392	2.8372	0.005
Health care assistant – Educator/ professional educator	1.04813	0.37801	2.7727	0.006
Psychologist – Educator/ professional educator	0.65517	0.44683	1.4663	0.143
Administrative / technical staff – Educator/ professional educator	1.16216	0.42787	2.7161	0.007

Continues

Table 3
Continued

	Estimate	SE	Student's *t*	*p*-value
Department:				
Emergency – Addiction	1.08427	0.34621	3.1319	0.002
Mental health – Addiction	0.23964	0.32693	0.7330	0.464
Other – Addiction	0.54229	0.27334	1.9839	0.047
Setting:				
Missing – Nursing home	0.02976	1.50260	0.0198	0.984
Hospital – Nursing home	0.30145	1.25887	0.2395	0.811
Territorial/ambulatory – Nursing home	-0.03521	1.26616	-0.0278	0.978
Personal stigma - DUD				
Intercept	14.49541	2.6728	5.423	<0.001
Age	0.04037	0.0152	2.653	0.008
Psychological well-being (WHO-5)	0.14574	0.0331	4.409	<0.001
Emotional exhaustion (MBI_EE)	0.05703	0.0199	2.863	0.004
Depersonalization (MBI_D)	0.04655	0.0331	1.406	0.160
Personal accomplishment (MBI_PA)	-0.00718	0.0223	-0.321	0.748
Sex:				
Male – Female	0.36483	0.3550	1.028	0.304
Marital status:				
Single – Married	-0.06622	0.3448	-0.192	0.848
Separated, divorced – Married	0.74098	0.4562	1.624	0.104
Profession:				
Social worker – Educator/ professional educator	1.07270	0.8872	1.209	0.227
Nurse or health professional – Educator/ professional educator	2.30607	0.6481	3.558	<0.001
Medical doctor – Educator/ professional educator	0.76327	0.7523	1.015	0.310
Health care assistant – Educator/ professional educator	3.36710	0.7219	4.664	<0.001
Psychologist – Educator/ professional educator	1.28608	0.8533	1.507	0.132
Administrative / technical staff – Educator/ professional educator	3.25051	0.8171	3.978	<0.001
Department:				
Emergency – Addiction	3.80929	0.6612	5.761	<0.001
Mental health – Addiction	1.94748	0.6244	3.119	0.002
Other – Addiction	3.39874	0.5220	6.511	<0.001
Setting:				
Missing – Nursing home	0.96626	2.8696	0.337	0.736
Hospital – Nursing home	1.59075	2.4041	0.662	0.508
Territorial/ambulatory – Nursing home	0.63027	2.4180	0.261	0.794
Social distance - DUD				
Intercept	13.86342	1.54812	8.955	<0.001
Age	-0.01476	0.00881	-1.675	0.094
Psychological well-being (WHO-5)	-0.00235	0.01915	-0.123	0.902
Emotional exhaustion (MBI_EE)	0.01700	0.01154	1.473	0.141
Depersonalization (MBI_D)	0.00209	0.01918	0.109	0.913
Personal accomplishment (MBI_PA)	-0.03093	0.01293	-2.392	0.017
Sex:				
Male – Female	-0.40538	0.20565	-1.971	0.049
Marital status:				
Single – Married	-0.16212	0.19972	-0.812	0.417

Continues

Table 3
Continued

	Estimate	SE	Student's *t*	*p*-value
Separated, divorced – Married	0.21590	0.26423	0.817	0.414
Profession:				
Social worker – Educator/ professional educator	0.76898	0.51387	1.496	0.135
Nurse or health professional – Educator/ professional educator	1.12885	0.37541	3.007	0.003
Medical doctor – Educator/ professional educator	1.56228	0.43574	3.585	<0.001
Health care assistant – Educator/ professional educator	0.95142	0.41814	2.275	0.023
Psychologist – Educator/ professional educator	0.97543	0.49426	1.974	0.049
Administrative / technical staff – Educator/ professional educator	0.91688	0.47329	1.937	0.053
Department:				
Emergency – Addiction	1.46026	0.38296	3.813	<0.001
Mental health – Addiction	0.58359	0.36164	1.614	0.107
Other – Addiction	0.90502	0.30236	2.993	0.003
Setting:				
Missing – Nursing home	-0.39312	1.66211	-0.237	0.813
Hospital – Nursing home	-0.29011	1.39251	-0.208	0.835
Territorial/ambulatory – Nursing home	-0.69615	1.40057	-0.497	0.619

AUD: alcohol use disorder; DUD: drug use disorder (cocaine, amphetamine, or opioid); MBI_D: Maslach Burnout Inventory Depersonalisation Scale; MBI_EE: Maslach Burnout Inventory Emotional Exhaustion Scale; MBI_PA: Maslach Burnout Inventory Personal Accomplishment Scale; SE: Standard Error; WHO-5: The World Health Organisation- Five Well-Being Index.

higher levels of emotional exhaustion, and counterintuitively with higher levels of psychological well-being showed higher levels of personal stigma towards SUDs. Moreover, nurses, health professionals, and administrative/technical staff exhibited greater personal stigma, while working in addiction departments was associated with lower levels of stigma. In terms of social distance, sex, specific profession, department, and the burnout dimension of personal accomplishment played key roles. Decreasing levels of personal accomplishment, indicative of increased burnout, are associated with higher levels of social distance. Females, nurses, physicians, health professionals, and administrative/technical staff reported higher social distance, and again professionals in addiction departments displayed lower social distance.

Previous literature also showed a positive correlation between burnout scores and stigma levels [26, 27], proposing that professional burnout is an important variable in the development of negative feelings towards patients, including stigmatizing attitudes. In particular, this might be due to the fact that workers who experienced burnout tend to feel to no longer have the necessary resources to deal with the more complex situations faced at work, and SUD patients are consistently considered as more dangerous, more unpredictable, and more difficult to deal with [4, 5] constituting important work challenges for healthcare personnel. A peculiar result was found concerning the positive correlation between psychological well-being and personal stigma. Psychological well-being is typically related to burnout [28, 29], so that we expected that lower levels of psychological well-being would have predicted higher levels of stigma, aligning with the trend observed in burnout. However, this discrepant result might be attributed to the perception of SUD as not being a real medical condition and of SUD patients as being more responsible for their condition compared to people with other disorders [30, 31]. These types of beliefs might not be influenced by the level of psychological well-being one has, as stereotypes might be developed earlier in life and may not be easily modified by a transient state of psychological well-being [26]. The results of the present study concerning the impact one's profession on stigma levels are in line with previous studies demonstrating that health professionals who work more frequently or have more contact with SUD patients have more positive attitudes towards the latter as compared to other health professionals [5]. This phenomenon could be attributed to familiarity with a particular condition, as suggested by the contact hypothesis [5]. Individuals, such as professionals in addiction departments, who have greater exposure, knowledge, and experience with the stigmatized condition, are more likely to demonstrate increased tolerance and develop more positive attitudes toward people with the condition [32, 33].

There are some important limitations worth considering that may restrict the generalizability of the results of the present study. First, data were collected through a self-reported questionnaire and may not accurately reflect participant's stigmatizing attitudes and behaviours. This limitation particularly applies to the results regarding the prescription of examinations and visits to SUD patients compared to persons without these disorders, in which marked differences were not found reflecting a positive and correct medical conduct; however, we cannot clearly state whether this is the real behaviour of physicians given that the results were self-reported. Our results could be affected by social desirability bias, where the physicians answered the questions to pres-

ent themselves in more socially acceptable terms. Furthermore, the ad-hoc questionnaire used to fulfil the objectives of the study is not a validated instrument of measurement; even if this allowed us to analyse different aspects of stigma, the resultant data might not be replicable in future studies. Finally, the present study utilized a cross-sectional design and surveyed a non-representative sample of healthcare workers. Therefore, our results cannot be used to make inferences to other healthcare contexts.

Future research should consider using validated and objective tools to assess the different facets of stigma. For example, future works should evaluate clinical practice with more objective methods analysing the prescribed examinations during emergency visits of SUD patients and non-SUD patients. Moreover, future studies should expand the investigation by adopting a longitudinal study design, recruiting a more representative sample of healthcare personnel, including workers of other Italian Local Health Units.

CONCLUSIONS

In conclusion, healthcare workers show a more pronounced stigma towards people with cocaine, amphetamine, or opioid use disorder than towards people who use alcohol. In general, stigma is higher towards people suffering from SUDs than towards people suffering from other psychiatric or physical disorders. Importantly, high level of burnout results in higher levels of stigma towards SUDs patients. Furthermore, stigma levels differ between staff working in different departments, highlighting that those working in addiction departments show less stigma than those working in mental health, emergency, or other departments. Interestingly, although counterintuitive, it was found that higher levels of psychological well-being were linked to higher levels of stigma.

Further research is needed to explore whether stigma could be related to beliefs and biases about addiction causes and to poor levels of medical, psychological, and psychiatric knowledge on addiction clinical issues. Indeed, attitudes regarding the willingness to work with individuals with SUDs, patient treatment adherence, and motivational changes often seem to be influenced more by common beliefs and preconceptions rather than scientific knowledge. It is crucial to enhance healthcare professionals' knowledge, expertise, and adherence to effective guidelines, especially concerning addiction aetiology, diagnosis, and treatment. As previous literature suggests [34-36], specific training should be provided to address stigma, particularly among psychiatrists and mental healthcare professionals, in order to improve the personnel attitudes towards SUD patients and increase overall knowledge about the condition and its implications. Furthermore, training should also focus on improving the psychological well-being, including the prevention and management of burnout, of healthcare professionals not only to reduce the possibility of encountering stigmatizing behaviours in clinical contexts but also to cultivate a healthier and more resilient workforce.

Ultimately, reducing stigma and improving attitudes towards individuals with SUDs is essential to foster better patient-provider relationships and promote more effective treatment outcomes. By prioritizing education and providing targeted interventions against stigma, healthcare professionals can play a pivotal role in enhancing the overall well-being of patients facing addiction challenges.

Authors' contributions

Conceptualization: MS and DS; data curation: AV; formal analysis: AV and SP; investigation: DS, GZ, AM, RM, AP, VP, GG, VS; methodology: MS and DS; project administration: DS; resources: GZ; supervision: DS and MS; writing – original draft: AV; writing – review and editing: AV, DS, EB, AM, RM, AP, VP, GZ, VS, GG, SP, and MS.

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Conflict of interest statement

The Authors declare no conflict of interest.

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Use of antidepressant and antipsychotic drugs in subjects with hemophilia of the Umbria Region in the period 2011-2022

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Abstract

Introduction. Chronic diseases, such as hemophilia, can evoke psychological sequelae and be associated with a higher risk of mental health disorders. The utilization of antidepressant and antipsychotic drugs in subjects with hemophilia is not completely understood and few data are available.

Objectives. The aim of this analysis is to describe use of antidepressant and antipsychotic drugs in subjects with hemophilia of the Umbria Region in the period 2011-2022.

Methods. A descriptive, cross-sectional, and retrospective analysis based on data on filled prescriptions for antidepressants and antipsychotics has been carried out. The overall and annual prevalence of drugs use and consumption were calculated based on pharmaceutical prescriptions charged to the National Health Service in subjects with hemophilia and matched controls from general population.

Results. In the study period 170 subjects with hemophilia were identified; about 80% were male. About 20% and 8.2% received antidepressants and antipsychotics, respectively. A higher percentage of users and consumption were found in subjects with hemophilia compared to matched controls, although no statistically significant differences were observed.

Conclusions. Our analysis suggests that depression and psychosis are important comorbidities in subjects with hemophilia. Further larger studies are needed in order to confirm these data and better define the burden of mental health disorders in subjects with hemophilia.

Key words

- inherited blood coagulation disorders
- hemophilia
- antidepressants
- antipsychotics
- drug consumption

INTRODUCTION

Hemophilia is a rare inherited blood coagulation disorder caused by a deficiency of clotting factor VIII (hemophilia A) and factor IX (hemophilia B) characterized by spontaneous and post-traumatic bleeding events in the joints, muscles, and other soft tissues [1]. The treatment of hemophilia has progressively reached new landmarks and with advances in diagnosis and the development of safe and effective treatment modalities, subjects with hemophilia now have an almost average life expectancy [2]. Despite evolving from a fatal disease to a chronic disorder, hemophilia causes significant morbidity and its psychosocial impact on patients and their caregivers remains considerable [3].

Data on the use of antidepressants and antipsychotics in the adult general population of high-income countries showed a meaningful use (up to 17% of adults are prescribed antidepressants and up to 2% antipsychotics) which is steadily increasing compared to the previous decades [4]. In 2022, 6.7% of the Italian population used antidepressants and 1.8% used antipsychotics [5]. Consumption of antidepressants is higher in fe-

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males and increases with age, reaching a prevalence of 27.7% in women aged more than 85 years. Conversely, the prevalence of use of antipsychotics increases with age and men use more doses than women on average in all age groups, with the exception of persons aged more than 85 years [5].

Chronic diseases are associated with a higher risk of mental health disorders and hemophilia is no exception [5] considering several factors that significantly impact quality of life such as the consequences of bleeding episodes, frequent hospital admissions, chronic arthropathy, and functional disability. These factors contribute to a high rate of mental health disorders, particularly depression, in patients with haemophilia, with more than 30% affected in several studies [6-24]. A systematic literature review and meta-analysis by Al-Huniti A and colleagues reported that at least 2 out of every 5 subjects with hemophilia suffer from depression and/or anxiety [13]. Across studies, differences exist in the methodologies including questionnaires, face-to-face interviews and data from health data registries used. These differences were also influenced by demographic, socio-political, and health care system between countries. A recent descriptive, longitudinal, and retrospective analysis based on information from administrative health data registries found an increased consumption of antidepressant and anti-anxiety medications among subjects with haemophilia compared with controls, regardless of age or sex [25].

To date there is a lack of studies, especially large national studies, analysing broad hemophilia populations with a specific focus on strategies for management of depression, anxiety and psychiatric disorders. The aim of this analysis is to describe the prevalence of antidepressant and antipsychotic drugs in subjects with hemophilia in the Umbria Region in the period 2011-2022 and to evaluate the trend over this period. This study represents the first attempt to evaluate the burden of mental health disorders in the haemophilic population based on the drug prescription from a regional health data registry over a long time period. It could confirm data from international and national studies on this topic.

METHODS

All Italian citizens are enrolled in the Italian National Health Service (Servizio Sanitario Nazionale, SSN), which provides health care free of charge. We obtained data from the regional archive of drug prescriptions for the period 2011-2022, which contains all outpatient prescriptions filled within the SSN, and from the archive of SSN enrolees, which contains demographic data about inhabitants of Umbria Region.

We performed a descriptive, cross-sectional, and retrospective analysis based on data on filled prescriptions for antidepressant (Anatomical Therapeutical Chemical classification, ATC, N06A) and antipsychotic (ATC N05A) drugs in subjects with hemophilia. This study compares the prevalence of use of antidepressant and antipsychotic drugs, defined as the proportion (%) of a population with at least one prescription of aforementioned drugs either in each year during the whole study period, in subjects with hemophilia and matched controls from the general population.

The study population comprised subjects with hemophilia identified through:

- ≥1 prescription of factor VIII or factor IX concentrates (ATC code B02BD02 or B02BD04) or
- bypassing agents during the study period or hospitalization between January 2000 and December 2022 with a diagnosis of "congenital factor VIII disorders" (International Classification of Disease – Clinical modification, ICD-9-CM, 286.0) or "congenital factor IX disorders" (ICD-9-CM 286.1).

Subjects diagnosed with other congenital hematological disorders (ICD-9-CM 286.2-Congenital factor XI deficiency, 286.3-Congenital deficiency of other clotting factors, 286.4-von Willebrand's disease, 286.5-Hemorrhagic disorder due to intrinsic circulating anticoagulants, antibodies, or inhibitors, 286.6-Defibrination syndrome, 286.7-Acquired coagulation factor deficiency, and 286.9-Other and unspecified coagulation defects) were excluded. For each year analysed, the proportion of subjects treated with antidepressants and antipsychotics was calculated, stratified by age, and gender.

Controls from the general population were identified through the same regional archive of drug prescriptions of the Umbria Region and randomly matched at a ratio of 1:100 using gender, age, and health district of reference. The study cohort was dynamic, including births and deaths as observed.

The defined daily dose (DDD) is the unit of measurement defined as the assumed average maintenance daily dose for a drug, approved and recommended by the World Health Organisation (WHO) for drug use studies and surveys (https://atcddd.fhi.no/atc_ddd_index_and_guidelines/guidelines/). The "DDDs per user" measure the mean duration of treatment per user. This measure has been used for many years in drugs consumption studies and comparisons at national and international level [5]. The total DDDs used were computed by summing all the DDDs for each prescribed package to obtain antidepressant and antipsychotic drugs consumption during the study period.

Differences in the main characteristics and drug use between subjects with hemophilia and controls were tested through the Chi-Square, Wilcoxon rank-sum and T-tests, with the significance level set at a p-value <0.05.

RESULTS

During the study period 170 subjects with hemophilia (both A and B) were identified, of whom 79.4% were male (n=135) and 20.6% female (n=35) *(Table 1)*. The mean age was 42.7 years: 40.3 for males and 52.3 years for females. Approximately 76% of subjects (129 cases) had factor VIII deficiency while 24% (41 cases) had factor IX deficiency. Most subjects were identified through diagnosis codes (77%, 131 cases) while the remaining 23% (39 cases) through the prescription of factor VIII or factor IX concentrates. *Table 1* summarises key demographic and pharmacoepidemiological characteristics of the study population (n=170) and controls from the general population (n=16,916). As

Table 1
Demographic characteristics of subjects with hemophilia and matched controls from the general population

	Subjects with hemophilia	Matched controls	p
Total	170	16,916	
Mean age (±SD)	42.7 (±24.1)	43.0 (±23.9)	0.904
Gender (% male)	79.4	79.3	0.974
Age groups n. (%)			
<18 years	26 (15.3)	2,611 (15.4)	0.960
18-39 years	55 (32.4)	5,368 (31.7)	0.863
40-64 years	48 (28.2)	4,861 (28.7)	0.886
65-84 years	35 (20.6)	3,476 (20.5)	0.990
85+ years	6 (3.5)	600 (3.5)	0.990
Coagulation factors use (%)*	60.6	–	–

SD: standard deviation; *At least 1 prescription of factor VIII or factor IX concentrates or bypassing agents during the study period.

expected, no significant differences between these two groups in terms of distributions of age and gender was observed *(Table 1)*.

In the period 2011-2022, the consumption between two groups was comparable except for the median DDD (p-value <0.001), mean number of prescriptions (p-value <0.001), and in the use of specific drug categories or classes. In particular, the use of drugs in the "Blood and blood forming organs" (ATC code B), "Systemic hormonal preparations, excluding sex hormones and insulins" (ATC code H) and "Nervous system" (ATC code N) categories has been found higher in subjects with hemophilia compared to matched controls *(Table 1)*. These differences were especially driven by antihemorrhagics (ATC code B02) and antianemic preparations (ATC code B03) for the ATC Category "B" and by desmopressin (ATC code H01BA02) and Corticosteroids for systemic use (ATC code H02) for the ATC Category "H". Moreover, a higher use of drugs for Nervous system (ATC code N) was found in subjects with hemophilia, with Analgesics (ATC code N02) and Antidepressants (ATC code N06A) being among the fifteen most used therapeutic classes *(Table 2)*.

In order to verify the results of the main analysis, data on drug utilisation in the last year available have been analysed. In 2022, a higher prevalence of use in subjects with hemophilia compared to the matched controls was confirmed (p-value <0.05). The consumption between two groups was comparable except for mean number of active principles (p-value <0.001). No significant differences compared to 2011-2022 were found for categories and therapeutic classes *(Table 2)*.

The prevalence of use of antidepressants during the study period was 19.4% in subjects with hemophilia and 17.2% in matched controls. Concerning antipsychotics 8.2% of subjects with hemophilia and 5.9% of matched controls received at least one prescription during the study period *(Table 3)*. Higher prevalence of use was found in both males and females with hemophilia compared to matched controls. The analysis by gender in both groups showed higher prevalence of use in female subjects for antidepressant and antipsychotic drugs.

Regarding the trends of the antidepressant drugs, an increase in prevalence of use was observed in Umbria Region from 2011 to 2022 for both subjects with hemophilia and matched controls. In subjects with hemophilia, the percentage of users increased from 4.79% in 2011 to 8.70% in 2022 (the highest observed value), with values remaining above 4% since 2012 except for the lowest value of 3.70% in 2017. A constant slight increase in prevalence of use of antidepressant drugs, from 3.90% in 2011 to 6.79% in 2022, was observed in matched controls *(Figure 1)*. Notably, the prevalence of antidepressant use was higher (about 1.5-fold) in subjects with hemophilia compared to matched controls in each year considered, with the exceptions of 2017 and 2020. However, for each year considered, the difference between the two groups was not statistically significant.

The trend analysis of antipsychotic drugs showed an increase in their prevalence of use in Umbria Region from 2011 to 2022 both in subjects with hemophilia and matched controls. In subjects with hemophilia, the percentage of users increased from 0.60% in 2011 to 3.73% in 2022 (the highest observed value), with the prevalence remaining stable at 2.45% in the 2018-2020 period. A steady, slight increase in the prevalence of use of antipsychotic drugs was observed in matched controls, rising from 0.67% in 2011 to 2.26% in 2022, *(Figure 2)*. The difference between the two groups for each year considered was not statistically significant.

Regarding the DDDs per user of antidepressant drugs, values showed a slight increasing tendency from 2011 to 2022 in subjects with hemophilia and a stable trend in matched controls. The DDDs per user in subjects with hemophilia showed higher values during the 2016-2020 period, reaching a peak in 2017 (320 DDDs per user). In the last two years (2021 and 2022), they showed a decrease returning to a level comparable with those registered in the 2011-2014 period. On the other hand, the DDDs per user in matched controls remained quite stable throughout the study period, ranging from 205 in 2011 to 221 DDDs per user in 2022 with a peak in 2015 (233 DDDs per user). For each year considered, the difference between the two groups was not statistically significant *(Figure 3)*.

Regarding the DDDs per user of antipsychotic drugs, values showed a decreasing trend over time in subjects with hemophilia and a generally constant trend in matched controls. The DDDs per user in subjects with hemophilia showed higher values in 2011, 2013, and 2016 reaching a peak in 2017 (448 DDDs per user). In the 2018-2022 period they showed a steady decline to values lower than 170 DDDs per user with the lowest value of 71 DDDs per user registered in 2022. On the other hand, the DDDs per user in matched controls remained quite stable throughout the study period, ranging from 140 in 2011 to 91 DDDs per user in 2022 reaching a peak in 2012 (161 DDDs per user). The difference between the two groups was not statistically sig-

Table 2
Drug utilization in subjects with hemophilia and matched controls from the general population in the 2011-2022 period and year 2022

	2011-2022			2022		
	Subjects with hemophilia	**Matched controls**	***p***	**Subjects with hemophilia**	**Matched controls**	***p***
Prevalence of use (%), any drugs	99.4	94.1	**<0.05**	80.7	62.6	**<0.05**
Defined daily dose median*	2,213	700	**<0.001**	390	495	0.186
Mean number of active principles	14.9	13.1	0.075	4.6	5.8	**<0.001**
Mean number of prescriptions	393	243	**<0.001**	48.3	41.5	0.281
ATC≠ 1st level categories n. (%)						
Alimentary tract and metabolism (A)	110 (64.7)	10,370 (61.3)	0.822	54 (33.5)	5,492 (33.9)	0.915
Blood and blood forming organs (B)*	149 (87.6)	7,202 (42.6)	**<0.05**	77 (47.8)	3,380 (20.9)	**<0.05**
Cardiovascular system (C)	84 (49.4)	7,799 (46.1)	0.389	52 (32.3)	5,544 (34.3)	0.601
Dermatologicals (D)	12 (7.1)	1,054 (6.2)	0.657	1 (0.6)	221 (1.4)	0.417
Genitourinary system and sex hormones (G)	30 (17.6)	2,701 (16.0)	0.552	16 (9.9)	1,213 (7.5)	0.243
Systemic hormonal preparations, excluding sex hormones and insulins (H)	109 (64.1)	7,618 (45.0)	**<0.05**	37 (23.0)	2,291 (14.2)	**<0.05**
Antiinfectives for systemic use (J)	155 (91.2)	14,699 (86.9)	0.099	59 (36.6)	5,787 (35.8)	0.817
Antineoplastic and immunomodulating agents (L)	14 (8.2)	879 (5.2)	0.077	6 (3.7)	398 (2.5)	0.303
Musculo-skeletal system (M)	76 (44.7)	8,078 (47.8)	0.429	25 (15.5)	2,864 (17.7)	0.472
Nervous system (N)	82 (48.2)	5,745 (34.0)	**<0.05**	30 (18.6)	2,205 (13.6)	0.066
Antiparasitic products, insecticides and repellents (P)	10 (5.9)	1,207 (7.1)	0.527	1 (0.6)	171 (1.1)	0.590
Respiratory system (R)	80 (47.1)	7,121 (42.1)	0.192	25 (15.5)	1,747 (10.8)	0.055
Sensory organs (S)	8 (4.7)	974 (5.8)	0.558	2 (1.2)	430 (2.7)	0.265
Various (V)	3 (1.8)	189 (1.1)	0.426	0 (0.0)	49 (0.3)	0.484
ATC≠ 2nd level therapeutic classes n. (%)						
Antibiotics	152 (89.4)	14,556 (86.0)	0.208	55 (34.2)	5,607 (34.7)	0.896
Corticosteroids for systemic use	87 (51.2)	6,965 (41.2)	**<0.05**	25 (15.5)	1,639 (10.1)	**0.024**
Anti-peptic, antiulcer and GERD***	86 (50.6)	7,861 (46.5)	0.284	40 (24.8)	3,126 (19.3)	0.078
Antihypertensives	80 (47.1)	7,221 (42.7)	0.252	49 (30.4)	5,040 (31.1)	0.845
Antihemorrhagics	77 (45.3)	377 (2.2)	**<0.05**	9 (5.6)	57 (0.4)	**<0.05**
Drugs for asthma and COPD***	74 (43.5)	5,871 (34.7)	**<0.05**	21 (13.0)	1,250 (7.7)	**<0.05**
NSAIDs£	66 (38.8)	7,240 (42.8)	0.297	17 (10.6)	1,921 (11.9)	0.608
Analgesics	56 (32.9)	3,623 (21.4)	**<0.05**	12 (7.5)	899 (5.6)	0.296
Antianemic preparations	41 (24.1)	2,979 (17.6)	**<0.05**	10 (6.2)	939 (5.8)	0.826
Drugs for osteoporosis	36 (21.2)	3,149 (18.6)	0.394	12 (7.5)	1,192 (7.4)	0.967
Anticoagulants	34 (20.0)	4,449 (26.3)	0.063	4 (2.5)	1,180 (7.3)	**<0.05**
Antidepressants	33 (19.4)	2,913 (17.2)	0.452	14 (8.7)	1,099 (6.8)	0.340
Systemic hormone preparations, excluding sex hormones and insulins	28 (16.5)	71 (0.4)	**<0.05**	3 (1.9)	16 (0.1)	**<0.05**
Antibiotics for topical use	27 (15.9)	2,701 (16.0)	0.976	6 (3.7)	455 (2.8)	0.486
Drugs for genitourinary disorders	26 (15.3)	2,293 (13.6)	0.510	15 (9.3)	1,117 (6.9)	0.230

≠ATC: Anatomical Therapeutic Chemical Classification System; *Excluding coagulation factors and bypassing agents; **GERD: Gastroesophageal reflux disease; ***COPD: chronic obstructive pulmonary disease; £NSAIDs: Nonsteroidal anti-inflammatory drug.

nificant for most years; however, according to Wilcoxon rank-sum test a statistically significant difference was found only in 2016 (p-value 0.029) and 2017 (p-value 0.021) *(Figure 4)*.

DISCUSSION

Our descriptive, cross-sectional, and retrospective analysis showed that 20% of subjects with hemophilia received at least one antidepressants prescription and

Table 3
Prevalence of use and consumption of antidepressant and antipsychotic drugs in subjects with hemophilia and matched controls from the general population

	Hemophilia			Matched controls		
	Males	**Females**	**Total**	**Males**	**Females**	**Total**
N. of subjects (%)	135 (79.4)	35 (20.6)	170 (100)	13,416 (79.3)	3,500 (20.7)	16,916 (100)
Mean age in years (±SD)	40.3 (23.4)	52.3 (24.5)	42.7 (24.1)	40.5 (23.2)	52.2 (24.3)	43.0 (23.9)
Antidepressant drugs						
Users n. (%)	22 (66.7)	11 (33.3)	33 (100)	1,900 (65.2)	1,013 (34.8)	2,913 (100)
DDDs per user	942.4	1,035.1	973.3	717.9	1,004.6	817.6
Mean age in years (±SD)	57.4 (17.8)	72.9 (20.9)	63.2 (20.2)	58.9 (19.7)	67.8 (18.1)	62.5 (19.8)
Prevalence of use (%)	16.3	31.4	19.4	14.2	28.9	17.2
Antipsychotic drugs						
Users n. (%)	10 (71.4)	4 (28.6)	14 (100)	675 (67.1)	331 (32.9)	1,006 (100)
DDDs per user	535.6	181.2	434.3	368.9	193.4	311.1
Mean age in years (±SD)	61.2 (20.6)	74.8 (11.1)	65.8 (19.2)	64.9 (22.3)	76.2 (18.1)	69.2 (21.9)
Prevalence of use (%)	7.4	11.4	8.2	5.0	9.5	5.9

SD: Standard Deviation; DDD: defined daily dose.

8.2% at least one antipsychotics prescription during the study period. A higher percentage of users and higher consumption were found in subjects with haemophilia compared to matched controls, although no statistically significant differences were observed. Antidepressants use was highest among users aged 70 or older, especially females. Additionally, antidepressant users increased from 7.1% in 2011 to 10.4% in 2022, while antipsychotic users increased from 0.6% in 2011 to 4.4% in 2022.

In 2022, 6.7% of the Italian population used antidepressants and 1.8% antipsychotics [5]. Consumption of antidepressants is higher in females and increases with age, reaching a prevalence of 27.7% in women aged over than 85 years. On the other hand, the prevalence of antipsychotics use increases with age and men use more doses than women on average in all age groups, except for those aged over 85 years [5]. In particular, 8.5% of the Umbria Region population used antidepressants and 2.3% antipsychotics with differences in terms of consumption between genders (11.2% in females *vs* 5.3% in males for antidepressants and 2.2% in females *vs* 1.8% in males for antipsychotics) [5]. These data place the Umbria Region among the Italian region with the highest consumption of antidepressant and antipsychotic drugs [5].

Previous studies have reported a higher rate of mental health disorders in patients with hemophilia compared to controls [6-24], with depression (formal diagnosis) and depressive symptoms/anxiety interesting 40-50% of subjects with hemophilia. The methodology used in the abovementioned studies varied significantly and demographic, health care and social care differences between studied populations should be taken into account. Our findings are substantially in line with a recent systematic review and meta-analysis, which reported about two-fold or higher increased risk

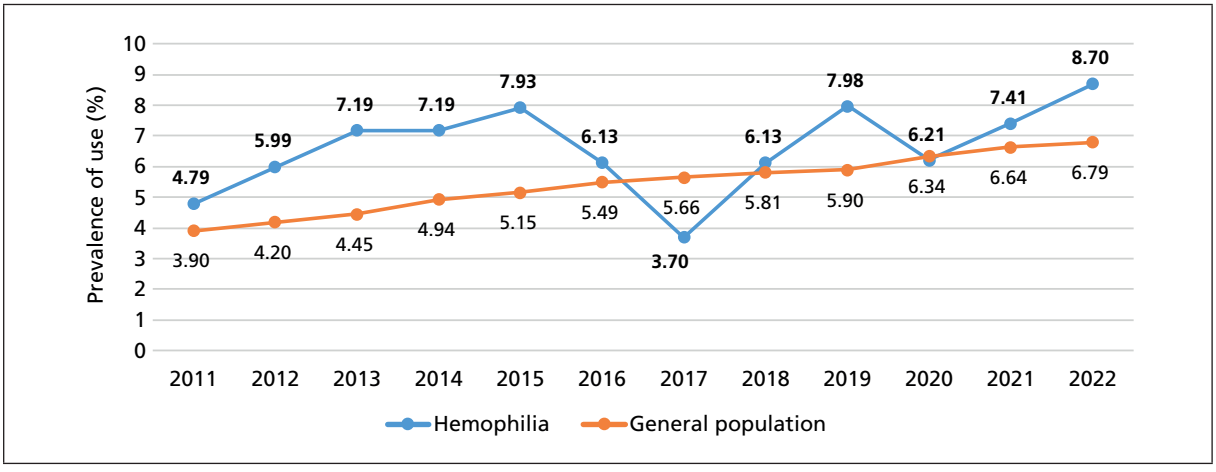

Figure 1
Prevalence of use of antidepressant drugs trend in subjects with hemophilia and matched controls from general population (Umbria Region, 2011-2022).

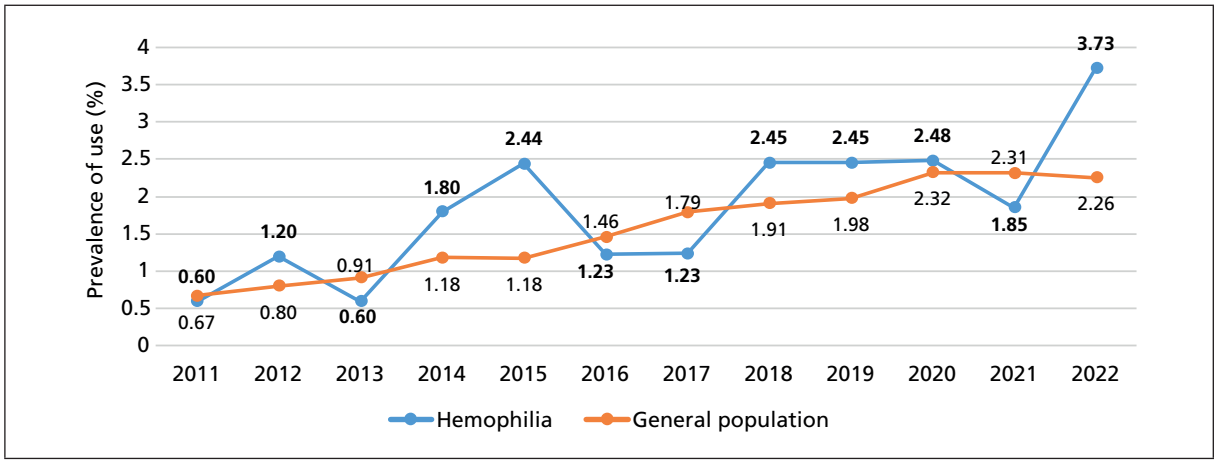

Figure 2
Prevalence of use of antipsychotic drugs trend in subjects with hemophilia and matched controls from general population (Umbria Region, 2011-2022).

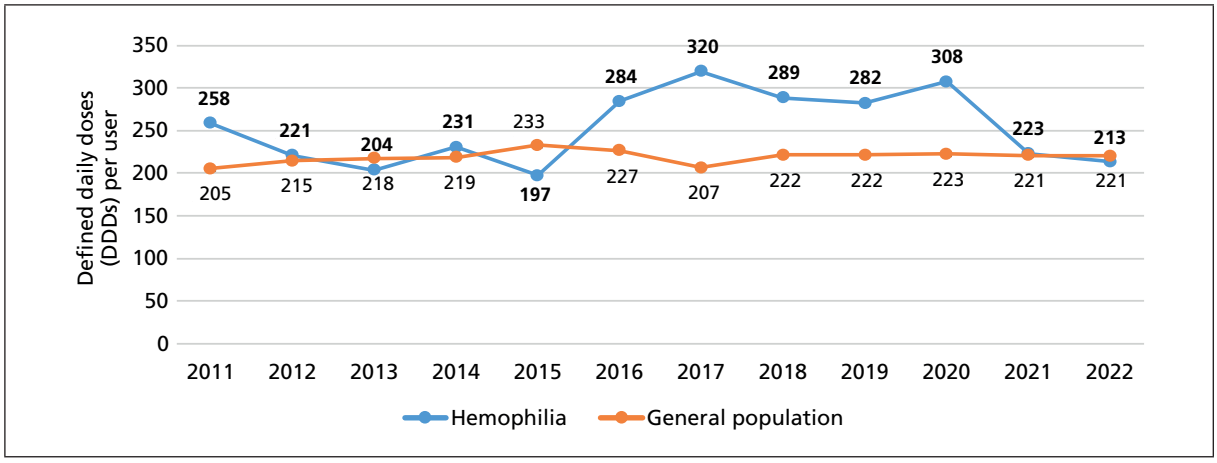

Figure 3
Trend of defined daily doses (DDDs) per user of antidepressant drugs in subjects with hemophilia and matched controls from general population (Umbria Region, 2011-2022).

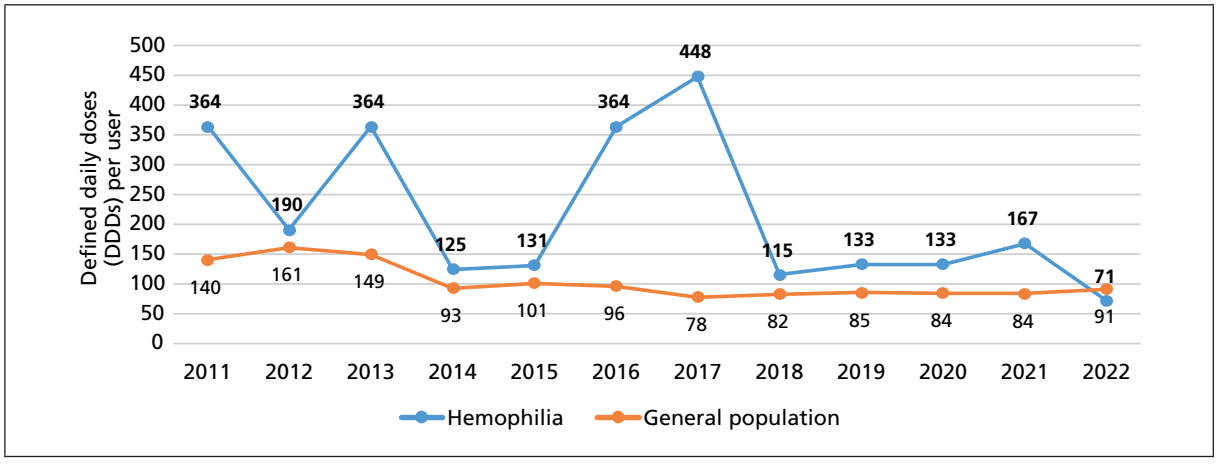

Figure 4
Trend of defined daily doses (DDDs) per user of antipsychotic drugs in subjects with hemophilia and matched controls from general population (Umbria Region, 2011-2022).

of depression, anxiety, or both in subjects with hemophilia compared with the general population [13], as well as with those from a descriptive, longitudinal, and retrospective analysis based on data from four Nordic countries National Health Data Registers during 2007-2017 [25]. This study showed higher likelihood of antidepressants use in subjects with hemophilia compared to matched controls, especially in women and carriers subgroups [25].

Considering that no information was available in our health flow data about private purchases by citizens, the use of drugs (e.g., benzodiazepines) and non-pharmacological interventions in mild to moderate mental health disorders, the prevalence of antidepressants and antipsychotics use observed in our study underestimates the real burden of mental health disorders, especially depression and depressive symptoms. Our study had some limitations: the relatively small number of patients identified in the study explains the variability in the prevalence of use and consumption trends in subjects with hemophilia. Some variables that are significant predictors of depression, such as the severity of hemophilia, persistent pain, and joint impairment, were not considered. The definition of subject with haemophilia based on diagnosis in hospital care and prescriptions of factor VIII or factor IX concentrates includes also female carriers of hemophilia. Moreover, the broad inclusion criteria could include people with other bleeding disorders where hemophilia A or B had been registered with an uncorrected code. Finally, information about diagnosis of depression and psychotic disorders was unavailable.

Despite these limitations, we believe this study is of particular importance as it provides data on the use of antidepressants and antipsychotics in subjects with haemophilia. A strength of the study is that information on all filled prescriptions for drugs used in the management of depression, and psychosis was available during the 12-year study period.

CONCLUSIONS

Despite significant improvements in morbidity and mortality outcomes, the quality of life for subjects with haemophilia remains endangered, with emerging evidence suggesting that chronic diseases are associated with mental health disorders. In addition to direct or indirect impact that mental health disorders have on physical health of subjects, some evidence includes depression and anxiety among modifiable factors that can decrease adherence to factor replacement therapy, thus increasing the risk of disease complications [26, 27]. This study suggests that mental health disorders, such as depression and psychosis, are relevant comorbidities in subjects with hemophilia and should be considered by clinicians to ensure appropriate treatment and improve patients' quality of life. Although our sample size was sufficient considering the prevalence of haemophilia, the generalizability of the results should be interpreted with caution. Further studies with larger, preferably multicenter, regional, or national cohorts are warranted to validate these findings and establish more robust conclusions.

Authors' contributions

GM, RA and RDC designed the study. RER, GB and MR retrieved and prepared the data. RDC, MC, AA and GM carried out the statistical analysis. GM, RA, RER, AA, MC, GB, RDC and MR wrote the manuscript. All Authors critically revised and approved the final version of the manuscript. The corresponding Author attests that all listed Authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Conflict of interest statements

The Authors disclose no conflicts of interest.

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Responding to healthcare needs of different religious communities: implications for the Italian National Health Service

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Abstract

Background. One of the challenges that our Italian National Health Service is facing is the structural change of society, regarding the migratory flows recorded in the last thirty years with the consequent increase in faithful who follow religions other than the Catholic one.

Aim of the study. This study highlights the critical issues due to religious indications of different faiths which can have implications for our healthcare system. The study analyses the different concept of health, illness, well-being and pain, life and death, gender issues, rules regarding diet, fasting and drugs that can be taken by the patients. Religious norms regarding procreation, termination of pregnancy, and the use of contraceptive methods are also considered; as well as euthanasia, organ donation and the specific needs for end-of-life rites in different religious faiths, as they are presented in the literature and as they emerged in the dialogue with the national representatives of the religious faiths that make up the Interreligious Table of Rome.

Conclusions and future perspective. The complexity of this relatively recent Italian reality necessarily leads to an in-depth analysis of religious and cultural diversity. The National Health Service must face a series of changes which concern both the adaptation of health structures and the adequate preparation of health workers, who are called upon to know how to communicate and offer care and assistance to all.

Key words

- religions
- immigration
- delivery of healthcare
- healthcare workers
- patient rights

INTRODUCTION

The migratory flows that have characterized the last thirty years have led to an exponential increase in Italy of believers belonging to religions other than the Catholic one.

Compared to what happened in other European countries, immigration in Italy presents some peculiarities such as the short period in which it developed (about thirty years) and the great diversity of origin of the immigrants (over 200 countries from all continents). According to Fondazione Iniziative e Studi sulla Multietnicità (ISMU) calculations and estimates [1] on Istituto Nazionale di Statistica (ISTAT) data [2], the total number of foreigners regularly present in Italy on 1 January 2022 is 6,003,000 of which 5,194,000 residents, 303,000 non-residents (but with regular residence) and 506,000 irregular foreigners without a residence permit (estimated data).

The people who profess a religion other than Catholic Christianity in Italy are approximately 2.2 million Italians and 3.9 million foreigners. Among Italians, 82.1% are Christian (79.7% Catholic Christian), 16.2% atheist or agnostic and 1.7% profess other religions; mainly Islam, Buddhism, Hinduism and Judaism. Among foreigners, 51.8% are Christian (28.8% Orthodox, 17.7% Catholic), 33.3% Muslim, 4.5% are atheist or agnostic and the remaining share professes other religions; such as Hinduism, Buddhism and other oriental religions (Center for Studies on New Religions – Centro Studi sulle Nuove Religioni, CESNUR – elaboration based on the estimate of the 2022 Immigration Statistical Dossier) [3]. Religions followed by Italian citizens and immigrants are shown in *Figure 1*.

This found our institutions, and in particular public health, unprepared. The concepts of health and disease

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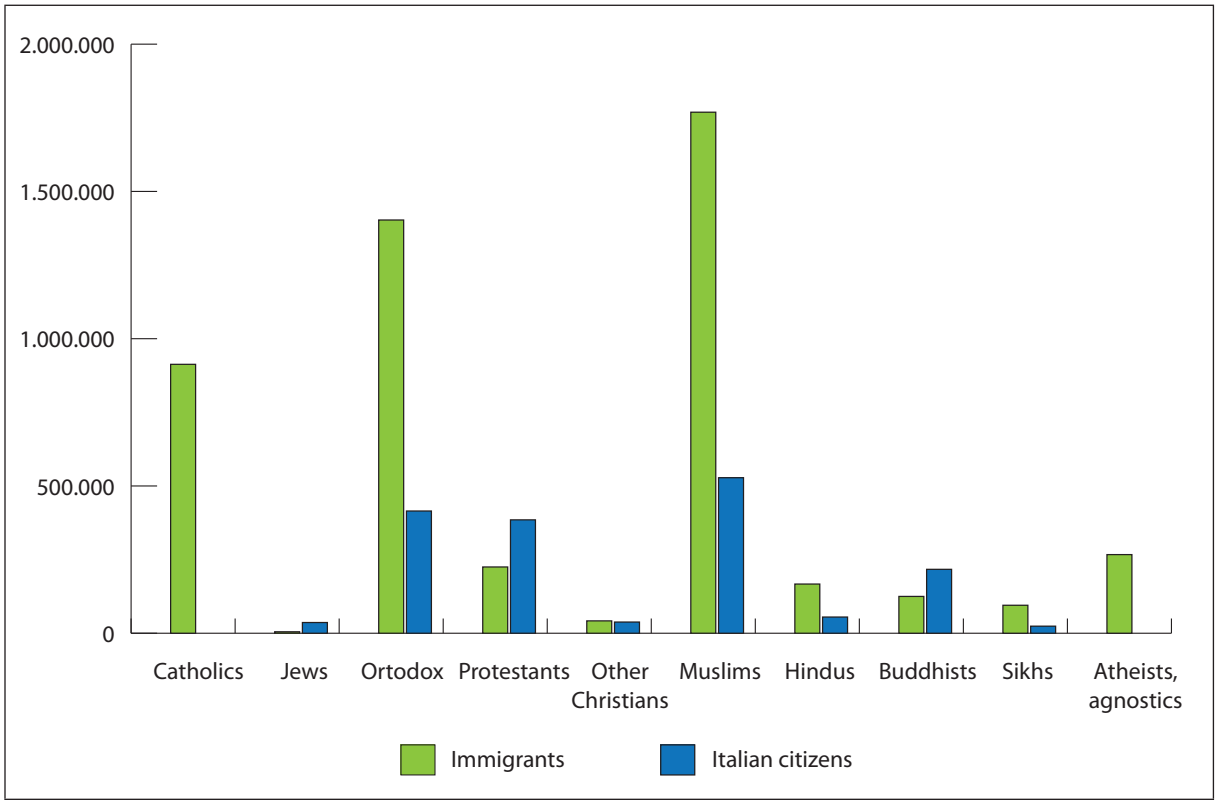

Figure 1
Religions followed by Italian citizens and immigrants. Italian Catholics, Italian atheists and agnostics are not shown in the graph because the numbers are too high.

take on multiple meanings and values with a consequent plurality of behaviors, which must be constantly investigated and considered. In the case of disease, for example, there is substantial mistrust towards official medicine, especially on the part of groups of immigrants belonging to oriental religions or coming from African countries who continue to follow the traditional medicines of their own country or who associate them with prescribed therapies, resulting in problems regarding the effectiveness of the drug and interactions.

The rules dictated by religious faiths may concern the type of diet to follow, fasting periods but also the refusal of certain therapies and the type and composition of drugs that can be prescribed.

Sexuality, abortion and assisted fertilization follow precise rules dictated by the religion to which one belongs. There are also rules that the faithful must follow for organ donation, end-of-life rites, autopsies and burials.

In general, all the different religious confessions also present specific gender problems, complicated by the connection with the culture of the country of origin, which make the relationship with healthcare workers difficult and complicated.

Italy, later than other European states, is rapidly transforming into a multicultural and multi-religious society. Public health is called upon to provide a whole series of adequate responses to the new requests for assistance and care linked to individual cultural-religious specificities.

METHODS

This article analyzes in succession the general principles of the religious faiths present in Italy, focusing on the religious norms and the needs of patients who follow different religions, which have implications for our National Health Service (NHS). Judaism, Islam, Hinduism, Buddhism, Sikhism, the Orthodox Christian Churches and the Protestant Christian Churches were analyzed.

The study is based on bibliographic searches of studies published in Italian and English on the PubMed and Google Scholar databases and on publications available online.

PubMed and Google Scholar databases were searched until the 4th of June, 2023 (without starting date) to retrieve peer reviewed studies and grey literature relevant to the search question. Key words such as "religion", "religious" "faith", "health", "disease", "belonging", "affiliation", "behavior" and "well-being" and synonyms – plus the name of the most common religion faiths – were used with different combination with Boolean operators. Only studies published in Italian and English and publicly available were selected.

Bibliographic search and consultation with experts were used in order to capture information regarding the impact of different religious faiths on health.

The study also made use of targeted interviews on health issues of the national representatives of the religious faiths that make up the Interreligious Table of

Rome. The Interreligious Table of Rome brings together national representatives of 8 different religious confessions (Buddhism, Reformed Christianity, Judaism, Hinduism, Islam, Orthodoxy, Seventh-day Adventist Church and Italian Buddhist Institute Soka Gakkai). As an official body of the Municipality of Rome, from 1998 to 2011, it promoted interventions aimed at intercultural and interreligious education with respect for differences, in schools, universities and municipalities in the Roman territory. As a Cultural Association since 2011, it collaborates with local hospitals and healthcare companies in the creation of information and training projects aimed at healthcare workers involved in welcoming the sick, as a consultant for the processes of adapting care and assistance procedures in healthcare facilities.

The questions that guided the discussion with the religious representatives focused on any critical issues perceived by the religious representatives in the protection of health, in reference to topics such as the health of women and minors, the organization of health services and the relationship with the sanitary system.

In February 2023, 8 different in person focus groups, moderated by a researcher of the Center for Global Health Research and Studies of Università Cattolica del Sacro Cuore, Rome, Italy, were organised consulting one by one the different religious representatives. The focus groups lasted 90 minutes each. Key question leading the discussion with religious representatives was "are there any critical issues perceived by faithful of religion you represent in terms of health protection and healthcare?". Moreover, the key question was further detailed with specific questions regarding any possible barriers encountered with reference to gender issues, children assistance, medicines uptake, healthcare services organisation. At the end of the meeting, the guiding questions were sent to the religious representatives that were also given the opportunity to add additional elements after further reflection.

RELIGIOUS FAITHS

This part will analyze the basic principles of the different religions currently present in Italy and the religious norms that follow their adherents, delving into all the problems and critical issues that NHS practitioners necessarily need to be aware of and deal with.

Judaism

There are approximately 13 million Jews in the world and they live mainly in Israel and the United States. The number of faithful in Italy is 37,000 (less than 2% of the national population) and the vast majority are Italian citizens [3].

In Judaism, illness is considered as a failure to comply with divine provisions and therefore is a consequence of the person's lack of caution in prevention and treatment, it must be accepted as part of one's nature and as evidence sent by God [4].

Observant Jews follow a particular diet called Kosher: they can eat ruminant animals such as cows, calves, sheep, goats (artiodactyl mammals with the hoof divided into two parts), poultry such as chickens, fish with scales and fins. Slaughter must be carried out by a qualified and trained person in order to follow the dictates of the Torah. Milk and dairy products cannot be consumed together with meat and poultry [5].

During the Jewish Passover (lasting 8 days, normally in April) the intake of leavened foods is prohibited and bread is replaced with unleavened bread. This celebration is very heartfelt. The patient may request that relatives bring particular foods, in particular for the traditional dinner which takes place on the first and second evening of Easter.

Kippur, the Day of Atonement (between September and October), is dedicated to fasting and prayer.

For Jews, male circumcision is mandatory. It is linked to the pact stipulated between God and Abraham (Genesis 17.10-14), of which circumcision becomes the physical sign that is repeated throughout the generations. Circumcision is performed on babies as young as 8 days old. In the Jewish community, ritual circumcisions are performed in compliance with medical-health protocols and in safe conditions, therefore Jewish newborns can be circumcised in Jewish community facilities. Law 101 of 1989, which approved the agreement between Italy and the Italian Jewish communities, recognized the conformity of the practice of Jewish circumcision with the principles of our legal system [6].

Saturday is a public holiday for Jews. Sabbath begins from sunset on Friday and lasts until Saturday evening. Patients may wish to light two lights at the beginning of the Sabbath and celebrate its beginning with kosher wine or grape juice and bread, and they may ask relatives to provide it. It is forbidden to work on Saturdays, this category also includes non-urgent surgical interventions. In case of hospital discharge on a Saturday, the patient must be able to stay until the evening (even without a bed). The same rules apply on other public holidays.

Judaism forces men to procreate and not waste semen, while women can use contraceptives. Among the contraceptive methods currently in use, the pill is considered the best aid because it interferes less with normal sexual intercourse.

Abortion is not permitted, but if it is intended to protect the physical or mental health of the woman, which could be damaged by a pregnancy, it may be permitted [7].

In Jewish tradition, the fetus is protected from the moment of conception, but its right does not prevail over that of the mother to life [4].

There are no limitations regarding the taking of drugs, organ transplants and transfusions.

Fundamental to Judaism is the centrality of human life. Life is considered inviolable, which is why euthanasia is prohibited [8].

The autopsy is considered an act of disfigurement and any improper use of the body is expressly prohibited. An autopsy may only be permitted in exceptional cases, for example when it is requested by the criminal court when there is uncertainty about the cause of death.

Before burial, the body must be subjected to a washing ritual, which serves to honor the deceased by removing any type of dirt or bad smell. Cremation is prohibited by Jewish law.

Islam

Islam is the world's second largest religion after Christianity, with followers equal to a quarter of the world's population. There are over two billion Muslims in the world. Over fifty countries have Muslim-majority populations, including 22 nations in the Middle East, while other groups of believers are clustered in minority communities in nations on nearly every continent.

In Italy there are approximately two million three hundred thousand Muslims of which 528,000 Italian citizens, the majority of whom are of foreign origin who have acquired citizenship over the years and 1,769,000 resident foreign citizens [3].

According to Islam, God is believed to have created human beings and given them their bodies as gifts to be cared for. Therefore, keeping one's body healthy is important and sick people are expected to look for solutions to restore their physical and mental well-being [9].

Islam has generally encouraged the use of science and biomedicine to alleviate suffering, with Muslim patients seeking medical solutions to their health problems.

Muslims are required to follow a diet, similar to the Jewish Kosher diet, which involves the consumption of foods considered legal (halal), foods subjected to a specific ritual. It is not permitted to eat pork and animals that have not been slaughtered according to Islamic custom; alcohol is strictly prohibited. If halal meals are not available, kosher Jewish meals or vegetarian meals are acceptable. Utensils used in the preparation of non-halal foods should not be used to prepare meals intended for a Muslim patient [9].

Medicines containing alcohol or derived from non-halal animal products are prohibited by the Islamic religion.

Ramadan is the holy month of fasting, dedicated to prayer, meditation and self-discipline. Fasting is an obligation for all healthy adult practicing Muslims. Fasting is one of the five duties of the Islamic faith. During Ramadan, Muslims do not ingest food or liquids, including water, between sunrise and sunset. During this month, medications taken orally, auricularly or nasally, suppositories or inhalations are not permitted because they could interrupt the fast. The patient can only perform certain treatments or take defined medications (drugs absorbed through the skin, injections and gargles, as long as no liquids are ingested). Minors, the elderly, the sick and women who are breastfeeding or pregnant are exempt from fasting. Women during their menstrual cycle and people traveling are exempted only temporarily [10].

Male circumcision, although not mentioned in the Quran, and therefore not obligatory, is practiced almost universally by Muslim males. Islam bases the practice of circumcision on the seventeenth chapter of Genesis, the same biblical chapter referenced by the Jews. For Muslims, circumcision is a matter of cleanliness, purification and self-control. It can be done from after birth up to about fifteen years of age. Unlike Jews, Muslims do not have an agreement with the Italian state. This is mainly due to the lack of a hierarchical clerical structure as well as the lack of a single representation of the different Muslim communities present in Italy [11].

The Italian regional health system does not guarantee the possibility of carrying out non-therapeutic circumcision in a homogeneous way throughout the national territory. In most regions the surgery can only be done privately. The cost, which can vary between 2,000 and 4,000 euros, can be prohibitive for an immigrant family. Often, Muslim immigrant communities, are forced to resort to unqualified personnel, without adequate medical training and in hygienically unsafe environments, putting the very lives of children at risk [6].

Muslim patients from some countries generally do not accept being examined or treated by doctors or other healthcare personnel who are not of the same gender. Women in particular may be less willing to see a male doctor. In addition to the refusal to be assisted by male healthcare personnel, there is the use of delegation to the male companion (father, husband, brother) both for the listing of symptoms and for the approval of therapeutic prescriptions.

Visiting the sick is an important task in the life of a Muslim, so Muslim patients may receive a large number of visits.

Muslims are allowed to use temporary contraceptives, while permanent contraceptive methods (such as vasectomies and tubal closures) are only permitted if the woman's health is at risk.

Assisted reproduction is allowed, however there are some techniques and practices that are not allowed such as using a sperm donor and cryopreserved sperm after the death of the husband (donor).

A fetus is considered alive after 120 days of gestation, therefore abortion after 120 days of gestation is not permitted unless the pregnancy poses a serious threat to the mother's life, or in the case of fetal anomalies.

Muslims believe that death is predestined by God, therefore they accept both death and illness as a natural path of life. Islam does not accept treatment aimed at prolonging the final stages of a terminal illness. Under these circumstances it is permissible to shut down life support systems. Islam considers human life sacred, so suicide and euthanasia are prohibited; however, if a patient finds himself in a condition in which he has no life expectancy, he is allowed to stop medical treatment.

In the event of the patient's death, relatives may want the face (or entire body) to be turned towards Mecca and for the entire body to be covered with cloth and handled as little as possible by healthcare workers. Burial should be carried out as soon as possible after death, sometimes relatives request that burial take place on the same day as death. Islam prohibits the disfigurement of corpses and, for these reasons, some Muslims reject autopsies even though some Muslims (Shiites) favor organ donation and transplantation [9, 12].

When healthcare providers interact with a Muslim patient, they should follow certain recommendations whenever possible [12]. Islamic prayer times may interfere with healthcare facility meal times and special arrangements may be necessary. Before praying, Muslims must wash themselves with water; prayers are recited facing Mecca and performed on a prayer rug, but in case of illness they can be performed in bed or sitting. For those who are not physically confined to bed, you may need a clean, quiet space to pray.

If the staff were to carry out the cleaning, it is a gesture of courtesy to ask the patient himself to move the sacred text which is only touched in a state of ritual purity.

Muslims prefer to use the right hand for eating and drinking. A water container should be placed next to the Muslim patient for washing hands after each meal. Islam places great importance on personal hygiene (washing with water after urination or defecation, removing hair from the pubic area and armpits, keeping nostrils and nails clean) [12].

Hinduism

Hinduism is a religion of Indian origin and, with almost a billion practitioners, it is the third largest religious community in the world, after Christianity and Islam. Hindus are mainly found in India, Nepal and Bali. There are over a billion Hindus in the world. In Italy there are two hundred and twenty-two thousand Hindus, of which 55,000 Italian citizens and 167,000 resident immigrants [3].

It is difficult to define guidelines for healthcare workers because the term Hinduism does not mean a single religious structure, but a myriad of faiths, cultures and philosophies, sometimes even theologically distant from each other, but with common convergent principles. These differences are found in ritual and religious practices. A preliminary interview with the patient and family members is advisable to learn about the religious tradition and related observances.

According to the Hindus, the state of health is a state of balance of vital energies, it is not just one or more organs of the body that become ill, but there is an imbalance of the vital force which alters the functioning of one or more organs, in attempt to re-establish one's balance. Health is a piece within a complex system of relationships with the environment, emotions and feelings.

The relationship with the family unit is very important, it has a central role in the life of a Hindu, for this reason the visits could be very crowded [13].

The diet includes a ban on the consumption of beef. Many followers of Hindu religions are vegetarians and generally tend to avoid the consumption of milk, meat and eggs.

Hindu women wish to be cared for, bathed only by women and may wish to be examined by a doctor of the same sex. Hindu women are generally reluctant to go to the doctor and be examined and, if pregnant, only go to the doctor close to giving birth [14]. The Hindu woman is reluctant to show parts of her body so it is advisable to limit the affected area as much as possible and carry out the visit in the presence of her husband or another family member. Married women wear necklaces, bracelets or toe rings which have a very sacred value, they should never be taken off without their consent. The same goes for the sacred thread that some men wear around their chest.

There is no official position on contraception, for Hindus life is extremely sacred, birth control is considered a practice not to be encouraged. The only accepted form of contraception is moderation in sexual activity.

Termination of pregnancy is not permitted except in cases where it poses a serious risk to the mother's life.

As for drugs, natural ones are preferred, while those of animal origin are avoided.

There are conflicting opinions on transplantation and organ donation.

Hinduism encourages acceptance of pain and suffering (Hinduism and death with dignity: historical and contemporary cases) [15].

Hindus believe that the moment of death is determined by fate. The anxiety to prolong life as much as possible, denying imminent death is an undoubted consequence of the illusion of immortality, therefore they are not in favor of the long term use of life sustaining treatment [16].

Hindus believe that all living things, including animals, have a soul that transmigrates from one life to another. Consequently, they do not see death as the end of life but as a passage to rebirth, from one life to another [17].

An autopsy is usually not accepted and, if necessary, it is important to consult the family first.

Hindus practice cremation which according to their religion should take place immediately after death.

Buddhism

Buddhism originated in north-eastern India and then spread from India to central and south-eastern Asia, China, Korea and Japan and recently also to the West.

Buddhism is the fourth largest religion in the world with over 500 million followers. In Italy there are approximately three hundred and forty thousand Buddhists. Italian citizens of the Buddhist faith, including those who have acquired citizenship over the years, are 215,000, while resident Buddhist immigrants are 125,000 [3].

Buddhist women prefer to be visited and cared for by female healthcare personnel, while monks are prohibited from being cared for by personnel of the opposite sex. Often women only turn to health facilities at the end of their pregnancy.

There are no dietary restrictions due to religion, but many Buddhists are vegetarian or vegan.

According to Buddhist teachings, the value of life is sacred, taking life is the negative act par excellence, not only the life of man, but also that of other living beings must be respected.

Life begins at the very moment of conception. Therefore, the voluntary termination of pregnancy is in itself a very negative act. In some situations, for example in danger for the mother, in cases of physical violence or similar, the termination of the pregnancy may be permitted, but it is always the termination of a life. This has moral implications from the perspective of the woman's karma.

Illness and suffering are an integral part of man's life, and as such they must be realistically considered not a punishment for a fault committed, a misfortune, but a fact that must be addressed carefully from a therapeutic and psychological point of view. Any intervention and therapy aimed at improving the patient's condition is accepted.

As regards the approaching moment of death, a treatment is strongly recommended that guarantees the patient maximum tranquility and serenity so as to be able to best prepare for the moment of passing away. However, Buddhism often opposes the use of opioid medications at the end of life due to the undesirable consequence of a reduced level of consciousness at the time of death.

From the Buddhist perspective, the patient in a persistent vegetative state is a living human being. Such a patient should not, in principle, be treated differently from any other patient. Therefore, euthanasia is not permitted [18].

Death is the fundamental act of life as it indicates the possibility of a positive rebirth. There is a lot of attention to the passage, which does not end with cardiac arrest, but requires more time to allow consciousness to move away from the body. Buddhists believe that the body is not immediately devoid of spirit after death. According to Tibetan tradition, the body should not be handled for 72 hours, and many Buddhist families may request that the body remain at their disposal for several hours after death to perform religious rites [19].

From this perspective, the autopsy is seen as a bloody act and is therefore accepted with great difficulty.

In Buddhism there are no injunctions for or against organ donation. Central to Buddhism is the desire to alleviate suffering, so organ donation can be seen as an act of generosity [19].

Sikhism

The Sikh religion, the fifth religion in the world by number of believers, was born in northern India in the Panjab. It has around 30 million believers distributed throughout the world, in Italy the number of believers is around 150/180 thousand [3].

For Sikhs, hair (hair, beard and perineal hair for women) must not be removed from any part of the body without their consent. In the event that a patient's life is in danger and in the event that urgent medical care is required (which cannot be carried out without their removal), medical care must be provided without hesitation. If a Sikh patient refuses medical treatment on the basis of his religious beliefs (because his hair cannot be shaved), these wishes must be listened to and the patient informed of the potential risks arising from such a decision is required to sign a document in which he assumes all responsibility [20].

Cleanliness is very important as Sikhs follow a ritual of cleanliness and prayer each morning and evening, that healthcare workers should try to respect.

Given that the religion prohibits alcohol consumption and smoking and that most Sikhs are vegetarians, some medicines may not be suitable because they contain alcohol or are derived from animals. Healthcare professionals should inform patients: about the pharmaceutical composition and the production process of the proposed medicinal product (for example whether the use of materials of animal origin is foreseen in the manufacture of the product).

Prayer is an integral part of their daily routine. Sikh patients may wish to have a prayer book with them during their hospital stay. The prayer book is usually covered with a piece of cloth and should be kept in a clean place at bed height. It is important to wash your hands before handling any prayer book.

For a Sikh, the family is fundamental, therefore the family unit must always be kept informed and represents an excellent interlocutor for the medical and paramedical staff, in fact many decisions regarding the patient's health are made in agreement with the relatives.

Sikh patients prefer to be seen by healthcare professionals of the same sex and may request the presence of a family member during any clinical examination.

Healthcare professionals must ask permission from the patient or a family member before remove any article of faith; cut hair and hair from any part of the body; remove the turban [20].

Orthodox Christianity

The Orthodox Church does not have a single structure like the Catholic Church but is made up of local "autocephalous" Churches. An autocephalous church possesses the right to resolve all internal problems on its own authority and the ability to choose its own bishops, including the Patriarch, Archbishop or Metropolitan who heads the church. While each autocephalous church acts independently, they all remain in full sacramental and canonical communion with one another. The Orthodox currently number around 130 million and are widespread especially in Eastern Europe, the Balkan peninsula and the Middle East, but also in North Africa, Japan and North America. In Italy there are approximately two million Orthodox Christians: 400,000 Italians plus approximately 1,600,000 non-Italian citizens (resident immigrants), originating mainly from Romania, Ukraine and Moldavia [3].

The Orthodox Church considers human life and well-being as gifts from God, perceives the healing of physical illnesses by the doctor as also a divine action. Therefore, to achieve healing, most Orthodox Christians turn to both modern medicine and the spiritual resources of their ancient faith. The Orthodox Christian sees suffering as a consequence of man's sinful condition which manifests itself in various ways: through human mortality, individual sin, and the evil prevalent in society and nature.

There are no restrictions on diet but the Orthodox fast for many days a year: every Wednesday and Friday, and at the start of Great Lent, and on Great Friday of Lent. Fasting consists of excluding alcohol, oil and animal proteins and consuming only bread, pasta, rice, olives, vegetables and fruit.

The Orthodox Church does not oppose the use of drugs and blood transfusions as therapeutic measures, and in the case of a dying patient, palliative care should be provided to relieve pain.

Orthodox Churches generally have a more nuanced position on contraception than the Catholic Church. However, artificial contraception is not seen as evil, but can be considered lawful under certain conditions within marriage (for example if the spouses have already had more children) [21].

Only the Ethiopian Orthodox Church, the Eritrean Orthodox Church and the Coptic Orthodox Church advise to perform male circumcision.

The Orthodox Church condemns euthanasia as a mortal sin. If the patient's health condition is critical and there is no hope of recovery, interruption of life support systems may be allowed.

Once death has occurred, the presence of an Orthodox priest is necessary who, in addition to reciting prayers, will provide family members and/or medical personnel with information on the procedures to be performed. Since the faithful often ask the hospital to be able to place a candle near the patient's bed in the last moments of life and since this need is often not permitted for safety reasons, the Orthodox priest is the only person able to mediate between the hospital norms and tradition.

Autopsies should only be performed if clearly necessary.

The Orthodox religion only provides for burial in the ground (inhumation) [21].

Protestantism

There is no "Protestant religion" as such. "Protestant" is a term that applies to various Christian groups that do not accept the authority of the Pope of Catholicism or the Patriarch of Orthodox Christianity [22, 23].

According to estimates by the Center for Studies on New Religions (CESNUR), in 2021 among Italian citizens (excluding foreign citizens resident in Italy) there were 383,100 Protestants, whose main Churches of belonging were: Pentecostal, Evangelical (Lutheran and Reformed), Waldensian, Baptist, Methodist, Seventh Day Adventist, Anglicans. Among foreigners, residents and irregulars, CESNUR estimates 224,400 units [3].

Protestant Christians have a different way of understanding the cause of illness, some see it as a consequence of personal behavior and an expression of guilt or shame, others see illness as a cause derived from situations over which they have no control, others as a punishment or personal test from God.

Since these ideas are often linked to personal experiences, it is appropriate for healthcare professionals to discuss them with the patient. For example, a small number of Protestants from a tradition that practices faith healing will be reluctant to trust today's medical practices and may wish to be treated by faith healers in addition to the care provided by medical personnel.

There is no universal agreement between different Protestant groups regarding abortion [23].

Many Protestant groups affirm gender equality even though individual families may not practice it. Healthcare personnel may find themselves in situations where the males of the family are responsible for every decision regarding practical and therapeutic measures.

There are no specific diet-related prohibitions, however some Protestants may prefer to avoid the consumption of caffeine, meat, and alcohol. The Seventh-day Adventist Church, for example, shows particular attention to healthy and sober lifestyles. Adventists strictly follow a lacto-ovo-vegetarian diet. They refrain from eating meats such as pork, rabbit, horse and fish that do not have fins and scales. They also abstain from the use of alcohol, tobacco and any type of drug [24].

Most groups do not ban cremation. Some Protestant groups perform specific rituals and practices at the time of death, while others prefer that family, friends and their clergy be present to comfort the patient at this delicate time.

In general, Protestant groups do not prohibit organ and tissue donation, in fact most groups encourage it because it is a way of caring for others. Both blood transfusions and autopsies are permitted.

RELATIONSHIP BETWEEN STATE AND RELIGIOUS FAITHS IN ITALY

The Italian Constitution recognizes (article 19) the right to freely profess one's religious faith and practice worship, excluding "rites contrary to good customs", and prohibits regulatory limitations on ecclesiastical bodies, which can organize themselves according to their own statutes. Relations between the State and religious confessions other than the Catholic one, according to Article 8 of the Constitution, are regulated by law on the basis of agreements that must be stipulated with the relevant representatives [11]. The confessions with and without agreement are shown in *Table 1*. The Agreement with the State guarantees, among other things: spiritual assistance in compulsory institutions, such as the armed forces, places of health and penal institutions; the right not to make use of religious teaching; recognition of the civil effects of marriages celebrated before the ministers of worship of the respective religious confessions; the protection of places of worship and the valorization of assets relating to the historical and cultural heritage of each confession; free exercise of their ministry by ministers of religion; the recognition of the religious holidays of each religious confession.

In the case of the Confessions that have stipulated the Agreement, hospital spiritual assistance is entrusted to ministers of religion registered in the appropriate certi-

Table 1
Religious faiths who have or have not entered into the agreement with the Italian state, as required by article 8 of the Constitution

Religious faiths that have entered into an Agreement with the Italian State
• Waldensian Table
• Union of Italian Jewish communities
• Union of Seventh-day Adventist Christian Churches
• Assemblies of God in Italy
• Evangelical Baptist Christian Union of Italy
• Evangelical Lutheran Church in Italy
• Sacred Orthodox Archdiocese of Italy and Exarchate for Southern Europe
• The Church of Jesus Christ of Latter-day Saints
• Apostolic Church in Italy
• Italian Buddhist Union
• Italian Hindu Union
• Soka Gakkai Italian Buddhist Institute
Religious faiths that have not entered into an Agreement with the Italian State
• Several independent Evangelical Churches
• Islam
• Jehovah's Witnesses
• Romanian Orthodox Diocese of Italy
• Sikhism

fied lists. They enjoy free access to institutions even on their own initiative, without time limitations; in any case the hospital is required to promptly communicate requests for assistance made by patients or their families.

For religions without convention the regulatory basis remains Royal Decree no. 289 of 1930, according to which ministers of religion admitted to the State can be authorized to frequent places of treatment, to provide religious assistance to patients who request it, by the administrative management of the institute itself (art. 5). For the latter, spiritual assistance is not always guaranteed.

THE INTERVIEWS: OTHER CRITICAL ISSUES

The interviews with the representatives of the religions of the "Interreligious Table of Rome" confirmed the critical issues previously listed for the individual religious faiths.

Representatives of Hindus, Buddhists and Muslims reiterated the problems relating to the relationship of immigrant faithful with social and healthcare personnel, the poor adherence to female cancer prevention campaigns and the poor access to gynecological visits and pre- and post-natal procedures. The representative of the Buddhist faith also underlined the difficulty of health integration of the Chinese community, essentially due to linguistic barriers.

Another critical issue noted is the lack of trust that Eastern faiths share in official medicine and the fact that immigrants often prefer to return to their country of origin to undergo treatments and surgeries. As regards Islam, it should be added that in the Italian school population there are very few girls originating from Bangladesh, precisely because some groups of immigrants, originating from Bangladesh, send their daughters to study in their country of origin.

Some religions such as Islam and Judaism, which give great importance to end-of-life rites, complain about the general impossibility of carrying them out in healthcare facilities.

All the representatives, both of the faiths affiliated with the State and those not affiliated with the State, underlined the difficulty of having their religious ministers access hospitals to assist their faithful, in addition to the lack of places in our hospital facilities dedicated to the prayer of patients hospitalized.

CONCLUSIONS

In this study we have considered the main needs of believers of religions other than the Catholic one who turn to healthcare, and we have tried to indicate the consequent behaviors that all healthcare workers should take into consideration to guarantee adequate assistance in structures of the Italian health services, as required by our Constitution.

The task of the NHS is to guarantee access to prevention, diagnosis and treatment services to every individual present on the national territory, without distinction of gender, religion or ethnicity. Religious beliefs influence choices regarding procreation, organ donation and transplantation, palliative care and end-of-life rituals; adherence to pharmacological prescriptions and dietary indications and different attitudes towards prevention. Structural change in society also requires change in the healthcare sector.

However, in the management of the doctor/patient relationship and in the assistance/care spaces there is still a general lack in the implementation of active practices and positive actions with respect to the need to guarantee adequate religious and spiritual support aimed at alleviating suffering, pain and illness, to promote individual well-being

It is often the citizens themselves, of faiths other than the Catholic religion, who report a certain inadequacy of health facilities in dealing, in the treatment and care sector, with specific needs relating to aspects of a cultural and religious nature, with the emergence of possible inequalities. Places of care and assistance are also called to be spaces of attention to intercultural dialogue and respect for religious differences. To support care processes it is also necessary to intervene on the quality and comfort of the hospital environment; propose adequate menus; ensure support for the spiritual and religious needs of all patients; facilitate the entry and presence of ministers of worship for the spiritual assistance of both the patient and his family, prepare spaces for the prayer needs of the faithful.

The change towards a multi-religious and multicultural society requires that healthcare workers equip themselves with new professional skills, suited to the health needs of citizens of other cultures and religions.

In conclusion, healthcare is called to renew itself and adapt to changes in needs and expectations that affect the population. This is why it is increasingly important to build a healthcare system based on integration, dignity and respect for the person as a whole.

It is therefore impossible to ignore adequate information/training courses on the fundamental principles, rules and observances dictated by the different religions followed by patients.

Authors' contributions

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

Conflicts of interest statement

The Authors declare to have no conflict of interest.

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Analysis of suspected adverse reactions to food supplements containing beehive products: an update from the Italian Phytovigilance System

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Abstract

Introduction. Beehive products are widely used in food supplements; however, their composition variability and allergenic components have raised some concerns. This work aims to provide information about the beehive products safety profile by evaluating the suspected adverse reactions (ARs).

Methods. The suspected report of ARs collected within the Italian Phytovigilance System (IPS) were evaluated. The clinical and demographic characteristics of the cases were described, and the causality assessment performed.

Results. 61 reports were analysed, mainly concerned women. Serious events were reported in 17 forms (28%). The ARs (n=116) referred to respiratory (25.0%), skin (24.1%), and gastrointestinal disorders (21.5%). Label warnings for atopic subjects were present only in 7 food supplements. The causality assessment was mostly probable (54.1%).

Conclusions. Present findings outline relevant information about the safety issues of beehive product consumption, especially in atopic or allergic subjects, and strengthen the importance of IPS to point out safety signals.

Key words
- allergy
- atopy
- safety
- dietary supplements
- honeybee products

INTRODUCTION

In the last years, beehive products, namely honey, propolis, and royal jelly, have attracted a great attention of the scientific community owing to their presumed beneficial effects on human health. Indeed, several studies have highlighted a plethora of biological properties of these products, including antiseptic, anti-inflammatory, wound-healing, antioxidant, antibacterial, antimycotic, antifungal, antiulcer, anticancer, anti-allergy, and immunomodulatory ones [1-3]. Therefore, some attempts have been made to exploit the benefits of these products at a clinical level, albeit with limited results. Indeed, the high variability at chemical level, makes difficult the standardization of their preparations and, consequently, the reproducibility of the expected effects [3]. Several parameters contribute to the composition variability, such as the honeybee varieties, the plant species, the geographical area, and the harvesting season. Therefore, currently, beehive products have few applications, mainly as dietary supplements to relief minor ailments, in both adults and children [4]. Particularly, people resort to them to counteract respiratory tract diseases, to boost the immune system, and to increase body energy. However, at present, no health claim have been attributed to dietary supplements containing beehive products due to the high variability of their composition [5].

Despite the potential beneficial properties ascribed

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to beehive products, some concerns have emerged with respect to their safety. Particularly, the esters of caffeic acid (phenylethyl caffeate and methylbutenyl caffeate) seem to be responsible for the strong sensitizing properties of propolis [6]. Indeed, contact dermatitis and severe systemic allergies have been reported [7, 8]. Accordingly, propolis has been recently added in Europe to the test battery of compounds used in routine diagnosis of allergic contact dermatitis (ACD) [8, 9]. However, also other substances, such as isoferulates, flavonoid aglycones, and free aromatic acids, may play a role in propolis allergy [7]. Some cases of ACD have been ascribed also to royal jelly and honey. In the latter case, the presence of propolis and pollen in honey could be the culprits. The presence of essential oils in beehive products contributes to the occurrence of allergic reactions, being contact allergens. Moreover, substances secreted by the bees themselves may be involved in allergies [7].

Currently, there is a lack of knowledge about the efficacy and safety profile of these products due to both the absence of clinical trial and pharmacoepidemiological studies. In fact, absence of information about their use in the population makes it impossible to conduct studies for risk quantification. Therefore, at the moment, spontaneous reports of adverse reactions (ARs) represent the only tool to collect information related to the safety profile of these natural products.

In this context, in the present paper, the suspected ARs associated with the consumption of products containing, among others, beehive ingredients, collected within the Italian Phytovigilance System (IPS), have been evaluated to monitor their safety profile. The paper represents an update and a widening of a previous work [10] in which reports of ARs to food supplements containing propolis were analysed.

METHODS

All spontaneous reports of ARs referred to beehive products gathered within the IPS were analysed. IPS was set up in 2002 to collect spontaneous reports of suspected ARs related to products of natural origin, so improving the information about the safety profile of dietary supplements, galenic and/or herbal preparations. IPS is coordinated by the Italian National Institute of Health (Istituto Superiore di Sanità, ISS) and operates separately from the Italian Pharmacovigilance network, which collects ADRs (adverse drug reactions) related to registered drugs. The ARs concerning products of natural origin can be reported online by health professionals, companies, and citizens through the website www.vigierbe.it. ARs are coded according to the medical dictionary of regulatory activities (MedDRA) and the composition of the product (ingredients and dosages) is verified trough the label notified to the Italian Ministry of Health.

In the present study, an in-depth analysis of ARs related to beehive products, collected within the IPS between March 2002 and August 2023, has been performed by excluding the reports that have been already analysed in the previous publication [10]. All available information on the reports was retrieved and the demographic, clinical and pharmacological characteristics of cases were collected and analysed. In particular, data referred to: 1) patient characteristics, namely age, sex, and clinical history or status; 2) suspected product information, such as product type, dosages, composition, duration and reason for use; 3) concomitant products and predisposing conditions (e.g., previous allergies); 4) ARs description (i.e., seriousness, dechallenge, rechallenge, and outcome).

A multidisciplinary group evaluated each report and estimated the causality assessment (categorized as certain/definite, probable/likely, possible, unlikely, or un-assessable/unclassifiable) according to the World Health Organization (WHO) system for standardized case causality assessment criteria. When more than one active compound was present in the suspected product, the attribution of causality concerned the whole commercial product. The composition of products was reported, excluding excipients, as on the label of the package. Continuous data were expressed as mean ± standard deviation (SD) and categorical variables were expressed as count or percentages.

RESULTS

From March 2002 to August 2023, 79 spontaneous reports of suspected ARs related to beehive products were collected. Excluding the 18 cases previously published [10], 61 reports were analysed in the present study. Clinical and demographic characteristics of cases are provided in *Table 1*. The median age of patients who experienced ARs was 37.5 years (Inter Quartile Range=9.75-53.25 years); women were involved in 32 cases (52%), men in 26 (43%) while in 3 cases (5%) the information was lacking. Serious reactions occurred in 17 cases (28%). The ARs reported (n=116) were mainly related to "Respiratory diseases" (n=29; 25.0%), "Skin and subcutaneous tissue" (n=28; 24.1%), and "Gastrointestinal disorders" (n=25; 21.5%), mostly not serious (*Figure 1* and *Figure 2*).

The products involved in ARs were food supplements (n=45; 72.6%), herbal products (n=5; 8.1%), medical devices (n=4; 6.4%), herbal medicinal products (n=3; 4.8%), food (n=1; 1.6%) and others (n=4; 6.4%). About the composition, propolis was present in 59.7% of products (n=37), honey in 32.3% (n=20), royal jelly in 29% (n=18), and pollen in 4.8% (n=3) (See *Supplementary Material* available online). In 18 products, a combination of these components was present; moreover, in most of the cases, suspected products also contained different herbal extracts. The reason of use referred to two main reasons: coughs/pharyngitis/colds (44.3%; n=27) and asthenia/tonic (16.4%; n=10); the information was unknown in 21 cases (34.4%) and in 3 (4.9%) cases "other reasons" were reported (See *Supplementary Material* available online). Predisposing conditions, as atopy or allergy, were indicated in 30% of reports. Concomitant products were reported in 35.4% (n=22) of cases, however, in 17 cases (27.9%) the information was not available. From the label analysis, only 7 suspected products carried warnings for atopic subjects. Healthcare professionals reporting the suspected ARs were mainly physicians (n=31; 50%) and pharmacists (n=22;

Table 1
Clinical and demographic characteristics of patients showing adverse reactions to dietary supplements containing beehive products collected from the Italian Phytovigilance System

Characteristics	Overall (61)	Serious (17)	Not serious (44)
Age median (range) (1 NR)	37.5 (2-94) IQR (9.75-53.25)	34 (4-71) IQR (10.25-57.25)	36.5 (2-94) IQR (10-54.25)
Sex			
Male	26	5	21
Female	32	9	23
Unknown	3	3	0
Predisposing conditions			
Yes	18	6	12
No	26	4	22
Unknown	17	7	10
Concomitant products	18	6	12
≥5	3	0	3
Between 1 and 4	19	8	11
No	22	3	19
Unknown	17	6	11
Reason of use			
Coughs/pharyngitis/colds	27	9	18
Asthenia/tonic	10	2	8
Other	3	0	3
Unknown	21	6	15
Type of product			
Food supplement	45	14	31
Herbal product	5	1	4
Medical device	4	1	3
Herbal drug	3	0	3
Food	1	0	1
Other	4*	1	3
Report qualification			
Physician	31	10	21
Pharmacist	22	4	18
Citizen	4	1	3
Other	3	1	2
Unknown	1	1	0
Outcome			
Recovered	30	6	24
In recovering	7	3	4
Improvement with sequalae	4	3	1
Not recovered	2	1	1
Unknown	18	4	14
Dechallenge			
Positive	30	9	21

Continues

Table 1
Continued

Characteristics	Overall (61)	Serious (17)	Not serious (44)
Negative	1	0	1
Unknown	30	8	22
Rechallenge			
Positive	2	0	2
Negative	2	0	2
Not executed	46	15	31
Unknown	11	2	9
Causality assessment	2	0	2
Probable	33	6	27
Possible	21	8	13
Unlikely	1	0	1
Not related	3	1	2
Unassessable	3	2	1

*One report contained two suspected products; NR: not reported; IQR: interquartile range.

35.5%). In term of outcome, the clinical condition was mostly "recovered" (n=30; 49.2%), "in recovering" (n=7; 11.5%), "improvement with sequelae" (n=4; 6.6%), and "not recovered" in 2 cases (3.3%); the information was lacking in 18 reports (29.5%). Dechallenge resulted positive in 49.2% of reports (n=30); rechallenge was positive in 2 cases (3.3%); however, in most cases it resulted as "not executed". The causality assessment performed was mostly probable (54.1%; n=33) and possible (n=21; 34.4%); in 7 cases (11.5%) the assessment resulted as unlikely (1 case), unrelated (3 cases) or unassessable (3 cases), detailed information is presented in *Table 1*.

DISCUSSION

Nowadays, beehive products are found in many commercial products, among which dietary supplements, resulting in a widespread human exposure and an increased risk of adverse reactions, particularly hypersensitivity [8, 11]. Propolis has been recognized as one of the most used honeybee allergenic products, causing symptoms ranging from mild to severe reactions, such as anaphylaxis [12-14]. Particularly, documented cases of oral sensitization to propolis are rare, while allergic reactions resulting from local administration of propolis are significantly more common [15]. Caffeic acid and its esters have been found as the primary chemical constituents responsible for haptenic activity and allergenicity [8]. Along with propolis products, some cases of suspected allergic reactions to honey and royal jelly, have been also reported [16, 17]. Honey allergy may be caused by pollen content (especially Compositae pollen) or bee-derived proteins, while in the case of royal jelly the major protein 3 (MRJP3) has been identified as the main culprit [16, 18]. Moreover, allergen cross-reactivity between bee products can also occur [18].

Overall, the study retrieved 61 reports of ARs related to the consumption of beehive-derived products. Particularly, 17 reports pointed out serious ARs, 12 of which were related to products containing propolis (n=12), so confirming the trend highlighted in the literature [11]. The symptoms were mostly related to an allergic condition exacerbated in respiratory, cutaneous, or gastrointestinal disorders.

Commonly, beehive-derived products are used to alleviate the inflammatory status of the upper airways or to decrease states of fatigue after flu [19]. This was confirmed by the analysis where the reason for use referred to coughs/pharyngitis/colds in 43.5% of cases and asthenia/tonic in 16.1%. The study, also highlights the short duration of use of these products, being the median of 2 days with an interquartile range between 1 day and 4 days. This brief duration of use could be also related to the occurrence of ARs, mostly acute reactions with short-term onset that required the discontinuation of the products. In support, dechallenge, when reported, resulted as positive in about 50% of cases, reinforcing this hypothesis. Details of the reports are described in *Supplementary Material* available online.

The present work offers several points for discussion. Firstly, in some cases the patients had only taken one product derived from bees, such as propolis (in cases 1, 10, 19 and 31) or royal jelly (in cases 12, 13, 18 and 29); furthermore, concomitant factors or predisposing conditions were absent: this fact makes the association between consumption of bee product and AR more likely. However, in most cases, several ingredients were present in the reported food supplements making it difficult to establish the role of the beehive products in the ARs. Furthermore, other dietary supplements or drugs were often assumed concomitantly, making the picture more complex. As an example, in the case 4, a 10-year-old child experienced toxic epidermal necrolysis, a type IV delayed hypersensitivity reaction [20], one day after consuming a supplement containing propolis and rose-

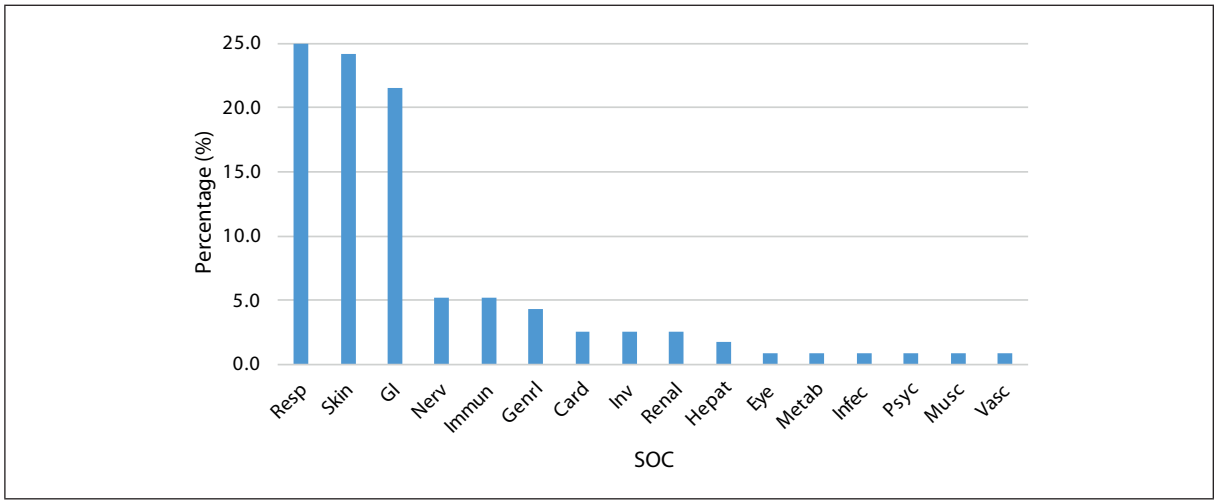

Figure 1
Frequency of system organ class (SOC) – overall.
Card: cardiac disorders; Eye: eye disorders; Genrl: general disorders and administration site conditions; GI: gastrointestinal disorders; Hepat: hepatobiliary disorders; Immun: immune system disorders; Infec: infections and infestations; Inv, investigations; Metab: metabolism and nutrition disorders; Musc: musculoskeletal and connective tissue disorders; Nerv: nervous system disorders; Psyc: psychiatric disorders; Renal: renal and urinary disorders; Resp: respiratory, thoracic and mediastinal diseases; Skin: skin and subcutaneous tissue disorders; Vasc: vascular disorders.

hip. He was also in therapy with gentamicin sulfate and betamethasone valerate for treating erythema and took another food supplement for pharyngolaryngeal pain. Moreover, about one week before the onset of the reaction, he was treated with the anesthetic lidocaine for the application of three stitches for a head wound. The AR was life-threatening and the patient did not recover yet, when the AR was reported. Previous evidence has shown that the intake of propolis can trigger skin reactions [9, 21]. However, the occurrence of toxic epidermal necrolysis has also been associated with products containing rose hips [22] and gentamicin, the antibiotic taken by the patient in addition to the food supplement [23]. Furthermore, lidocaine has also been reported to induce late hypersensitivity reactions [24]. Regarding the concomitant supplement, it was not possible to hypothesize its contribution to the AR, being its composition unknown. Therefore, although an association between product intake and onset of the AR has been highlighted, the actual contribution of the product to the reaction cannot be established owing to concomitant drugs/supplements taken by the patient whose

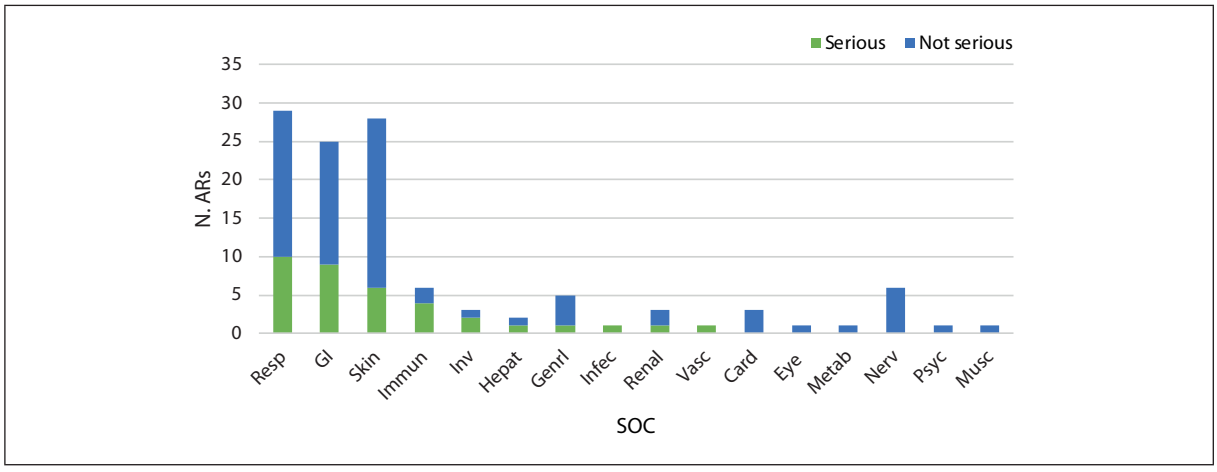

Figure 2
Number of adverse reactions (serious and not serious) grouped by system organ class (SOC).
Card: cardiac disorders; Eye: eye disorders; Genrl: general disorders and administration site conditions; GI: gastrointestinal disorders; Hepat: hepatobiliary disorders; Immun: immune system disorders; Infec: infections and infestations; Inv: investigations; Metab: metabolism and nutrition disorders; Musc: musculoskeletal and connective tissue disorders; Nerv: nervous system disorders; Psyc: psychiatric disorders; Renal: renal and urinary disorders; Resp: respiratory, thoracic and mediastinal diseases; Skin: skin and subcutaneous tissue disorders; Vasc: vascular disorders.

contribution in the AR cannot be excluded. As result the causality assessment resulted "possible".

Case 58, a 7-year-old child, experienced an allergic reaction characterized by generalized rash on the face, trunk, limbs, itchy and warm to the touch. She had assumed a food supplement containing concentrated apple juice, honey, fructose, ginger dry extract, and another food supplement based on agrimonia and tormentilla (See *Supplementary Material* available online). Honey consumption has been linked to several cases of allergic-type ARs, especially in children [16]. However, it should be also considered that plants of the Rosaceae family have recently emerged as the most frequent cause of allergic symptoms among foods, being responsible for the lipid transfer proteins (nsLTPs) syndrome, which may range from local manifestations (e.g., mild contact urticaria, oral allergy syndrome, gastrointestinal issues) up to anaphylaxis and even anaphylactic shock [25]. Therefore, in the present case, both supplements could have played a role in the triggering of ARs.

Sometimes, people who experienced ARs were also affected by serious conditions, thus making it difficult to establish whether the AR was due to the product consumption or to an exacerbation of the disease. For example, case 34, a 71-year-old woman, experienced oedema, ascites, oliguria, and toxic erythema after taking a supplement for flu syndrome with cough. The product contained propolis, thyme, rose hip, and echinacea. She was also assuming bisoprolol fumarate and was affected by liver cirrhosis. Hypersensitivity reactions and skin irritation have been reported for echinacea, propolis, and thyme [26-28]. However, liver cirrhosis worsening could explain to the occurrence of ascites and oliguria [29, 30]. Moreover, case 35, a 60-year-old female, experienced an allergic reaction characterized by acute respiratory failure after assuming a medical device syrup, containing propolis, which have been reported to cause ARs at respiratory levels [11]. However, the presence of goiter in the patient could have worsened the respiratory symptoms, due to the trachea compression. Another important aspect to consider is that the predisposing condition could be also represented by the reason for the use of the product such as sore throat or pharyngodynia. Therefore, it could be supposed that the beehive product intake worsens respiratory symptoms even if supporting literature is lacking. In addition to respiratory reactions, many skin events (mostly non-serious) have been collected in this study and have been already reported in numerous case reports [21, 31-36]. Even if these events are mostly not serious, it is desirable to consider the benefit-risk profile for these natural products, especially because they are usually used for minor ailments. Moreover, even if rarely, beehive products have been also associated with major dermatological adverse events, such as in the cases 4, 7, 12, 34, 49, 58 and 60.

Another important element of discussion is represented by the consumption of beehive-derived products by atopic subjects. In general, there is no evidence of toxicity of beehive products; however, numerous ARs appear in atopic subjects; therefore, they could be predisposed to allergic-type and inflammatory manifestations [37]. According to the most traditional classification [38], adverse reactions occur in individuals with a certain predisposition and are not readily anticipated; thus, from a pharmacological perspective, they are called "bizarre". Based on present results, it was found that in 30% of the reports (see cases 10, 11, 30, 40, 48, 49, 50, 53 and 55) predisposing conditions, such as atopy or previous allergy manifestation, were indicated (in 28% cases no information was reported). As an example, case 10, a 32-year-old woman, experienced pharyngodynia after taking a product containing propolis, to relieve dry cough due to pollen allergy. To be noted that in this case dechallenge was positive. In case 40, palate and tongue edema, and dyspnea affected a 65-year-old woman after assuming a supplement (propolis agrimony, rose hip, and zinc gluconate) for pharyngodynia. The patient's clinical history highlighted previous allergies to grasses, mites, mosquitoes and horseflies. Similar scenarios were also reported in cases 49 and 53. Therefore, atopic subjects should be discouraged from using beehive-derived products to avoid possible risk of allergic reactions.

Besides atopy, other predisposing conditions, such as autoimmune diseases, could represent an important factor in triggering the AR. For example, in case 56, the subject (a 36-years-old female) suffered of life-threatening sore throat and oedema after the intake of a supplement containing propolis (multifraction hydroalcoholic extract standardized on total flavonoids) and *Citrus limon* L. essential oil. Moreover, she presented several predisposing conditions, namely multiple sclerosis, fibromyalgia, osteoarthritis, and thyroiditis. These are immune-mediated diseases with an upper-activation of inflammatory mechanisms [39-41], so a condition which could possibly generate an inflammatory response after the intake of beehive-derived products. Each of these conditions requires a specific pharmacological treatment (although the concomitant medications were not specified in the report form); therefore, it is not possible to exclude a potential drug-natural product interaction. Both atopy and autoimmune diseases could be considered as predisposing the ARs due to their inflammatory physiopathology; however, up to now there is no evidence supporting this association; thus, this hypothesis is merely spurious and highlights the need to perform more studies aimed at analyzing the correlation between the inflammation in these pathologies and the response of the immune system to beehive products.

In this in-depth analysis it was observed that patients with predisposing conditions experienced more severe reactions. This issue should not be underestimated, considering that, very often, users do not receive adequate information about products of natural origin before their intake. Indeed, health professionals not always investigate the concomitant and/or predisposing conditions of patients; moreover, the operators of the food sector do not highlight on the product label the potential risks for predisposed individuals, perhaps for both marketing reasons and because there is no legal requirement to state such warnings. Nevertheless, this information would lead an increased consumer awareness, so guiding them in making the most targeted, safe, and conscious choice for the use of such products

and, thereby, stemming or limiting the ARs risk.

Noteworthy, Northern Italy was the area mostly involved in reporting the potential ARs to beehive products (51 cases); the Southern and Central areas contributed less, having only sent 5 and 4 reports, respectively, while in one case no information was reported. This disproportion in reporting between Italian areas could be due to the greater sensitivity of the North to report ARs related to natural products rather than by a greater frequency of events in these areas. However, it is also possible that the difference highlighted could be due to both a major consumption of natural products and a higher level of pollution which could be related to the highest frequency of respiratory problems [42].

At last, another point worthy of discussion is the large number of product categories in which beehive products can be found, thus causing some confusion among users. Indeed, in the reports analyzed within the analysis, beehive products were present in food, herbal products, herbal medicinal products, food supplements, and medical devices. Moreover, it should be outlined that suspected ARs to medical devices and herbal medicinal products are out of the scope of the IPS being a specific one already in place [43, 44]. However, to avoid losing information, we included them in the analysis. Therefore, it is important to increase the knowledge of health professionals and the general population on products of natural origin.

CONCLUSIONS

Based on the best available knowledge, the present study along with the previous published one [9] are the only focusing on the analysis of ARs to beehive products. Indeed, while some case reports are present in the literature, no clinical trials or observational studies, aimed at characterizing the safety profile of beehive products, were retrieved. Particularly, this study was conceived as an observational retrospective analysis of spontaneous reports collected from the IPS to characterize the safety profile of beehive products, thus allowing to: (a) identify safety issues; (b) highlight potential subgroup of people at major risk due to predisposing conditions, and (c) provide awareness of consumers concerning beehive products in a public health perspective. Present findings outline relevant information about the safety profile of beehive products consumption in atopic subjects. On the current legislation it is not mandatory to indicate beehive ingredients as allergic compounds. However, atopic or allergic people could take advantage on finding adequate information on the product label. The insertion of an information on the label could be an important help for at risk consumers who could consciously evaluate the benefit/risk profile of the beehive product consumption. Furthermore, several issues related to the complexity of natural products have been highlighted such as the fact that several ingredients were often present; thus, it is impossible to determine with certainty the role played by beehive products in the observed reactions. These results strengthen the importance of IPS as an irreplaceable method to monitor food supplements' risk signals, which otherwise would be lost, considering that safety studies are not required for their commercialization.

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Conflict of interest statement

The Authors declare no conflicts of interest.

Ethics approval

The present study does not require any institutional or national ethical committee approval. Moreover, personal data were processed according to the current legislation.

Availability of data and material

The Authors confirm that the data supporting the findings of this study are available within the article and the *Supplementary Materials* available online.

Authors' contributions

II: data analysis; investigation; writing; original draft. SDG: data analysis; investigation; writing; original draft. GM: supervision; writing; review and editing. MS: supervision; review and editing. FMI: supervision; writing; review and editing.

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BRIEF NOTE

Precision prevention network: new pathway for supporting women victims of violence

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Abstract

Introduction. Violence against women (VAW) is a persistent global public health problem that runs across all social classes and ethnicities with a considerable negative influence on women's health and behaviour. Early detection, appropriate interventions and multidisciplinary cooperation are crucial factors in tackling gender violence.

Objectives. This note describes "The Violence against women: long-term health effects for precision prevention" transdisciplinary and multicenter project that aims to implement the National Guidelines with two sets of questions: the European Injury Database (EU-IDB) violence module and the Post-Traumatic Stress Disorder (PTSD) questionnaire for improving innovative approaches to limit the long-term health effect of VAW. Furthermore, the analysis of epigenetic profile in women's DNA may contribute to the knowledge of molecular mechanisms underlying PTSD and other non-communicable diseases. Epigenomic research in parallel with rigourous guidelines and social, educational, clinical and community interventions could accomplish innovative precision prevention protocols.

Conclusions. Public health plays essential role in identifying risk factors and strengthening the support for women victims of violence.

Key words

- violence against women (VAW)
- intimate partner violence (IPV)
- post traumatic stress disorder (PTSD)
- long-term effect
- precision prevention

INTRODUCTION

Violence against women (VAW) may determine higher physical health morbidity and mortality [1]. It is one of the most devastating plagues worldwide with a considerable negative influence on women's health and behaviour [2].

The United Nations defines VAW as "any act of gender-based violence that results in, or is likely to result in, physical, sexual, or mental harm or suffering to women, including threats of such acts, coercion or arbitrary deprivation of liberty, whether occurring in public or in private life" [3].

Furthermore, the Council of Europe Convention on preventing and combating VAW and domestic violence, the so-called Istanbul Convention (2011), defines gender-based violence as any violence directed against a woman as such, or that affects women disproportionately (art. 3) [4].

A data analysis conducted from 2000 to 2018, across 161 countries, by WHO and UN Interagency Working Group on Violence against Women, found the prevalence of nearly 30% of women subjected to physical and/or sexual violence by an intimate partner or non-partner sexual violence or both [1].

In addition, the Italian National Institute of Statistics reported that about 31.5% of women have experienced some form of violence at least once in their life [5].

Current data confirm the very high prevalence of all types throughout the world [6, 7]: 35% of women worldwide have experienced either physical and/or sexual violence, 7% have been sexually assaulted by someone other than a partner, and 200 million have experienced female genital mutilation/cutting [8].

Worldwide, almost one-third (27%) of women aged 15-49 years, who have been in a relationship, reported that they have been subjected to some form of physical and/or sexual violence by their intimate partner [1]. An increasing research demonstrates the associations between intimate partner violence (IPV) and women's mental health problems, in particular, depression and stress related disorders [9] affecting woman's physical and mental health, reducing sexual autonomy, and in-

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creasing the risk for unintended pregnancy and multiple abortions [10].

According to the European Injury DataBase (EU-IDB) [11], the two most common forms of VAW are IPV and violence by acquaintances or friends (39% and 17% respectively).

Thus, violence has long-term consequences even if the violence has stopped or has been limited to a single abuse episode making the victims vulnerable to many diseases and conditions [10] (*Figure 1*). Among the mental health and behavioural disorders, the most prevalent is the Post Traumatic Stress Disorder (PTSD), a stress-related disorder triggered by sudden traumatic events and multiple genomic factors [1, 12].

In analogy to the Istanbul Convention, the current Italian National Strategic Plan on male violence against women [13] includes 4 pillars: *i)* prevention, *ii)* protection and support, *iii*) prosecution and punishment, *iv)* assistance and promotion.

The Decree of the President of the Council of Ministers (November 24, 2017) introduced the National Guidelines for Health Authorities and Hospitals concerning rescue and socio-medical assistance to women victims of violence, adopted in accordance with the objectives of the Italian National Strategic Plan [14]. The aim of the National Guidelines is to provide an adequate and integrated intervention in the treatment of the physical and psychological consequences of violence starting from timely care of women victims of violence up to accompaniment to local services. This pathway encompasses both the Emergency Department (ED) and the dedicated medical services in the territory (*Figure 2*).

MEASURES TO IMPROVE THE PATHWAY FOR SUPPORTING WOMEN VICTIMS OF VIOLENCE

National Guidelines path provides a triage code (for confirmed or suspected violence) and, according to the severity of the trauma, an *ad hoc* protocol, as the result of the activation of fast track to psychological assessment in case of less serious health conditions; otherwise, in the case of hospitalization, the psychological assessment will be performed when the health conditions improve. In order to better understand the context of violence, our project proposes to collect information concerning: *i)* sex of the perpetrator, *ii)* age of the perpetrator, *iii)* setting of the assault *iv)* relationship victim/perpetrator *(see Supplementary Material available online in italian version, in order to meet the objectives of the project; Figure 2)* through the EU-IDB violence module [11].

In addition to the physical and medical examination, a psychological interview is submitted for assessing re-victimization risk. If, following the psychological assessment, as already suggested by National Guidelines (*e.g.* with the Brief Risk Assessment for ED-DA-5; see *Supplementary Material available online*) [15], a medium/high risk of relapse emerges, the woman is entrusted to an emergency shelter or similar facilities, otherwise she is discharged. In both cases, the objective is the activation of her entry into the territorial anti-violence network.

Finally, the PTSD assessment is carried out when patient has established a relationship with the psychologist. After the discharge from hospital to her place to an emergency shelter, the PTSD assessment can be performed using the International Trauma Questionnaire-ITQ (*see Supplementary Material available online; Figure 2*) [16].

One of the new tasks of the Central Actions Area (*Centro Nazionale per la Prevenzione e il Controllo delle Malattie, CCM*) "Violence against women: long-term health effects for precision prevention" requires the integration of EU-IDB violence module and ITQ in the National Guidelines [14].

This integration is part of a multicentric and transdisciplinary project, "The Violence against women: long-term health effects for precision prevention", aiming at defining new strategies and models for supporting wom-

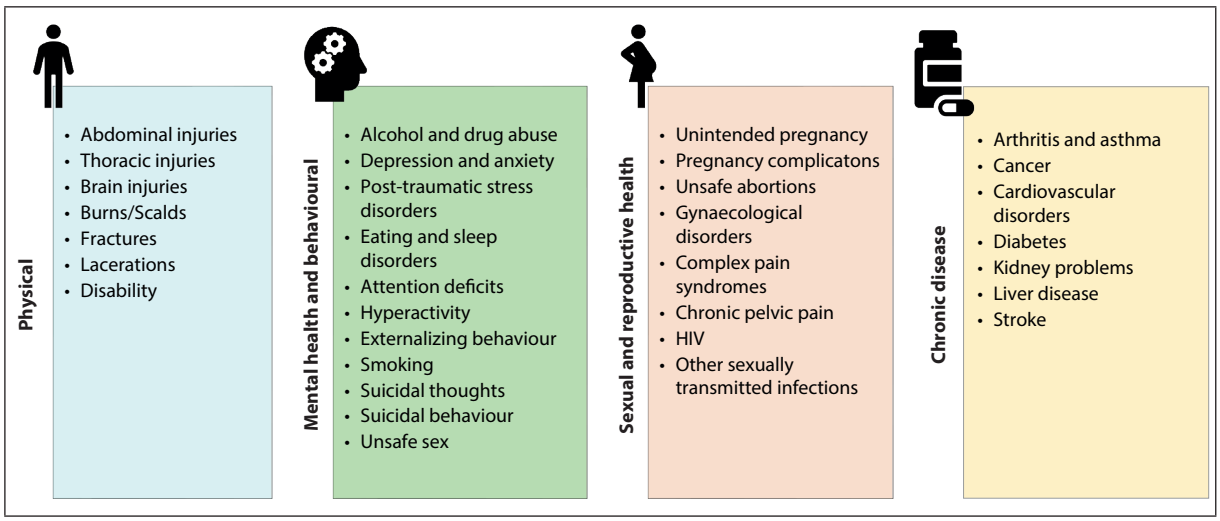

Figure 1
Behavioural and health consequences of violence (adapted from WHO. Global status report on violence prevention 2014. Available from: https://www.who.int/publications/i/item/9789241564793, last access August 2024. WHO is not responsible for the content or accuracy of this adaptation).

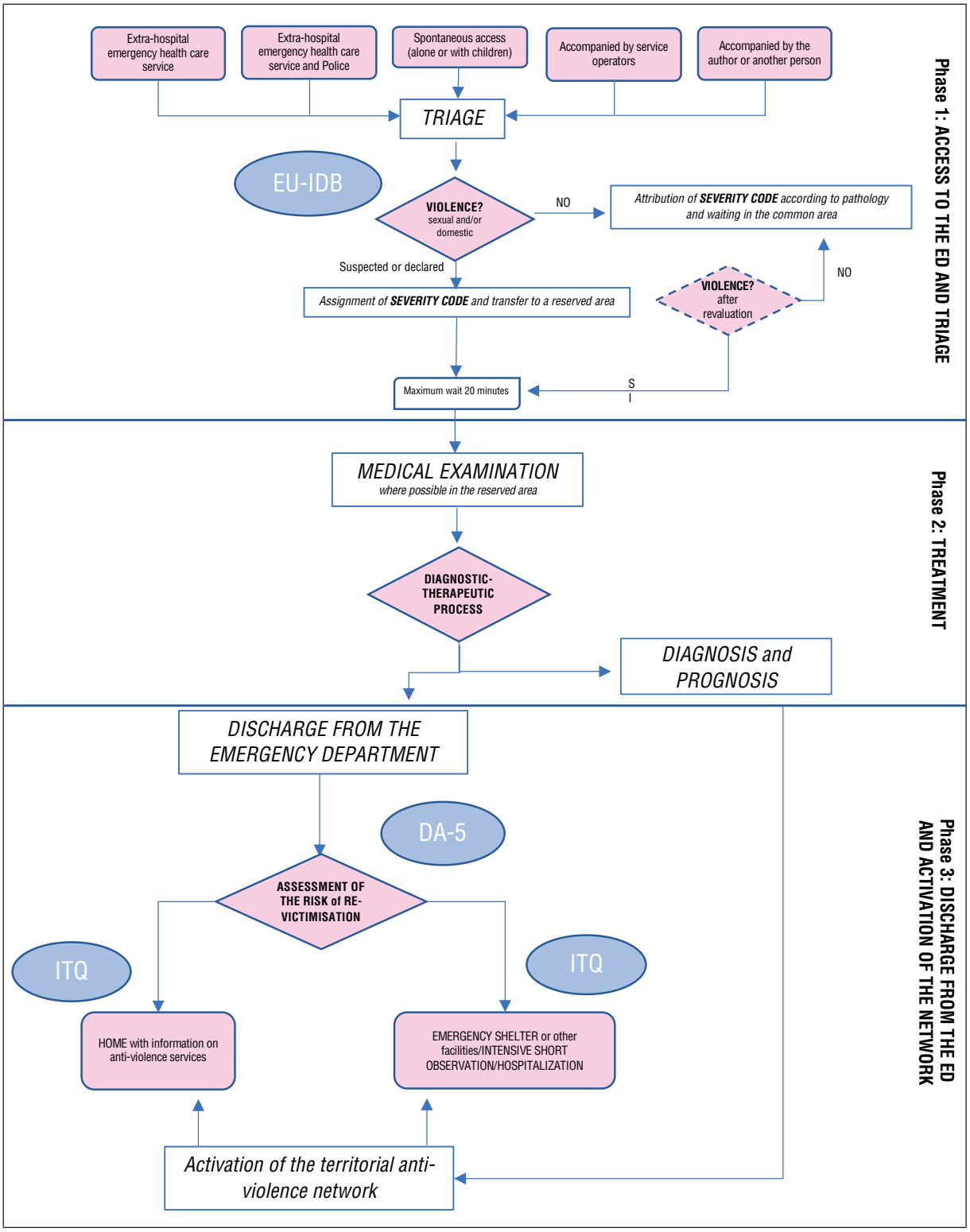

Figure 2
The pathway for supporting women victims of violence. In the circle the assessment tools are shown: EU-IDB violence module revised; Brief Risk Assessment (DA-5) and PTSD questionnaire (International Trauma Questionnaire-ITQ). (Modified from "Linee guida nazionali per le Aziende sanitarie e le Aziende ospedaliere in tema di soccorso e assistenza socio-sanitaria alle donne vittime di violenza. Gazzetta Ufficiale della Repubblica Italiana, Serie generale - n. 24 del 30.01.2018).

en and at creating new territorial models to counteract long-term health effects. In fact, most epidemiological studies on VAW focus on short-term effects, while long-term ones are neglected or marginally included even if they involve serious and complex consequences.

Early detection of chronic and non-communicable diseases that originate from the trauma is crucial to face their onset.

EPIGENETICS OF VIOLENCE AGAINST WOMEN

Violence, as a negative "socio-environmental" factor, is able to influence and modify the functionality of our genome through epigenetic modifications. Studying the genome and identifying epigenetic markers is an innovative approach to understanding the effects of violence on women's psychophysical health. In fact, the consequences of violence remain in the psyche and can also affect the structure and functionality of the DNA (deoxyribonucleic acid) compromising women's health.

It has already been demonstrated that violence interferes with genome plasticity and gene expression through epigenetic mechanisms [17]. Differentially regulated methylation levels of genes associated with Hypothalamic-Pituitary-Adrenal (HPA) axis, neurotransmission and inflammation genes were found to be linked to PTSD [18, 19]. Among long-term psychiatric disorders, PTSD is the most prevalent and is triggered by sudden traumatic events and multiple genomic factors and influenced by duration and severity of violence [1, 12].

In 2016, the Italian National Institute of Health (Istituto Superiore di Sanità, ISS) in collaboration with the University of Milan and the Cà Granda Foundation of the Ospedale Maggiore Policlinico di Milano, conducted the pilot study "Epigenetics for women" (EpiWE) that highlighted the presence of epigenetic markers associated with PTSD arising from violence in the relational and/or sexual environment compared to the control population.

The EpiWe study represented a preliminary attempt to link PTSD and stress relatated disorders in women who have been exposed to IPV or sexual violence to epigenetic changes detected in their DNA samples [20]. In particular, three genes brain-derived neurotrophic factor (BDNF), dopamine receptor D2 (DRD2), and insulin-like growth factor 2 (IGF2) have been found to be differentially expressed (hypermethylated) indicating that violence can interfere with genome plasticity and gene expression regulation. This finding, although preliminary, is promising in revealing epigenetic markers in genes mediators of brain plasticity, which can modulate learning and memory in response to stress associated with IPV and violence-induced PTSD. By contributing to the knowledge of epigenetic signature underlying PTSD and stress-related disorders in the context of VAW, we could derive clues about better treatments and innovative protocols of precision medicine for limiting the long-term effects [20].

The EpiWe pilot project developed into a multicentric project, "Violence against women: long-term health effects for precision prevention", that intends to collect biological samples for a follow-up study to detect the epigenetic signature of the entire genome.

DISCUSSION AND CONCLUSIONS

VAW has different dimensions in different cultures and, clearly, encompasses very different levels of traumatic injuries. This leads to the need of a unescapable systematic multidisciplinary approach.

The "Violence against women: long-term health effects for precision prevention", a transdisciplinary and multicenter project, aims to implement the National and Territorial Health Services for tackling the long-term health consequences by means of dedicated health and social services. It is necessary to build up the entire health history of women to correlate violence and the early onset of some non-communicable diseases.

In our project, a substantial premise is represented by the creation of a unique individual personal code that will enable to set up the personal clinical history of the patient (DMdS 262 of 7 December 2016).

Moreover, during our pilot study we faced various problems in particular, the patient dropout, which means the abandon of the care pathway. This results in the lack of DNA samples acquisition, necessary to the follow-up study (2 years, at least). The epigenomic analysis of the samples could be of use as a biomarker of the consequences of the violence that sometimes could emerge even many years after the event.

The implementation of the ViVa biobank within the ISS, ensures the first collection of biological samples of women who have survived violence, and violence for the first time is considered as a social health determinant that causes diseases.

The earlier is the detection of PTSD in association with the epigenetic markers, the faster will be the development of resilience.

Our objective consists in improving Public Health research by creating and interconnecting innovative strategies to ensure long-term care and limit the costs of violence weighing heavily both on women for women who have suffered violence and on the National Health Service (NHS).

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Authors' contributions

AC, MG and SG conceived and designed the study and wrote the manuscript. EC revised and edited the manuscript. All Authors revised the manuscript for important intellectual content, and agreed with this article's contents.

Conflict of interest statement

The Authors declare no competing interests.

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Book Reviews, Notes and Comments

Edited by
Federica Napolitani Cheyne

DIZIONARIO DEI BIBLIOTECARI ITALIANI DEL NOVECENTO
Simonetta Buttò, Alberto Petrucciani (Eds).
With the collaboration of Andrea Paoli
Roma: Associazione Italiana Biblioteche; 2022
882 p.
ISBN 978-88-7812-362-5
€ 60,00

[Dictionary of Italian librarians of the Twentieth Century]

The publication of a biographical dictionary dedicated to members of a profession is always to be hailed as good news, because it constitutes a valuable element for the reconstruction of the often complex and articulated history of that same profession, but above all it is good news if it concerns the profession of the librarian, perhaps little known but fundamental in the organization of knowledge and in supporting scientific research.

The origin of the *Dizionario dei bibliotecari italiani del Novecento* goes back more than two decades, when the volume *Per una storia dei bibliotecari italiani del XX secolo: dizionario bio-bibliografico 1900-1990*, edited by Giorgio De Gregori and Simonetta Buttò (Rome: AIB, 1999) came out, then in 2000 the online version was produced, which has been continuously enriched and updated (https://www.aib.it/aib/editoria/dbbi20/dbbi20.htm).

This new printed edition of the *Dictionary* presents 826 concise, accurate and reliable biographical profiles, the result of bibliographical and archival research, as well as an extensive bibliography, so that readers can continue with further reading if they are interested in a particular character. The set of biographies makes it possible to reconstruct the different aspects of the librarian's profession in Italy, developments and critical issues, in a century of great political, social and technological changes.

What emerges is a varied and complex physiognomy of the Italian library system, in which librarians, known or little known, represent its connective tissue, regardless of the different types of libraries in which they work, e.g., national, public, religious, university or research libraries.

Here, it seems appropriate to point out, among others, the presence of biomedical librarians who, despite their small number, assume a significant role because of the complex disciplinary field in which they work, the highly specialized and technical documentary and bibliographic resources they manage, their very specific skills, and the type of users they serve (researchers, physicians, medical students, nurses, as well as patients).

The *Dictionary* includes profiles of a number of librarians at the Italian National Institute of Health (Istituto Superiore di Sanità, ISS) who have played a significant role in the development of the library and, more generally, in the growth of the profession: Elena Pinto Vecchi, who worked in the ISS Library from 1947 to 1973, later becoming its director from 1965; Maria Valenti, from 1951 to 1973, from 1965 as deputy director and head of the Information and Loans Section; and Vilma Alberani, from 1961, then head of the Editorial Activities Service.

Also present are Lamberto Bravi, who worked from 1915 at the library of the Bacteriological Laboratory of Health, directed by Bartolomeo Gosio, where he was, among other things, editor of the "Annuario bibliografico italiano delle scienze mediche ed affini" (1916-1926), and Nello Vian, responsible for the foundation of the library of the Faculty of Medicine of the Università Cattolica in Rome, which he directed from 1959 to 1975, as well as a number of librarians who worked at the State Medical Library (Elena Amico Moneti, Ada Caputi Moricca, Maria Teresa Danieli Polidori, Luciana Mancusi Crisari, Giuliana Persichelli Nibaldi, and Maria Schellembrid Buonanno).

Finally, it is striking that most of the librarians mentioned join the AIB, the Italian Library Association (Associazione Italiana Biblioteche), highlighting the fact that a profession, to be such, needs to find itself in a professional community with which to freely compare itself.

In conclusion, this *Dictionary* represents an important repertoire for the history of librarians and of those institutions of knowledge that are libraries, and while we remember – as the editors point out in the *Introduction* – "the women and men who have gone before us, we cannot escape the reflection that the value of libraries, for those who use them, depends first and foremost on the people who work in them".

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Publications from International Organizations on Public Health

Edited by
Annarita Barbaro

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS (FAO)

Food Outlook – Biannual report on global food markets. Rome: Food and Agriculture Organization of the United Nations 2024; 144 p. ISBN 978-92-5-138860-0. Food Outlook is published by the Markets and Trade Division of FAO under the Global Information and Early Warning System (GIEWS). It is a biannual publication focusing on developments affecting global food and feed markets. Each report provides comprehensive assessments and short-term forecasts for production, utilization, trade, stocks and prices on a commodity-by-commodity basis and includes feature articles on topical issues. This June issue offers FAO's reviews of market supply and demand trends for the world's major foodstuffs, namely cereals, oil crops, sugar, meat, dairy and fish. It also looks at trends in food import bills, Ocean freight rates, international food prices and futures markets.

The State of Food Security and Nutrition in the World 2023. Urbanization, agrifood systems transformation and healthy diets across the rural–urban continuum. Rome: FAO, IFAD, UNICEF, WFP and WHO 2023; 316 p. ISBN 978-92-5-137226-5. This report provides an update on global progress towards the targets of ending hunger (SDG Target 2.1) and all forms of malnutrition (SDG Target 2.2) and estimates the number of people who are unable to afford a healthy diet. Since its 2017 edition, this report has repeatedly highlighted that the intensification and interaction of conflict, climate extremes and economic slowdowns and downturns, combined with highly unaffordable nutritious foods and growing inequality, are pushing us off track to meet the SDG 2 targets. However, other important megatrends must also be factored into the analysis to fully understand the challenges and opportunities for meeting the SDG 2 targets. One such megatrend, and the focus of this year's report, is urbanization. New evidence shows that food purchases in some countries are no longer high only among urban households but also among rural households. Consumption of highly processed foods is also increasing in peri-urban and rural areas of some countries. These changes are affecting people's food security and nutrition in ways that differ depending on where they live across the rural-urban continuum. This timely and relevant theme is aligned with the United Nations General Assembly-endorsed New Urban Agenda, and the report provides recommendations on the policies, investments and actions needed to address the challenges of agrifood systems transformation under urbanization and to enable opportunities for ensuring access to affordable healthy diets for everyone.

UNITED NATIONS EDUCATIONAL, SCIENTIFIC AND CULTURAL ORGANIZATION (UNESCO)

State of the ocean report, 2024. Paris: UNESCO Publishing 2024; 89 p. The State of the Ocean Report (StOR) has the ambition to inform policymakers about the state of the ocean and to stimulate research and policy actions towards "the ocean we need for the future we want", contributing to the 2030 Agenda and in particular SDG 14, which reads "Conserve and sustainably use the oceans, seas and marine resources", as well as other global processes such as the UNFCCC, the Convention on Biological Diversity and the Sendai Framework for Disaster Risk Reduction. Structured around the seven outcomes of the UN Decade of Ocean Science for Sustainable Development, the report provides important information about the achievements of the UN Ocean Decade and, in the longer term, about ocean well-being. The StOR will be used to inform policy and administrative priorities and identify research focus areas that need to be strengthened or developed. More than 98 authors from 25 countries contributed to the report. The different sections provide insights on ocean related scientific activities and analyses describing the current and future state of the ocean, addressing physical, chemical, ecological, socio-economic and governance aspects.

JOINT UNITED NATIONS PROGRAMME ON HIV/AIDS (UNAIDS)

UNAIDS DATA 2023. Geneva: United Nations Programme on HIV/AIDS 2023; 436 p. Every year UNAIDS provides revised global, regional and country-specific modelled estimates using the best available epidemiological and programmatic data to track the HIV epidemic. Modelled estimates are required because it is not possible to count the exact number of people living with HIV, people who are newly infected with HIV or people who have died from AIDS-

related causes in any country: doing so would require regularly testing every person for HIV and investigating all deaths, which is logistically infeasible and ethically problematic. Modelled estimates – and the lower and upper bounds around these estimates – provide a scientifically appropriate way of describing HIV epidemic levels and trends.

HIV Prevention: From Crisis to Opportunity. Key findings from the 2023 Global HIV Prevention Coalition scorecards. Geneva: United Nations Programme on HIV/AIDS 2024; 107 p. This sixth progress report of the GPC reviews the status of HIV prevention in 40 countries: the 28 initial focus countries of the Coalition and the 12 countries that were invited to join the Coalition in 2023. It tracks progress in the 28 initial focus countries and serves as a baseline assessment for the 12 newly invited countries. This report describes and analyses key developments in HIV prevention by 2022, identifies the main challenges and opportunities and outlines priorities for the years ahead. It is divided into two main sections. The main body of the report reviews progress made across the five main prevention pillars, examines implementation of the ten action points in the 2025 HIV Prevention Road Map and discusses key priorities for the immediate future. The Annex comprises country fact sheets for all 40 focus countries. Those fact sheets present in detail the progress made in implementing HIV prevention programmes at the country level, as represented by country HIV prevention scorecards and Road Map action plans in the 28 initial focus countries and as a baseline for the 12 newly invited countries.

ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT (OECD)

OECD-FAO Agricultural Outlook 2024-2033. Paris: Organization for Economic Co-operation and Development and Food and Agriculture Organization of the United Nations 2024; 335 p. ISBN 978-92-64-72259-0 (print) ISBN 978-92-64-59211-7 (PDF) ISBN 978-92-64-94407-7 (HTML) ISBN 978-92-64-38550-4 (epub). This report provides a comprehensive assessment of national, regional and global agricultural commodity markets over the next ten years. This 20th joint edition of the Agricultural Outlook comprises four parts: Agricultural and food markets. Trends and prospects which outlines key projections and insights on challenges facing agri-food systems over the coming decade; Regional briefs which explores key trends and issues in the agricultural sector across the seven FAO regions, the third part, Commodity, which describes recent market developments and medium-term projections for consumption, production, trade, and prices for the commodities covered in the Outlook, and a fourth part, Statistical Annex, presenting projections for production, consumption, trade, and prices for agricultural commodities, fish, and biofuels, as well as macroeconomic and policy assumptions

INTERNATIONAL LABOUR ORGANIZATION (ILO)

World Employment and Social Outlook: Trends 2024. Geneva: International Labour Organization 2024; 120 p. ISBN 978-92-2-040041-8 (print) ISBN 978-92-2-040042-5 (web PDF). This report reveals a complex global employment scenario. It forecasts a slight increase in global unemployment in 2024, signalling emerging labour market challenges. The report highlights also disparities between high and low-income countries, noting higher unemployment and poverty rates in lower-income nations. It also points out that a significant portion of the global workforce remains in informal employment. Key concerns include worsening income inequality and the impact of inflation on real incomes, especially in G20 countries. The report underscores the need for policy interventions focused on social justice to ensure a fair and sustainable global economic recovery.

WORLD HEALTH ORGANIZATION (WHO)

Intersectoral global action plan on epilepsy and other neurological disorders 2022–2031: implementation toolkit. Geneva: World Health Organization 2024; 160 p. ISBN 978-92-4-009635-6 (electronic version) ISBN 978-92-4-009636-3 (print version). This toolkit operationalizes the implementation of the Intersectoral global action plan on epilepsy and other neurological disorders 2022-2031 (IGAP), directed at reducing the burden and strengthening services for people with neurological disorders. The implementation toolkit is intended to be a "go-to" resource for those involved in IGAP implementation in countries. It lists actions and suggests tools and resources that can be utilized to realize fully the vision of IGAP and progress towards achieving the 10 global targets of the action plan. It is primarily intended for use by policymakers at national and subnational levels as well as programme managers and service planners across various sectors such as health, social services, education, environment, finance, employment, justice, and housing. The toolkit is also relevant for academics and the donor and development community as a blueprint for meeting the targets in the action plan. People with neurological disorders, their carers and families and associations that represent them are an essential part of the implementation process and are placed at the heart of all actions.

Prevention and control of iodine deficiency in the WHO European Region: adapting to changes in diet and lifestyle. Geneva: World Health Organization 2024; 122 p. ISBN 978-92-890-6119-3 (PDF). Iodine deficiency, especially mild deficiency, is still a widespread problem in the WHO European Region. Since the last WHO report on iodine deficiency in the Region was published 15 years ago, a wealth of new data on io-

dine status has become available, particularly concerning vulnerable population groups. This report reviews the iodine status in the WHO European Region, as well as current scientific knowledge on the consequences of mild iodine deficiency, dietary sources of iodine and the present effectiveness of iodine deficiency prevention measures. This report is also unique as it combines information sourced not only from scientific publications and public health reports, but also animal husbandry science and reporting, and the food industry.

Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection. Geneva: World Health Organization 2024; 272 p. ISBN 978-92-4-009090-3 (electronic version) ISBN 978-92-4-009091-0 (print version). The 2024 HBV guidelines provide updated evidence-informed recommendations on key priority topics. These include expanded and simplified treatment criteria for adults but now also for adolescents; expanded eligibility for antiviral prophylaxis for pregnant women to prevent mother-to-child transmission of HBV; improving HBV diagnostics through use of point-of-care HBV DNA viral load and reflex approaches to HBV DNA testing; who to test and how to test for HDV infection; and approaches to promote delivery of high-quality HBV services, including strategies to promote adherence to long-term antiviral therapy and retention in care. These guidelines include 11 updated chapters with new recommendations. There are also updates to five chapters relating to monitoring with unchanged recommendations from the 2015 guidelines, but these have been updated with new context, additional studies and research gaps.

Instructions to Authors

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They should be understandable also without reference to the text and should be numbered in Arabic numerals in a consecutive and independent way according to their citation within the paper.
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Figures should be loaded as separate files. The following file formats are acceptable: JPEG, TIFF or EPS. Vectorial images (graphs, flow charts, schemes, and other non bitmap material) should be in Excel, Adobe Illustrator, Microsoft Power Point so as to allow the editorial formatting of the material.
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Articles in journal

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

Books and chapters in a book

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

Proceedings

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

Technical reports

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

Legislation

Italia. Decreto legislativo 29 ottobre, n. 419. Riordinamento del sistema degli enti pubblici nazionali, a norma degli articoli 11 e 14 della legge 15 marzo 1997, n. 59. Gazzetta Ufficiale – Serie Generale n. 268, 15 ottobre 1999.
US Social Security Administration. Evidentiary require-

ments for making findings about medical equivalence. Final rules. Fed Reg. 2006 Mar 1;71(40):10419-33.
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