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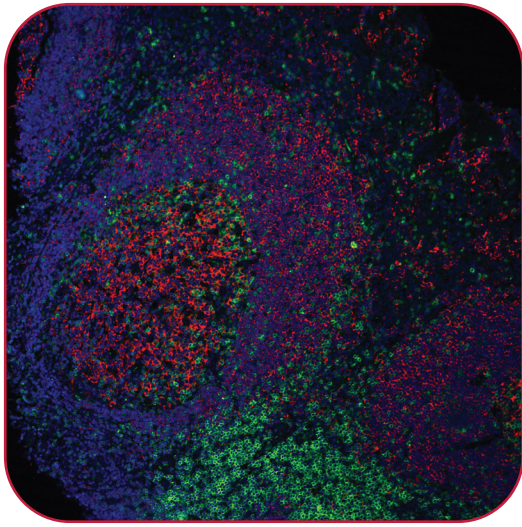
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The photograph on the cover is a triple immunofluorescence staining of a human tonsil, showing a secondary B cell follicle with germinal center. CD20+ B cells are in red and CD3+ T lymphocytes are in green; nuclei are in blue. The image is provided by Barbara Serafini, Department of Neuroscience, Istituto Superiore di Sanità, Rome, Italy



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First detection of SARS-CoV-2 lineage A.27 in Sardinia, Italy

Alessandra Lo Presti¹, Ferdinando Coghe², Angela Di Martino¹, Sara Fais³, Riccardo Cappai², Manuela Marra⁴, Maria Carollo⁴, Marco Crescenzi⁴, Germano Orrù³, Giovanni Rezza⁵ and Paola Stefanelli¹

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Abstract

Introduction. Multiple variants of SARS-CoV-2, since the end of 2020 have emerged in many geographical areas and are currently under surveillance worldwide highlighting the continuing need for genomic monitoring to detect variants previously not yet identified.

Methods. In this study, we used whole-genome sequencing (WGS) and phylogenetic analysis to investigate A.27 lineage SARS-CoV-2 from Sardinia, Italy.

Results. The Italian A.27 lineage genomes from Sardinia appeared related in a clade with genomes from France. Among the key mutations identified in the spike protein, the N501Y and the L452R deserve attention as considered likely vaccine escape mutations. Additional mutations were also here reported.

Conclusion. A combination of features could explain our data such as SARS-CoV-2 genetic variability, viral dynamics, the human genetic diversity of Sardinian populations, the island context probably subjected to different selective pressures. Molecular and genomic investigation is essential to promptly identify variants with specific mutations with potential impact on public health and vaccine formulation.

Key words

- SARS-CoV-2
- lineage A.27
- phylogenetic analysis
- Italy

INTRODUCTION

Human coronaviruses (CoV) are enveloped positive-stranded RNA viruses belonging to the order *Nidovirales*, mostly responsible for upper respiratory and digestive tract infections [1]. An outbreak of a febrile respiratory illness due to the newly discovered Coronavirus (officially named by the World Health Organization as SARS-CoV-2) occurred in mid-December 2019, in the city of Wuhan, Hubei province (China). The virus spread across most countries in all the continents, causing a pandemic event [2-4]. Multiple variants of SARS-CoV-2, since the end of 2020 have emerged in many geographical areas and are currently under surveillance worldwide, highlighting the continuing need for genomic and epidemiological surveillance to detect variants previously not yet identified.

In particular, those viruses belonging to lineage B.1.1.7, B.1.351, P.1 and more recently to B.1.617, which contains three sub-lineages [5-10] have been considered of concern regarding a high transmissibility and/or potential immune escape [10]. During a recent

survey of the diversity of SARS-CoV-2 in Mayotte, a cluster of divergent sequences within lineage A (clade 19B) was reported [11].

Specifically, SARS-CoV-2 lineage A.27, as of March 2021, was prevalent in Slovenia, France, Germany, Switzerland and the United Kingdom [12]. In this study, we report whole-genome sequencing (WGS) and phylogenetic analysis of the first three linked cases of the SARS-CoV-2 lineage A.27 in Italy.

MATERIALS AND METHODS

Patient data

Three members of the same family resulted COVID-19 positives. One patient suffers for chronic obstructive pulmonary disease (COPD), hypertensive heart disease and high BMI. He/She has been symptomatic since February 13, 2021 with a lab-confirmed COVID-19 diagnosis on February 17. At first, the patient showed symptoms characterized by osteo-muscular pain and fever (37.5 °C - 38 °C), followed by cough and dyspnea; on February 26, his/her condition worsened and intersti-

tial pneumonia was diagnosed. The second patient has been symptomatic at February 15, confirmed two days later. Symptoms like pharyngodynia, dry cough and mild headache were reported. The clinical picture was mild with a duration of three days. The third patient, resulted positive on February 17 and asymptomatic. The younger and the third patients did not infect any other persons, despite the occurrence of not protected contacts with several colleagues for business purposes and with other family members.

Whole-genome sequencing and phylogenetic analysis

Hereby, it was reported whole-genome sequencing (WGS) and a complete molecular characterization and phylogenetic analyses of the three SARS-CoV-2 strains collected from the patients whose clinical conditions are reported above. Total nucleic acids were extracted from the naso-pharyngeal swab, collected on February 17, using QIAamp viral RNA mini kit (Qiagen, Hilden, Germany), according to the manufacturer's recommendations. SARS-CoV-2 RNA were analysed for N1, N2 and RP genes by in-house rt-Real-time PCR through the Applied Biosystems 7500 Fast System instrument using reagents and protocol from CDC (Division of Viral Diseases, Centers for Disease Control and Prevention-USA) [13].

The RNA samples were quantified using Qubit™ RNA HS Assay Kit (Q32854, Invitrogen) and 10 ng were reverse-transcribed using SuperScript™ VILO™ cDNA+ Synthesis Kit (cod 1175-4050, ThermoFisher Scientific).

Whole-genome sequencing analysis was performed using the Ion GeneStudio S5™ Series System with the Ion AmpliSeq™ SARS-Cov-2 Research Panel (Supplementary Material).

Libraries were prepared manually with the Ion Ampliseq Library Kit Plus according to the manufacturer's protocols (Pub. No. MAN0017003), quantified by Agilent 2100 Bioanalyzer (Agilent Technologies) and then pooled together in equimolar amounts.

The diluted multiplexed library was sequenced using an Ion S5™ System semiconductor-based device (Thermo Fisher scientific), according to manufacturer's protocols (Pub. No. MAN0017003; Supplementary Material).

The consensus sequences were assembled by IRMA (Iterative Refinement Meta-Assembler) Assembly method (Supplementary Material) under the Ion Torrent sequencing technology [14, 15].

The generated sequences were submitted to GISAID (accession numbers: EPI_ISL_2244910, EPI_ISL_2244911 and EPI_ISL_2244912) [16].

To explore the lineages of the new sequences the "Pangolin COVID-19 Lineage Assigner" was used [17] in order to assign the lineages. The assignment of the clade was performed according to Nextstrain classification [18] (<https://Nextstrain.org/>).

The identification of the amino acid mutations was performed through visualization of the alignments compared to Wuhan-Hu-1 Reference SARS-CoV-2 genome (Accession Number: NC_045512.2).

For phylogenetic analysis, 181 additional complete

genome foreign SARS-CoV-2 sequences lineage A.27 were retrieved from GISAID [16] database (last access 23 March 2021) to investigate the relationships among strains. All the sequences were aligned using MAFFT [19] under the Galaxy platform Galaxy Version 7.221.3 [20] (<https://usegalaxy.org/>) (Supplementary Material) and manually edited through Bioedit software [21]. The best fitting substitution model, together with the maximum likelihood (ML) phylogenetic tree, were obtained with IQ TREE [22]. Support for the tree topology and clades was estimated with the bootstrap test (1000 bootstrap replicates).

RESULTS

The lineage analysis showed that the three SARS-CoV-2 sequences belonged to lineage A.27 and the clade assignment was 19B (last access to Pangolin COVID-19 Lineage Assigner and Nextstrain: 23 March 2021).

The maximum likelihood phylogenetic tree (Figure 1) shows a supported cluster including four genomes from Germany, and a main supported clade.

The sequences of the three patients identified as lineage A.27, appeared located in the main clade related (bootstrap value 81%) with eight genomes from France.

The A.27 lineage genomes collected from other countries were distributed in other statistically supported clusters within the main clade.

The non-synonymous amino acid variations identified in the three A.27 lineage Italian genomes compared to the Wuhan-Hu-1 reference NC_045512.2, were reported in Table 1.

In particular, the variations identified inside the spike protein were: L18F, T95I, L452R, N501Y, T572S, A653V, H655Y, D796Y, S939F, H1083Y, G1219V.

DISCUSSION

We described whole-genome sequencing (WGS) and phylogenetic analysis of the first three linked cases of the SARS-CoV-2 lineage A.27.

The three genomes here investigated belonged to lineage A.27 and represent, to the best of our knowledge, the first identification of this lineage in Italy at that time (February 17, 2021). In fact, other A.27 genomes deposited in GISAID in Italy with older collection dates were related to 18 March 2021.

Phylogenetic analysis consistently placed the three Italian genomes related among them and showed the Italian patient's strain in a supported cluster mainly related with genomes from France. Among the amino acids mutations found in the three A.27 genomes if compared to other A.27 genomes present on GISAID from other countries, the following: T572S, H1083Y (spike), L146F (*nsp12*), E261D (*nsp13*) were identified only in Italian A.27 genomes from Sardinia region.

Our data could be the result of a combination of events, such as the SARS-CoV-2 genetic variability, the viral dynamics (within and between individual hosts), and the island context probably promoting a different selective pressure [23, 24].

These observations reinforce the need for a continuous genomic surveillance. The rise in mutational variants of SARS-CoV-2, especially with changes in the Spike

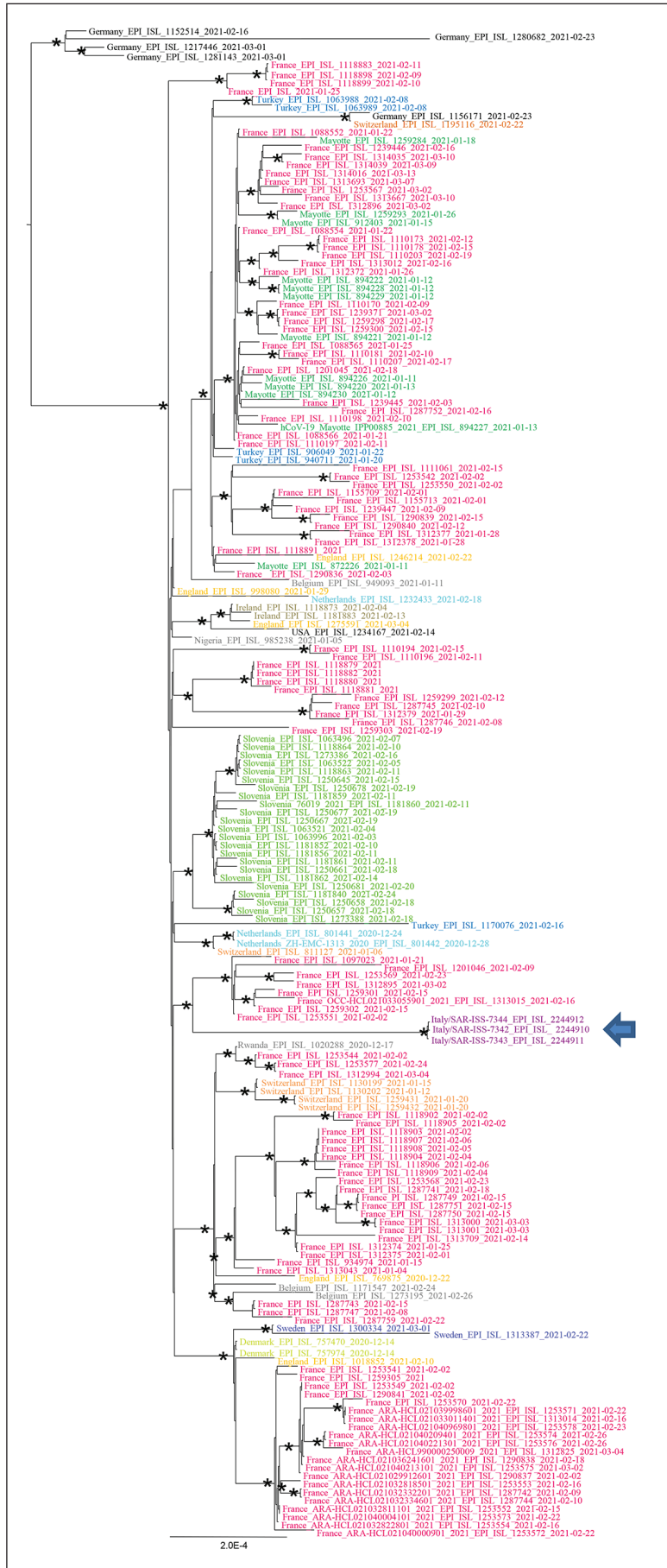


Figure 1
 Maximum Likelihood Phylogenetic analysis of three SARS-CoV-2 lineage A.27 Italian complete genomes from Sardinia, plus 181 lineage A.27 downloaded from GISAID (collected from other countries). The tree was rooted by using the midpoint rooting method. Branch lengths were estimated with the best-fitting nucleotide substitution model according to a hierarchical likelihood ratio test. The scale bar at the bottom represents nucleotide substitutions per site. An asterisk along a branch represents significant statistical support for the clusters subtending that branch (bootstrap support and aLRT >80%). The colors of the tips represent genomes from different countries (Germany, black; France, red; Turkey, blue; Switzerland, dark orange; Mayotte, dark green; England, ocra yellow; Netherlands, celestial blue; Belgium, grey; Ireland, brown; Nigeria and Rwanda, dark grey; Slovenia, light green; Italy, violet; Sweden, intermediate blue; Denmark, super light green).

Table 1

The non-synonymous amino acid mutations harbored by the three Italian SARS-CoV-2 genomes lineage A.27 here investigated

Mutation	Target
L18F	<i>spike</i>
T95I	<i>spike</i>
L452R	<i>spike</i>
N501Y	<i>spike</i>
T572S	<i>spike</i>
A653V	<i>spike</i>
H655Y	<i>spike</i>
D796Y	<i>spike</i>
S939F	<i>spike</i>
H1083Y	<i>spike</i>
G1219V	<i>spike</i>
S202N	<i>nucleocapsid</i>
P106L	<i>nsp2</i>
D217G	<i>nsp4</i>
N82S	<i>nsp6</i>
L146F	<i>nsp12</i>
P77L	<i>nsp13</i>
E261D	<i>nsp13</i>
V50A	<i>ORF3a</i>
L84S	<i>ORF8</i>

protein, is of significant concern due to the potential ability for these mutations to increase viral infectivity, virulence and/or ability to escape immune response.

In particular, the lineage A.27 was interesting because comprises a combination of different amino acid changes and in particular the N501Y and L452R amino acid substitutions. The N501Y in the spike also found in the alpha, in the beta and in the omicron variant (<https://outbreak.info/situation-reports/omicron>) is associated with an increased viral transmission [25]. The mutation L452R first got attention at that time, as part of the epsilon variant, but additional evidences have shown that several lineages carried L452R mutations [26], also including the delta variant [27]. The findings seem to suggest that the L452R may provide a competitive advantage, and that the replacement with the arginine may create a much stronger attachment of the virus to the human cells, and might allow it to avoid the neutralizing antibodies trying to interfere with this attachment [26, 27]. Ongoing molecular surveillance is essential to promptly identify variants with specific mutations that may act as trigger to an increase of COVID-19 cases.

CONCLUSION

Molecular and genomic investigation is essential to promptly identify variants with specific mutations

with potential impact on public health and vaccine efficacy.

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Authors’ contributions

ALP contributed to the conception, design of the study, to investigation, to phylogenetic analysis, and writing original draft. FC contributed to patient data curation, clinical picture, resources, writing, review and editing. ADM contributed to investigation, data curation, writing, review and editing. SF and RC contributed to data curation, writing, review and editing. MM and MC contributed to whole-genome sequencing, consensus assembly, with the supervision of MC. GO contributed to resources, data curation, writing, review and editing. GR contributed to supervision, writing, review and editing. PS contributed to project administration, supervision, writing, review and editing. The first draft of the manuscript was written by ALP. All Authors commented on earlier version of the manuscript. All Authors have read and approved the final manuscript.

Ethical considerations

This study is a part of a larger research approved by the Ethics Committee of the ISS (Prot. PRE BIO CE n. 0026259).

Conflict of interest statement

The Authors declare that they have no conflict of interest.

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Alcohol consumption and COVID-19 in Europe: how the pandemic hit the weak

Alice Matone, Silvia Ghirini, Claudia Gandin and Emanuele Scafato for the European Study Group on Alcohol Use and COVID-19

Osservatorio Nazionale Alcol, WHO Collaborating Centre for Health Promotion and Research on Alcohol and Alcohol-related problems, Centro Nazionale Dipendenze e Doping, Istituto Superiore di Sanità, Rome, Italy

Abstract

Introduction. The COVID-19 pandemic came along with several health and social unprecedented emergencies, among which handling people with substance use disorder issues.

Methods. In this work, data from a cross-sectional online survey conducted among more than 40,000 adults in 21 European countries during the spring of 2020 are analyzed. The survey recorded participants drinking habits during the year preceding the survey and the changes in alcohol consumption during lockdown. The analyses focused on alcohol consumers' type, investigating on the behavioral change in people who already had a problematic alcohol consumption attitude.

Results and conclusion. The results show how subjects with risky or hazardous use of alcohol increased both drinking quantity and frequency in most European countries, underlining the urge to establish regulations on online and home delivered alcoholic beverages availability and reinforcing and restructuring health care services.

Key words

- alcohol consumption
- COVID-19
- Europe
- hazardous drinking

INTRODUCTION

The global outbreak of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2, henceforth: COVID-19) at the beginning of 2020 led to an unprecedented worldwide health, social and economic crisis. On March 11, 2020 World Health Organization (WHO) declared COVID-19 to be a pandemic disease, and reports, as of October 7th 2021, over 235 million confirmed cases and almost 5 million deaths [1]. In order to halt the spread of the virus many countries have dramatically curbed public life, often with nationwide lockdowns. Particularly in Europe, across the months of March and April, most of the region's population was suddenly confined at home, often facing a number of personal and social consequences [2, 3].

It has been reported how the COVID-19 pandemic increased the levels of stress, depression and anxiety, implying a very strong psychological impact on the global population [4, 5]. Among the several consequences on society, change in alcohol consumption is one of these: social isolation is a major risk factor for alcohol misuse, while social support is a protective factor against it [6, 7]. It follows that the effects of forced home isolation added to the lack of support from social services have been detrimental, especially for the populations subgroups that already had a hazardous alcohol consumption. To mention one example, data from a survey

conducted in Italy between April and June 2020 reports that social isolation during the SARS-CoV-2 pandemic a noteworthy increase in sedentariness, tobacco smoking and alcohol consumption [8]. A similar scenario has been observed in Germany [9] and Belgium [10].

Changes in alcohol consumption attitudes are undoubtedly one of the detrimental social consequences of the COVID-19 restrictive measures [11]. Every year alcohol consumption contributes to 3 million deaths and to the disabilities and poor health of millions of people all over the world. Harmful use of alcohol is responsible for 5.1% of the global burden of disease and alcohol is the leading risk factor for premature mortality and disability in people from 15 to 49 years old: it accounts for 10 percent of all deaths in this age group [12]. The higher rates of alcohol-related death and hospitalization affect especially disadvantaged and vulnerable populations [13].

As recently reported, the pandemic and necessary public health response have exacerbated individual-level and population-level substance use problems [14, 15]. Dramatic increases in alcoholic beverages sales were recorded [16], for instance in the US online sales increased 262% from 2019 [17]. Some evidences show how there has been an increase in alcohol consumption frequency, quantity and risky behavior such as binge drinking [18-25], while a reduction in use support for

alcohol reduction by high-risk drinkers has been reported [26]. On April 14th WHO warned on alcohol harm during the pandemic and encouraged governments to enforce measures which limit alcohol consumption [27].

Several surveys have been carried out during the past year since the beginning of the pandemic, with the scope to retrieve information on people's alcohol and substance use behavior [10, 28-32]. The results from such studies are to be interpreted cautiously because of the many biases that surveys may imply, such as sample collection and self-reporting bias [33, 34]. Nevertheless, some useful and precious information may be extrapolated if properly analyzed and interpreted.

Between April 24 and July 22 of 2020 a cross-sectional online survey was conducted among more than 40,000 adults in 21 European countries [35-37]. The survey recorded participants drinking habits during the last year and the changes in alcohol consumption during the last month (*i.e.*, during lockdown), specifically in their drinking frequency, the quantity they consumed, and incidence of heavy episodic drinking events. As previously shown [36, 38], data collected from the survey globally shows that, since the beginning of the pandemic, alcohol consumption has decreased on average and that the decline is primarily due to a reduction in heavy episodic drinking occasions. However, in the present study, we propose a different perspective analysis, approaching the data with a focus on drinking behaviors, particularly analyzing subjects that already had a hazardous alcohol consumption. We aim at investigating alcohol consumption change during lockdown in subjects with a hazardous drinking behavior, compared to low-risk drinkers. In fact, we hypothesize that people mostly affected from lockdown measures in terms of alcohol consumption have been those with previous hazardous drinking patterns, which suddenly found themselves without social connections, deprived of all the support instruments that were usually available for alcohol related issues, and with a high availability of online alcoholic products for sale. Furthermore, while for those who were used to "social drinking" the lockdown could have represented a deterrent for alcohol consumption, those who had the dangerous tendency to drink alone found themselves with unprecedented occasions to drink [39, 40], without a social context that would usually hold them back from drinking. A further element in support of our hypothesis is the fact that many people – once more those from the lower socioeconomic status – found themselves temporarily laid off, if not unemployed, lacking therefore of another strong deterrent from drinking.

METHODS

This study fully complies with the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) statement [41].

Data

A cross-sectional online survey was developed to investigate on changes in alcohol consumption among European adults during the first COVID-19 emergency period. Answers were collected between April 24 and July 22 of 2020. The survey used fixed standard ques-

tions, and researcher-led outcome measures, to ensure comparability across countries and to other studies.

The questionnaire was written in English, and then translated into 20 languages and disseminated in 21 European countries. In some countries a targeted sampling was used to ensure sufficient representation across gender, age, and educational attainment (*e.g.*, via paid ads on social media websites) [35].

The survey section of interest for the present work regards the questions on the consumer type – *i.e.*, alcohol consumption attitudes of the respondent during the 12 months prior to completing the questionnaire – and the change in alcohol consumption during the lockdown experience – *i.e.*, in the month prior to completing the questionnaire. The questions related to the former are the ones from the AUDIT-C test [42], while for the latter are the following: "Did you drink alcohol less or more often in the past month?", "Did the amount of alcohol you usually drink on each drinking occasion (*i.e.*, the volume of alcohol consumed) change in the past month?". The answer was in a scale from 1 to 5 as follows: 1 "much less", 2 "slightly less", 3 "no change", 4 "slightly more", 5 "much more". The consumer type questions regard alcohol frequency, quantity and binge drinking, and the results are summed into a final score. Participants that did not respond to all three AUDIT-C questions were considered as non-responders, therefore, they were not included in the final analysis.

Summary of study protocol

The cross-sectional online survey consisted of five sections covering: (i) sociodemographics; (ii) the AUDIT-C; (iii) perceptions of measures employed to contain the pandemic; (iv) changes in personal alcohol consumption; and (v) changes in the personal use of other substances. The target population was adults aged 18 years or over and there were no further inclusion or exclusion criteria. Participation was voluntary and fully anonymous. Respondents could select not to answer any of the questions and opt to terminate participation in the survey at any time. The survey was designed to take a maximum of 10 minutes to complete, and participants could complete the survey in any of the languages provided, irrespective of their location. The current country of residence was recorded in a separate question. The survey was conducted using the open source survey tool LimeSurvey [43]. Anonymity of respondents was ensured by not collecting data such as the referral URL, HTTP cookies, internet protocol (IP) address, or the exact time of completing the survey. Sampling procedures differed between countries: decentralized snowball technique was used to reach as many people as possible. Amongst the channels used for dissemination of the surveys were alcohol research and policy networks, social media, web pages, press releases, and institutional or interest group mailing lists. Further details about the study design and implementation can be found elsewhere [35].

Definitions

Standard alcohol unit: in the questionnaire, one standard alcohol unit is defined as 11 grams of pure alcohol

based on the average of the most widely used definitions in Europe, except for those countries where a different definition is employed: Czech Republic (16 grams), Denmark and Sweden (12 grams), Slovenia (10 grams) and the UK (8 grams), for further details see [35].

Alcohol consumer: participants that declared to have consumed at least one standard alcohol unit within the 12 months prior compiling the questionnaire.

Consumer type: the hazardous alcohol consumer has an AUDIT-C sum score higher or equal to 5 for males and higher or equal to 4 for females. Conversely, we defined low-risk consumer the responder with an AUDIT-C sum score below 5 and 4 for males and females, respectively.

Non-responder: participants that did not respond to all three the AUDIT-C questions, and therefore when it was not possible to compute the AUDIT-C sum score, where classified as non-responders.

Change in alcohol consumption: participants that responded 1 or 2 (“much less” or “slightly less”) to the questions about alcohol consumption change in the month prior compiling the questionnaire (*i.e.* the lockdown period) where grouped into the “decrease” category, while participants that responded 4 or 5 (“much more” or “slightly more”) where grouped into the “increase” category.

Statistical analyses

We analyzed the data for each of the European countries involved in the study. Non-consumers and non-responders (see above definitions) were not included in the analysis (see flow chart reported in Figure 1). In order to investigate whether people that were already showing an inappropriate drinking behavior increased their consumption during lockdown, we grouped consumers in “Hazardous” and “Low risk” as described above. We investigated, in the two identified groups, if there has been an increase or decrease in alcohol consumption quantity or in alcohol consumption frequency during lockdown. Change in alcohol consumption was grouped into “Decrease” (1 or 2) and “Increase” (4 or 5), no change was not included in the analysis.

We implemented a logistic regression model, where change in alcohol consumption (quantity or frequency) is the dependent variable, and hazardous, sex and age are the independent variables. Survey weight were used to account for the respective population distributions of each country, weights computation has been described elsewhere [38]. Statistical analyses were performed in R version 3.6.1 [44].

RESULTS

A total of 40,064 people participated to the survey, the sample numerosity is described in the flowchart in Figure 1, while data for each participating country are reported in Table 1. 130 subjects were not eligible for the analyses as data was not sufficient to compute their consumer type. Final survey population resulted in 39,934 (11,800 males and 28,134 females) with an average of 41.13 years of age. Alcohol consumers (at least one consumption in the last 12 months) in Europe are 35,637 (89.2%). Non-responders to AUDIT-

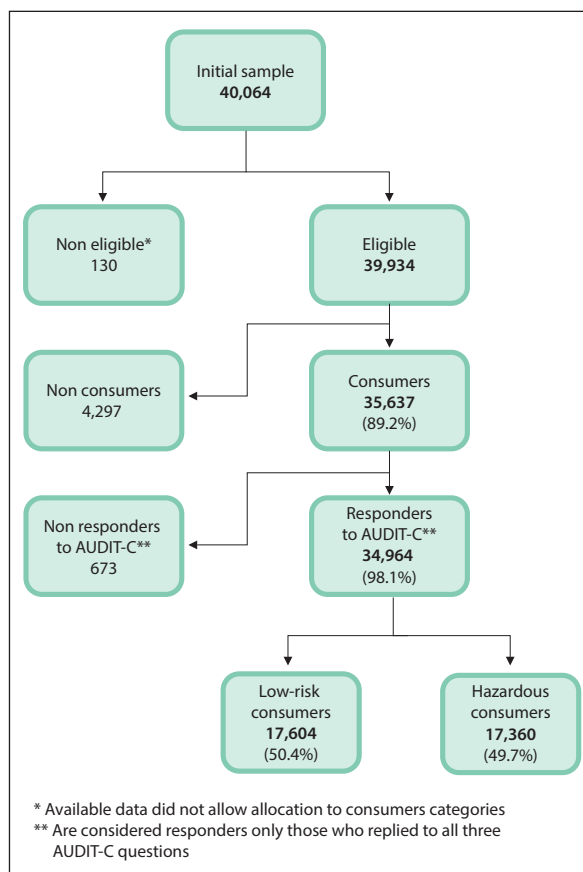


Figure 1 Flowchart describing numerosity of the sample.

C among consumers were 673, and responders are 34,964. Overall hazardous consumers are 17,360 and low-risk consumers are 17,604 (see Table 1). During lockdown, alcohol consumption quantity decreased for 9,921 responders and increased for 5,362, while alcohol consumption frequency decreased for 10,865 and increased for 8,345. For 19,481 and 15,123 responders there was no change for quantity nor frequency, respectively.

In Table 2 changes in alcohol consumption quantity and frequency for each country and for alcohol consumption groups are reported, as well as the Bonferroni adjusted p-value for each logistic regression model implemented. Change in alcohol consumption quantity during lockdown (increase *vs* decrease) was found to be positively significantly correlated with consumer type (hazardous *vs* low risk), after correcting for sex and age and adjusting for multiple testing ($p < 0.001$) for 15 out of 21 countries (except for Albania, Iceland, Ireland, Slovakia, Slovenia and the United Kingdom). Similarly, change in alcohol consumption frequency during lockdown was positively significantly correlated with consumer type (hazardous *vs* low risk) for 16 out of 21 countries (except for France, Slovakia, Slovenia, United Kingdom and Ukraine). Figure 2 illustrates, for each country, the percentage increase in alcohol quantity (2A) and frequency (2B) for hazardous (red) and low-risk (green) consumers. It can be observed how the

Table 1

Participants details by country. In the column indicating the percentage of hazardous consumers, the highlighted cells indicate whether hazardous consumers are more than half of the responders

Country	N	Consumers	% Consumers	Non responders*	% Non responders* (% among consumers)	Hazardous	% Hazardous (% among consumers who responded)	Low-risk	% Low-risk (% among consumers who responded)
Albania	574	201	35.02%	34	16.92%	29	17.37%	138	82.63%
Czechia	1,552	1,431	92.20%	33	2.31%	729	52.15%	669	47.85%
Denmark	2,556	2,427	94.95%	50	2.06%	1542	64.87%	835	35.13%
Finland	3,761	3,437	91.39%	50	1.45%	1713	50.58%	1,674	49.42%
France	389	312	80.21%	8	2.56%	150	49.34%	154	50.66%
Germany	1,644	1,502	91.36%	35	2.33%	774	52.76%	693	47.24%
Greece	553	529	95.66%	15	2.84%	184	35.80%	330	64.20%
Hungary	544	433	79.60%	16	3.70%	155	37.17%	262	62.83%
Iceland	601	477	79.37%	7	1.47%	166	35.32%	304	64.68%
Ireland	541	480	88.72%	12	2.50%	296	63.25%	172	36.75%
Italy	990	686	69.29%	18	2.62%	184	27.54%	484	72.46%
Norway	17,061	15,497	90.83%	158	1.02%	7821	50.99%	7,518	49.01%
Poland	1,145	1,087	94.93%	19	1.75%	638	59.74%	430	40.26%
Portugal	704	607	86.22%	13	2.14%	161	27.10%	433	72.90%
Russia	815	698	85.64%	32	4.58%	251	37.69%	415	62.31%
Slovakia	506	453	89.53%	13	2.87%	187	42.50%	253	57.50%
Slovenia	560	497	88.75%	9	1.81%	145	29.71%	343	70.29%
Spain	3,135	2,769	88.33%	94	3.39%	1154	43.14%	1,521	56.86%
Sweden	807	720	89.22%	10	1.39%	245	34.51%	465	65.49%
Ukraine	537	477	88.83%	16	3.35%	150	32.54%	311	67.46%
United Kingdom	959	917	95.62%	31	3.38%	686	77.43%	200	22.57%
Europe	39,934	35,637	89.24%	673	1.89%	17,360	49.65%	17,604	50.35%

*Consumers that did not respond to one or more AUDIT C questions.

increase is almost always higher for the hazardous consumers compared to the low-risk.

DISCUSSION AND CONCLUSIONS

With the COVID-19 outbreak, and in particular during the lockdown period, managing healthcare and prevention, among the others, became one of the most problematic issues of everyday life. All of the common activities aimed at detecting, preventing, responding and recovering from all of the acute and chronic diseases, became extremely complicated, not only as reported by the scientific literature but mainly as testified by people themselves [45, 46]. Many have been the missed prevention opportunities due to a blocked health system, trying to ensure the COVID cases management as the main Public Health priority endangering controls, screening and diagnosis of a number of chronic and acute conditions [47]. The impact of this has been experienced particularly by the most fragile patients always in need for a very sensitive, usually hardly planned management in the treatment of problematic mental health disorders and addictions, who experienced a dis-

ruption in the continuity of care, due to closures of specialized treatment services during lockdown [48, 49].

In particular, people with alcohol addiction issues found themselves without psychological and motivational support and without the opportunity for a correct pharmacological treatment and lack of symptoms control, such as craving [50]. During a period in which loneliness, pressure by not easy social dynamics, difficult working and family conditions may have influenced mental health and led to behavioral changes, lack of self-control, pushing people into a new, unrealistic dimension where progress towards the final goal of abstinence was lost. Loneliness has been identified as a health concern during the pandemic, and its association with alcohol consumption has been investigated, although it is not yet very well understood. For example, a pilot study conducted in the USA during the 2020 summer of the COVID-19 pandemic – in which restrictions were in place – reported that adults who felt lonelier on average across 30 days consumed more alcohol each day [51]. Loneliness can be a factor that triggers or increases mental health frailty, and it has indeed

Table 2

Change in alcohol consumption quantity and frequency during lockdown. The table shows, for each country, the number and percentage of hazardous or low-risk consumers who increased or decreased alcohol consumption and frequency. Bonferroni adjusted p-value refers to the output of the logistic regression model, where significance ($p < 0.05$) indicates that change in alcohol consumption (quantity or frequency) depends on the consumer type (hazardous or low risk), after correction for sex and age and multiple testing. In the columns indicating the percentages of increase in alcohol consumption (quantity and frequency), the highlighted cells indicate whether consumers that increased consumption are more than half

Country	Consumer type	Change in alcohol consumption quantity					Change in alcohol consumption frequency				
		Increase		Decrease		Bonferroni adjusted P-value"	Increase		Decrease		Bonferroni adjusted P-value
		n	%	n	%		n	%	n	%	
Albania	Hazardous	8	40.00%	12	60.00%	P=0.4329	9	42.86%	12	57.14%	P=0.0067
	Low-risk	13	19.12%	55	80.88%		10	13.33%	65	86.67%	
Czechia	Hazardous	174	45.31%	210	54.69%	P<.001	262	54.58%	218	45.42%	P<.001
	Low-risk	46	23.12%	153	76.88%		123	39.81%	186	60.19%	
Denmark	Hazardous	306	34.19%	589	65.81%	P=0.0017	500	41.32%	710	58.68%	P<.001
	Low-risk	73	33.33%	146	66.67%		159	44.41%	199	55.59%	
Finland	Hazardous	319	33.76%	626	66.24%	P<.001	469	41.14%	671	58.86%	P<.001
	Low-risk	40	9.71%	372	90.29%		121	18.11%	547	81.89%	
France	Hazardous	52	52.00%	48	48.00%	P=0.0053	61	56.48%	47	43.52%	P=1
	Low-risk	15	30.00%	35	70.00%		37	49.33%	38	50.67%	
Germany	Hazardous	266	57.95%	193	42.05%	P<.001	351	65.12%	188	34.88%	P<.001
	Low-risk	83	36.89%	142	63.11%		137	42.41%	186	57.59%	
Greece	Hazardous	66	53.66%	57	46.34%	P<.001	74	52.86%	66	47.14%	P<.001
	Low-risk	28	22.05%	99	77.95%		39	22.94%	131	77.06%	
Hungary	Hazardous	27	42.86%	36	57.14%	P=0.0207	42	51.85%	39	48.15%	P<.001
	Low-risk	9	20.93%	34	79.07%		25	35.21%	46	64.79%	
Iceland	Hazardous	34	44.16%	43	55.84%	P=1	56	55.45%	45	44.55%	P=0.001
	Low-risk	11	13.41%	71	86.59%		27	22.13%	95	77.87%	
Ireland	Hazardous	96	45.71%	114	54.29%	P=0.0608	148	61.41%	93	38.59%	P=0.0024
	Low-risk	35	43.21%	46	56.79%		67	60.91%	43	39.09%	
Italy	Hazardous	79	63.20%	46	36.80%	P<.001	91	66.42%	46	33.58%	P<.001
	Low-risk	57	28.36%	144	71.64%		76	34.08%	147	65.92%	
Norway	Hazardous	1,551	36.94%	2,648	63.06%	P<.001	2,679	51.92%	2,481	48.08%	P<.001
	Low-risk	357	17.98%	1,629	82.02%		905	29.86%	2,126	70.14%	
Poland	Hazardous	169	48.84%	177	51.16%	P<.001	269	61.84%	166	38.16%	P<.001
	Low-risk	38	25.85%	109	74.15%		93	40.97%	134	59.03%	
Portugal	Hazardous	62	65.26%	33	34.74%	P<.001	66	64.08%	37	35.92%	P<.001
	Low-risk	42	35.00%	78	65.00%		63	41.18%	90	58.82%	
Russia	Hazardous	60	53.57%	52	46.43%	P<.001	109	68.55%	50	31.45%	P<.001
	Low-risk	30	23.81%	96	76.19%		71	37.57%	118	62.43%	
Slovakia	Hazardous	36	37.89%	59	62.11%	P=1	53	44.17%	67	55.83%	P=1
	Low-risk	14	21.54%	51	78.46%		22	24.44%	68	75.56%	
Slovenia	Hazardous	42	54.55%	35	45.45%	P=0.0531	56	54.37%	47	45.63%	P=1
	Low-risk	25	24.51%	77	75.49%		45	37.19%	76	62.81%	
Spain	Hazardous	405	45.30%	489	54.70%	P<.001	486	52.03%	448	47.97%	P<.001
	Low-risk	267	31.08%	592	68.92%		330	35.07%	611	64.93%	
Sweden	Hazardous	36	39.13%	56	60.87%	P<.001	63	51.64%	59	48.36%	P<.001
	Low-risk	9	7.96%	104	92.04%		22	14.86%	126	85.14%	
United Kingdom	Hazardous	287	57.40%	213	42.60%	P=1	390	69.03%	175	30.97%	P=1
	Low-risk	46	54.76%	38	45.24%		75	61.98%	46	38.02%	
Ukraine	Hazardous	34	47.22%	38	52.78%	P<.001	57	57.00%	43	43.00%	P=1
	Low-risk	15	16.48%	76	83.52%		57	41.91%	79	58.09%	

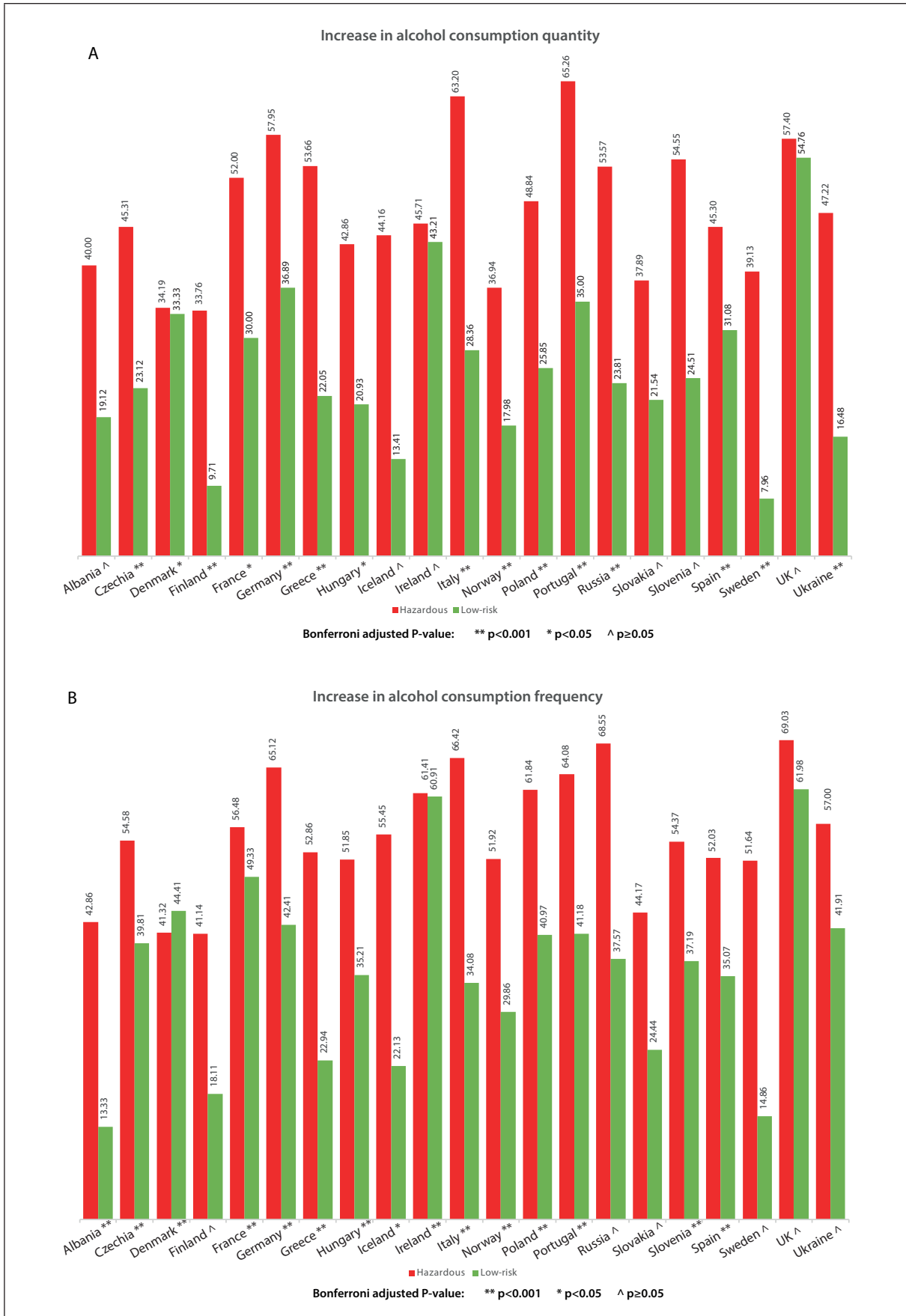


Figure 2 Increase in alcohol consumption quantity (A) and frequency (B) for hazardous and low-risk consumers.

been reported as the quarantine, during the COVID-19 pandemic, has affected mental health indicators, such as anxiety symptoms, depression, and various measures of psychological distress: all factors that have been associated with alcohol misuse [14, 52].

In the present study we highlight that, in a pan-European survey with more than 40 thousand participants, the majority of alcohol consumers that already were hazardous consumers before the pandemic outbreak, increased their alcohol intake during lockdown, both in terms of quantity and frequency. In fact, despite the general decrease in alcohol consumption that was detected from the survey data analyzed as a whole [36, 38], this tendency is mostly driven from those consumers that are classified as low-risk. In fact, giving a deeper look at the data, the story to be told is different [53, 54]: the percentage of hazardous drinkers who increased alcohol consumption quantity and frequency is higher than those who decreased it in 8 and 17 – respectively for quantity and frequency – out of 21 European countries where the survey was conducted. In Ireland and the United Kingdom also low-risk drinkers increased alcohol consumption quantity (only UK) and frequency. If we consider that in Europe half (49.65%, see *Table 1*) of the consumers that responded to the survey are hazardous consumers (more than half in Czech Republic, Denmark, Finland, Germany, Ireland, Norway, Poland and United Kingdom), this analysis sheds light on the very critical situation that emerged during the COVID-19 pandemic. Vulnerable subjects, that already had a dangerous attitude towards drinking for their health, increased alcohol intake, especially frequency, as being isolated at home, with no social and medical support, and often without an occupation, increased the occasions for drinking. To support our results, one recent Italian study [55] based on hair samples of 30 subjects with drug and/or alcohol disorders, showed that consumption of benzodiazepines and alcohol increased. Interestingly, the trend was opposite compared to heroin, cocaine, MDMA and cannabis, all of which decreased during the lockdown and went back to pre-lockdown levels after the period of confinement. Both the number of benzodiazepine-positive samples and the level of alcohol consumption increased and remained high, even at the end of the lockdown: during home isolation, people with substance use disorder shifted toward what was more easily accessible, used as self-medication for negative feelings and to alleviate the effects of abstinence from drugs that were no longer readily available, producing significant changes in substance use patterns [55].

The herein presented results shed light on the urgent need to take action on two main fronts: regulations on online and home delivered alcoholic beverages availability and reinforcing and restructuring health care services for people with alcohol use issues [56]. Increases in alcoholic beverages sales have been reported widely since the outbreak of the pandemic – not to mention unrecorded alcohol consumption [57] – partner in crime the ease in purchasing alcohol online and having it home delivered [58-60], new habits where regulations are not yet established. For this reason it is essential that evidence-based restrictions on alcohol prices, avail-

ability and marketing are introduced, such as increases in taxation coupled with minimum unit pricing [61, 62]. On the other end, much is to be accomplished for health services: first of all, care should be warranted and systems should for no reason be interrupted, remote health delivery is to be structured and fine-tuned and individualized practices planned [63, 64]. Nonetheless the overall decrease in the frequency and volume of alcohol consumption – as detected by the survey – the increase in the frequency of hazardous drinkers, those who were already in a need-for-treatment situation, represents the most relevant and neglected result to be reported, whereas the decrease of drinkers not at risk, represents an empty prize.

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Authors' contribution

Alice Matone: methodology, software, data curation, formal analysis, writing - original draft preparation, vi-

sualization; Silvia Ghirini: data curation, methodology, validation, writing, review and editing, visualization; Claudia Gandin: writing, review and editing, visualization; Emanuele Scafato: conceptualization, writing, review and editing, visualization, supervision, project administration.

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Conflict of interest statement

All the Authors of the manuscript have no conflict of interest to declare.

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Cancer screening programmes in Italy during the COVID-19 pandemic: an update of a nationwide survey on activity volumes and delayed diagnoses

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Abstract

Introduction. In Italy, regional governments are in charge of implementing cervical, breast and colorectal cancer screening programmes. The 2020 Coronavirus pandemic led to a national lockdown and the temporary suspension of several non-urgent health-care activities, including cancer screening. This paper aims to describe the results of a national survey carried out by the National Centre for Screening Monitoring (ONS) on cervical, breast and colorectal cancer screening activities in 2020.

Materials and methods. A national survey was conducted by ONS in 2020 to assess: the number of screening invitations by Region; the volumes of screening tests and the attitude to attend the screening programme compared to 2019; the number of delayed diagnoses of malignant or pre-malignant lesions caused by the slowing down of screening programmes, based on the average Region-specific screening detection rate for cervical, breast and colorectal cancers.

Results. Screening tests for breast, colorectal and cervical cancer decreased by 37.6%, 45.5% and 43.4% in 2020 compared with 2019. In 2020 the estimated numbers of undiagnosed lesions are: 3,324 breast cancers, 1,299 colorectal cancers, 7,474 colorectal advanced adenomas and 2,782 CIN2 or more severe cervical lesions. Participation in cancer screening programmes decreased by 15%, 15% and 20%, for cervical, breast and CRC screening, respectively.

Discussion and conclusions. An urgent call to action is needed to prevent further delays and to limit the impact of the pandemic on cancer diagnosis and prevention.

Key words

- cancer screening
- COVID-19
- delayed diagnosis
- Italy
- survey

INTRODUCTION

In Italy, Regions are responsible for organizing cancer screening programmes, aiming at early detection of cervical, breast and colorectal cancer. Indeed, a national law included these screening programmes among the public health interventions that all Regions must implement [1]. The outbreak of the Coronavirus infection (COVID-19) severely hit Italy, and led the

Italian Government to adopt severe containment measures, such as a nationwide lockdown that started the 9 March 2020 [2]. The response to the pandemic (in Italy as well as in other countries) had an impact on the health system and resulted in a sudden suspension of several non-urgent health care activities, including cancer screening services, offered to the asymptomatic population [3]. However, referrals for subjects with

a previous positive cancer screening test were maintained [4].

The effectiveness of cancer screening programmes is entangled with a timely management of patients. This is because timely lesion identification might allow for an early-stage diagnosis, that would lead to more conservative treatments, and prevent severe complications. The risk associated with the delay of the diagnosis of cancer due to COVID-19 has increasingly drawn the scientific community attention. Several studies are ongoing, aiming to assess the impact of interruption of routine screening services on cancer diagnosis and deaths. Simulation modelling studies, even if based on different assumptions, showed that an interruption of screening activity is associated with an increased number of cancer deaths, in particular in the years immediately following the suspension of screening programmes [5-8]. The main determinants of the impact of the interruption of the screening activities on health were: the duration of the suspension; the strategy adopted for catching up those who, even if invited, could not participate in the screening due to the lockdown restrictions/suspension; and the participation rate of the invited population [9]. For example, for stage 3 colorectal cancer, a recent study demonstrated that a 2-month delay to surgery is predicted to cause more than 9% reduction in survival across all age groups, while for a 6-month delay, this reduction is estimated to be >29% [7]. Moreover, the differential impact of stopping screening activity by SES (Socioeconomic Status) as well as the equity implications of adopting different recovery strategies has been debated [10].

In Italy, the National Centre for Screening Monitoring (ONS) and the Italian Group for Colorectal Screening (GISCoR) formulated the criteria to orient decisions about the design of recovery plans, prioritizing people whose screening was delayed because of the lockdown [11, 12]. In Italy, the suspension of screening services lasted from March until April 2020, even though in a non-homogeneous way among the different Regions. In the same way, programmes were restarted in May 2020, with relevant differences among Regions [13]. ONS – a technical network of Italian screening regional centers supporting Regions and the Ministry of Health in screening programmes monitoring and quality assurance – has conducted periodic national surveys to monitor cancer screening programmes during the COVID-19 emergency. The main aim of the surveys was to describe accrued delays by comparing 2019 and 2020 data, to evaluate the reboot velocity after the lockdown and to provide estimates of missed diagnoses – i.e., malignant or pre-malignant lesions subjected to a diagnostic delay due to the slowdown of screening programmes. The first survey showed that, between January and May 2020, half as many tests were done in 2020 at a national level, compared with the same period of 2019. In addition, the survey highlighted that not every regional programme restarted in May 2020 [13]. The survey was designed as a three waves study (Jan-May 2020; June-Sep 2020; Oct-Dec 2020). This paper aims to describe the results of the national survey to closely monitor screening programmes delays and reboots.

MATERIALS AND METHODS

Setting

In Italy, regional governments are in charge of implementing cervical, breast and colorectal cancer screening programmes through local health authorities. Breast cancer screening programmes invite women aged between 50 and 69 for a mammogram every two years (in some Regions target age is extended from 45 to 74, with annual screening from 45 to 49). Cervical screening programmes invites all women aged between 25 and 30 for a Pap test every three years, and those aged between 30 and 35 for an HPV test every 5 years until age 64. Finally, colorectal cancer screening programmes invite women and men aged between 50 and 70 (or 74 in some Regions) for a fecal immunochemical test (FIT) every two years. Some Regions also provide the option of one sigmoidoscopy at the age of 58/60.

In Italy, the first COVID-19 case was diagnosed on 21 February 2020. The lockdown was implemented on 8 March 2020, and the infections peaked at the end of March 2020. The lockdown was gradually removed in May/June 2020. As in other European countries, the virus transmission was lower during the summer until October 2020. To face the second wave of COVID-19 infections, the Italian Government implemented a series of new restrictions, but not a complete lockdown (www.salute.gov.it/portale/nuovocoronavirus/archivio-MonitoraggiNuovoCoronavirus.jsp).

Survey procedures

Methods have been described elsewhere [13]. A quantitative survey was conducted by ONS administering an *ad hoc* questionnaire to all 21 regional cancer screening coordinators in October 2020 (first update) and January 2021 (last update). Data were referred to the target population of the breast (women aged 50-69 years old), cervix (women aged 25-64 years old), and colorectal cancer screening (women and men aged 50-69 years old) and concerned:

- screening invitations (i.e. absolute number of subjects contacted either by mail or by phone, counting every subject one time only) between January and December 2020, compared to the same period in 2019;
- absolute number of screening tests performed between January and December 2020 compared to the same period in 2019.

The following estimates, based on the abovementioned data, were then calculated:

- “standard months” of delay (SM), i.e. number of months of activity that would be required to catch up if the programmes were conducted with the same capacity of the pre-COVID era. This parameter is obtained by multiplying the proportion of fewer tests carried out in 2020, in a certain time interval, by the number of months that make up the period;
- missed diagnoses, i.e. the number of malignant or pre-malignant lesions (breast carcinomas, advanced adenomas and colorectal carcinomas, cervical lesions CIN2 or more severe) that will face a diagnostic delay due to the slowing down of screening tests’ offer. The estimates are obtained applying the Region-specific screening detection rate (DR) of the three cancer

screening programmes to the absolute difference of the number of tests performed. The following DRs were applied: (i) breast cancer screening: average DR of years 2016-2018 except for some Regions where data was not available (for Puglia, data relating to the years 2014-2016 were used; for Molise 2014, 2016, 2017; for Calabria 2015, 2016, 2018); (ii) cervical cancer screening: DR of 2017; (iii) colorectal cancer screening: average DR of years 2016-2018 for Fecal Immunochemical Test (FIT)-based programmes (except for Molise where DR was inconsistent and Puglia where the program started in 2019 – for these Regions the average DR from South Italy was applied) and average 2015-2017 DR for flexible-sigmoidoscopy-based programmes;

- attitude to attend the screening test after the invitation, i.e. the comparison of the relative curtailment of screening test performed and with that of screening invitations. The assumption is that if the same number of invitations corresponded to the same participation in 2019, the ratio between exams carried out in 2020 compared to 2019 would correspond to the ratio between invitations made in 2020 compared to 2019.

Twenty-one Regions out of 21 participated in the survey, whereas the results of 2 out of 5 programmes in Calabria are missing. Results are presented for the entire study period (January-December 2020) and sub-periods (Jan-May 2020; June-Sep 2020; Oct-Dec 2020) to monitor reboot speed. However, the data from Basilicata are referred to the whole period of the study and are therefore were not analysed for sub-periods. Secondly, colorectal cancer screening data from Umbria are referred to the 50/74-year-old target population.

RESULTS

Between January and December 2020, there were 980,994 fewer invitations than 2019 for mammography screening (-26.6%; range Marche -0.5% / Trento -60%), 1,929,530 for colorectal cancer screening (-31.8%; range Basilicata -70.5% / Umbria +6.8%; Puglia not evaluated because the colorectal cancer screening programme started in the second half of 2019), and to 1,279,608 for cervical cancer screening (-33%, range Basilicata -71.3% / Umbria +19.8%) (Table 1). Screening programmes are working hard to recover the delay, even if from the comparison of the three-time periods (January-May, June-September, and October-December) emerged that the recovery is still incomplete. Indeed, the invitations gap between 2020 and 2019 of breast cancer screening decreased from -41.7% to -23.3% and -2.7% in the three-time periods. Similarly, for colorectal cancer screening the gap between 2020 and 2019 decreased from -47.0% to -32.9% and 0.0%; finally, for cervical cancer screening from -41.5% to -38.8% and -13.0%.

The gap of screening tests performed between 2019 and 2020 was of 751,879 exams for breast cancer screening (-37.6 %, range: Umbria -9.1% / Calabria -63.3%), with an average delay of 4.5 SM; of 1,110,414 tests for colorectal cancer screening (-45.5%, range: Umbria -0.2% / Campania -78.6%) with an average delay of 5.5 SM; of 669,742 tests for cervical screening

(-43.4%, range: Basilicata -74% / Umbria +1.8%) with an average delay of 5.2 SM (Table 2, Table 3). However, a large variability was observed among Regions for all three screening programmes.

We estimate that the number of undiagnosed lesions is 3,324 breast cancers; 1,299 colorectal cancers; 7,474 colorectal advanced adenomas; and 2,782 CIN2 or more severe cervical lesions (Table 4). The participation decreased in all three screening programmes: compared with 2019, the attendance rate to screening invitation was 56.6%/67.0%=0.85 for cervical, 62.4%/73.4% = 0.85 breast and 54.5%/68.2% = 0.80 for colorectal cancer screening. These data show a decreased participation by 15%, 15% and 20% in each screening programme.

DISCUSSION

This paper provides an update of the quantitative estimate of the accumulated delays in cancer screening programmes, due to the COVID-19 epidemic in Italy. While the first survey included data on the lockdown period (March and April 2020), this second one includes data until December 2020, a period of potential recovery. The latest data show that although organized screening restarted after the lockdown, delays did not recover by the end of 2020 and they are increasing compared with the previous year. Despite the efforts, it is complicated to recover the backlog, also because the longer operating time necessary for each exam cause a slowing downtime of screening performance. Indeed, a set of new measures were introduced to reduce risk of contagion - such as disinfection, personal protective equipment, lowered number of people in waiting rooms, reduced availability of personnel and medical rooms. For these reasons delays were still growing in the second (June-September) and third (October-December) observation period, even if slower than in the first period (January-May). Variability in the recovery pace was observed across Regions and programs. After May 2020 Umbria, Emilia-Romagna, and Tuscany invited more individuals than in previous years, showing a commitment to the screening coverage recovery. On the other hand, other Regions (i.e., Campania, Lombardy, Basilicata) showed an opposite trend. Among the three programmes, breast cancer screening showed a faster recovery, as evidenced by the 0.9 and 0.8 SM of the second and third periods.

Analyzing these data, it is worth mentioning that the volumes of screening activities in 2019, which were used as a reference in this study, are intended to represent the pre-pandemic routine healthcare offer rather than a gold standard. Furthermore, results of cervical cancer screening may be influenced by the progressive transition from invitation to Pap test every 3 years to HPV test every 5 years [14]. For instance, the target population in 2020 is lower than in 2019, also because some programmes started HPV test invitations in 2017 (the next invitation will be in 2022 instead of 2020). In addition, some programmes invited more people to the HPV test in 2017 than in 2016. It should be noted that using the data of only one year as a reference (namely those from 2019) is a limit for this analysis. Nevertheless, 2019 data have been chosen because very similar

Table 1

Difference of screening invitations performed in 2020 vs 2019, by screening programme and time period

Regions/ Autonomous Province	Invitations											
	Jan-May			June-Sept			Oct-Dec			January-December 2020 (%)		
	CS	BCS	CCS	CS	BCS	CCS	CS	BCS	CCS	CS	BCS	CCS
Abruzzo	-6,984	-624	-11,630	-7,803	-6,801	-6,241	18,906	2,576	24,221	4,119 (5.9%)	-4,849 (-11.8%)	6,350 (4.0%)
Basilicata§										-22,541 (-71.3%)	-17,726 (-44.6%)	-51,993 (-70.5%)
PA Bolzano	-2,113	-10,924	-5,462	7,104	-955	15,769	-9,658	-104	13,151	-4,667 (-8.0%)	-11,983 (-35.5%)	23,458 (54.9%)
Campania	-4,7212	-75,635	-71,619	-108,283	-35,071	-69,431	-95,300	-10,403	-35,209	-250,795 (-56.5%)	-121,109 (-44.3%)	-176,259 (-65.5%)
Calabria^	-6,677	-7,882	-9,252	-534	-2,903	-358	-9,021	-855	-1,738	-16,232 (-54.6%)	-11,640 (-55.4%)	-11,348 (-64.8%)
Emilia Romagna	-73,336	-70,445	-119,548	-24,899	12,842	51,981	-4,538	9,503	36,669	-102,773 (-33.5%)	-48,100 (-15.7%)	-30,898 (-5.2%)
FVG	-16,350	-25,756	-33,553	-13,448	21,698	-8,315	-10,658	-9,415	1,643	-40,456 (-41.4%)	-13,473 (-15.2%)	-40,225 (-24.0%)
Lazio	-58,095	-77,572	-161,500	-62,392	-22,125	-100,638	77,883	49,502	113,382	-42,604 (-9.3%)	-50,195 (-12.2%)	-148,756 (-19.4%)
Liguria	-18,627	-25,570	-52,582	-36,012	-14,735	-54,098	14,908	2,546	8,594	-39,731 (-33.9%)	-37,759 (-33.0%)	-98,086 (-43.2%)
Lombardia	-45,350	-159,111	-378,491	-35,527	-59,783	-364,673	-40,949	-33,892	-95,015	-121,826 (-62.3%)	-252,786 (-39.2%)	-838,179 (-64.5%)
Marche	-29,500	-22,900	-45,500	9,587	776	23,350	-7,592	21,624	6,913	-27,505 (-21.6%)	-500 (-0.5%)	-15,237 (-7.6%)
Molise	-2,208	-150	-4,151	931	-1,051	-14,618	-1,280	-464	0	-2,557 (-36.2%)	-1,665 (-21.8%)	-18,769 (-60.6%)
Piemonte# FIT	-81,406	-68,732	-24,377	-21,677	-36,218	-3,839	-29,587	-32,609	7,664	-132,670 (-42.8%)	-137,559 (-42.8%)	-20,552 (-20.3%)
Piemonte FS			-23,608			-17,648			883			-40,373 (-59.0%)
Puglia*	-47,720	-13,224	50,132	-73,513	-48,492	-3,610	-45,284	-29,410	-29,156	-166,517 (-52.6%)	-91,126 (-51.0%)	17,366 (21.2%)
Sardegna	-8,466	5,191	-17,608	-22,047	-19,263	-23,412	-25,687	-12,001	-23,966	-56,200 (-47.0%)	-26,073 (-37.6%)	-64,986 (-57.2%)
Sicilia	-91,889	-32,526	-137,787	19,089	7,310	10,732	-3,427	-5,332	-74,222	-76,227 (-17.1%)	-30,548 (-9.4%)	-201,277 (-38.1%)
PA Trento	-7,083	-7,577	-12,201	-6,717	-7,913	-346	-247	-6,116	3,649	-14,047 (-34.0%)	-21,606 (-60.0%)	-8,898 (-13.3%)
Toscana	-52,349	-25,128	-94,404	-26,376	-24,671	-24,182	17,241	19,944	20,834	-61,484 (-20.7%)	-29,855 (-11.0%)	-97,752 (-19.4%)
Umbria	-9,112	-12,515	-16,867	-588	-435	6,757	19,700	8,650	19,110	10,000 (19.8%)	-4,300 (-6.4%)	9,000 (6.8%)
Valle d'Aosta	-1,926	-3,155	-3,698	1,454	559	-2,174	-413	-1,907	-3,674	-885 (-9.9%)	-4,503 (-56.1%)	-9,546 (-56.8%)
Veneto	-61,788	-50,160	-89,851	-48,136	-16,792	-28,449	-4,086	3,313	5,730	-114,010 (-33.3%)	-63,639 (-19.2%)	-112,570 (-18.5%)
ITALY	-668,191	-684,395	-1,263,557	-449,787	-254,023	-613,443	-139,089	-24,850	-537	-1,279,608	-980,994	-1,929,530
	(-41.5%)	(-41.7%)	(-47.0%)	(-38.8%)	(-23.3%)	(-32.9%)	(-13.0%)	(-2.7%)	0.0%	(-33.0%)	(-26.6%)	(-31.8%)

CS= cervical screening, BCS= breast cancer screening, CCS= colorectal cancer screening, FIT=faecal immunochemical test, FS=flexible sigmoidoscopy

*colorectal cancer screening programme was not activated in 2019

Data referring to the whole region except for CCS

^ Data of 3 programmes out of 5

§ Data are not provided for subperiods

to what we would expect in terms of invitation and participation rates in 2020 and for this reason, these data should give a realistic estimate of delays.

Referrals for second-level care for positive screening tests have been guaranteed, even if with a lower capacity than before the pandemic, because of organizational needs (i.e., physical distancing and sanitification measures). These new organizational needs may have contributed, after the lockdown, to limit the recovery of the first-level screening tests, and so in further delays in the diagnostic assessment. Additional resources (more professionals, equipment and logistics) are needed as soon as possible to counterbalance the delays accumulated over the whole of 2020.

We estimated that the accumulated delay of 2020, concerning more than two and a half million fewer screening tests being performed, resulted in around 3,300 breast cancers, 1,300 colorectal carcinomas, 7,400 colorectal advanced adenomas and 2,800 CIN2 or more serious cervical lesions facing a diagnostic delay.

The clinical consequences of these delays are more severe for breast and colorectal cancer screening, because those programs are characterized by a relevant detection of invasive cancers (i.e., respectively 4.4 and 1.1 x 1,000 screened compared with 0.15 x 1,000 of cervical cancer screening in 2018-2019) [15]. Therefore, a possible advance in stage at diagnosis would concern a greater amount of cases. Furthermore, a proportion of undetected advanced adenomas could evolve to invasive colorectal carcinoma. [9] Recent studies on the effects of delays in performing a colonoscopy in FIT positive individuals showed that a delay of at least 7-9 months is necessary to observe an increase of the detection of invasive carcinoma and the worsening of the distribution by stage [16, 17].

However, the results of simulation modelling studies on the impact of screening suspension suggest that 3 to 12 months interruptions of screening activity are associated with an increase of mortality and a shift in the diagnosis toward a less favourable stage distribution of screen-detected CRCs [9, 18, 19].

Table 2
Difference of screening tests performed in 2020 vs 2019, by screening programme and time period

Regions/ Autonomous Province	Tests performed																							
	Jan-May				June-Sept				Oct-Dic				January-December 2020											
	CS	%	BCS	%	CCS	%	CS	%	BCS	%	CCS	%	CS	%	BCS	%	CCS	%						
Abruzzo	-4,779	-48.9	-6,030	-52.9	-5,264	-39.6	-5,070	-44.2	-7,066	-57.2	-251	-1.5	-1,809	-20.8	-6,451	-48.6	-2,313	-21.2	-11,658	-38.9	-19,547	-52.8	-7,828	-19.3
Basilicata [§]	-1,188	-72.4	-4,832	-53.6	-2,761	-53.5	144	4.1	1,417	35.7	-2,954	-23.3	-407	-2.4	-4,074	-46.6	629	14.2	-1,451	-6.5	-7,489	-34.5	-5,086	-22.8
PA Bolzano	-19,488	-58.7	-23,311	-60.8	-15,622	-54.1	-8,270	-39.4	2,681	21.2	-22,202	-90.6	-24,160	-75.4	-20,133	-93.1	-22,571	-96.3	-5,1918	-60.2	-40,763	-56.1	-60,395	-78.6
Campania	-3,536	-75.2	-3,670	-71.2	-1,224	-88.8	1,901	319.0	-597	-42.5	-1,156	-99.9	-2,288	-76.2	-1,191	-57.7	-1,477	-78.0	-3,923	-47.3	-5,458	-63.3	-3,857	-87.1
Calabria [^]	-51,854	-62.9	-49,527	-49.1	-71,363	-53.1	-20,658	-33.5	6,364	12.1	12,308	16.7	3,541	9.5	7,311	12.0	21,514	31.1	-68,971	-38.0	-35,852	-16.7	-37,541	-13.5
Emilia Romagna	-11,419	-42.5	-15,144	-53.6	-15,584	-38.6	-5,650	-35.0	7,103	51.4	-7,282	-24.0	-6,164	-35.0	-1,987	-11.9	-998	-3.7	-23,233	-38.3	-10,028	-17.1	-23,864	-24.5
FGV	-30,024	-56.5	-48,910	-65.8	-64,367	-72.0	-12,339	-44.5	-8,103	-20.9	-46,914	-62.4	-21,113	-47.7	-21,986	-37.1	-17,387	-39.7	-63,476	-50.7	-78,999	-45.9	-128,668	-61.7
Lazio	-11,232	-60.5	-16,531	-58.9	-18,995	-61.1	-7,568	-78.4	-8,419	-54.9	-20,157	-84.2	-2,260	-26.4	-13,462	-53.9	-11,108	-64.0	-21,060	-57.3	-38,412	-56.2	-50,260	-69.4
Liguria	-21,275	-62.5	-93,399	-61.5	-181,441	-68.6	-17,720	-80.6	-59,195	-47.0	-190,358	-91.3	-26,528	-78.1	-23,926	-24.9	-64,210	-54.8	-65,524	-72.8	-176,520	-47.2	-436,009	-73.9
Lombardia	-12,700	-55.0	-10,900	-51.9	-16,200	-55.5	-4,133	-25.2	-7,192	-40.4	4,285	22.7	-9,144	-33.9	-2,334	-13.6	-2,215	-11.2	-25,977	-39.1	-20,426	-36.5	-14,130	-20.8
Marche	-667	-42.6	-1,420	-50.1	1,381	66.1	141	17.6	-375	-21.5	-6,517	-100.0	-360	-43.7	-1,077	-44.7	0	0.0	-886	-27.8	-2,872	-41.1	-5,136	-59.7
Molise	-38,845	-55.4	-40,160	-52.9	-15,954	-53.7	-26,622	-58.5	-21,774	-41.0	-13,566	-57.4	-23,273	-53.0	-17,963	-36.9	-4,367	-24.0	-88,740	-55.6	-79,897	-45.0	-33,887	-47.4
Piemonte# FIT	-21,680	-50.6	-18,906	-50.6	7,700	(nv)	-20,179	-62.4	-16,829	-59.4	-188	-19.1	-3,997	-22.0	-9,098	-34.6	-7,344	-49.0	-45,856	-49.1	-44,833	-48.7	168	1.1
Piemonte FS	-8,502	-45.1	-5,754	-45.3	-7,308	-56.0	-6,735	-50.1	-7,508	-69.5	-9,177	-80.1	-7,399	-53.6	-5,211	-53.5	-6,647	-71.0	-22,636	-49.1	-18,473	-55.6	-23,132	-67.6
Puglia*	-27,883	-63.1	-22,921	-55.7	-6,982	-43.3	-2,806	-11.3	-10,681	-35.9	-20,342	-52.1	-15,112	-45.3	-13,186	-39.7	-26,452	-80.1	-45,801	-44.8	-46,788	-44.9	-53,776	-61.0
PA Trento	-5,985	-50.5	-5,979	-50.8	-6,716	-45.7	-1,945	-23.9	-6,071	-72.1	1,277	24.9	-1,693	-21.0	-4,051	-60.7	-1,743	-12.1	-9,623	-34.3	-16,101	-59.9	-7,182	-21.0
Toscana	-31,309	-45.0	-31,996	-40.3	-66,393	-57.6	-12,328	-25.0	-5,951	-12.0	-16,921	-27.5	9,336	22.5	2,804	6.0	-993	-1.8	-34,301	-21.4	-35,143	-20.0	-84,307	-36.2
Umbria	-8,013	-48.2	-12,053	-53.4	-6,689	-32.6	-387	-3.5	-1,277	-10.0	-3,581	-16.4	9,100	78.4	8,830	61.4	10,170	69.6	700	1.8	-4,500	-9.1	-100	-0.2
Valle d'Aosta	-1,551	-54.9	-2,001	-48.9	-2,240	-43.4	570	28.1	147	22.9	-3,617	-100.0	-585	-33.1	-1,265	-67.5	-2,839	-100.0	-1,566	-23.7	-3,119	-51.8	-8,696	-74.8
Veneto	-42,735	-56.5	-41,181	-44.7	-100,018	-55.1	-22,006	-39.4	-6,212	-9.8	-836	-0.7	-5,837	-12.3	-6,746	-11.3	1,901	2.1	-70,578	-39.5	-54,139	-25.1	-98,953	-25.6
ITALY	-354,665	-55.3	-454,625	-53.6	-600,664	-57.6	-171,660	-39.6	-149,538	-27.1	-352,795	-45.3	-130,152	-28.9	-135,196	-23.7	-140,938	-23.8	-669,742	-43.4	-751,879	-37.6	-1,110,414	-45.5

CS= cervical screening, BCS= breast cancer screening, CCS= colorectal cancer screening, FIT=faecal immunochemical test, FS=flexible sigmoidoscopy

*colorectal cancer screening programme was not activated in 2019

Data referring to the whole region except for CCS

[^]Data of 3 programmes out of 5

[§]Data are not provided for subperiods

Table 3
Standard months of delay in 2020, by screening programme and time period

Regions/ Autonomous province	Cervical cancer screening				Breast cancer screening				Colorectal cancer screening			
	Jan- May	Jun- Sep	Oct- Dic	Jan- Dic	Jan- May	Jun- Sep	Oct- Dic	Jan- Dic	Jan - May	Jun - Sep	Oct - Dic	Jan - Dic
Abruzzo	-1.9	-2.0	-0.7	-4.7	-2.0	-2.3	-2.1	-6.3	-1.6	-0.1	-0.7	-2.3
Basilicata§				-8.9				-5.2				-8.1
PA Bolzano	-0.6	0.1	-0.2	-0.8	-2.7	0.8	-2.3	-4.1	-1.5	-1.6	0.3	-2.7
Campania	-2.7	-1.2	-3.4	-7.2	-3.9	0.4	-3.3	-6.7	-2.4	-3.5	-3.5	-9.4
Calabria^	-5.1	2.7	-3.3	-5.7	-5.1	-0.8	-1.7	-7.6	-3.3	-3.1	-4.0	-10.5
Emilia Romagna	-3.4	-1.4	0.2	-4.6	-2.8	0.4	0.4	-2.0	-3.1	0.5	0.9	-1.6
FVG	-2.3	-1.1	-1.2	-4.6	-3.1	1.5	-0.4	-2.0	-1.9	-0.9	-0.1	-2.9
Lazio	-2.9	-1.2	-2.0	-6.1	-3.4	-0.6	-1.5	-5.5	-3.7	-2.7	-1.0	-7.4
Liguria	-3.7	-2.5	-0.7	-6.9	-2.9	-1.5	-2.4	-6.7	-3.1	-3.3	-1.8	-8.3
Lombardia	-2.8	-2.4	-3.5	-8.7	-3	-1.9	-0.8	-5.7	-3.7	-3.9	-1.3	-8.9
Marche	-2.3	-0.7	-1.6	-4.7	-2.3	-1.5	-0.5	-4.4	-2.9	0.8	-0.4	-2.5
Molise	-2.5	0.5	-1.4	-3.3	-2.4	-0.6	-1.8	-4.9	1.9	-9.1	0.0	-7.2
Piemonte# FIT	-2.9	-2.0	-1.8	-6.7	-2.7	-1.5	-1.2	-5.4	-2.7	-2.3	-0.7	-5.7
Piemonte FS									-3.3	-3.3	-1.8	-8.4
Puglia*	-2.8	-2.6	-0.5	-5.9	-2.5	-2.2	-1.2	-5.8				
Sardegna	-2.2	-1.8	-1.9	-5.9	-2.1	-2.7	-1.9	-6.7	-2.6	-3.2	-2.3	-8.1
Sicilia	-3.3	-0.3	-1.8	-5.4	-2.6	-1.2	-1.5	-5.4	-0.9	-2.8	-3.6	-7.3
PA Trento	-2.6	-0.8	-0.7	-4.1	-2.7	-2.7	-1.8	-7.2	-2.4	0.4	-0.6	-2.5
Toscana	-2.3	-0.9	0.7	-2.6	-2.2	-0.4	0.2	-2.4	-3.4	-0.9	-0.1	-4.3
Umbria	-2.4	-0.1	2.8	0.2	-2.9	-0.3	2.1	-1.1	-1.4	-0.8	2.1	0.0
Valle d'Aosta	-2.8	1.0	-1.1	-2.8	-4	0.3	-2.5	-6.2	-2.3	-3.7	-2.9	-9.0
Veneto	-2.9	-1.5	-0.4	-4.7	-2.3	-0.3	-0.4	-3	-3.1	0	0.1	-3.1
ITALIA	-2.8	-1.3	-1.0	-5.2	-2.8	-0.9	-0.8	-4.5	-3.0	-1.8	-0.7	-5.5

CS= cervical screening, BCS= breast cancer screening, CCS= colorectal cancer screening, FIT=faecal immunochemical test, FS=flexible sigmoidoscopy.

*colorectal cancer screening programme was not activated in 2019

Data referring to the whole region except for CCS

^ Data of 3 programmes out of 5

§ Data are not provided for subperiods

Similar results have been reported from modelling studies on breast cancer mortality and stage shift, as a result of delayed diagnosis following screening suspension [8, 19]. For cervical lesions, consequences could be less severe because this screening aims at identifying pre-neoplastic lesions with a natural history characterized by a slow progression and sometimes a possible regression [20]. If a CIN 3 lesion is detected instead of a CIN 2, the standard treatment is not more invasive and the prognosis is similar. Anyway, a more accurate estimate of the impact of the lockdown on cancer screening will be possible by comparing the stage at diagnosis of cancers detected in 2020 with the ones detected in the previous years.

Modelling studies are also showing that the impact of screening suspension is related to some factors: the duration of the suspension, the participation rate during the recovery period, and the catch-up strategy adopted by the screening center. An immediate catch-up of all delayed invitations would minimize the negative impact of the suspension. However, the observed trend in the recovery progression suggests that such an option is un-

likely to be feasible in every setting. Recovery strategies based on the adoption of priority criteria may, however, mitigate the negative effects of the screening suspension [8, 9, 11, 12, 19]. As an example, the approach of the Dutch breast cancer screening program to first invite those women who were not able to previously attend due to the suspension, might explain the unobserved shift towards a higher tumor stage at diagnosis. Nevertheless, a decreased incidence of screen-detected tumors was reported [21]. To allow directing limited resources to people who may benefit the most, the screening centers should adopt risk-based approaches to screening, following frameworks established before the pandemic, or adopting the expected Positive Predictive Value of the test as a priority criterion for the invitation. At the same time, the screening interval for lower-risk subjects should be extended. The implementation of these strategies may ensure equity of access to screening.

Low participation is still limiting the impact of the recovery strategies. Following the lockdown, in Italy as in other countries, patients were frightened, especially those with comorbidities, and sometimes they try to

Table 4

Quantitative estimate of lesions that may face a diagnostic delay due to the screening interruption by screening programme, 2020 vs 2019

Regions/ Autonomous Province	Cervical cancer screening			Breast cancer screening			Colorectal cancer screening				
	Gap of screening test in 2020 vs 2019	Detection Rate of CIN2+ (per 1000 screened)	Missed diagnosis of CIN2+ (estimate)	Gap of screening test in 2020 vs 2019	Detection Rate of breast cancer (x 1000 screened)	Missed diagnosis of breast cancer (estimate)	Gap of screening test in 2020 vs 2019	Detection Rate of colorectal cancer (x 1000 screened)	Missed diagnosis of colorectal cancer (estimate)	Detection Rate of Advanced adenoma (x 1000 screened)	Missed diagnosis of advanced adenoma (estimate)
Abruzzo	-11,658	5.7	-66	-19,547	4.5	-88	-7,828	3	-23	11.8	-92
Basilicata§	-13,264	1.8	-24	-12,520	4.1	-51	-16,017	1.1	-18	1.2	-19
PA Bolzano	-1,451	NA		-7,489	4.8	-36	-5,086	1.1	-6	4.3	-22
Campania	-51,918	2	-104	-40,763	2.9	-118	-60,395	1.6	-97	4.5	-272
Calabria ^	-12,383	10	-39	-5,458	4	-22	-3,857	3.1	-12	3.4	-13
Emilia Romagna	-68,971	5.2	-362	-35,852	5.5	-197	-37,541	0.9	-34	7.6	-285
FVG	-23,233	4.9	-114	-10,028	5.7	-57	-23,864	1	-24	4.2	-100
Lazio	-63,476	4.4	-278	-78,999	4.2	-332	-128,668	1.9	-244	10.4	-1,338
Liguria	-21,060	5.4	-114	-38,412	3.1	-119	-50,260	0.8	-40	4.4	-221
Lombardia	-65,524	3.8	-250	-176,520	4.4	-777	-436,009	0.9	-392	4.9	-2,136
Marche	-25,977	2.8	-73	-20,426	4	-82	-14,130	1.1	-16	6.8	-96
Molise	-886	1.0	-1	-2,872	3.5	-10	-5,136	1.7	-9	5.6	-29
Piemonte# FIT	-88,740	6.4	-568	-79,897	5.5	-439	-33,887	1.7	-58	12.2	-413
Piemonte FS							-11,758	2.8	-33	46.1	-542
Puglia*	-45,856	0.4	-18	-44,833	4.3	-193					
Sardegna	-22,636	5.1	-116	-18,473	3.3	-61	-23,132	2.1	-49	6	-139
Sicilia	-45,801	1.8	-84	-46,788	3	-140	-53,776	1.1	-59	5.7	-307
PA Trento	-9,623	5.2	-50	-16,101	6	-97	-7,182	1	-7	7.4	-53
Toscana	-34,301	6.4	-220	-35,143	5.2	-183	-84,307	0.9	-76	5.6	-472
Umbria	-700	12.3	9	-4,500	3.4	-15	-100	0.6	0	5.8	-1
Valle d'Aosta	-1,566	3	-5	-3,119	4.5	-14	-8,696	0.5	-4	6	-52
Veneto	-70,578	4.3	-307	-54,139	5.4	-292	-98,953	1	-99	8.8	-871
ITALY	-669,742	4.5	-2,782	-751,879	4.7	-3,324	-1,110,582	1.1	-1,299	6.7	-7,474

CS= cervical screening, BCS= breast cancer screening, CCS= colorectal cancer screening, FIT=faecal immunochemical test, FS=flexible sigmoidoscopy.

*colorectal cancer screening programme was not activated in 2019

Data referring to the whole region except for CCS

^ Data of 3 programmes out of 5

§ Data are not provided for subperiods

NA: not available

avoid healthcare settings that they perceived as at high risk of infection. Studies showed that even severe symptomatic patients avoided searching for medical assistance in emergency departments [22, 23]. Our results confirm that the attitude of the invited population to attend screening invitations was lower than before the pandemic, with a reduction in participation of 15% for cervical, 15% for breast and 20% for colorectal cancer screening. A decrease in screening uptake is not reported everywhere: the Scottish experience shows that pandemic represented an opportunity to transform and renew screening services with a robust recovery plan and a clear practical implementation of the restart. Such an approach led to greater participation levels than in previous years for breast, colorectal, and cervical screening [24]. It will therefore be of the utmost importance to develop communication strategies suitable for promoting

participation during this emergency, as well as to pursue new possible organizational features, such as postal delivery of self-sampling devices for HPV test or FIT test [14]. These measures will be of particular relevance also to counterbalance the possible search of opportunistic screening, not adequately monitored, and to prevent inequity issues that may arise from this tendency.

CONCLUSIONS

Although organized screening restarted after the 2020 lockdown, delays have not been recovered yet. For this reason, 3,324 breast cancers, 1,299 colorectal cancers and 7,474 colorectal advanced adenomas, and 2,782 CIN2 or more severe cervical lesions may have potentially missed an early diagnosis in Italy in 2020. Effective recovery strategies would involve the adoption of explicit priority criteria, the implementation of well-

designed communication strategies to promote participation, and the allocation of the necessary resources to ensure the implementation of the recovery plans and the sustainability of the programme activities over time.

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Authors' contribution

Mantellini P, Zappa M: conception and design, critical revision of the article for important intellectual content, final approval of the article; Battisti F: drafting of the article, critical revision of the article for important intellectual content, final approval of the article; Falini P, Gorini G: acquisition of the data, data analyses, critical revision of the article for important intellectual content, final approval of the article; Armaroli P, Giubilato P, Zorzi M, Battagello J: data analyses, critical revision of the article for important intellectual content, final approval of the article; Sassoli de Bianchi P, Giorgi Rossi P, Senore C: critical revision of the article for important intellectual content, final approval of the article.

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All Authors declare that they have no conflict of interest.

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A population-based cohort approach to assess excess mortality due to the spread of COVID-19 in Italy, January-May 2020

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Abstract

Aims. To assess the impact of the COVID-19 pandemic on all-cause mortality in Italy during the first wave of the epidemic, taking into consideration the geographical heterogeneity of the spread of COVID-19.

Methods. This study is a retrospective, population-based cohort study using national statistics throughout Italy. Survival analysis was applied to data aggregated by day of death, age groups, sex, and Italian administrative units (107 provinces). We applied Cox models to estimate the relative hazards (RH) of excess mortality, comparing all-cause deaths in 2020 with the expected deaths from all causes in the same time period. The RH of excess deaths was estimated in areas with a high, moderate, and low spread of COVID-19. We reported the estimate also restricting the analysis to the period of March-April 2020 (first peak of the epidemic).

Results. The study population consisted of 57,204,501 individuals living in Italy as of January 1, 2020. The number of excess deaths was 36,445, which accounts for 13.4% of excess mortalities from all causes during January-May 2020 (i.e., RH = 1.134; 95% confidence interval (CI): 1.129-1.140). In the macro-area with a relatively higher spread of COVID-19 (i.e., incidence rate, IR): 450-1,610 cases per 100,000 residents), the RH of excess deaths was 1.375 (95% CI: 1.364-1.386). In the area with a relatively moderate spread of COVID-19 (i.e., IR: 150-449 cases) it was 1.049 (95% CI: 1.038-1.060). In the area with a relatively lower spread of COVID-19 (i.e., IR: 30-149 cases), it was 0.967 (95% CI: 0.959-0.976). Between March and April (peak months of the first wave of the epidemic in Italy), we estimated an excess mortality from all causes of 43.5%. The RH of all-cause mortality for increments of 500 cases per 100,000 residents was 1.352 (95% CI: 1.346-1.359), corresponding to an increase of about 35%.

Conclusions. Our analysis, making use of a population-based cohort model, estimated all-cause excess mortality in Italy taking account of both time period and of COVID-19 geographical spread. The study highlights the importance of a temporal/geographic framework in analyzing the risk of COVID-19-epidemy related mortality.

Key words

- COVID-19 epidemic
- spread
- mortality
- excess mortality
- cohort
- surveillance
- Italy

INTRODUCTION

Italy was the first European country to be hit by the COVID-19 pandemic. The first confirmed case of COVID-19 was reported on February 20, 2020 [1], and the first related death occurred in February; it was a man in his 70s who suffered from pre-existing cardiovascular disease. Since then and until the end of May 2020, Italy experienced a strong epidemic wave that, particularly in the months of March and April, put the national health services under pressure, especially in the regions with the highest cases of COVID-19 [2]. Excess mortality, defined as the difference between the total and expected mortalities, is one of the main epidemiological tools for the measurement of the effects of a pandemic [3].

In Italy [4, 5], as in the rest of Europe [6-8], numerous studies have already been conducted with the aim of estimating excess mortality caused by COVID-19. Studies that compared the estimates among European countries [8] demonstrated that during the first wave of the epidemic, Italy was among the countries that had the highest number of excess deaths. The differences in the estimates between countries depended, as already observed [8], on the different characteristics of the populations. However, studies that estimate excess mortality in relation to the geographical spread of the disease are scarce.

The data on the first wave in Italy, due to the high geographical heterogeneity of the COVID-19 incidence rates throughout the national territory [1], can help estimate excess mortality in relation to the geographical spread of the disease. On these grounds, we conducted an analysis of the overall mortality based on the data supplied by the National Institute of Statistics (Istituto Nazionale di Statistica, ISTAT) and the Italian National Integrated COVID-19 Surveillance System, managed by the National Institute of Health (Istituto Superiore di Sanità, ISS). This study aimed to describe all-cause excess mortality from January to May 2020, integrating all existing information on a national basis. In particular, we focused on the quantification of the excess of deaths from all causes in Italy in relation to the spread of COVID-19.

METHODS

Study population

The study population consisted of Italians living in Italy at the start of the study period, i.e., the resident population released by the Italian National Institute of Statistics on January 1, 2020. (ISTAT; <http://dati.istat.it>). In the current analysis, the resident population was considered by Italian administrative units (107 provinces), age (from 0-9 years to 90+ years by intervals of 10 years), and sex.

Deaths from all causes. ISTAT releases estimates per day of the number of deaths from all causes by age, sex, and municipality of residence drawing from population and taxpayers' registries (National Register of Resident Population and the information provided by the municipalities themselves). For the present analysis of the year 2020, deaths from all causes referred to 7,357 municipalities out of the 7,904 existing ones (for 93% of Italian municipalities corresponding to 95% of all Ital-

ian residents); for further details, see published report [9]. For the purpose of our study, the dataset of deaths from all causes was aggregated by day, provinces (107 provinces), age, and sex.

COVID-19 surveillance and deaths in COVID-19 cases. COVID-19 cases are microbiologically (SARS-CoV-2-positive nasopharyngeal swabs) diagnosed and collected daily by the Italian Regions through a dedicated web platform (Italian National Surveillance System for COVID-19). This surveillance system is monitored and updated daily by the ISS as per the case definition published and regularly updated online by the European Centre for Disease Prevention and Control (ECDC) [10-12]. Clinical and epidemiological information (e.g., age, sex, municipality/province of residence, comorbidity, vital status, and date of death) are also collected.

For the present analysis, we extracted from the dataset all cases and deaths (SARS-CoV-2 infections confirmed by RT-PCR) between January 1 and May 31, 2020, by province of residence (107 provinces), age classes (from 0-9 years to 90+ years, aggregated over a 10-year interval), sex, and day of death.

Primary outcomes: i) observed number of deaths from all causes per day in 2020; ii) expected number of deaths from all causes in the same day (estimated as the average number of deaths from all causes occurring daily in the previous 5 years, i.e., 2015-2019); iii) observed excess number of deaths per day in 2020, calculated as the difference of the first two outcomes: i)-ii).

Secondary outcomes: i) observed number of deaths "with a COVID-19 diagnosis" per day in 2020; ii) number of deaths "without a COVID-19 diagnosis" per day in 2020 (calculated as the difference between the total number of deaths from all causes per day in 2020 and the number of deaths "with a COVID-19 diagnosis" per day); and iii) incidence of COVID-19 cases per day (incidence rates $\times 100,000$).

Study design

Retrospective cohort study.

Statistical analyses

All datasets were aggregated and merged by day, age group, sex, and province of residence. The count-time aggregate data were converted to frequency-weighted survival-time data. We considered in detail the survival times going from January 1, 2020, to the end of the study period, which was May 31, 2020, or to the date of death if the person died before the end of the study period.

We obtained interpolating curves for the outcomes per day (all-cause deaths, expected deaths, and difference between all-cause deaths and deaths with a COVID-19 diagnosis) using the locally estimated scatterplot smoothing method (LOESS) [13]. The LOESS method was further used as a supplementary analysis to compare the main characteristics (age and sex) of the outcomes.

To estimate the cumulative incidences of the outcomes, we employed the Kaplan-Meier method [14]. In addition, we applied Cox models [14] on aggregated data, as aforementioned, to estimate the relative hazards (RHs) of deaths from all causes in 2020 compared

with the expected number of deaths from all causes in the same year, i.e., the RHs of excess deaths. The same model was used to estimate the RHs of deaths without a COVID-19 diagnosis, defined above, in 2020 compared with the expected deaths from all causes in the same year. The analyses were also repeated separately by geographical areas. For this purpose, we considered different levels of COVID-19 diffusion according to the tertiles of the COVID-19 incidence rates per 100,000 residents, and we classified provinces accordingly. In detail, we assumed “low spread of COVID-19” when the incidence rates by province were less than the first tertile, “moderate spread of COVID-19” when the rates ranged from the first to the second tertile, and “high spread” when the COVID-19 rates were over the third tertile.

Finally, we restricted the analysis to the period of March-May 2020 (first peak of the epidemic) to estimate again the RH excess mortality from all causes and calculate the RH of excess deaths for COVID-19 incidence rate increments.

Data were analyzed using the SAS software version 9.4.

RESULTS

Demographic characteristics of the cohort and the COVID-19 diagnoses

In total, 57,204,501 individuals were included in the analysis (*Supplementary Figure 1* available online and demographic description in *Table 1*). The geographical distribution of the excluded population (5%) was similar to that of the included population: of the excluded individuals, 41% lived in the north, 22% in the center, and 37% in the south; of those included, 44% lived in the north, 21% in the center, and 35% in the south.

The age and sex distributions of the cohort (*Table 1*) were similar to those of the whole Italian population (*Table 1*): young people accounted for less than 20%

(people younger than 20 = 10,176,681, accounting for 17.8%), and people older than 60 accounted for almost 30% (25,513,208, accounting for 29.7%), with a male-to-female ratio of about 0.95.

Most of the deaths from all causes (*Table 1*) occurred in the age group of 80-89 years (121,055; 39.3%) and in females (158,613; 51.5%). The age distribution of COVID-19-related deaths was similar to that of all-cause deaths in the Italian population, except for individuals aged 70-79 years for whom the percentage was higher (26.7% vs 19.7%), as well as among individuals aged 90+ years for whom, however, the percentage was lower (17.6% vs 26.5%); with regard to gender, the majority of COVID-19 deaths were males (18,842; 58.5%).

Table 2 (part a) presents a brief description of the COVID-19 cases confirmed by the Italian National Surveillance System on COVID-19. The majority of cases of COVID-19 was concentrated in 36 provinces (33.6%), where the National Surveillance System reported during the studied period an incidence rate of at least 450 COVID-19 cases per 100,000 residents (high diffusion area). Conversely, lower spread of the disease was observed in the remaining provinces (*Table 2, part a*, low and moderate spread of COVID-19). It should be noted that the distribution by sex and age of COVID-19 cases was quite similar in the three COVID-19 diffusion macro-areas (*Table 2, part b*). In addition, it should be noted that among individuals aged 80+ years, the highest percentage was reported in the area with high incidence, especially in comparison with the estimate reported in low spread area (27.1% in the area with high incidence vs 14.1% in the area with low incidence).

Temporal patterns of the main outcomes according to the geographical spread of COVID-19

Overall, the ISTAT reported 307,809 deaths from all causes in Italy from January 1, 2020, to May 31, 2020

Table 1

Population description, corresponding to 94.9% of all residents in Italy at January 1st 2020; deaths occurred from Jan 1st to May 31 2020

Demographic features	Groups	Total cohort	Deaths for any causes	COVID-19 related death
Totals		57,204,501	307,809	32,236
		frequency (%)	frequency (%)	frequency (%)
Age	0-9	4,702,210 (8.2%)	564 (0.2%)	3 (<1%)
	10-19	5,474,471 (9.6%)	263 (0.1%)	0 (0%)
	20-29	5,846,300 (10.2%)	594 (0.2%)	14 (<1%)
	30-39	6,601,399 (11.5%)	1,248 (0.4%)	64 (0.2%)
	40-49	8,586,396 (15.0%)	4,178 (1.4%)	285 (0.9%)
	50-59	9,021,150 (15.8%)	12,080 (3.9%)	1,129 (3.5%)
	60-69	7,053,315 (12.3%)	25,850 (8.4%)	3,282 (10.2%)
	70-79	5,703,289 (10.1%)	60,537 (19.7%)	8,594 (26.7%)
	80-89	3,460,872 (6.0%)	121,055 (39.3%)	13,179 (40.9%)
	≥90	755,099 (1.3%)	81,440 (26.5%)	5,686 (17.6%)
Sex	males	27,858,592 (48.7%)	149,196 (48.5%)	18,842 (58.5%)
	females	29,345,909 (51.3%)	158,613 (51.5%)	13,394 (41.5%)

Table 2 (part a)Description of COVID-19 cases occurred in Italy from Jan 1st to May 31 2020

Demographic features		
Total		223,937
		frequency (col %)
Age groups		
0-9		1,818 (0.8%)
10-19		3,364 (1.5%)
20-29		12,391 (5.5%)
30-39		17,248 (7.7%)
40-49		29,046 (13.0%)
50-59		40,208 (18.0%)
60-69		29,948 (13.4%)
70-79		32,243 (14.4%)
80-89		39,460 (17.6%)
≥90		18,211 (8.1%)
Sex		
males		102,640 (45.8%)
females		121,297 (54.2%)
Spread level of COVID-19*		
low (30-149 cases per 100,000)		18,517 (8.3%)
moderate (150-449 cases per 100,000)		42,323 (18.9%)
high (450-1,610 cases per 100,000)		163,097 (72.8%)

(Table 1); of these deaths, 36,445 were in excess relative to the expected numbers in the same period ($36,445 = 307,809 - 271,364$; $271,364.2 =$ average in the previous 5 years (from January 1 to May 31 during the years: 2015-2019). Of these 36,445 excess deaths, the majority occurred in laboratory-confirmed COVID-19 cases, registered by the Italian National Integrated COVID-19 Surveillance System (32,236 “deaths with a diagnosis of COVID-19”; COVID-19 deaths as in Table 1), whereas the remaining 4,209 (11.5%) were deaths “without a COVID-19 diagnosis.”

Figure 1 (part A) clearly shows an increase in the excess number of deaths (red line vs blue line) from early March 2020, with a peak at the end of March, which exactly followed the peak of “deaths with a COVID-19 diagnosis” (in March 27, Supplementary Figure 2 available online). The excess number of deaths was lower in provinces reporting low to moderate levels of COVID-19 incidence (Figure 1, parts B and C) and higher in those with a higher diffusion of COVID-19 (Figure 1, part D).

When considering temporal patterns in the excess number of deaths by sex and age (Supplementary Figure 3 available online), we observed that the excess number of all-cause deaths was higher in males than in females in all age groups, except for females aged 90+ years. Similarly, the number of deaths “diagnosed as non-COVID-19” was higher in males aged 80-89 years respect the number of females of the same age group. Furthermore, the number

Table 2 (part b)

Description of COVID-19 cases by COVID-19 spread

Demographic features	Low spread	Moderate spread	High spread
Total	18,517 (8.3%)	42,323 (18.9%)	163,097 (72.8%)
		freq. (col. %)	freq. (col. %)
Age groups			
0-9	315 (1.7%)	452 (1.1%)	1,051 (0.6%)
10-19	641 (3.4%)	903 (2.1%)	1,820 (1.1%)
20-29	1,646 (8.9%)	2,918 (7.0%)	7,827 (4.8%)
30-39	2,004 (10.9%)	3,579 (8.5%)	11,665 (7.1%)
40-49	2,726 (14.7%)	5,830 (13.8%)	20,490 (12.7%)
50-59	3,665 (20.0%)	8,129 (19.2%)	28,414 (17.4%)
60-69	2,721 (14.6%)	5,512 (13.0%)	21,715 (13.3%)
70-79	2,172 (11.7%)	5,311 (12.5%)	24,760 (15.2%)
80-89	1,933 (10.4%)	6,455 (15.2%)	31,072 (19.0%)
≥90	694 (3.7%)	3,234 (7.6%)	14,283 (8.8%)
Sex			
males	9,527 (51.5%)	18,673 (44.1%)	74,440 (45.6%)
females	8,990 (48.5%)	23,650 (55.9%)	88,657 (54.4%)

*Levels were obtained on the basis of the tertiles of the distribution of the incidence rates of COVID-19 by province of residence.

Note: the Italian provinces with *low incidence* were: Agrigento, Ascoli Piceno, Bari, Barletta, Benevento, Cagliari, Caltanissetta, Caserta, Catania, Catanzaro, Cosenza, Crotone, Enna, Foggia, Frosinone, Isernia, L'Aquila, Latina, Lecce, Livorno, Matera, Messina, Napoli, Nuoro, Oristano, Palermo, Potenza, Ragusa, Reggio Calabria, Roma, Salerno, Siracusa, Sud Sardegna, Taranto, Trapani, Vibo Valentia, Viterbo; *moderate incidence*: Ancona, Arezzo, Brindisi, Campobasso, Chieti, Cuneo, Fermo, Ferrara, Firenze, Forlì-Cesena, Gorizia, Grosseto, La Spezia, Lucca, Macerata, Padova, Perugia, Pisa, Pistoia, Pordenone, Prato, Ravenna, Rieti, Rovigo, Sassari, Siena, Teramo, Terni, Treviso, Udine, Varese, Venezia, Vicenza; *high incidence*: Alessandria, Aosta, Asti, Belluno, Bergamo, Biella, Bologna, Bolzano, Brescia, Como, Cremona, Genova, Imperia, Lecco, Lodi, Mantova, Massa Carrara, Milano, Modena, Monza e della Brianza, Novara, Parma, Pavia, Pesaro e Urbino, Pescara, Piacenza, Reggio Emilia, Rimini, Savona, Sondrio, Torino, Trento, Trieste, Verbano-Cusio-Ossola, Vercelli, Verona.

of deaths “diagnosed as non-COVID-19” was higher in females aged 90+ vs males aged 90+ years (Supplementary Figure 3, parts B, C, E, and F available online).

Estimates of the cumulative incidences of deaths from all causes and comparison with the expected number of deaths according to the COVID-19 diffusion over time

The observed and estimated cumulative mortalities from all causes of death are reported by month in Supplementary Table 1 available online. The observed estimates of mortality were lower than expected until February 2020 (i.e., the observed mortality was 0.19% on February 2020 vs the expected mortality of 0.21%) and higher afterwards, ranging from 0.34 in March to 0.54 in May 2020 (Supplementary Table 1 available online).

In areas with a high spread of COVID-19 (Figure 2, part B), the observed rates increased from 0.10% in January 2020 to 0.66% in May 2020, whereas in those with a lower spread, the all-cause mortality decreased from 0.10% to 0.44% over the same period, respectively.

These results were confirmed by the Cox models, which yielded RH of observed to expected numbers of

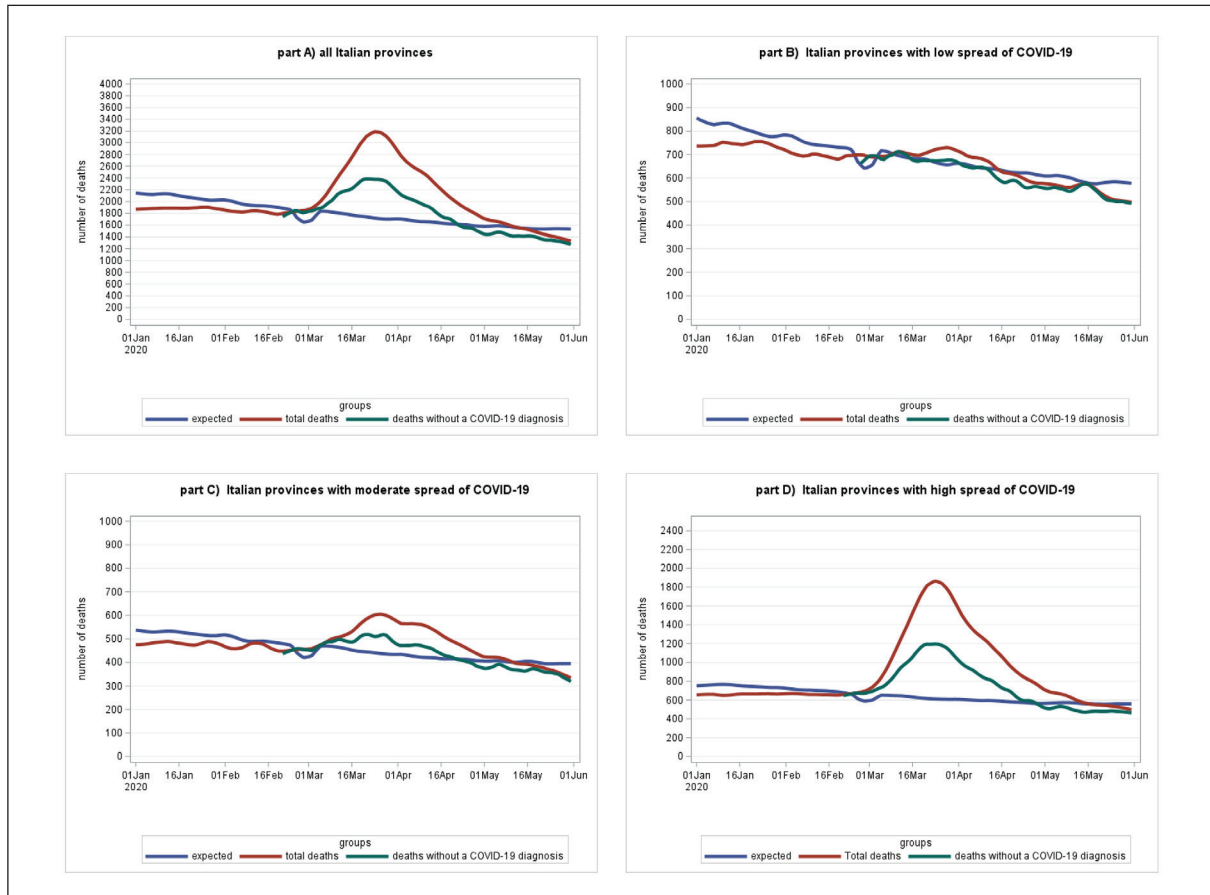


Figure 1

All-cause daily deaths from January 1 to May 31, 2020 (red curve); average number of deaths (blue curve) that occurred between 2015 and 2019 in the same study period (expected deaths); deaths without a COVID-19 diagnosis (green curve, i.e., difference between all-cause deaths and deaths with a COVID-19 diagnosis); curves fitted by locally estimated scatterplot smoothing (LOESS), local regression method. Described graph curves in: part A) all Italian provinces; part B) Italian provinces with low spread of COVID-19; part C) Italian provinces with moderate spread of COVID-19; part D) Italian provinces with high spread of COVID-19.

deaths from all causes of 1.375 (95% CI: 1.364-1.386), 1.049 (95% CI: 1.038-1.060), and 0.967 (95% CI: 0.959-0.976), respectively, in areas with a high, moderate, and low spread of COVID-19, for the year 2020 (January-May).

In *Figure 2 (part E)*, the observed mortality from deaths without a COVID-19 diagnosis is graphed together with the expected mortality from all causes of death; therefore, the RH of the observed number of deaths without a COVID-19 diagnosis relative to the expected number of deaths was 1.016 (95% CI: 1.011-1.022), accounting for about 2% of excess mortality.

Restricting the analysis to the period of March-April 2020 (peak of the epidemic), the RH of excess deaths was 1.435 (95% CI: 1.424-1.446). We also estimated that the excess mortality increased by 35.2% for every 500 increase per 100,000 residents in the number of new cases of COVID-19 (*Table 3*).

DISCUSSION

Applying a population-based cohort approach, we estimated excess mortality attributable to the COVID-19 epidemic according to different geographical spread of the virus during the first 5 months in 2020. This was

possible, thanks to the use of two nationwide data sources (ISS and ISTAT).

The study highlights an “excess” in mortality, an epidemiological term used to give an estimate of the difference between the observed number of deaths in a specific period and the expected number of deaths in the same period [3]. This could be due to both the direct and indirect effects of the pandemic. Direct effects take into consideration the number of deaths diagnosed as “COVID-19.” All the excess deaths may be due to COVID-19, but they might have occurred before a possible diagnosis of SARS-CoV-2 infection (for instance, deaths from organ dysfunctions, such as heart or kidney failures, are likely to be triggered by the virus).

The indirect effects include the deaths of patients suffering from serious diseases other than COVID-19 due to the overload of the National Health Service, especially in the most affected areas, as also observed in the USA [15, 16]. The anticipated deaths of fragile people, such as the elderly, could be considered as another indirect effect of the pandemic. Only future analyses extended to the entire period of 2020-2021 will be able to assess the full impact of the pandemic, including a possible “collection” phenomenon, the so-called “har-

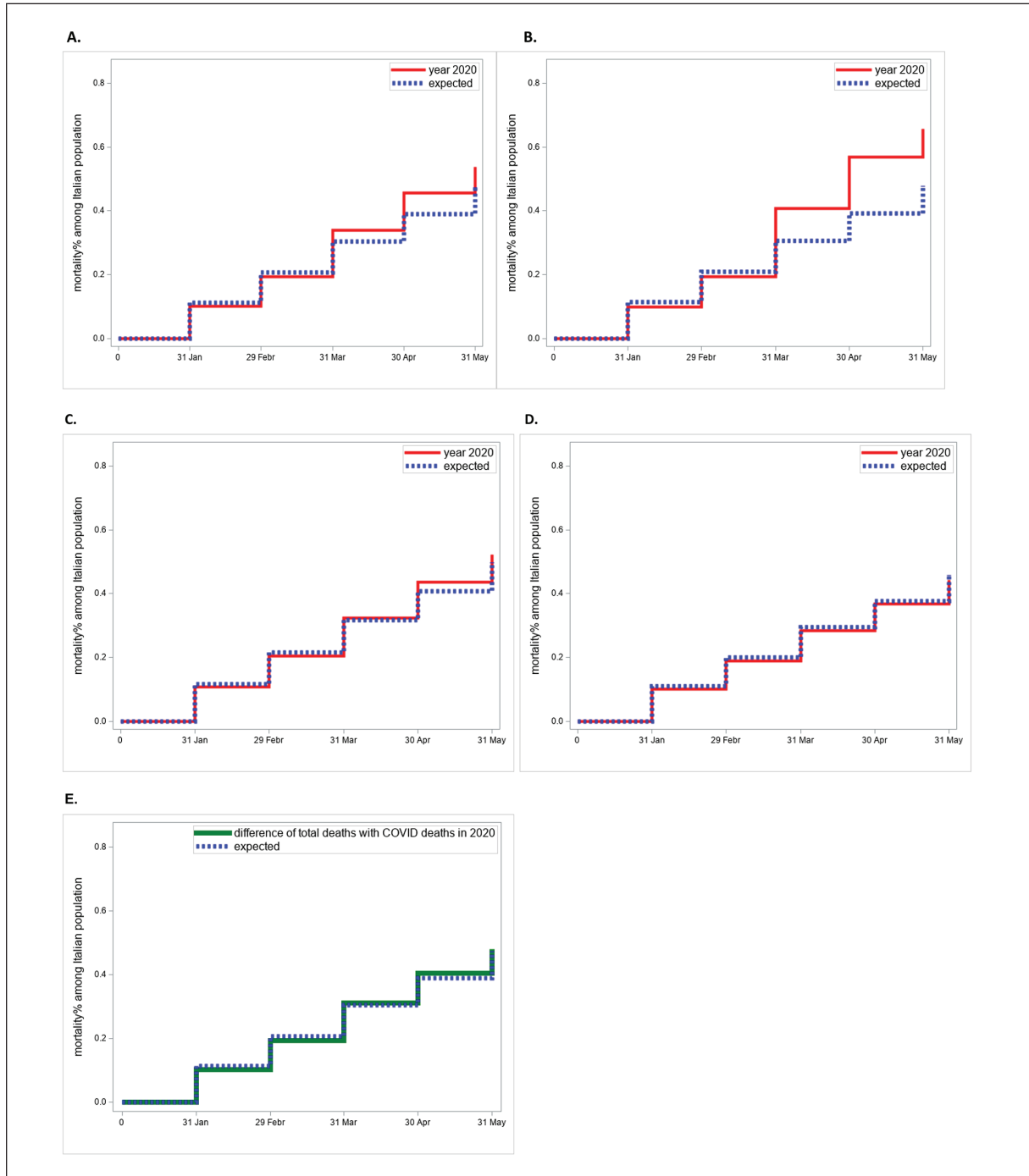


Figure 2

Part A) all-cause mortality in Italy during the study period; all provinces throughout Italy (part A), $RH = 1.134$ (95% CI: 1.129-1.140); part B) provinces with a high spread of COVID-19, RH of mortality observed in 2020 vs all-cause expected mortality = 1.375 (95% CI: 1.364-1.386); part C) provinces with moderate spread, RH of 2020 vs expected deaths = 1.049 (95% CI: 1.038-1.060); part D) provinces with low spread, RH of 2020 vs expected = 0.967 (95% CI: 0.959-0.976); part E) cumulative incidences of deaths without a COVID-19 diagnosis vs expected deaths, $RH = 1.016$ (95% CI: 1.011-1.022).

vesting effect.” Furthermore, the sanitary containment measures taken to tackle the health crisis during the first wave have significantly reduced violent deaths, such as traffic accidents.

In Italy, mortality from any cause started to rise quickly since the beginning of March 2020 and declined after a peak of more than 3,000 deaths in March 27.

The same trends were observed for COVID-19-related deaths and deaths registered without a COVID-19 diagnosis. Therefore, the excess deaths gradually diminished after the peak in March 27.

We estimated a RH of excess deaths of 1.13 between January 1 and May 31/2020, i.e., an excess of 13% in the observed number of deaths from all causes com-

Table 3

Relative hazard (RH) of excess mortality (year 2020 vs expected) and RH for increments of 500 cases per 100,000 residents during the peak months of epidemic (March and April 2020)

	RH of death for any cause	95% CI
Year 2020 vs expected	1.435	(1.424-1.446)
Incidence rate of COVID-19 per increments of 500 x 100,000 residents	1.352	(1.346-1.359)

pared with the number of expected deaths from all causes. In the same period, the RH of the observed deaths without a COVID-19 diagnosis compared with the expected deaths from all causes was equal to 1.016, indicating that about 2% of the excess deaths occurred in subjects without a diagnosis of COVID-19. This percentage may partly reflect a delay in the diagnosis and/or access to health services (individuals may have died before being tested). It should be noted that these findings should be confirmed by analyzing all the causes of deaths. In this regard, the Italian National Institute of Statistics recently analyzed all the causes of death observed in March-April 2020 (the period of the first epidemic wave in Italy), considering deaths obtained from the death certificate data (https://www.istat.it/it/files//2021/04/Report-Cause-di-Morte_21_04_2021.pdf). They found that COVID-19 was the leading cause of death among males and the second (after neoplasms) among females.

When exploring excess deaths by sex and age groups, we observed that the all-cause excess deaths were higher in males than in females in all age groups, except for females aged 90 years or older. Notably, we observed in both sexes, aged 80 years or older, a higher number of deaths “diagnosed as non-COVID-19” during the peak months, especially in females aged 90 years or older. Unsurprisingly, this result reflected the structure of the Italian population, as in the rest of Europe, where females account for more than 70% of individuals aged 90 years or older (https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Population_structure_and_ageing). Furthermore, these results could prompt further research on the origins and causes of under-reporting of COVID-19 deaths.

We also demonstrated that the largest increase in mortality was observed in provinces with a COVID-19 incidence rate of 450-1,610 cases per 100,000 residents, with an overall increase in mortality of about 37%. Conversely, the RH of excess deaths decreased to 5% in provinces with a moderate level of COVID-19 incidence (150-449 cases per 100,000 residents); we observed an RH of death lower than 1 in provinces with a COVID-19 incidence lower than 30-149 cases per 100,000 residents, i.e., the mortality observed in 2020 was lower than expected. Our results are only in part consistent with a recent study conducted in Italy [17]. The authors reported “an estimated increase of 47,490 (95% eCI: 43,984-50,362) from the expected baseline numbers when accounting for temporal trends and differences in temperature distribution,” corresponding

to a percentage excess of 29.5% (95% eCI: 26.8-31.9). Even if not directly comparable because of differences in the periods analyzed and in the design and method used, we obtained a high percentage (43%) of excess mortality in March and April. Again, even if direct comparison with our results was impossible, our study partially replicates findings from a population-based cohort study conducted on a large sample of the UK population (3,862,012 of adults), in which the different scenarios hypothesized by the UK model approximately correspond to the three levels of COVID-19 spread in Italy (low, moderate, and high) [7]. We also estimated the increase in the RH for all-cause mortality with the increase in the incidence rate of COVID-19 (for increments of 500 cases per 100,000 residents), which was equal to 1.352 (95% CI: 1.346-1.359), corresponding to an increase of about 35% in the excess deaths for every 500 increase in the number of diagnoses per 100,000 residents. The last estimate could be a benchmark: for example, the excess mortality would be almost double (70%) for incidences of 1,000 new COVID-19 cases per 100,000, and this is what happened unfortunately in many municipalities in the north during the first wave [10, 17].

We also observed that among subjects aged 80 years, those who were living in areas with a high spread of COVID-19 were relatively more affected than those of the same age who were living in areas with a low spread of COVID-19 (27.1% vs 14.1%). This result highlights that, during the first wave, a high proportion of COVID-19 cases was reported in nursing homes, especially in the area with a high spread of the epidemic, i.e., in the northern regions [18].

Several studies have been published in Europe [6, 7], in USA [15, 16], and Italy [4, 5], taking into account excess deaths; however, this is one of the first studies to summarize all the available information on mortality, integrating data from two national data sources, namely, the National Institute of Statistics and COVID-19 Surveillance Data from the National Institute of Health. Therefore, the strength of this study relies on the fact that it was based on almost the entirety of the Italian resident population. Furthermore, the heterogeneity in the geographical spread of the epidemic allowed for the estimation of the different impacts on excess deaths in different areas according to different levels of COVID-19 incidence.

This study has some limitations. First, we applied a cohort approach without using individual data, but using aggregated data. While we could apply survival techniques as we knew the individual death dates, we were not able to be as accurate on COVID-19 exposure: given the association between aggregated cases/deaths at the province level, we cannot ignore the possible impact of ecological fallacy on our estimates of excess deaths. Furthermore, we assumed that the entire Italian population was exposed to the virus starting from an arbitrary date (January 1, 2020), and as a result, we have presumably underestimated the excess mortality. However, a recent study in Italy showed virus detection in wastewater since December 2019 in large cities in the north [20], confirming the appropriateness of this

date as time zero of our analysis, especially as regards the northern regions.

Second, we used the COVID-19 incidence rate per 100,000 residents as a measure of the spread of the virus. Moreover, at the beginning of the epidemic, the incidence rates of COVID-19 were mostly representative of symptomatic people [1]. Therefore, when including asymptomatic cases, the estimates of COVID-19 incidence would have been much higher, as was the case in subsequent epidemic waves including the different geographical patterns of the Sars-Cov2 diffusion [21]. Finally, we defined deaths as “COVID-19-related” when occurring in patients who tested positive for SARS-CoV-2 by RT-PCR, regardless of pre-existing diseases that may have caused the death, as previously reported [1, 19]. This also reflected the unclarity of the definition of COVID-19-related death at the start of the epidemic.

In conclusion, our analysis, in which we used a population-based cohort approach, provided estimates of mortality excess due to COVID-19 in Italy, in particular during the first wave of the epidemic, when the surveillance system had just been established.

Authors' contributions

MD performed the statistical analyses and drafted the manuscript; GM contributed to the design of the study and revised the advanced draft of the manuscript; SB elaborated surveillance data and revised critically the manuscript; VM elaborated mortality data; SP coordinated and supervised National mortality data; MB and GC elaborated National mortality data and revised critically the manuscript; XA elaborated surveillance data and critically revised the manuscript, FR, MF, MFV elaborated surveillance data and critically revised the manuscript, MS, AMU and MDM elaborated surveillance data; PP is the head of the Italian coronavirus disease surveillance system and revised the manuscript; AB coordinated and supervised the surveillance data collection, contributed to the conception and design of the study, critically revising the manuscript; all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Conflict of interest statements

The Authors declare that they have no competing interests.

The Authors declare that data on excess mortality in year 2020 has been published previously, but not in the same form, with different objectives and statistical methods (Dorrucchi M, Minelli G, Boros S, et al. Excess Mortality in Italy During the COVID-19 Pandemic: Assessing the Differences Between the First and the Second Wave, Year 2020. *Front Public Health*. 2021; doi: 10.3389/fpubh.2021.669209).

Patient consent for publication

Not required.

Ethics approval

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

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Knowledge and attitudes towards Zika virus: an Italian nation-wide cross-sectional study

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Abstract

Background. Zika virus (ZIKV) is an arthropod-borne virus transmitted through infected mosquitoes. The aim of this Italian nation-wide study was to evaluate general population's knowledge and attitudes towards ZIKV, its transmission, and travel-related preventive measures.

Methods. This cross-sectional study was conducted between July and August 2017, through a validated questionnaire. Predictors of knowledge were analysed through multivariate regression.

Results. Among 1119 respondents, 20% and 71% knew etiological agent and transmission route of ZIKV infection, respectively. Approximately 43% ignored the preventive measures to be taken after returning from endemic areas. At multivariate analysis, predictors of poor knowledge were age, living in Central or South Italy and Islands, being poorly educated, having never heard of or attended a travel clinic.

Conclusions. This study captures an overall poor knowledge of Zika among general public. This research highlights the need of designing and implementing measures to improve travellers' awareness and protection against ZIKV.

Key words

- arthropod-borne viruses
- flavivirus
- travel medicine
- tropical disease
- Zika

INTRODUCTION

Recently, a series of emerging and re-emerging infectious diseases have constituted major public health challenges globally, with a major impact of Severe Acute Respiratory Syndrome (SARS) [1], Middle East Respiratory Syndrome (MERS), Ebola virus disease (EVD), Malaria, the Zika virus (ZIKV) infection and, lately, the novel Coronavirus Disease 2019 (COVID-19) [2]. Although firstly described in limited specific geographical areas (for instance, MERS-Coronavirus infection in middle-Eastern countries, ZIKV in South America, and EVD in the Western Africa), they have quickly spread worldwide, due to globalization, migration, and the creation of conditions for the smooth travelling of people (e.g., decrease in transport fares, packaged holidays, easier backpacking) [3-5].

Among all, one of the most impacting diseases – af-

ter the challenge posed by SARS-CoV-2 [6, 7] –, is the infection due to ZIKV. This is an arthropod-borne virus (arbovirus) of the family Flaviviridae, genus Flavivirus, which was firstly isolated in sentinel rhesus macaque in the Zika forest of Uganda in 1947 [8]. Although mosquito vectors represent the main route of transmission (primarily *Aedes* spp, like *A. aegypti*), post-transfusion, sexual, maternal-to-foetus and intrapartum transmissions have been described [9, 10]. In fact, ZIKV genome has been isolated in saliva, blood, cerebrospinal fluid, urine, breast milk, and amniotic fluid, being ZIKV also responsible for congenital infections and malformations (e.g., microcephaly, cerebral calcifications, severe brain malformations including Guillain-Barre syndrome), and other birth defects [11]. Indeed, from a public health perspective, the great interest on ZIKV is not solely associated with the spread of the infection,

but mostly attributable to severe congenital malformations in new-borns.

For this reasons, when ZIKV caused an important outbreak in early 2016, started in Brazil and then crossed different international borders, mainly in the Americas [12], the World Health Organization (WHO) Emergency Committee declared it an international public health emergency [13]. This action severely impacted on travelling and travel medicine at that time, during which Brazil was preparing to host the 2016 Olympic Games, with more than 200 nations, 10,000 athletes [14, 15], and hundreds of thousands of tourists from all over the world [16]. Despite the whole situation and the several recommendations (advising, in particular, pregnant women and those planning a pregnancy, athletes, and general public) issued by the WHO [17, 18], the real risk of transmission of ZIKV was valued to be low, since the Olympic Games were held during the winter months, when the distribution of mosquitoes was expected to be low [19]. Moreover, extensive use of insecticides eradicated mosquito population and, most importantly, athletes, trainers and visitors were instructed to use individual protection (wearing appropriate clothing with skin coverage, sleeping under mosquito nets, using contact insecticides for clothing and mosquito nets, and applying insect repellents on a regular basis). Despite all these precautions, many imported cases were registered in several European countries, including Italy [20]. Here, sexual secondary autochthonous cases have been also reported in recent years [21]. Eventually, even though no autochthonous cases of Zika transmission have been notified in Europe and the vast majority of mosquito populations endemic in Italy have proved to be less or not suitable for ZIKV (compared to *A. aegypti*), the identification of mosquitoes belonging to the *Aedes* spp. (such as *A. albopictus*, *A. koreicus* and *A. japonicus*) in certain areas of the country has raised concerns regarding the possibility of their colonization by ZIKV and a consequent virtual autochthonous spread of the disease [22, 23].

Considering the above, the aim of this nation-wide study was to evaluate the general population's knowledge and attitudes towards prevention of Zika in Italy. The final goal was to detect possible drivers of the compliance towards preventive measures in the general population, as well as identify critical educational needs, useful for developing new methods of empowerment of general public and containing the future transmission of the disease, especially considering the expected high number of travellers to Middle East for the upcoming 2022 FIFA World Cup in Qatar, which harbours *A. aegypti* mosquito [24].

METHODS

Study design

This cross-sectional study was conducted between July and August 2017, assessing knowledge and attitudes toward ZIKV, its transmission, and the preventive measures by means of modified version of a validated Italian-38-item questionnaire available in literature [25]. This was shortened in order to make the questionnaire easier and to increase the total number of respon-

dents. The new version of the survey was re-validated, and the validation process consisted of the administration of the full questionnaire to 28 adult subjects (not included in the final analysis), to gauge feedback on the overall consistency, reliability, and acceptability in terms of clarity and question formats. The final version of the survey was included in the Supplementary material, available online (*Appendix 1*).

The questionnaire was administered twice, two weeks apart, in order to obtain knowledge and attitude measurements both representative and stable over time. We assessed the test-retest reliability and internal consistency of the questionnaire using the Cronbach's α . It is a measure of how a set of items are related as a group [26]. Higher is the Cronbach's α value higher is the intercorrelations among tested items. A value α greater than 0.70 is generally considered as the minimum acceptable cut-off [27]. Initial Cronbach's α was <0.70 ; thus, in order to achieve a satisfactory value, surveys' items were iteratively eliminated until an acceptable value was reached. The final, simplified version of the questionnaire included eight items, with a α of 0.81, together with the socio-demographic questions (*Table S1*, available online as Supplementary material). Overall test-retest concordance was 0.86, ranging from 0.76 to 0.94 according to each item (*Table S2*, Supplementary material). The validation process took place between January and February 2017.

The new version of the questionnaire was based on a total of 15 items: the first seven investigated socio-demographic characteristics (sex, age, citizenship, area of residency, education, occupation, and partner status), the remaining eight were about the knowledge on ZIKV aetiology, transmission route, preventive measures, and attitude about consultation of travel medicine clinic before travelling abroad. The questionnaire was administered on-line and developed via Google forms®, a user-friendly and free tool used to create survey and collect data. All subjects were voluntary enrolled and questions collected anonymously and no personally identifiable information (as for instance name, and date of birth) were required and stored. Participants were invited through social networks and no inclusion/exclusion criteria were set, establishing a convenient and purposive sample of general population. All data were stored electronically in a database protected by password, known only to the data manager.

Ethical approval

Ethical approval was given by the local Ethics Committee of the University of Perugia (Comitato Universitario di Bioetica), reference number 2016-09R.

Variables and statistical analysis

Descriptive statistics included counts (percentages, %) for categorical data and mean (and standard deviation, SD) for continuous variables. Since the main endpoint of the study was the assessment of knowledge and attitude of the general population towards ZIKV, these two were assessed as a binary variable, since only one of the possible responses was correct. Specific scores from the survey responses were created and medians used as

a cut-off point. Participants with scores equal or below the median were classified as very knowledgeable. The Italian region of residence of respondents categorized into: "South Italy and Islands" (Sicily, Sardinia, Calabria, Basilicata, Apulia, Campania, Molise, Abruzzo), "Central Italy" (Toscana, Umbria, Lazio, Marche) and "Northern Italy" (Lombardy, Piedmont, Liguria, Veneto, Emilia-Romagna, Aosta Valley, Trentino-Alto Adige, Friuli-Venezia Giulia) according to the territorial division of the National Institute of Statistics (ISTAT, www.istat.it).

For the purpose of the multivariate analysis, variables were handled as follows. The variable "employment" was aggregated into three categories: student, worker, and unemployed. The divorced/widowed responses at "partner status" variable was classified as single. The age was subsequently categorized into pre-defined intervals, generating the new variable "age class". For the multivariable analysis, the independent variable "I know of the existence of the travel medicine clinic" was generated starting from the question "Clinic consultation frequency", if "Never/I never heard of it" the answer of the new variable is "No", if "Whenever before making a trip/Only for travel outside of Europe" the response of the new variable is "Yes". Both absolute and relative frequencies were calculated for all qualitative variables; Pearson's chi-square test (χ^2) was used to analyse categorical variables. A multivariable logistic regression was performed, considering low knowledge as a dependent variable (median of error >3).

The statistical significance level for the analyses was 0.05. In model 1 we did not perform any adjustment, model 2 was adjusted for age and gender. Results are expressed as crude odds ratio (OR) (model 1) and adjusted OR (aOR) (model 2) with 95% confidence intervals (95% CI). The data were analysed using the STATA statistical software version 14 (StataCorp. 2015. College Station, TX, US).

RESULTS

Descriptive characteristics of the sample (n = 1119) are presented in *Table 1*. Respondents had a mean age of 37.3 year (with 12.4 SD) and 68.4% were women. On average, they were mainly Italian (98.8%), highly educated (59.1%) and employed (41.6). In most of the cases (55%) respondents had never heard about or never attended travel medicine clinic. *Table 2* shows the frequency of replies on knowledge and attitude regarding ZIKV in the total sample stratified by level of knowledge. In total, 20.2% (n = 226) and 71.4% (n = 798) of the sample knew the etiological agent and transmission route of ZIKV infection, respectively. Among those with an overall good level of knowledge, only 27.3% correctly identified a virus as etiological agent, whilst the majority (67.2%) thought that the cause of the infection was a mosquito. As regards the need of prevention measures to be taken before travelling abroad, 59.3% of the total sample was aware of them, and 83.1% among those very knowledgeable about ZIKV. Approximately 43% of the sample declared to not knowing the measures to prevent the risk of transmission of infection after returning from endemic areas, both in case of ex-

Table 1
Descriptive characteristics of the study population

Variables		N	%
Sex	Female	765	68.4
	Male	354	31.6
Age (mean \pm SD)		37.3 \pm 12.4	
Age class	18-25	167	14.9
	26-35	463	41.4
	36-45	215	19.2
	46-55	154	13.8
	56-65	94	8.4
	>65	26	2.3
Nationality	Italian	1106	98.8
	Other	13	1.2
Region	North Italy	378	33.8
	Central Italy	299	26.7
	South Italy and Islands	442	39.5
Education	Lower than university degree	661	59.1
	University degree or higher	458	40.9
Employment	Student	240	21.4
	Employee	465	41.6
	Freelancer	251	22.4
	Unemployed	115	10.3
	Retired	48	4.3
Partner status	Engaged	620	55.4
	Single	461	41.2
	Divorced/widowed	38	3.4
Travel clinic consultation frequency	Whenever before travelling abroad	95	8.5
	Only for travel outside of Europe	411	36.7
	Never attended/I never heard of it	613	54.8

SD: standard deviation.

periencing ZIKV symptoms or not (42.3% and 42.8%, respectively). More than 80% of these showed low level of knowledge about ZIKV (83.8% and 80.4%, respectively). Specifying a multivariate regression model (*Table 3*), the analysis found that the lower level of knowledge was associated with increasing age (aOR = 1.03; 95% CI 1.02-1.04), living in central Italy (aOR = 1.38; 95% CI 1.01-1.90) or in South Italy and Islands (aOR = 1.52; 95% CI 1.14-2.02), being poorly educated (aOR = 1.54; 95% CI 1.20-1.98), having never heard of travel medicine clinic (aOR = 3.66; 95% CI 2.15-6.23), or having never attended a travel clinic (aOR = 4.03; 95% CI 2.36-6.89).

DISCUSSION

The presented nation-wide cross-sectional study yielded important results on the level of knowledge and attitudes towards the travel-related risk due to

Table 2
Frequency of replies on knowledge and attitude regarding Zika virus provided by respondents, total and stratified by knowledge. The correct answer is highlighted in grey

Variables		Total	Good knowledge	Low knowledge	χ^2
		N (%)	N (%)	N (%)	p-value
What is the cause of Zika infection?	A virus	226 (20.2)	179 (27.3)	47 (10.1)	<0.001
	Drinking contaminated water	19 (1.7)	8 (1.2)	4 (0.9)	
	Dirty environments	12 (1.1)	11 (1.7)	8 (1.7)	
	Mosquito	621 (55.5)	440 (67.2)	181 (39.0)	
	I do not know	241 (21.5)	17 (2.6)	224 (48.3)	
Which is the transmission route of the Zika infection?	Through contact with saliva	24 (2.1)	16 (2.4)	8 (1.7)	<0.001
	By means of air particles (examples: coughing or sneezing)	33 (2.9)	17 (2.6)	16 (3.5)	
	Infected mosquito bite	798 (71.4)	609 (93.0)	189 (40.7)	
	I do not know	264 (23.6)	13 (2.0)	251 (54.1)	
What do you need to do before travelling to endemic areas (where Zika virus is highly prevalent)?	Bed nets, previously treated with repellents	31 (2.8)	20 (3.0)	11 (2.4)	<0.001
	Repellent sprays in sufficient quantities for the duration of the trip	136 (12.5)	68 (10.4)	68 (14.6)	
	All of the above	664 (59.3)	544 (83.1)	120 (25.9)	
	I do not know	288 (25.7)	23 (3.5)	265 (57.1)	
If Zika symptoms appear after returning from an endemic area, what should be done to prevent transmission of the infection?	Practicing protected sex (condoms) for at least 6 months following the onset of symptoms	567 (50.7)	522 (79.7)	45 (9.7)	<0.001
	It is not necessary to take any preventive measures	79 (7.0)	49 (7.5)	30 (6.5)	
	I do not know	473 (42.3)	84 (12.8)	389 (83.8)	
If after returning from an endemic area, NO symptoms of Zika appear, what should be done in order to reduce the risk of transmission of the infection?	Practicing protected sex (condoms) for at least 8 weeks after returning from the endemic area	479 (42.8)	453 (69.2)	26 (5.6)	<0.001
	It is not necessary to take any preventive measures	178 (15.9)	113 (17.2)	65 (14.0)	
	I do not know	462 (42.8)	89 (13.6)	373 (80.4)	
Which of the following preventive measures is necessary to take after returning from an endemic area, if the symptoms related to Zika have NOT appeared?	Avoid donating blood for at least 28 days after returning	743 (66.4)	598 (91.3)	145 (31.2)	<0.001
	It is not necessary to take any preventive measures	48 (4.3)	18 (2.8)	30 (6.5)	
	I do not know	328 (29.3)	39 (5.9)	289 (62.3)	
Before planning to travel abroad, do you check if your destination is an endemic area and/or there are high-risk factors for Zika infection?	Yes	632 (56.5)	502 (76.6)	130 (28.0)	<0.001
	No	487 (43.5)	153 (23.4)	334 (72.0)	
Median of error = 3	Subject equal or below the median of error (if ≤ 3 errors)	655 (58.5)	-	-	
	Subject over the median of error (if >3 errors)	464 (41.5)			

^Good knowledge: median of error ≤ 3 errors; low knowledge: median of error > 3 errors.

ZIKV infection among general public. The first important finding is the low level of awareness and basic knowledge of ZIKV among the participants. If from one hand only 20.2% the respondents knew that responsible of Zika is a virus, from the other, the survey captured that more than two-third (71.4%) of the sample was aware of ZIKV transmission via the bite

of an infected mosquito. This proportion was slightly lower than that observed in a few similar studies, in which disparities may be attributable to differences in characteristics of the study population and settings. For instance, most of these researches were conducted among health care providers [28, 29] or in countries with a history of previous ZIKV transmission [30],

Table 3
Multivariable logistic regression model based on 1119 observations. Crude and adjusted odds ratio are presented

		Dependent variable: Low knowledge (median of error >3)			
		OR (95% CI)	p-value	aOR (95% CI)	p-value
Sex*	Female	1		1	
	Male	1.01 (0.77-1.30)	0.978	0.99 (0.77-1.29)	0.977
Age** (continuous)	Per unit increase	1.03 (1.02-1.04)	<0.001	1.03 (1.02-1.04)	<0.001
Citizenship	Italian	1		1	
	Other	0.42 (0.11-1.53)	0.189	0.38 (0.10-1.44)	0.157
Region	North Italy	Ref.		Ref.	
	Central Italy	1.51 (1.10-2.06)	0.018	1.38 (1.01-1.90)	0.045
	South Italy and Islands	1.61 (1.21-2.13)	<0.001	1.52 (1.14-2.02)	0.005
Education	University degree or higher	Ref.		Ref.	
	Lower than university degree	1.75 (1.36-2.20)	<0.001	1.54 (1.20-1.98)	<0.001
Occupation	Student	1		1	
	Worker	1.70 (1.25-2.31)	0.001	1.08 (0.76-1.54)	0.675
	Unemployed	2.09 (1.32-3.29)	0.002	1.49 (0.92-2.40)	0.104
Partner status	Engaged	1		1	
	Single	0.77 (0.61-0.98)	0.039	1.09 (0.84-1.44)	0.496
Travel clinic consultation	Whenever before travelling abroad	Ref.		1	
	Only when travelling outside Europe	1.35 (0.80-2.27)	0.257	1.41 (0.83-2.40)	0.198
	Never heard of it	3.42 (2.03-5.79)	<0.001	3.66 (2.15-6.23)	<0.001
	Never	4.01 (2.36-6.81)	<0.001	4.03 (2.36-6.89)	<0.001

OR: odds ratio; 95%CI: 95% confidence interval; aOR: adjusted OR for age and sex; *adjusted only for age; **adjusted only for sex.

where the awareness about the diseases is expected to be higher. Contrarywise, the overall level of knowledge regarding the correct use of repellent and bed net was found in approximately half of the sample. In previous literature, prevalence of knowledge and use of bite-prevention measures varied greatly, according to different aspects of surveys design and conduction, including type and ages of travellers, studied disease, and local availability of travel medicine clinic [31, 32]. Interestingly, more than a quarter respondents reported inaccurate ZIKV transmission routes and prevention practices, mostly not knowing the correct answer for the selected items. In travel medicine research, knowledge of the infection cause and transmission route has been correlated to better compliance towards the use of prevention measures [5, 33]. In particular, mosquito-bite prevention is a basic strategy to protect from numerous vector-borne diseases. Therefore, general public should be informed and instructed on the correct use of bite-prevention measures (e.g., use of repellent, appropriate clothing, sleeping under bed net, etc.) when travelling abroad [5, 34].

Less than half of the interviewed knew the importance of practicing protected sex (through condom use) on the returning from an endemic area, over a period that ranging from 8 weeks to 6 months, based on the appearance of Zika-related symptoms. This can be considered a proxy of respondents' very low knowl-

edge of the sexual transmission of ZIKV, also in case of asymptomatic infection, and related consequences of infection during pregnancy. The finding is concerning and reflects missed opportunities for prevention of ZIKV infection through correct practices and behaviours, as highlighted in previous studies [35-37]. Having a third of the sampled general public unaware of the importance of avoiding blood donation for at least 28 days after returning is a substantial public health issue. In fact, this might lead blood donors to not declare recent travels in Zika endemic areas. In this context, the US Centers for Disease Control and Prevention highlighted that blood donor screening on the basis of a questionnaire, without a laboratory test, is insufficient for identifying Zika-infected serum [38], likely due to donors' under-reporting of previous travels. As a matter of fact, ZIKV ribonucleic acid (RNA) persists in serum during weeks [39], and a systematic review and meta-analysis on the prevalence of ZIKV in blood donations indicated that RNA prevalence showed a high variability, reaching high-risk level in most of the situations [40].

The current study was also designed to investigate the respondents' overall level of knowledge on ZIKV. Self-reported surveys displayed a worrisome extremely high proportion of interviewees (41.5%) with an unsatisfactory awareness of ZIKV, risk of infection, and the important precautions to be taken to avoid transmis-

sion and consequences of infection during pregnancy. In multivariable analysis, increasing age, low education level, region of residence and the behaviour of not attending travel clinic before travelling predicted respondents' poor knowledge. These results can be easily explained as younger age is associated to more access to information on travel-related risk and illness, by virtue of great abilities to easily seek and obtain health information online [41], and, as expected, education background was found to influence knowledge about Zika, in line with previous surveys [42, 43]. The multivariate model also suggested that highly knowledgeable respondents were those living in the North of Italy. The country has a universal coverage National Health System that is organised on national, regional and local levels; the regional or local organization of Preventive Departments – which include Travel Clinic – may explain disparities on ZIKV-related knowledge across regions [44]. However, the regional gap in travel health information in Italy deserves further research.

As regards the behaviour of seeking medical care before travelling abroad, it is worth also noting that this study investigated respondents' knowledge and attitude towards travel medicine clinic consultation before travelling abroad. Self-reported surveys displayed a worrisome extremely low proportion of its utilization among general public. Pre-travel medical advice before travelling is the first important tool for the prevention of travel-associated illness and injuries [45, 46], and these results spotlight that specific interventions are needed to promote correct pre-travel behaviours and practices among general public, pointing key messages that focus on the most relevant aspects of a healthy and safe travel, as well as to achieve an optimal level of protection against travel-related risks [4, 47, 48].

Limitations and strengths

Although it was a nation-wide study, one of the main limitations includes the use of a convenience sample, as well as the administration of the survey via social network. These two elements may have led to a selection bias, in particular a non-response bias. In fact, individual who decided to participate may differ from those who did not apply. Participants may be more highly educated, healthier and more informed on the topic compared to non-responders. However, we believe that if any selection bias has occurred, this would have resulted in selecting more conscious people, which would result in an underestimation of the true association. Moreover, since the recruitment took place via internet, only people with available electronic device and internet connection could take part of the study. Nevertheless, approximately 60% of the Italian population has a personal computer and more than 70% has a stable connection [49], limiting the possible impact of a selection bias. Using self-reported data is another potential limitation and information bias may have been introduced into this study. In fact, self-reporting data may be prone to recall bias or social desirability bias. However, in order to mitigate this risk, we anonymized the questionnaire without including sensitive information. Moreover, it was administered

on-line, which is usually associated with a lower level of social desirability bias [50]. Further, we used a validated questionnaire, and even if an information bias may not be completely excluded, this is a well-known method to reduce it.

Another limitation is associated with the lack of questions investigating the travel frequency of the interviewed people in the used research survey [25], preventing from adjusting the results according to this information, which may be considered a predictor of respondents' knowledge and risk perception towards ZIKV.

Despite these limitations, this study has some important strengths. First, since the questionnaire was based on mandatory answers, there were no missing data. Second, the administration way was very unexpensive, easy to fill and allowed to reach a high number of subjects in all the Italian regions, achieving a large and representative sample size of the Italian general population. Lastly, the questionnaire was based on multiple-choice that largely facilitate the analysis, even if it may have probably limited further exploration of such a composite phenomenon.

CONCLUSION

In the next years, the number of international travellers visiting Zika-endemic areas is expected to increase. This study offers an important insight on the low levels of knowledge and attitude towards ZIKV in Italy. The specific recommendations and information to the travellers who visit ZIKV endemic areas are available on the institutional and travel's medicine websites, but they should also be made available to the general public through dedicated websites and social media, to increase risk perception and ensure appropriate protection measures to be taken to avoid the infection and its consequences.

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Conflict of interest statement

Authors have no competing interests to declare.

Author's contribution statement

VG and DN conceived the work, performed the study, collected data and performed data curation. OES performed data analysis. SP contributed in reporting. FP helped in collecting evidence. All authors wrote the first draft of the manuscript. VG critically revised the manuscript. All Authors read and approved the final version of the manuscript.

Data availability statement

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

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Styloid process elongation and temporomandibular disorders: a pilot study in the Albanian population

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Abstract

Introduction. Patients with an elongated styloid process (SP) presented related symptoms as deep neck pain, foreign body sensation in the throat, pain on turning the head, and odynophagia. These symptoms are the source of misdiagnosis of this syndrome since these clinical manifestations are like those of temporomandibular disorders (TMD). This study aimed to investigate a possible correlation between the TMD and elongation of the SP.

Materials and methods. The case-control study included 60 participants between 25-60 years of age and was carried out at University Dental Clinic, Department of Maxillo-Facial Surgery, Tirana, Albania during the period November 2020 – March 2021. The study group consisted of 30 patients diagnosed with TMD (21 females and 9 males) and the control group consisted of 30 individuals without TMD (18 females and 12 males). The diagnosis of TMD was performed according to Research Diagnostic Criteria for Temporomandibular Disorders axis I and the SP measurement was performed by a single experienced examiner. The normal range of SP length was considered 20-30 mm.

Results. SP >30mm was found in 86.67% of patients with TMD group and 43.33% of individuals of the control group. There was a significant difference between the TMD group and the control group in regards to SP length ($p < 0.001$).

Conclusions. There is a significant association between the elongation of the SP and TMD. Dental clinicians should recognize the morphological changes in the length of SP on the panoramic radiographs, which could be a hint in the proper diagnosis of TMD.

Key words

- temporomandibular disorders
- styloid process
- masticatory muscles

INTRODUCTION

The styloid process (SP), an integral part of the styloid complex chain is derived from the second pharyngeal arch (Reichert's cartilage). The tip of SP is positioned between the internal carotid artery, internal jugular vein, and cranial nerves V, IX. With this critical anatomical location, variations in the length of SP, which according to Langlais *et al.* [1, 2] results from ossification in the stylohyoid ligament, may be associated with a group of clinical symptoms that require surgical intervention [3]. O'Carroll reported that 8 of 103 (8%) patients with an elongated SP presented with related symptoms of deep neck pain, foreign body sensation in the throat, pain on turning the head, and odynophagia which are the source of misdiagnosis of this syndrome

since these clinical manifestations are like those of Temporomandibular disorders (TMD) [4].

TMD encompasses many clinical problems involving the masticatory muscles, the temporomandibular joint and associated structures or both [5]. An elongated SP is present in 2% to 30% of adults and the prevalence among patients with classic TMD pain symptoms is unknown.

This study aimed to investigate a possible correlation between the TMD and elongation of SP in the Albanian population.

MATERIALS AND METHODS

The study protocol consisted of a pilot case-control study carried out at University Dental Clinic, Depart-

ment of Maxillo-Facial Surgery, Tirana, Albania during the period November 2020 – March 2021. The study was approved by the Bioethical Commission of the Medical University of Tirana [Protocol no: 2020/11-16]. From each patient enrolled in this study informed consent was obtained before the beginning of the study.

Cases group (n = 30) included patients diagnosed with TMD and the control group (n = 30) with no history of TMD.

Subjects who do not have reached skeletal maturity (<25 years old), pregnant women, and individuals who have undergone radiation treatment were not allowed to participate in the study.

The diagnosis of TMD was performed according to Research Diagnostic Criteria for Temporomandibular Disorders axis I [6], with the symptoms lasting at the last 3 months.

For both groups in the study, the SP length was assessed bilaterally from the digital panoramic images [7], and only the side with a higher length of SP was taken into consideration. The digital panoramic radiographs evaluated in this study were taken using 2D Units Dentsply Sirona at the Faculty of Dental Medicine, Tirana, Albania. To have a good visualization and accurate measurements, the images were calibrated properly by adjusting the contrast and brightness. The length of SP from 20-30 mm is considered normal, and the length longer than 30 mm is considered elongated SP [8-10]. To obtain high reproducibility and reliability of the data and to reduce bias the clinical and radiographic examinations were done by a single trained examiner. Digital measurement calibration was performed before each radiographic measurement.

Reporting of this observational case-control study was conforming with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [11].

STATISTICAL ANALYSIS

To test whether the relationship between a categorical variable (control and TMD subjects) and a continuous numerical variable (SP length) is statistically significant, we used the Mann-Whitney non-parametric test.

Fisher's exact test was used to test whether the differences between the control and TMD subjects and the elongated and normal SP variables are statistically significant or not. A p-value <0.05 was the criteria for considering the result statistically significant.

To test whether there were any differences in the length of the SP between different ages and genders in the TMD group and control group, a two-way ANOVA without replication test was used.

The statistical analysis has been performed using Bio-Stat 4.0.

RESULTS

The sample size consisted of 60 individuals (40 females and 20 males), with an average age of 42.53 years. The gender ratio in TMD cases (female:male) was 2.3:1. A gender ratio in favor of the females was found also in control group (1.5:1). The higher participation of the female gender, perhaps, is related to the fact that females are more concerned about oral health and oral esthetics, and hence had more frequent dental controls. The average SP length was statistically significantly higher in TMD cases (mean = 35.7) compared to controls (mean = 30.73) (p-value <0.001 using Mann-Whitney nonparametric test) (Table 1).

There was a significant difference for the SP length between cases and controls subjects (p value = 0.009). In particular, the TMD group has a higher percentage of SP length (>30 mm) compared to the control group (87% versus 43% respectively) (Table 2).

The Table 3 shows the results of two-way ANOVA without replication test, in order to describe the effect

Table 1
Demographic characteristics of the subjects included in our study

Variable	Controls (n=30)	TMD (n=30)	P-value *
Sex			
Male (n, %)	12 (40%)	9 (30%)	
Female (n, %)	18 (60%)	21 (70%)	
Age in years (mean, SD)	42.3 (12.15)	42.76 (11.64)	
SP length (mean, SD)	30.73 (3.54) †	35.7 (4.12)	<0.001

* P value using Mann-Whitney nonparametric test.

Table 2
Distribution of cases and controls by selected variables and Fisher's Exact Test between case and control subjects

Variable	Controls (n=30)	TMD (n=30)	P-value*
SP length			
> 30 mm (n, %)	13 (43%)	26 (87%)	0.009
≤ 30 mm (n, %)	17 (57%)	4 (13%)	

*P value using Fisher's Exact Test (2-sided).

Table 3

Results of two-way ANOVA without replication test; the effect of age and gender in the length of the SP in the TMD and control group respectively

Source of Variation	SS	df	MS	F	P-value	F crit
TMD group						
Age	2490.30933	29	85.8727356	1.28683792	0.25068731	1.86081144
Gender	747.654	1	747.654	11.2038997	0.00227172	4.18296429
Error	1935.216	29	66.7315862			
Total	5173.17933	59				
Control group						
Age	2363.51483	29	81.5005115	1.01627929	0.48280813	1.86081144
Gender	1984.90017	1	1984.90017	24.7509235	2.7189E-05	4.18296429
Error	2325.65483	29	80.1949943			
Total	6674.06983	59				

SS: sum of squares; Df: degrees of freedom; MS: mean squares; F crit: critical value for F score.

of gender and age in the length of the SP in the TMD and control group respectively (Table 3).

The results of two-way ANOVA without replication test, show that, in the TMD group, there is a significant effect of the gender variable in the length of the SP (p-value = 0.002), and no discernible effect of the age variable in the length of the SP (p-value = 0.25). In the control group, the results show that there is a discernible effect of the gender variable in the length of the SP (p-value = 2.7189E-05) and no effect of the age variable in the length of the SP (p-value = 0.48).

DISCUSSION

The etiology of elongated SP under the current knowledge is unknown, even though this condition has a prevalence in the range of 1.4-83.6% [7-9].

The percentage of female gender in controls was 60% and in cases it was 70%. The gender ratio is shown to be 2:1 with female risk three times greater compared with male in development of TMD [6]. In literature, the relationship between gender and SP length has shown controversial results. Some studies report that there is no association [12, 13] between gender and SP length, and others report that there is an association [14, 15].

The mean lengths of SP were 35.7 and 30.73 mm in TMD and control groups respectively. These values are higher than those reported by Andrade *et al.* 2012 [8]. This difference could be explained by the small sample size, which could bias to some extent the results of this study. The current study was limited by its non-randomized nature, as well as the small number of patients.

In our study, we found that there is an association between gender and elongation of SP in both groups (p-value = 0.002 and 0.003 in TMD and control group respectively).

Also, in our study we found that there is no association between age and elongation of SP, which is consistent with the results of studies of Rizzatti-Barbosa *et al.* 2005; Okabe *et al.* 2006 [14, 15].

The relationship between TMD and elongated SP is

poorly investigated in epidemiological studies. Existing studies again offer controversial results. In 2013 Sancio-Gonçalves *et al.* [13] reported no significant relationship between TMD and SP length. But other studies [16, 17] reported a significant association between the length of the SP and TMD. In our study, we found that 87.7% of patients with TMD had elongated SP, versus 13.33% with normal SP. In the control group, 43.3% had elongated SP, versus 56.7% with normal SP. This data clearly showed a significant association between the elongation of the SP and TMD in the Albanian population.

CONCLUSIONS

The present study attempts to investigate a possible correlation between the TMD and elongation of SP. Although the results are interesting and show a significant association between TMD and elongation of SP, a possible bias to our result is the fact that we considered as the normal range of length of SP from 20-30 mm and elongated SP when the length was >30 mm, but we do not have data that show the normal range of length of SP in Albanian ethnic group. Further investigations must be conducted to examine the normal range of length of SP in Albanian ethnic groups to clarify if there are differences in the morphology of SP with other ethnic groups and the prevalence of elongation of SP in Albanian ethnic groups.

There is a significant association between the elongation of the SP and TMD. Dental clinicians should recognize the morphological changes in the length of SP on the panoramic radiographs, which could be a hint in the proper diagnosis of TMDs. Further follow-up studies are necessary to confirm this evidence.

Conflict of interest statement

The Authors declare that there is no conflict of interest.

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Psychological care for infertile couples undergoing assisted reproductive technology: a national study on the characteristics of counselling services

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Abstract

Introduction. Infertility has an impact on the psychophysical health of individuals and couples, and its treatment through an assisted reproductive technology (ART) is a very exacting experience. The aim of this study was to explore the characteristics of psychological counselling services in Italian ART centres through a specially designed questionnaire administered to the physicians in charge of the centres.

Methods. The questionnaire online was sent to 306 ART authorized centres. It consisted of 26 questions. A total of 15 were single-selection questions, 5 were multiple-choice and the remaining 6 were open-ended.

Results. 113 (37%) ART centres responded to the questionnaire. All the ART centres offered psychological counselling, but only in 47% of them the psychologist is a permanent staff member. In 69% of the centres, 10 to 20% of couples use the psychological counselling service.

Discussion. Although the Italian Guidelines under Law 40/2004 stress the need to provide couples with psychological support and counselling and the literature highlights the efficacy of such interventions, the results of our study show that psychological counselling services are not yet fully operational in Italian ART centres or integrated into their day-to-day medical practice.

Conclusion. In conclusion, the results show that psychological services in Italian ART centres are not yet fully operational and integrated in the ART procedure. All of this highlights the importance of further investigations with the aim to shared information to use to establish common protocols for psychological interventions in ART centres.

Key words

- infertility
- assisted reproductive technology
- psychological interventions
- psychological counselling services

INTRODUCTION

Infertility is defined as “the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse” [1]. Following on this definition, the WHO reported that in developed countries one in four couples experience infertility [2]; in Italy an infertility diagnosis involves an estimated 15% of couples [3].

Infertility affects women and men and can be accompanied by various psychological disorders [4-6] that are more frequent and severe in women [7-9]. Luk and Loke [10] showed that infertility mainly affects four aspects: (a) psychological well-being; (b) marital relationships; (c) sexual relationships; and (d) quality of life. Studies

on the negative psychological, behavioural and social impacts of infertility have shown that infertile couples tend to experience a wide range of negative emotions, including anxiety, fear, avoidance, depression, guilt and frustration [11-14].

Most couples diagnosed with infertility will pursue some form of medical treatment to overcome this obstacle to parenthood [15]. Assisted reproductive technology (ART) includes all fertility treatments that involve handling gametes and/or embryos outside the body to achieve reproduction [16]. ART treatments are very complex and emotionally challenging for the people involved; often both men and women experience various negative emotions such as guilt, disappointment,

frustration, fear, self-blame, pain, anxiety, sadness and depression during these medical procedures [17-21; 5]. The outcome of ART treatments is difficult to predict, and success rates are rather low, so it may take multiple attempts before achieving pregnancy [22, 7, 23]. In 2018 in Italy, 28.4% of women who underwent ART treatments became pregnant. This figure expresses the cumulative pregnancy rate, in that it takes account of all the embryo transfers from fresh and frozen cycles needed to establish a pregnancy [24]. However, the success of ART treatment varies greatly based on several factors, such as the type of infertility, the type of treatment and the age at which the latter is performed.

In Italy, ART is strictly regulated by Law 40/2004 which lays out the rules for assisted reproductive technology and contains the “Guidelines for the application of assisted reproductive techniques” [25, 26] that include the provision of psychological support for women and couples at any stage of the medical procedures (before and during treatment or in case of failure). Based on these Guidelines, the type of counselling to be provided by the clinics to couples are of three categories:

- decision-making counselling, to be offered prior to any treatment. It helps patients understand and ponder the implications of a treatment for themselves, their families and any children they have;
- support counselling, to be provided in times of stress or struggle. It is especially for individuals who are unable to undergo ART procedures, who find it hard to cope with a specific type of treatment, or who experience treatment failure; and
- therapeutic counselling, to help individuals, or couples develop coping strategies to deal with the consequences of infertility treatments, temper their expectations and accept the reality of difficult diagnoses or intensive assessments.

The Guidelines reflect current knowledge regarding the effects of psychological interventions on ART outcomes [14, 6] and are in line with the recommendations of regulatory bodies in many countries and of professional associations involved in the management of couples with infertility [27-29].

The European Society of Human Reproduction and Embryology (ESHRE) has produced guidelines regarding psychosocial care in infertility clinics and medically assisted reproduction [28]. According to these guidelines, all the infertility team members of a clinic are expected to share in caring for their patients' mental health throughout their treatments. Specialised services such as infertility counselling or psychotherapy should be provided when patients are considered to be at higher risk [28]. Several categories of patients are most in need of professional psychological aid in that they may experience high distress, have a history of psychiatric morbidity, perceive parenthood as their central life goal, deal with marital discord, have low social support, recurrent treatment or pregnancy failures, use donated gametes, face multiple pregnancies or plan medical treatment discontinuation [30, 31].

In Italy, there are no specific best practice recommendations for psychological interventions at ART centres and there is little or no research regarding psychological

services for fertility treatment recipients [32]. Following a research project jointly carried out by ART Italian National Register - Italian National Institute of Health and Department of Dynamic and Clinical Psychology and Health Studies – Sapienza University of Rome, this article presents the results of a survey on the psychological services in Italian ART centres.

METHODS

Participants

In 2020, a total of 341 ART centres (both public and private) were active in Italy according to the data from the Italian Assisted Reproductive Technology Register. The questionnaire was sent to the physicians in charge of 306 ART centres. The 35 centres in Lazio were excluded because they had already been investigated in a pilot study on the topic.

Procedure

An online questionnaire (Google Forms) was e-mailed to the physicians in charge of Italian ART centres on 13 January 2020, the deadline for returning it was 28 February 2020. Participation was voluntary and the survey was carried out in compliance with the World Medical Association's Code of Ethics (Declaration of Helsinki) for experiments involving human beings. Ethical approval was obtained from the Department of Dynamic and Clinical Psychology and Health Studies of the Sapienza University of Rome.

Questionnaire

The questionnaire was co-developed by ART Italian National Register – Italian National Institute of Health and Department of Dynamic and Clinical Psychology and Health Studies – Sapienza University of Rome. It consisted of 26 questions. A total of 15 were single-selection questions, 5 were multiple-choice and the remaining 6 were open-ended.

RESULTS

A total of 113 centres (37%) responded to the questionnaire; most of them (75 centres) offered II-III level (more invasive and complex) procedures and operated as public/NHS-contracted private services. 78% of the questionnaires were completed by the physicians in charge of the centres, while the remaining 22% were filled in by a staff member other than the physician in charge (via a written proxy). 48% (54) of responses came from private centres and 52% (59) came from public or NHS-contracted private centres.

48% of the public centres had a psychologist permanently on staff while 52% of them worked with an independent psychologist. Similarly, 45% of the private centres had a psychologist permanently on staff while 55% of them worked with an independent psychologist. In the public ART centres, the independent psychologist was present more often (once or twice a week in 30%) than in the private centres (13.3%). In 87% of the private centres, the independent psychologist worked at the centre only upon specific request or met with the referred patients at his/her own office. Patients in treatment made use of psychological counselling with a

similar frequency in the public and private centres, but couples' meetings were more frequent in private centres (80%), than in public ones (65.5%). No group meetings were held in either the public or the private centres.

In Table 1, the questionnaire items and the related answers were reported. Below, the answers to questions, from 4 to 26, were specifically described (each bullet point represents the answer to a question):

- in less than half of the centres (47%) the psychologist was a permanent staff member;
- in 38% of the cases, the psychologist worked at the ART Centre upon specific request, and in 32% of the cases he/she worked outside the centre at his/her own office with referrals. In the remaining cases, the psychologist worked at the centre once (10%) or twice a week (8%). 12% of the answers were "other", meaning that the psychologists worked at a hospital;
- in 69% of the centres, 10 to 20% of couples used the psychological counselling service. In 13% of the centres, 20% and 30% of couples used this service, in 5% of the centres 30% and 50% of couples used it and in 5% of the centres more than 50% of couples used it. In the remaining 8% of the centres all the couples used this service;
- in 47% of cases, referrals were made at the patient's or the doctor's request. All patients were referred to psychological counselling only in 14% of the centres. In 11% of the centres, referrals were made for patients who were identified by the staff as having specific needs. In 10% of the centres, the patients requested the aid and support of a psychologist. In 1% of the centres, referrals were made for all patients about to undergo ART techniques with donated gametes. In 17% of the cases more than one answer was provided;
- if the medical and/or /nursing staff suggested a referral, in 25% of the cases it was because the individual or couple showed evident psychological distress (extreme sadness, anxiety, crying, agitation, anger) coupled with problems in their relationship. In 19% of cases, the referral was made because the individual or couple showed evident psychological distress. In 16% of the cases, the referral was made for all the reasons indicated in the questionnaire answers: psychological distress, problems with treatment adherence, problems in the couple's relationship, difficulties in relating to the clinical staff. In 12% of cases, couples were referred to the psychologist because they showed evident psychological distress and had problems in their relationship as well as with treatment adherence. In 9% of cases, referrals were made for all of the following reasons: evident psychological distress, evident problems in the couple's relationship, and difficulty in relating to the clinical staff. In the other cases (19%) multiple reasons motivated the referrals and they only marginally concerned issues with treatment adherence and difficulties in relating to the clinical staff;
- in 32% of the cases, psychological counselling was proposed only prior to medical treatment; in 13% of the cases, it was proposed upon starting treatment and if ART was unsuccessful; in 10% of the cases, it was proposed upon starting treatment and throughout it. In 9% of the cases psychological counselling was proposed in all the scenarios envisaged in the answer options (During the first meetings at the centre before starting treatment; During treatment; When there was a drop-out risk; In cases where ART was unsuccessful; Upon completion of the process). The remaining centres (36%) provided multiple answers and each answer did not exceed 5%;
- in 29% of the cases the psychologist had three sessions, in 27% two, in 13% four and in 9% of the cases up to five. 10% of the responders indicated only one session. Only 4% of the responders stated 10 sessions. 3% of the cases indicated 6 sessions and another 3% indicated 8 sessions. 1% of the responders answered 7 sessions, 1% 18 sessions and the remaining 1% answered 20. This was an open-ended question, and the answers reflected the policies and procedures adopted at the centres;
- in most cases interventions were with couples (73%) or individuals (14%). In the remaining 13% of cases the answer chosen was "other", meaning that more than one type of session was proposed (e.g., couple and group meetings);
- in 22% of the cases the issues addressed were problems regarding infertility, the couple's relationship and the ART treatments. In 15% of the cases the topics regarded all the options proposed in the survey questionnaire: Infertility-related problems; Problems regarding the couple's relationship; Problems regarding the treatments; Family-of-origin issues; Problems regarding relations with the centre and its staff. In-

Table 1
Questions and answers in the survey on the characteristics of psychological services in Italian ART Centres

Questions	Answer options	Number of centres which responded to each question
1. Centre name	Free-form text response	100%
2. Centre's Identification Code assigned by the National ART Registry	Free-form text response	100%
3. Filled in by: (please add name, surname and job role)	Free-form text response	100%
4. Is the psychologist a permanent staff member at the ART centre, i.e., is he/she a regular member of the infertility team?	1) Yes 2) No, we employ an independent psychologist	1) 47% 2) 53%

Continues

Table 1
Continued

Questions	Answer options	Number of centres which responded to each question
5. If the Centre employs an independent psychologist, in what ways and how often does he/she work at the Centre?	He/she: 1) comes to the ART centre upon specific request 2) works at his/her office with referrals 3) comes once a month 4) comes one a week 5) comes twice a week 6) Other	1) 38% 2) 32% 3) 0% 4) 10% 5) 8% 6) 12%
6. What percentage of couples undergoing treatment at the Centre make use of psychological counselling?	1) Less than 10% 2) From 10% to 20% 3) From 20% to 30% 4) From 30% to 50% 5) More than 50% 6) All couples	1) 38% 2) 30% 3) 13% 4) 5% 5) 5% 6) 8%
7. How does referral of the individual or couple to the psychologist occur? <i>(more than one answer can be provided)</i>	1) All new patients at the ART Centre are referred to the psychologist 2) Patients who request the aid and support of a psychologist are referred to the psychologist 3) Patients who are identified by the staff as having specific needs are referred to the psychologist 4) All patients who will undergo ART techniques with donated gametes are referred to the psychologist 5) Other	2; 3) 47% 1) 14% 3) 11% 2) 10% 1;2;3) 8% 4) 1% Other 9% provided multiple answer (each one not more 3%)
8. If the medical and/or nursing staff suggest a referral, what aspects generally motivate the referral? <i>(more than one answer can be provided)</i>	1) Obvious psychological distress (extreme sadness, anxiety, crying, agitation, anger, etc.) 2) Problems with treatment adherence 3) Evident problems in the couple's relationship 4) Difficulty in relating to the clinical staff 5) Other	1;3) 25% 1) 19% 1;2;3;4) 16% 1;2;3) 12% 1;3;4) 9% Other 19% provided multiple answer (each one not more 4%)
9. At what stage of treatment is psychological counselling usually proposed? <i>(more than one answer can be provided)</i>	1) In the first meetings at the Centre, prior to the start of treatment 2) During treatment 3) When elements of drop-out risk are detected 4) In cases where the ART was unsuccessful 5) Upon completion of the process 6) Other	1) 32% 1;4) 13% 1;2) 10% 1;2;3;4;5) 9% Other 36% provided multiple answers (each did not exceed 5%)
10. How many sessions does the psychologist providing counselling/support at the ART centre have with each couple?	Free-form text response	Only one session: 10% Two sessions: 27% Three sessions: 29% Four sessions: 13% Five sessions: 9% Six sessions: 3% Seven sessions: 1% Eight sessions: 3% More than ten sessions: 2%
11. What types of psychological sessions are offered to patients?	1) Individual meetings 2) Couple meetings 3) Group meetings 4) Other	1) 14% 2) 73% 3) 0% 4) 13%
12. What topics are generally addressed in the counselling sessions? <i>(more than one answer can be provided)</i>	1) Problems regarding infertility 2) Difficulties in the couple's relationship 3) Difficulties regarding the ART treatments 4) Family-of origin issues 5) Problems regarding relations with the centre and its staff 6) Other	1;2;3) 22% 1;2;3;4;5) 15% 1;3) 13% 1;2) 12% 1) 11% 1;2;3;4) 7% 2) 3% 3) 2% Other 15% provided multiple answer (each one not more 4%)
13. Do you think that undergoing ART treatment with donated gametes increases the rate of recourse to psychological counselling?	1) Yes 2) No 3) We do not perform gamete donation techniques	1) 42% 2) 13% 3) 45%

Continues

Table 1
Continued

Questions	Answer options	Number of centres which responded to each question
14. If you have found that couples undergoing ART treatment with donated gametes are more likely to seek psychological counselling, what do you think determines this?	1) Physicians are more likely to propose counselling 2) Couples are more likely to request counselling 3) Both of the above 4) Other	1) 30% 2) 8% 3) 62% 4) 0%
15. Are the ART cycles involving donated gametes provided at your centre or are couples sent to other centres?	1) They are provided at our Centre 2) They are carried out at another Centre.	1) 43% 2) 57%
16. Do you think that undergoing ART techniques for the preservation of fertility in cancer patients increases the rate of recourse to psychological counselling?	1) Yes 2) No 3) We do not perform fertility preservation techniques	1) 25% 2) 40% 3) 35%
17. If you have observed a higher rate of recourse to psychological counselling of couples undergoing ART techniques as an onco-fertility course, what do you think determines this?	1) Couples are the ones who most frequently request counselling 2) Physicians are more likely to propose counselling 3) Both of the above. 4) Other	1) 4% 2) 21% 3) 71% 4) 4%
18. Are there policies and procedures in place in the ART centre that regulate the provision of psychological counselling?	1) Yes 2) No	1) 40% 2) 60%
19. If the answer is yes, please provide a short description of them	Free-form text response	Several common approaches emerged. Please see the text for more information.
20. Psychological counselling services for patients of the ART centre who wish to use them are: (choose from various payment options listed)	1) included in the ART treatment fee 2) paid via a fee charged for each counselling session. 3) paid via a fee charged for a standard number of sessions 4) Other	1) 31% 2) 34% 3) 15% 4) 20%
21. In which areas do you think psychological counselling is of greatest support for your work as a physician at the ART Centre? (more than one answer can be provided)	1) Adherence to medical prescriptions and treatment 2) Drop-out prevention 3) Promotion of ART outcomes 4) Managing the couple's emotional distress 5) Improving the couple's mood 6) Reducing the couple's stress 7) Facilitating physician-patient relationship 8) Facilitating management of the emotional burden of the staff working at the Centre 9) Facilitating team- work 10) Other	4;5;6) 9% Other 91% provided multiple answer (each one not more 7%)
22. Do you think it is useful for physicians to consult a psychologist when they are the ones providing decision-making and support counselling, as laid out in the 2015 Guidelines?	1) Yes 2) No	1) 87% 2) 13%
23. If your answer is yes, how do the consultations take place?	1) At structured times (team meetings, interdisciplinary interviews, etc.) 2) Informally, as needed 3) Discussion would be helpful but does not occur 4) Other	1) 26% 2) 64% 3) 9% 4) 1%
24. Do you hold team meetings in which the psychologist participates as a regular member of the therapeutic team to discuss jointly managed cases?	1) Yes 2) No	1) 60% 2) 40%
25. How often are team meetings attended by the psychologist?	1) Every week 2) Every month 3) Every 3 months 4) Other	1) 16% 2) 29% 3) 24% 4) 31%
26. Please leave your suggestions for improving this questionnaire	Free-form text response	Please see the text for more information

fertility-related problems and problems regarding the ART treatments were indicated in 13% of the cases; infertility-related problems and problems regarding the couple's relationship were indicated in 12% of the cases; and infertility-related problems were indicated in 11% of the cases. In 7% of the cases the following were addressed: Infertility-related problems; Problems regarding the couple's relationship; Problems regarding the treatments and Family-of-origin issues. Only problems regarding the couple's relationship were addressed in 3% of the cases, and only problems regarding the treatments in 2% of the cases. In the remaining 15% of the cases, a combination of more than one answer was provided, each combination did not exceed 4% of the cases;

- for 42% of the cases ART treatments with donated gametes increased recourse to counselling while for 13% they did not. 45% of the responders did not provide treatments with donated gametes;
- the greater use of counselling by couples undergoing ART treatments with donated gametes was determined by the requests of both the physicians and the couples (62% of responders). Physicians were more likely to propose counselling in 30% of the centres while counselling services were requested by the couples in only 8% of cases;
- in 57% of the cases ART cycles with donated gametes were carried out at other centres. This figure was higher than the one given for Question 13 (45%) because the 12% of the managers of centres not performing procedures with donated gametes responded to Question 13 by giving an opinion on how the gamete donation technique influenced the use of psychological counselling. In 43% of the cases ART cycles with donated gametes were carried out inside the centres;
- 40% of the responders did not think that cancer patients undergoing ART for fertility preservation used psychological counselling more frequently, while 25% believed that they did. 35% of the responding centres did not provide fertility preservation procedures;
- for 71% of responders, couples undergoing ART procedures for onco-fertility used counselling services both because they requested to do so and because their physicians proposed that they be counselled. 21% of responders said physicians were more likely to propose psychological counselling; 4% of responders said couples were more likely to request psychological counselling. The remaining 4% answered "Other";
- 60% of responders said there were no policies and procedures in place at the ART centres regulating the provision of psychological counselling while 40% said there were;
- several common approaches emerged from the descriptions. Here are some examples:
 - physicians proposed psychological counselling to all couples during their first visit; sometimes this was only addressed in the informed consent form or in a leaflet;
 - psychological support was mandatory for couples undergoing ART treatment with donated gametes or for couples undergoing preimplantation genetic testing;

- couples identified as having particular problems (signs of distress, risk factors, major psychopathological issues) were referred to psychological counselling;
- in 34% of the centres a fee was charged for each counselling session. In 31% of centres, the fee was included in the ART treatment fee. 15% of the centres had a fee for a standard number of sessions. 20% of the centres answered "Other";
- in 9% of the cases, the responders indicated: Managing the couple's emotional distress; Improving the couple's mood; Reducing the couple's stress. The other answers to the question were a combination of the proposed answer options: Adherence to medical prescriptions and treatment; Drop-out prevention; Promotion of ART outcomes; Managing the couple's emotional distress; Improving the couple's mood; Reducing the couple's stress. The single combinations did not exceed 7%. Since multiple, different answers were given, the percentages yielded were low, so it was difficult to determine which answer prevailed. However, this fragmentation highlighted the numerous different opinions of the physicians regarding the areas of their work at the ART centre that could most benefit from psychological counselling. It might be interesting to further investigate this point;
- in 87% of cases, the responders considered meetings with a psychologist useful for physicians who provide decision-making and support counselling;
- 64% of responders said that meetings were informal at their centres while 26% had structured meetings. 9% said meetings would be useful but did not take place. The remaining 1% answered "Other";
- 60% of responders said no team meetings were held with the psychologist present to facilitate a discussion on jointly managed cases;
- meetings were held every month in 29% of the centres, every 3 months in 24% and once a week in 16% of them. The remaining 31% answered "Other";
- the following could be observed from the suggestions made by the responding physicians to improve the questionnaire:
 - this field was not used to provide suggestions regarding the questionnaire, but rather to ask for support in adopting effective psychological counselling policies;
 - the importance of having a psychologist at the centre was reiterated;
 - the difficulty in completing the questionnaire was flagged up since responders knew little about the psychological service offered at the centres.

DISCUSSION

A survey regarding the characteristics of the psychological services offered by Italian ART centres has been a first step towards setting up a network of professionals through which models and procedures can be compared and practices established and shared.

With a 40% response rate, the representative features of the psychological assistance provided in the ART setting across Italy could not be itemized but insight could be gained into the assistance offered at the responding

centres. The overall picture is rather disappointing in that only half of the centres (47%) had a psychologist permanently on staff while most centres considered counselling services an “added asset” rather than an integral part of the treatment process as suggested by the Guidelines on Assisted Reproductive Technology [25, 26]. In 70% of centres the fee for psychological counselling was not included in the ART treatment fee. Furthermore, 30% of the responding centres worked with an independent psychologist who was called in upon request, knew little of the centre and was clearly not a full-fledged member of the resident therapeutic team.

Relatively few couples resorted to counselling (between 10% and 20% of couples in 70% of the responding centres) and very few of them were referred to a counsellor (about 10%). Although the Guidelines suggest incorporating counselling into the centres' routine practice and making it available at any time during the treatment course, the percentage of patients actually using such services was very low and in half of the cases referrals were either requested by the patients or recommended by the physicians. Moreover, in 45% of the cases referrals were requested either at the beginning of the ART process or following treatment failure. Referrals remained a central issue but they did not seem to be regulated by specific policies and procedures in 60% of the cases. Hence, the survey findings show that referrals to a psychologist for counselling occurred either when patients were sufficiently aware of their own distress and sought help, or when the treating physician was sensitive enough to do so. In a context with a strong medical orientation, where parenthood/childlessness was invested with a disease component and its solution exclusively involved the body, a place for thinking rather than acting was created only when distress and suffering were perceived by the patients or recognised by the treating physicians. Psychology, like medicine, was thus considered a “remedial profession” rather than a domain wherein new meanings are assigned to a disruptive experience like infertility and its treatment. Even the reasons for referral were mainly related to the psychological distress of individuals and couples (as indicated in 44% of cases) rather than to the treatment process or the relationship with a centre's staff. It is evident that psychological intervention continues to be considered as targeting the inner world of an individual or couple and not their relationship with the ART context. Treatments with donated gametes or for onco-fertility care enhanced the perceived importance of counselling and recourse to it, flagging up issues that clearly make the topic of parenthood more complex, and concerning which the Guidelines provide no specific indications.

It is interesting to observe that in almost all the cases (87%) physicians considered consultation with the psychologist useful when they were the ones providing decision-making and support counselling for couples. At the same time, however, 60% of the centres did not hold team meetings with the psychologist and the meetings held were unstructured and informal in 64% of the cases.

The data gathered at a national level confirmed the

information collected in the pilot study conducted on the ART centres in the Lazio region. A significant difference regarded the response rate, with 81% of the ART centres in Lazio responding compared to 37% of the national ART centres. The high response rate of the ART centres in the Lazio region may be due to a greater awareness raised among the physicians managing the centres when they attended a meeting where the pilot study was presented.

More ART centres in Lazio (62%) had policies and procedures regulating the provision of psychological counselling than the centres in the rest of the country (40%). This difference may be due to whether a centre operates as a public or as an NHS-contracted private service. Most of the centres participating in the survey in Lazio were private facilities while most of the responding centres in the rest of Italy were public facilities. This is an interesting finding that may warrant further investigation.

CONCLUSIONS

In conclusion, despite the limitation that only half of the centres responded to the questionnaire, the results of our survey support the perception that psychological counselling is not a fully operational service in Italian ART centres nor is it part of their routine practice even though the treatments they provide are known to have a strong emotional impact due to their own specific features and because they act on the effect (non-parenthood/childlessness) and not on the cause of infertility (the disease). The absence in most centres of policies and procedures for psychological interventions means that even where counselling is available, recourse to it is not fully structured or incorporated in the treatment process. At the same time, the need has been expressed by physicians to consult with psychologists before providing decision-making and support counselling.

Moreover, after the reorganization that has taken place in Italy's ART centres due to the health emergency caused by COVID-19, clear common policies and procedures for both in-person and online psychological counselling should be set up, shared by the infertility teams and incorporated into the treatment processes. This survey, carried out by the National ART Register, is a first step towards raising political awareness on the subject and creating specific good practices for psychological interventions within the ART setting in Italy.

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Authors' contribution

Conception design (RS, MDT) data extraction (RS), analysis (RS, MDT), interpretation (all Authors), drafting the manuscript (all Authors), supervision (GS). All the Authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Conflict of interest statement

Authors declare no conflict of interests.

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Implementation level of best practice policies by Italian Government for healthier food environments: Healthy Food Environment Policy Index (Food-EPI)

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Abstract

Background. This work aims to identify policies implemented for healthy food environments in Italy within The Healthy Food Environment Policy Index (Food-EPI) project.

Methods. Food-EPI tool, which includes two components, thirteen domains and fifty good practice indicators, was adapted for the Italian context. Evidence for implementation was gathered and summarized for all fifty indicators from data sources such as governmental websites, non-government organizations publications and websites and via direct contact with Government officials.

Results. The highest level of evidence was found within five domains: *food composition* (2/2 indicators), *labelling* (3/4), *promotion* (4/5), *provision* (4/5) and *leadership* (5/5). The domains with less identified evidence were *food prices* (1/4), *food in retail* (0/4), *trade and investment* (0/2) and *platforms and interaction* (1/4).

Conclusions. The evidence summarization and the upcoming stakeholders' meeting to rate the level of implementation for each indicator in Italy have the potential to improve Government commitment to shape healthier food environments.

Key words

- nutrition policy
- food
- food environments
- obesity
- policy implementation

INTRODUCTION

Overweight and obesity represent an increasing health problem worldwide [1]. These conditions have been associated with a number of non-communicable diseases [2] and higher all-cause mortality in several countries [3]. An important role in the increase of this phenomenon is played by unhealthy food environments which are a major driver of unhealthy population diets and obesity [4, 5].

Individuals interact with the environment in multiple settings, such as schools, homes and neighbourhoods, which are influenced by the education and health systems, Government, the food industry and a society's attitudes and beliefs [6]. Food environments are con-

trolled by higher-level instances and less by individuals. In this context, effective Government policies and actions are essential to increase the healthiness of food environments and to reduce the high levels of obesity, non-communicable diseases (NCDs) and all-cause mortality related to it [7]. Therefore, it is of utmost importance that Governments implement widely recommended preventive policies and actions to address the magnitude of the burden that unhealthy diets are creating [8].

Monitoring the degree of implementation of these widely recommended policies and actions is an important part of ensuring progress towards better population nutritional health [9].

In this context the International Network for Food and Obesity/Noncommunicable diseases Research, Monitoring and Action Support (INFORMAS) was created. INFORMAS is a global network of public-interest organizations and researchers that aims to monitor, benchmark and support public and private sector actions to create healthy food environments and reduce obesity, NCDs and their related inequalities. Key aspects of food environments are monitored over time and between countries, contributing to strengthening the accountability of Governments and the private sector for the impact of their policies and actions on food environments, obesity and NCDs. To do this, INFORMAS has developed a tool, the Healthy Food Environment Policy Index (Food-EPI) [8], to assess the extent of implementation of recommended food environment policies by national Governments compared to international best practice [10]. The Food-EPI tool and process have been through several phases of development, including a review of literature and policy documents, subsequent revision by a group of international experts from low-, middle- and high-income countries, and pilot testing. It has been pilot-tested [11] and used in different contexts to identify actions taken by Governments regarding policy implementation for healthy food environments [12-16].

The Food-EPI tool is part of the Science & Technology in childhood Obesity Policy (STOP) project, which is a European Commission-funded Horizon 2020 project, aiming to expand and consolidate the multidisciplinary evidence base upon which effective and sustainable policies can be built to prevent and manage childhood obesity. Based on the Food-EPI tool, in collaboration with the Italian National Health Institute (Istituto Superiore di Sanità, ISS), which is partner of the STOP project, we collected information and evidence for each indicator concerning the Italian context. The aim was to identify any actions taken by the Italian Government at the level of policy implementation for healthy food environments in Italy, which could serve as ground for subsequent rating and benchmarking the implementation of each policy with reference to international best practices, in order to make prioritized recommendations based on the identified gaps.

METHODS

The present study was carried out in two different steps. The first step included a narrative review to identify and collect pertinent documents concerning policy implementation for healthy food environments and benchmarks. The collected information was then sent to experts from the National Health Institute for validation. The second step consisted of a pilot study to measure the comprehensibility of the summarized information and easiness in conducting the rating process.

Search strategy

Institutional and non-institutional websites were searched by a team of five researchers on three levels: international, national and regional. At the international level websites of organizations such as World Health Organization, European Union and European

Parliament were searched to look for pertinent policies and actions that were adapted and implemented by the Italian Government. At the national level websites of institutions such as Ministry of Health, Ministry of Economic Development, Ministry of Agricultural, Food and Forestry Policies, Ministry of Education and National Health Institute, National Center for Diseases Prevention and Control (Centro Nazionale per la Prevenzione e il Controllo delle Malattie, CCM) were searched.

Furthermore, the websites of different non-profit organizations, scientific societies and food industries such as Italian Society of Human Nutrition (Società Italiana di Nutrizione Umana, SINU), National Agency for Regional Health Services (Agenzia Nazionale per i Servizi Sanitari Regionali, AGENAS), National Institute for the Promotion of the Health of Migrant Populations and for the Fight of Poverty Diseases (Istituto Nazionale per la Promozione della Salute delle Popolazioni Migranti e per il Contrasto delle Malattie della Povertà, INMP) Gaining Health, WHO Healthy Cities Network were explored. At the regional level, the websites of several municipalities were searched looking for initiatives, actions or policies implemented at a local level. The keywords used to search for pertinent documents were: policy; Government; Italy; national; regional; strategies; actions; implementation; initiatives; food composition; food labelling; food promotion; food prices; food provision; food retail; food trade; food investment; infrastructure; leadership; governance; food monitoring; funding; resources.

Definitions

For the purpose of this work the following definitions were used [11].

Food: food and non-alcoholic beverages, excluding breastmilk or breastmilk substitutes. *Food environments:* the collective physical, economic, policy and socio-cultural surrounding, opportunities and conditions that influence people's food and beverage choices and nutritional status.

Government: any Government departments and, where appropriate, other agencies (i.e., statutory bodies such as offices, commissions, authorities, boards, councils, etc.).

Government implementation: the intentions and plans of the Government and actions and policies implemented by the Government as well as Government funding for implementation of actions undertaken by non-governmental organizations, academic institutions, private companies (including consultants), etc.

Healthy/unhealthy food: categorization of foods as healthy/unhealthy in accordance with the WHO and EU guidelines or informed by rigorous criteria or the use of a nutrient profiling model.

Nutrients of concern: salt (sodium), saturated fat, trans fat, added sugar.

Systems-based approaches: a set of common objects or people and the relationships and interactions that make them part of a larger whole, working together towards a common purpose.

Policy actions: all Government policies, plans, strate-

gies and activities (evidence of policy implementation took into consideration the whole policy cycle, from agenda-setting, through to policy development, implementation and monitoring).

A strict collaboration and several consultations were conducted with experts from the National Health Institute during the research of websites and evidence collection process. The evidence collection was structured in several rounds, after each of which there was a feedback and evaluation from the National Health Institute expert.

Evidence compilation and synthesis

The Food-EPI tool is comprised of two components: *policies*, which is comprised of seven domains and *infrastructure support*, which is comprised of six domains. Each domain includes several indicators of good practice for a total of 50 indicators. The domains of the *policies* component are: *food composition* (2 indicators), *food labelling* (4 indicators), *food promotion* (5 indicators), *food prices* (4 indicators), *food provision* (5 indicators), *food retail* (4 indicators) and *food trade and investment* (2 indicators). The domains of the *infrastructure support* component are: *leadership* (5 indicators), *governance* (4 indicators), *monitoring and intelligence* (6 indicators), *funding and resources* (3 indicators), *platforms and interaction* (4 indicators) and *health in all policies* (2 indicators). An evidence document on the current degree of implementation of all 50 good practice *policy* and *infrastructure support* indicators across 13 domains was compiled from documents retrieved from institutional and non-institutional websites that were searched. Summaries of evidence of implementation in Italy, international best practice benchmarks and progress until March 2020 were compiled for each indicator. The international benchmarks were retrieved by the documents provided by INFORMAS and Food-EPI international group [16]. Five researchers worked independently to extract the relevant information from each document and synthesized it. For a summary of each document concerning each indicator see *Supplementary Material available online*.

Evidence verification

The evidence was comprehensively documented and returned to Government officials at the Ministry of Health to verify its completeness and accuracy. They gave their feedback on the evidence for each indicator, integrating new evidence, suggesting other websites to search, and adding recommendations. They added evidence regarding Veneto's experience on indicator 2 of *food provision* domain, as well as integrated new evidence on the *leadership* domain. The Government officials, also, integrated new evidence on indicator 2 of *governance*, indicator 2 of *monitoring and intelligence* and indicator 2 of *funding and resources* domains.

Experts' rating and prioritization

The next step in this project is the rating process from an expert panel at a national level, which will be formed by a wide range of public health experts, including academics, researchers, practitioners, and representatives

of non-governmental organisations. A formal invitation will be sent to identified experts who will be asked to rate the implementation of policies by the Italian Government for each of the 50 indicators of the Food-EPI tool, compared to international best practices (benchmarks).

The rating process was pilot tested to assess its comprehensibility and to identify and address any lack of clarity before carrying out a wider administration. The pilot testing included three experts identified through convenience sampling. They were sent a paper version of the evidence compilation document, reporting the degree of implementation of all good practice indicators. The rating was carried out in a Likert scale from 1 to 5, where: 1 was given when the specific policies were <20% implemented, 2 when were 20-40% implemented, 3 when were 40-60% implemented, 4 when were 60-80% implemented and finally 5 when were 80-100% implemented. International best practices (benchmarks), for each of the good practice indicators, were retrieved from INFORMAS and Food-EPI network and obtained from international food policy experts. These benchmarks include best examples from countries such as New Zealand, Chile, Australia, Argentina, Mexico, etc.

Once the rating process is finished and the data from the rating is collected, a prioritization action will follow, to evaluate the implementation gaps as identified from the ratings and to propose and prioritise concrete actions for implementation by the Italian Government. The domains with a lower implementation level and scores, as evaluated by the experts, are those needing prioritized policy actions to improve the situation, taking into account the impact, effects on equity, feasibility, acceptability, affordability and efficiency of the action.

RESULTS

Evidence identification and synthesis

The evidence for Government policy implementation and infrastructure concerning Italy varied among domains and indicators. We found the highest level of evidence within the following domains: *food composition* (2/2 indicators), *food labelling* (3/4 indicators), *food promotion* (4/5 indicators) and *food provision* (4/5). The domains with less identified evidence were *food prices* (1/4 indicators), *food in retail* (0/4 indicators), *food trade and investment* (0/2 indicators) and *platforms and interaction* (1/4 indicators) (see *Supplementary Material available online*).

Food composition

COMP1: the Italian Ministry of Health, in collaboration with food industries, has issued a national document, committing to containing sugars, saturated fats, salt trans fatty acids [17]. Moreover, Italy has ratified European regulation 1924/2006 on nutrition and health, which states that the definition of nutrient profiles should take into account the content of different nutrients and substances with a nutritional or physiological effect, in particular those such as fats, saturated fats, trans fatty acids, sugars, sodium or salt, whose excessive intake in the general diet is not recommended [18].

COMP2: Italy has also ratified the EU Regulation 1169/2011, establishing standards of “administered” products, in addition to those “sold” – i.e., restaurants, canteens and catering, at least as far as allergens are concerned [19].

Food labelling

LABEL1: the Italian legislation refers to the European one (EU Reg. 1169/2011), which implements the CODEX recommendations, stating the provision of food information to consumers and, also, promoting national provisions in labeling, presentation, and advertising of food [20, 21].

LABEL2: Italy has ratified the European regulation 1924/2006 on nutrition and health claims made on foods, which takes into account the content of different nutrients and substances focusing on fats, saturated fats, trans fatty acids, sugars, sodium or salt, poly- and monounsaturated fats, carbohydrates other than sugars, vitamins, minerals, proteins and fibers [18].

LABEL3: the Ministry of Health has issued a national document on food labelling, which provides food information to consumers and sets out the accepted levels of nutrients for a healthy diet. The logo of the food labels shows the amount of energy (expressed in Joules and calories), fats, saturated fats, sugars and salt (expressed in grams) present in a single portion of a given food. Furthermore, to communicate to the consumers how healthy or caloric the food they are about to buy is comes to the rescue the symbol of the battery, which indicates the percentage of each element present, in relation to the recommended daily amount of intake [19].

LABEL4: no evidence was identified on labelling the menu boards of all quick service restaurants (i.e. fast-food chains) applied by the Government.

Food promotion

PROMO1: the code of self-regulation for TV, which relies on a national law by the Italian Government, introduces a differentiated protection system for time slots. For example, it states that during the period from 16.00 to 19.00 must be avoided advertising in favour of soft drinks and alcoholic beverages within programmes that are aimed at minors [21].

PROMO1 and 2: the EU Pledge is a voluntary initiative by leading food and beverage companies to change food and beverage advertising to children under the age of twelve in the European Union. It aims at not advertising food and drinks to children under the age of 12 on TV, the press and the Internet, except for those products that meet precise nutritional criteria based on accredited scientific assessments (<https://eu-pledge.eu/>).

PROMO3: the document published by the Ministry of Health, entitled “Shared objectives for the improvement of the nutritional characteristics of food products with particular attention to the child population”, introduces, at a national level, specific limitations to the forms of promotion and advertising for soft drinks, including abstention of marketing in channels directed to children under 12 years of age and abstention of direct business activities in primary schools [17].

PROMO4: the Ministry of Health has issued na-

tional guidelines for school catering, whose objectives include facilitating correct eating habits through an effective model of health promotion and prevention [22].

PROMO5: no evidence was found on policies implemented by the Government to ensure that unhealthy foods are not commercially promoted to children, including adolescents on food packages.

Food prices

PRICES1: no evidence was identified regarding the minimisation of taxes or levies on healthy foods to encourage healthy food choices (e.g., low or no sales tax, excise, value-added or import duties on fruit and vegetables).

PRICES2: many attempts to tax unhealthy foods (sugar tax) have been made, but nothing has been finalised until now. Italy is cited in many articles as a case study on proposed but not introduced food taxes [23].

PRICES3: no evidence was identified on existing subsidies on foods, including infrastructure funding support (e.g., research and development, supporting markets or transport systems), to favour healthy rather than unhealthy foods.

PRICES4: there are some food related support programmes in Italy, however, it should be highlighted that the distributed food concerns the primary goods, without a specific focus on healthy or unhealthy food. Furthermore, these are not initiatives coming directly from the Government, but rather from non-profit organizations or EU (www.emporiosolidarieta.it/).

Food provision

PROMO1: the Ministry of Health has issued National guidelines for school catering (GU n. 134/2010), which aim to facilitate, from infancy, the adoption of correct eating habits for health promotion and the prevention of chronic degenerative diseases. It reports the recommended daily intake levels of energy and nutrients (LARN) (including salt, sugar, fat, fibre) diversified by sex, age and levels of physical activity [22].

“Fruits and vegetables in schools” is a Program promoted by Ministry of Agricultural, Food and Forestry Policies with the collaboration of CREA (Council for agricultural research and analysis of the agricultural economy) and ISMEA (Service institution for the agricultural food market), intended for schools, aiming to encourage children to consume fruit and vegetables and support them in conquering healthy eating habits, spreading educational messages about food waste generation and their prevention [24].

The Ministry of Agricultural, Food and Forestry Policies has also launched the initiative “Mense scolastiche biologiche”, in order to have more biological food in schools, reduce food waste and use local products [25].

Furthermore, a number of regional initiatives have been identified. Lombardy Region has issued guidelines for school catering, which include food and nutrient recommendations to compose a balanced menu by choosing adequate quantities of foods belonging to the different food groups. The recommendations include the adequate quantity of salt, fibre, sugar, fat, and drinks [26].

Veneto Region, as well, has published guidelines for school catering, which give recommendations on quality of food in the canteens and vending machines [27].

PROV2: as for the other public sectors, the Ministry of Health has issued national guidelines for hospital catering, aimed at improving nutritional quality and food safety in hospitalized subjects. The recommended daily intake levels of energy and nutrients (LARN) are diversified by the disease the patients are hospitalised for [28].

National guidelines exist also for pediatric hospital catering with the aim of guaranteeing the necessary nutrient reserve. The recommended daily intake levels of energy and nutrients (LARN), protein and lipid requirements, vitamin and mineral requirements are given for different age groups and sex [29].

Moreover, regional initiatives have been identified. Piemonte Region has issued an operating proposal for catering in nursing homes for the elderly, aiming to provide a dietetic guideline consisting of a minimum guaranteed number of different types of meals based on protein-energy content and/or consistency in relation to the clinical needs of the patients. It shows the adequate intake of proteins, fibres, carbohydrates, fat and vitamins [30].

Lastly, Lazio Region has published guidance on nutritional quality of meals provided in collective catering. It is composed of two parts: (1) Procedures and forms for the approval of the dietary tables and (2) Control and monitoring of meals' nutritional adequacy in collective catering [31].

PROV3: as for policies and guidance on food service activities, Emporia of Solidarity have emerged in recent years as a new form of regional food assistance provision programs in Italy, including a broad range of actors such as Caritas, Municipalities, Fondazione Banco Alimentare Onlus – FBAO and others. They do not focus solely on food provision, but offer, also, collateral services; e.g., guidance on balanced nutrition and education on how to manage expenditures (www.emporiosolidarieta.it/).

PROV4: no evidence was found on support and training systems implemented by the Government to help schools and other public sector organisations and their caterers meet the healthy food service policies and guidelines.

PROV5: finally, with regard to supporting private companies to provide and promote healthy foods and meals in their workplaces, the “Support for the implementation in Italian regional realities of the Health Promotion Network in the Workplace” program acts on the health promotion in the workplace, focusing on the prevention of behavioral risk factors of chronic and degenerative diseases (incorrect nutrition, sedentary lifestyle, smoking, harmful alcohol consumption) [32].

Food retail

No evidence was found for neither of the four indicators of the *food retail* domain (RETAIL 1-4), concerning the power of the Government to implement policies and programs to support the availability of healthy foods and limit the availability of unhealthy foods in

communities (outlet density and locations) and in-store (product placement).

Food trade and investment

No evidence was retrieved for neither of the two indicators of the *food trade and investment* domain (TRADE 1-2), concerning policies implemented by the Government that ensure that trade and investment agreements protect food sovereignty, favour healthy food environments, are linked with domestic health and agricultural policies in ways that are consistent with health objectives, and do not promote unhealthy food environments.

Leadership

LEAD1: several developed and implemented programs, including “Shared objectives for improving the nutritional characteristics of food products with particular attention to the infant population (3-12 years)” [16] and Regulation (EC) No 1924/2006 on rules on nutrition and health [18], show the political support expressed at both national as well as international level for improving food environments, population nutrition, diet related NCDs and their related inequalities.

LEAD2: clear population intake targets have been established by the Government for the nutrients of concern and/or relevant food groups in documents such as “The 4th Review of Nutrient Reference Energy Levels for the Italian Population”, published by the SINU [33]. Moreover, Italy shares the overview on dietary reference values for the EU population as derived by the EFSA (European Food Safety Authority) Panel on Dietetic Products, Nutrition and Allergies (NDA). This document gives the dietary reference values, which indicate the amount of an individual nutrient that people need for good health depending on their age and gender [34].

LEAD3: to establish clear, interpretive, evidenced-informed food based dietary guidelines the National Research Institute for Food and Nutrition has published “Guidelines for a healthy eating”. It gives recommendations on dietary requirements in order to create a healthy and balanced diet, guaranteeing more wellness and health [35].

LEAD4: the evidence regarding a comprehensive, transparent, up-to-date implementation plan linked to national needs and priorities, to improve food environments, reduce the intake of the nutrients of concern diet-related NCDs include:

1) evaluation of national critical issues in the nutritional field and intervention strategies 2016-2019, which is an agreement between the Government, the Regions and the autonomous Provinces of Trento and Bolzano [35]. It provides proposals for the planning of public intervention in the nutrition sector, above all in order to combat chronic diseases and their impact on the Italian population [36];

2) technical table on nutritional safety (Tavolo Tecnico sulla sicurezza nutrizionale, TaSiN), which is responsible for coordinating the initiatives related to nutritional surveillance and orientation, as the point of confluence of a national network to be implemented [37];

3) National prevention plan 2014-2018, which in-

tends to outline a system of health promotion and prevention actions that will accompany the citizen in all phases of life and in the workplaces [38].

LEAD5: finally, as for protecting vulnerable populations the program “Identification of surveillance systems and registers of mortality, tumors and other pathologies” [39], aims to ensure an active system of systematic collection of personal, health and epidemiological data to record and characterize all cases of risk to health, of a particular disease or of a relevant health condition, stratified for different population group, including the vulnerable ones. Moreover, the TaSiN, which is responsible for coordinating the initiatives related to nutritional surveillance and orientation, aims epidemiological surveillance and prevention, also, for vulnerable groups [37].

Governance

GOVER1: several initiatives have been implemented by the Ministry of Health and shared by food industries in Italy with regard to commercial restriction of unhealthy foods, such as:

- guidelines for commercial communication regarding food products and beverages, to protect children and their correct nutrition, which includes a national policy addressing commercial labelling of food and drinks and outlines the limits within which commercial communication must be maintained in this sector [40];
- the code of voluntary initiatives of the confectionery industry for the promotion of healthy eating behaviors, adopted by the Association of Italian confectionery industries [40];
- the self-regulation code for the promotion and marketing of the non-alcoholic beverage industry adopted by the Italian Association of Non-Alcoholic Beverages (ASSOBIBE) [40];
- the CONFIDA code for the operators of automatic food and beverage distribution which, among other things, provides guidelines related to nutritional parameters [40].

GOVER2: the document entitled “Health promotion in the third millennium: Facebook, social gaming and promotion of healthy lifestyles among adolescents” was drawn up for the purpose of constituting an operational tool for the realization of research and in-depth activities in the nutritional field relating to developmental age and in particular adolescence, in order to use evidence in the development of food and nutrition policies. It was structured and published by AGENAS, and SINU [41].

GOVER3: no evidence was identified on the implementation of policies and procedures for ensuring transparency in the development of food and nutrition policies.

GOVER4: INRAN (Istituto Nazionale di Ricerca per gli Alimenti e la Nutrizione, National Research Institute for Food and Nutrition), now incorporated in the CREA, in collaboration with the Ministry of Agriculture and Forestry Policies has issued a guideline for a healthy Italian diet, which aims to provide to consumers information and suggestion to eat better, both respecting cooking traditions and protecting the populations’ health [35].

Monitoring and intelligence

MONIT1: no evidence was identified on monitoring that systems implemented by the Government, are in place to regularly monitor food environments (especially for food composition for nutrients of concern, food promotion to children, and nutritional quality of food in schools and other public sector settings), against codes/guidelines/standards/targets.

MONIT2: the Health Behaviour in School-aged Children (HBSC) study is a multicentric study promoted by WHO Europe, including 50 countries and regions across Europe and North America, among which Italy. It aims at investigating adolescents’ (11-15 years) health and well-being in order to address health promotion policies. Among the investigation areas there is, also, nutrition (consumption of fruits, vegetables, sweets and sugared drinks) [42].

MONIT3: the surveillance system “OKKIO alla Salute” is aimed at monitoring overweight and obesity in children (6-10 y) and analysing related risk factors. It was first launched in 2007 promoted and funded by the Ministry of Health/ CCM, and is coordinated by ISS in collaboration with the Regions, the Ministry of Health and the Ministry of Education (www.epicentro.iss.it/okkioallasalute).

Passi and Passi d’Argento are, also, 2 surveillance systems for adults (18-65 ys, > 65ys), which aim at investigating lifestyles and behavioural risk factors linked to NCDs and the degree of knowledge and adherence to the intervention programs that the country is carrying out for their prevention. It is promoted and conducted by CCM, ISS and Local Health Authorities (www.epicentro.iss.it/passi/dati/temi).

MONIT4: the National Statistics Institute (Istituto Nazionale di Statistica, ISTAT) provides data in order to have a map on NCDs prevalence, their risk factors and occurrence rates. The main goal is to inform policy makers/Institutions (www.istat.it/).

MONIT5: no evidence was found that reported if major programs and policies are regularly evaluated to assess their effectiveness and contributions to achieving the goals of the nutrition and health plans.

MONIT6: regarding the progress towards reducing health inequalities there have been a number of initiatives including: 1) “Italy for health equity”. Starting from the best scientific evidence currently available on health determinants and outcomes, and from an analysis of the experiences and good practices implemented for the benefit of the most vulnerable groups at national and local level, this document presents possible shared intervention strategies to propose to policy makers and stakeholders involved in combating health inequalities [43].

2) the National Institute for the Promotion of the Health of Migrant Populations and for the Fight of Poverty Diseases (INMP) is an institution of the National Health Service (Sistema Sanitario Nazionale, SSN, supervised by the Ministry of Health, which was established in 2007 to address the socio-health challenges posed to the most vulnerable populations. The Institute welcomes and cares for all persons, Italians and migrants, who are in a condition of serious eco-

conomic and social hardship and encounter greater difficulties in accessing care [44]. No evidence on monitoring systems, implemented by the Government, are in place to regularly monitor food environments (especially for food composition for nutrients of concern, food promotion to children, and nutritional quality of food in schools and other public sector settings), against codes/guidelines/standards/targets.

Funding and resources

FUND1: the National Prevention Plan – which aims to reduce the preventable and avoidable burden of morbidity, mortality and disability of non-communicable diseases, prevent the consequences of neurosensory disorders, promote mental well-being in children, adolescents and young people, prevent addictions to substances and behaviors, reduce the frequency of infections/priority infectious diseases, implement the Integrated National Control Plan for food safety prevention and veterinary public health – has an allocated budget of 200 million euros. However, there is no evidence on what proportion of this budget is specifically dedicated to the nutrition [45]. Over the years, several campaigns have taken place in Italy regarding population nutrition promotion, such as:

- **Guadagnare Salute** (www.epicentro.iss.it/guadagnare-salute/programma/), aiming at promoting healthy lifestyles and acting in particular on the main risk factors of chronic degenerative diseases of great epidemiological relevance;
- **Capitan Kuk** (www.salute.gov.it/portale/news/p3_2_3_1_1.jsp?menu=dossier&id=3);
- **Canguro Saltalacorda** (www.salute.gov.it/portale/temi/p2_6.jsp?id=1715&area=stiliVita&menu=progetti);
- **Forchetta e scarpetta** (www.salute.gov.it/portale/temi/p2_6.jsp?id=1714&area=stiliVita&menu=progetti), which are all campaigns that have as target the nutrition of children;
- **Progetto Cuore** (www.epicentro.iss.it/alimentazione/progetto-cuore-riduzione-consumo-di-sale-2020), promoting reduction of salt and iodine to reduce cardio-vascular diseases.

However, documents that indicate the exact amount of spending on nutrition for each one of these projects are apparently absent [46].

FUND2: OKkio alla ristorazione [45] is an inter-regional network project for surveillance, monitoring and health promotion in collective catering. It aims to develop an effective collaboration between Food Hygiene and Nutrition Services (SIAN) and Collective Catering in Italy. Its objectives are monitoring user food consumption, promoting menus and healthy food, promoting national nutritional campaigns aimed at consumers.

FUND3: there is not an official national agency for health promotion in Italy. There's a Directorate-General office at Ministry of Health (Office No. 8), which is responsible for health promotion and prevention and control of chronic degenerative diseases. However, this office does not have a dedicated, secure funding stream [47].

Platforms and interaction

PLAT1: no evidence was identified regarding robust coordination mechanisms across departments and levels of Government (national, state and local) to ensure policy coherence, alignment, and integration of food, obesity and diet-related NCD prevention policies across Governments.

PLAT2: no evidence was identified on formal platforms (with clearly defined mandates, roles and structures) for regular interactions between Government and the commercial food sector on the implementation of healthy food policies and other related strategies

PLAT3: the only evidence found regarding this domain was The Healthy Cities Network, which is an initiative promoted by the World Health Organization (WHO) to help cities spread public health awareness, develop local policies for health and health programs, prevent and overcome threats and health risks and anticipate future health challenges (www.retecittasane.it/). On May 16, 2018 the Italian Ministry of Health and the Italian Healthy Cities Network signed a Memorandum of Understanding renewing, for another three years, the collaboration with The Healthy Cities Network. PLAT4: no evidence was found on Governments' work with a system-based approach with (local and national) organisations/partners/groups to improve the healthiness of food environments at a national level.

Health in all policies

HIAP1: Italy has approved the Understanding on the National Prevention Plan 2014-2018, for which 200 million euros were allocated, that dedicates special focus to health policies [38].

The essential levels of assistance (Livelli essenziali di assistenza, LEA) are the services that the SSN is required to provide to all citizens, free of charge or against the payment of a ticket. This document, last updated in 2017, represents the result of a shared work between Italian Government, Regions, autonomous Provinces and scientific societies and counts for 800 million euros.

HIAP2: no evidence was identified on processes such as health impact assessment's (HIAs) to assess and consider health impacts during the development of other non-food policies.

Results of the pilot rating

All three experts contacted to participate in the pilot rating accepted and rated the evidence provided to them. They were from non-academic and academic fields and had several years of experience. The mean of the experts' rating for each indicator is reported in *Table 1*. The areas that were rated by experts as the ones with more than 80% of policy implementation were *food provision* (indicator 1 and 2) and *food monitoring and intelligence* (indicator 3). the areas that were rated by experts as the ones with moderate level of policy implementation were *food label* (indicator 1), *food promotion* (indicator 4), *food prices* (indicator 4), *leadership* (indicator 3, 4, 5) and *food monitoring and intelligence* (indicator 2). The domains with the lowest rating were those concerning *platforms and interactions*, *health in all policies*, *food retail*, *food trade*, *food prices* (indicator 2), *governance*

Table 1
The mean rating for each indicator based on the pilot testing from three experts

Indicator	Mean
COMP1: Food composition targets/standards/restrictions have been established by the government for the content of the nutrients of concern (trans fats, added sugars, salt, saturated fat) in industrially processed foods, in particular for those food groups that are major contributors to population intakes of those nutrients of concern	3.67
COMP2: Food composition targets/standards/restrictions have been established by the government for the content of the nutrients of concern (trans fats, added sugars, salt, saturated fat) in meals sold from food service outlets, in particular for those food groups that are major contributors to population intakes of those nutrients of concern	1.67
LABEL1: Ingredient lists and nutrient declarations in line with Codex recommendations are present on the labels of all packaged foods	4
LABEL2: Evidence-based regulations are in place for approving and/or reviewing claims on foods, so that consumers are protected against unsubstantiated and misleading nutrition and health claims	3.67
LABEL3: One or more interpretive, evidence-informed front-of-pack supplementary nutrition information system(s) endorsed by the Government, which readily allow consumers to assess a product's healthiness, is/are applied to all packaged foods (examples are the Nutriscore and traffic lights)	3
LABEL4: A simple and clearly-visible system of labelling the menu boards of all quick service restaurants (i.e., fast food chains) is applied by the government, which allows consumers to interpret the nutrient quality and energy content of foods and meals on sale	3.5
PROMO1: Effective policies are implemented by the government to restrict exposure and power of promotion of unhealthy foods to children including adolescents through broadcast media (TV, radio)	2.33
PROMO2: Effective policies are implemented by the government to restrict exposure and power of promotion of unhealthy foods to children including adolescents through online and social media	3.67
PROMO3: Effective policies are implemented by the government to restrict exposure and power of promotion of unhealthy foods to children including adolescents through non-broadcast media other than packaging and online/social media	2.33
PROMO4: Effective policies are implemented by the government to ensure that unhealthy foods are not commercially promoted to children including adolescents in settings where children gather (e.g., preschools, schools, sport and cultural events)	4
PROMO5: Effective policies are implemented by the government to ensure that unhealthy foods are not commercially promoted to children, including adolescents on food packages	3
PRICES1: Taxes or levies on healthy foods are minimised to encourage healthy food choices (e.g., low or no sales tax, excise, value-added or import duties on fruit and vegetables)	2.33
PRICES2: Taxes or levies on unhealthy foods (e.g., sugar-sweetened beverages, foods high in nutrients of concern) are in place and increase the retail prices of these foods by at least 10% to discourage unhealthy food choices, and these taxes are reinvested to improve population health	1
PRICES3: The intent of existing subsidies on foods, including infrastructure funding support (e.g., research and development, supporting markets or transport systems), is to favour healthy rather than unhealthy foods	2.33
PRICES4: The Government ensures that food-related income support programs are for healthy foods	4
PROV1: The Government ensures that there are clear, consistent policies (including nutrition standards) implemented in schools and early childhood education services for food service activities (canteens, food at events, fundraising, promotions, vending machines etc.) to provide and promote healthy food choices	4.33
PROV2: The Government ensures that there are clear, consistent policies in other public sector settings for food service activities (canteens, food at events, fundraising, promotions, vending machines, etc.) to provide and promote healthy food choices	4.33
PROV3: The Government ensures that there are clear, consistent public procurement standards in public sector settings for food service activities to provide and promote healthy food choices	3
PROV4: The Government ensures that there are good support and training systems to help schools and other public sector organisations and their caterers meet the healthy food service policies and guidelines	3
PROV5: The Government actively encourages and supports private companies to provide and promote healthy foods and meals in their workplaces	3
RETAIL1: Zoning laws and policies are implemented to place limits on the density or placement of quick serve restaurants or other outlets selling mainly unhealthy foods in communities and/or access to these outlets (e.g., opening hours)	1.5
RETAIL2: Zoning laws and policies are implemented to encourage the availability of outlets selling fresh fruit and vegetables and/or access to these outlets (e.g., opening hours, frequency i.e., for markets)	1
RETAIL3: The Government ensures existing support systems are in place to encourage food stores to promote the in-store availability of healthy foods and to limit the in-store availability of unhealthy foods	1
RETAIL4: The Government ensures existing support systems are in place to encourage the promotion and availability of healthy foods in food service outlets and to discourage the promotion and availability of unhealthy foods in food service outlets	1

Continues

Table 1
Continued

Indicator	Mean
TRADE1: The Government undertakes risk impact assessments before and during the negotiation of trade and investment agreements, to identify, evaluate and minimize the direct and indirect negative impacts of such agreements on population nutrition and health	1
TRADE2: The Government adopts measures to manage investment and protect their regulatory capacity with respect to public health nutrition	1
LEAD1: There is strong, visible, political support (at the head of government or state/ ministerial level) expressed at both national as well as international level for improving food environments, population nutrition, diet related NCDs and their related inequalities"	1.5
LEAD2: Clear population intake targets have been established by the government for the nutrients of concern and / or relevant food groups to meet WHO and national recommended dietary intake levels	2.5
LEAD3: Clear, interpretive, evidenced-informed food based dietary guidelines have been established and implemented	4
LEAD4: There is a comprehensive, transparent, up-to-date implementation plan linked to national needs and priorities, to improve food environments, reduce the intake of the nutrients of concern to meet WHO and national recommended dietary intake levels, and reduce diet-related NCDs	4
LEAD5: Government priorities have been established to reduce inequalities or protect vulnerable populations in relation to diet, nutrition, obesity and NCDs	4
GOVER1: There are procedures in place to restrict commercial influences on the development of policies related to food environments where they have conflicts of interest with improving population nutrition. for example: restricting lobbying influences	1.5
GOVER2: Policies and procedures are implemented for using evidence in the development of food and nutrition policies	1
GOVER3: Policies and procedures are implemented for ensuring transparency in the development of food and nutrition policies	2.5
GOVER4: The Government ensures public access to comprehensive nutrition information and key documents (e.g., budget documents, annual performance reviews and health indicators) for the public	2
MONIT1: Monitoring systems, implemented by the Government, are in place to regularly monitor food environments (especially for food composition for nutrients of concern, food promotion to children, and nutritional quality of food in schools and other public sector settings), against codes / guidelines / standards / targets	1
MONIT2: There is regular monitoring of adult and childhood nutrition status and population intakes against specified intake targets or recommended daily intake levels	4
MONIT3: There is regular monitoring of adult and childhood overweight and obesity prevalence using anthropometric measurements	4.5
MONIT4: There is regular monitoring of the prevalence of NCD metabolic risk factors and occurrence rates (e.g., prevalence, incidence, mortality) for the main diet-related NCDs	5
MONIT5: Major programs and policies are regularly evaluated to assess their effectiveness and contributions to achieving the goals of the nutrition and health plans	3.5
MONIT6: Progress towards reducing health inequalities or health impacts in vulnerable populations and social and economic determinants of health are regularly monitored	3.5
FUND1: The "population nutrition" budget, as a proportion of total health spending and/or in relation to the diet-related NCD burden sufficiently contributes to reducing diet-related NCD's	1
FUND2: Government funded research is targeted for improving food environments, reducing obesity, NCDs and their related inequalities	2
FUND3: There is a statutory health promotion agency in place that includes an objective to improve population nutrition with a secure funding stream	1.5
PLAT1: There are robust coordination mechanisms across departments and levels of government (national, state and local) to ensure policy coherence, alignment, and integration of food, obesity and diet-related NCD prevention policies across governments	1
PLAT2: There are formal platforms (with clearly defined mandates, roles and structures) for regular interactions between Government and the commercial food sector on the implementation of healthy food policies and other related strategies	1
PLAT3: There are formal platforms (with clearly defined mandates, roles and structures) for regular interactions between government and civil society on the development, implementation and evaluation of healthy food policies and other related strategies	1
PLAT4: The Governments work with a system-based approach with (local and national) organisations/partners/groups to improve the healthiness of food environments at a national level	1
HIAP1: There are processes in place to ensure that population nutrition, health outcomes and reducing health inequalities or health impacts in vulnerable populations are considered and prioritised in the development of all government policies relating to food	1
HIAP2: There are processes e.g., Health Impact Assessment's (HIAs) to assess and consider health impacts during the development of other non-food policies	1

(indicator 2), *food monitoring and intelligence* (indicator 1). The feedback from experts was positive, reporting a high comprehensibility, clear language used and an easy, user-friendly rating process.

DISCUSSION

Despite growing interest worldwide for preventive action to be taken to tackle the obesity epidemic among all populations groups, there is the need for more evidence of the relative contribution of different recommended policies to improving population nutrition.

The present study utilized the Food-EPI tool, created by INFORMAS project [8] to collect evidence on good practice policies and infrastructures implemented by the Italian Government to improve population nutrition by improving food environments [16]. Government action indeed has been reported to be essential to implement policies to create healthier food environments.

In terms of policies implemented, the indicators for which a higher level of evidence was identified were: *food composition* (2/2 indicators), *food labelling* (3/4 indicators) and *food promotion* (4/5 indicators) and *food provision* (4/5 indicators). The research found a gap of evidence with regard to food in retail (0/4) and *food trade* and *investment* (0/2) indicators.

In terms of *infrastructure*, less evidence of implementation was identified compared to policies. The indicators with the highest level of evidence were *leadership* (5/5) and *funding* and *resources* (3/3), while the indicators with less evidence identified were *platforms* and *interaction* (1/4), *health in all policies* (1/2) and *governance* (2/4).

However, it should be highlighted that the evidence identified for each indicator was very heterogeneous in terms of quality of evidence, amount, and level, so a quantitative analysis among indicators would not be possible.

In order to test the rating process before a wider administration, a pilot test, including three experts, was conducted. The aim of this pilot testing was not to have results on the policy implementation level regarding healthy food environments in Italy, but rather to test the instrument and to receive feedback on the rating process and evidence compilation document, for as better wider administration. The pilot study showed a high comprehensibility and suitability of the rating process, which means that a *wider* administration can be carried out, using the evidence document that has been prepared by the research team. The areas with less evidence, where Government actions are needed the most according to the results of the pilot test were those concerning *platforms and interaction*, *health in all policies*, *food retail*, *food trade*, *food prices* (indicator 2), *governance* (indicators 2) and *monitoring and intelligence* (indicator 1). In line with the Food-EPI EU study, which reports an assessment of EU-level policies influencing food environments and priority actions to create healthy food environments in the EU, none of the EU-level policies with respect to the Food-EPI policy domains were rated as (very) strong. This study also reports policy implementation in the *food promotion*, *food prices*, *food in retail* domains as very weak or as non-existent [16].

However, the results of this pilot testing, being just preliminary, do not allow to drive final conclusions. Furthermore, since this work focuses more on the structuring and complication of the evidence document and reports only the results of a pilot rating process, it is not possible to compare the level of policy implementation in Italy with other countries. In this context, there is the need for the final results of the rating process, the wider administration of which will give more substantial and reliable information on the policies implemented in Italy and the prioritization of them by the Italian Government. Based on the results of this final rating, the experts will formulate recommendations for the Government on domains and indicators where further work and evidence is needed. The Expert Panel will give concrete actions for Italian Government, which will be prioritised by importance (need, impact, equity, other positive and negative effects) and achievability (feasibility, acceptability, affordability and efficiency) for both domains, i.e., policy and infrastructure support, separately.

Bringing together experts to systematically assess food environment policy has the potential to identify areas with broad expert recognition as important contributors to shaping a healthier food environment [7].

The Food-EPI provides a useful set of indicators focusing on where Government actions are needed most, and the process involves a wide range of stakeholders. The Food-EPI is currently being implemented by several countries globally.

The results and conclusions from different countries will be useful for the Decade of Action on Nutrition (<https://www.un.org/nutrition/>), which stimulates Governments to make relevant commitments on nutrition. The Decade of Action on Nutrition is a commitment by United Nations Member States to undertake 10 years of sustained and coherent implementation of policies, programmes and increased investments to eliminate malnutrition in all its forms, everywhere, leaving no one behind [48]. It is anticipated that benchmarking the extent of implementation of Government policies will increase accountability of Governments for their actions on food environments [49].

Moreover, Food-EPI has the potential to also enhance civil society's capacity to advocate for healthy food environments. This study contributes to the efforts of INFORMAS to broadly characterize the global food environment [8].

CONCLUSIONS

This study has provided a first step in identifying and summarizing Government action to improved food environments in Italy. Regular monitoring using Food-EPI plays a key role in creating awareness to address gaps in food environment policy in Italy to decrease the burden of diet-related NCDs.

Conflict of interest statement

Authors declare no conflict of interest.

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Improving the quality of care for people with chronic diseases: translating recommendations to practice

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Abstract

Introduction. Aim of this paper is to present a guide for translating to practice an evidence-based set of Quality Criteria and Recommendations (QCR) to promote the implementation of policies and practices in the field of health promotion, disease prevention and care for people with chronic diseases.

Methods. The guide is based on real-world experiences of eight European pilot actions using QCR as a framework for practice design, development, implementation, monitoring and evaluation. All partners implemented their respective practices by following the same agreed process.

Results. The implementation method was summarized in seven steps where each of one outline a particular phase of the process. The guide provides a step-by-step tutorial for the implementation of QCR.

Conclusions. Practical experiences from the pilot actions show the potential value of using the QCR in designing and implementing practices to improve the quality of care for people with chronic diseases.

Key words

- chronic diseases
- quality of care
- implementation
- intersectoral initiatives

INTRODUCTION

The burden of noncommunicable chronic diseases (NCDs) is steeply rising and although there is evidence of declining rates of premature mortality from NCDs in European region, improvements are not being implemented efficiently and fast enough [1]. Comprehensive and aligned health system response is needed including governance for intersectoral actions aligned at national, regional and local levels, well-resourced public health services supporting equity, multi-profile proactive primary care, efficient and timely care for acute states, person-centred care designed together with care users. Moreover it should include fit-for-purpose health force, adequate, prioritized financing aligned with service delivery goals, access to quality medicines and information solutions to support population health and individual seamless care including self-management [1]. Quality of care being one of the core processes is being improved in Europe using several strategies [2].

A first group of strategies focuses on healthcare structures and inputs, such as regulation of health profes-

sionals, technologies (through health technology assessment) and of healthcare facilities, including external institutional strategies (accreditation, certification, and supervision). A second group consists of strategies that steer and monitor quality of healthcare processes by setting standards (clinical guidelines for professionals and clinical pathways for provider institutions), by focusing on monitoring procedures and assuring improvements (audit and feedback directed to professionals), and patient safety strategies. The third group of strategies concerns leveraging processes and outcomes – the use of information to assure improvements (such as public reporting and pay-for-quality).

European Union (EU) supports numerous activities to increase quality of care in member states via health programs providing frameworks for sharing experiences and implementation across countries working in real world conditions [3]. EU co-funded the two most important Joint Actions on chronic diseases: JA CHRODIS – European Joint Action on chronic diseases and promoting healthy ageing across the life cycle and JA

CHRODIS PLUS – Implementing good practices for chronic diseases. The two Joint Actions aimed to support countries efforts, and transnational collaboration, for the improvement of prevention and quality of care for people with chronic diseases fostering integration of science-based interventions with community preferences mainly through carefully planned of pilot and innovative practices [3-5]. They produced a great deal of material (documents, guidelines, videos, etc.) useful for researchers but above all for health professionals, patients and decision makers. However, all these documents are published mainly on the JA dedicated sites, and often remain little known losing their potential impact on the quality of health of European citizens [http://chrodis.eu].

One of the results of JA CHRODIS was the definition of Quality Criteria and Recommendations (QCR) to improve prevention and quality of care for people with chronic diseases [6]. QCR definition involved, through a structured methodology, the community of partners of the Joint Action, and experts from a wide number of organizations across Europe and from a variety of professional backgrounds. The objective was to define an evidence-based set of quality criteria to assess whether a practice (i.e., interventions, policies, strategies, programs, and/or clinical practices) can be regarded as a “good practice” using Type 2 Diabetes as a model/example disease. The process led to the agreement on nine core quality criteria, with their essential components, that were the basis to formulate recommendations general enough to be applied in chronic diseases other than diabetes, in various domains (prevention, care, health promotion, education, and training), and in countries with different political, administrative, social and health care organization (Table 1).

Eight partners of JA CHRODIS PLUS engaged their communities in the co-creation of evidence, in real life conditions, using QCR to develop, implement and monitor innovative practices in the fields of disease prevention, health promotion and healthcare. They identified and prioritized improvement areas to be addressed in their interventions focusing on Type 1 and Type 2 diabetes, tinnitus, and complex chronic conditions [7-9]. Based on the experience of the eight pilot actions, we developed a guide to translate QCR into practice.

Aim of this paper is to present a guide for the use of QCR, and the overall process we followed for its definition, to contribute to dissemination and implementation research, and to support those who are going to lead the planning, implementation, monitoring and evaluation of practices in the field of health promotion, disease prevention and care for people with chronic diseases.

METHODS

Blueprint for action

We defined a “blueprint for action” to support partners, across European countries, to plan practices using QCR [10].

The general strategy for design, implementation, monitoring and evaluation of pilot actions was devel-

oped by the Asociacion Centro De Excelencia Internacional En Investigacion Sobre Cronicidad (KRONIK-GUNE) one of the JA partners. The strategy was then adapted by Authors (MM, JZ, AG) to include QCR providing a framework – structure, content, methodology – to enhance the adoption of QCR that could be applied in different settings and contexts.

The framework was comprised of a series of operational elements, methodological details, practical indications, and specific templates aimed to further support partners in the definition of the pilot plans:

- define a Local Implementation Working Group (LIWG) and identify key stakeholders;
- describe the scope of intervention by selecting, from QCR, the recommendations and related quality criteria, to be considered as the components of the intervention;
- conduct a Strengths, Weaknesses, Opportunities and Threats (SWOT) analysis of the context of pilot action using QCR;
- identify and prioritize improvement areas using QCR;
- plan actions for each identified improvement areas;
- define the key performance indicators;
- design the pilot implementation plan.

The strategy, templates and methods were discussed and agreed with partners during workshops and teleconferences in a participatory process.

Outline of eight pilot actions adopting QCR

Eight European partners from Bulgaria, Croatia, Finland, Germany, Greece, Spain, Serbia, and Slovenia, planned and conducted pilot actions to implement and test QCR in different settings and contexts for practice design, development, implementation, monitoring and evaluation [11].

Each participating Country followed the methodology defined by the blueprint for action, and used at least four out of the nine quality criteria: practice design, target population empowerment, education and training to promote empowerment, and sustainability and scalability. Moreover, at least one of the three criteria from the management perspective (Governance, Interaction with regular and relevant systems or Evaluation) was to be included. The partners used qualitative and quantitative methods of data analysis to assess the effectiveness both pilot action and QCR.

Croatia (Croatian Institute of Public Health in collaboration with the Primary Health Care Centres) tested structured education and performance feedback to increase the use of diabetes control checklist for improvement of quality care in diabetes, as well as to identify barriers for their full implementation in primary health care settings [12].

Finland (National Institute for Health and Welfare in collaboration with Primary health care and Family Federation of Finland) defined and tested a culturally sensitive lifestyle intervention model among a hard-to-reach and underserved population specifically tailored to the Somali population [13].

Greece (Aristotle University Hospital-AHEPA of Thessaloniki, Alexander Technological Educational Institute of Thessaloniki) provided structured education

Table 1
Quality Criteria and Recommendations (QCR) to improve prevention and quality of care for people with chronic diseases

Criteria	Recommendations
1 Practice design	The design should clearly specify aims, objectives, and methods, and rely upon relevant data, theory, context, evidence, and previous practices including pilot studies. The structure, organization and content of the practice is defined, and established together with the target population, that is clearly described (i.e., exclusion and inclusion criteria and the estimated number of participants). Human and material resources should be adequately estimated in relation with committed tasks. Relevant dimensions of equity have to be adequately taken into consideration, and targeted.
2 Target population empowerment	The practice should actively promote the empowerment of the target population by using appropriate mechanisms, such as self-management support, shared decision making, education-information or value clarification, active participation in the planning process and in professional training, and considering all stakeholders needs in terms of enhancing/acquiring the right skills, knowledge, and behaviour.
3 Evaluation	The evaluation outcomes should be linked to action to foster continuous learning and/or improvement and/or to reshape the practice. Evaluation and monitoring outcomes should be shared among relevant stakeholders, and linked to the stated goals and objectives, taking into account social and economic aspects from both the target population, and formal and informal caregiver perspectives.
4 Comprehensiveness of the practice	The practice should consider relevant evidence on effectiveness, cost-effectiveness, quality, safety, the main contextual indicators, as well as the underlying risks of the target population using validated tools to individual risk assessment.
5 Education and training	The practice should include educational elements to promote the empowerment of the target population (e.g., strengthen their health literacy, self-management, stress management etc.). Relevant professionals and experts are trained to support target population empowerment, and trainers/educators are qualified in terms of knowledge, techniques, and approaches.
6 Ethical considerations	The practice should be implemented equitably (i.e., proportional to need). The objectives and strategy are transparent to the target population and stakeholders involved. Potential burdens (i.e., psychosocial, affordability, accessibility, etc.) should be addressed to achieve a balance between benefit and burden. The rights of the target population to be informed, to decide about their care, participation and issues regarding confidentiality should be respected and enhanced.
7 Governance	The practice should include organizational elements, identifying the necessary actions to remove legal, managerial, financial, or skill barriers, with the contribution of the target population, carers and professionals that is appropriately planned, supported, and resourced. There is a defined strategy to align staff incentives and motivation with the practice objectives. The practice should offer a model of efficient leadership and should create ownership among the target population and several stakeholders considering multi-disciplinarity, multi/inter-sectoral, partnerships and alliances, if appropriate. The best evidence and documentation supporting the practice (guidelines, protocols, etc.) should be easily available for relevant stakeholders (e.g., professionals and target populations), which should support the multidisciplinary approach for practices. The practice should be supported by different information and communication technologies (e.g., medical record system, dedicated software supporting the implementation of screening, social media, etc.), defining a policy to ensure acceptability of information technologies among users (professionals and target population) to enable their involvement in the process of change.
8 Interaction with regular and relevant systems	The practice should be integrated or fully interacting with the regular health, care and/or further relevant systems, enabling effective linkages between all relevant decision-makers and stakeholders, and enhancing and supporting the target population's ability to effectively interact with the regular, relevant systems.
9 Sustainability and scalability	The continuation of the practice should be ensured through institutional anchoring and/or ownership by the relevant stakeholders or communities and supported by those who implemented it. The sustainability strategy should consider a range of contextual factors (e.g., health and social policies, sex and gender issues, innovation, cultural trends and general economy, and epidemiological trends), assessing the potential impact on the population targeted.

and training to medical and paramedical healthcare personnel for the management of cardiovascular risk factors (hypertension and diabetes) and for patient's education on lifestyles and self-management.

Serbia (University of Belgrade, Primary Health Care Centres, in collaboration with Republic Institute of Public Health and Ministry of Health) pilot action aimed at redesigning health care delivery to achieve better coordination of services to improve prevention and strengthening high quality care for chronic diseases, taking type 2 diabetes as a model disease [14].

Slovenia (General Hospital Novo mesto, and the Primary Healthcare Centre Novo mesto) developed a model to integrate care across levels of healthcare and the community based on a case study of chronic wound management. Special focus was paid to enhanced patient participation, and to sustainability through community partnership and support of the national policy-makers [15].

Spain (Regional Ministry of Health of Cantabria & Cantabrian Health Service), Bulgaria (National Centre of Public Health and Analyses), and Germany

(University Hospital Regensburg) aimed to assess to what extent mHealth tools (self-management and patient empowerment features) could contribute to patient control over their chronic disease, tinnitus, and diabetes [16].

Each partner prepared an implementation project report available at <http://chrodis.eu/07-fostering-the-quality-of-care-for-people-with-chronic-diseases/>, following the adapted version of SQUIRE 2.0 Guidelines [17].

Intermediary evaluation with the support of study visits

To support partners and evaluate the use of QCR, on-site assessment of the implementation process was performed in five pilot action sites. A concept note was defined that included rationale and general objectives of the study visits, expected outcomes, and methods being used by the LIWGs. During dedicated workshops the partners had the opportunity to discuss the concept note and identify ways to achieve meaningful patient involvement onto the implementation sites.

In general, the study visits were meant to foster the implementation activities via knowledge and experience exchange among partners. Moreover, the visits represented the opportunity to:

- conduct an interim implementation assessment with respect to outcome measures, as defined in the pilot action plan, with respect to QCR and with special focus to patient involvement and sustainability/scalability of the action;
- re-define, if needed, the action plan through a plan-do-study-act cycle;
- increase interest of the national stakeholders, including decision maker, creating the facilitatory context for the sustainability and spread of the action.

During the study visits, QCR usability was tested and evaluated by the participants and their opinions were heard and discussed. Participants were representatives of the LIWG, national/local stakeholders, including representatives of patients, experts from the JA (MM, JZ LN, VS, DS) and other representatives of European Health Futures Forum.

A questionnaire on the usability of QCR was submitted to partners when study visits were not performed.

RESULTS

Study visits lead the way to multi-stakeholder participation, meaningful patient involvement, and commitment from Health Authorities. The LIWGs considered all viewpoints and worked in a transparent manner, which facilitates the identification of possible enablers and barriers.

Based on the study visits, a valuable learning point was that all the LIWGs considered Quality Criteria and Recommendations as a valuable framework when it comes to the design, development and implementation of their pilot action and activities onto their respective sites. On some occasions, it was the QCR itself that triggered representatives from these groups to take new and different pathways. In general, it was considered a useful checklist, which supported implementation pro-

cess, to see the whole picture at the beginning of the project and to ponder the practical details in advance. A partner declared that “it makes you not forget anything and have it at the back of your mind all the time”. The added value of QCR was to be scientifically grounded. As a barrier, some implementers experienced less flexibility in practice development due to its use. Moreover, the criteria needed an introduction with explanations by trained experts because QCR is not a ‘plug in and play’ instrument. Without the external expert support its usage would have been questionable.

The guide for the use of QCR was developed in accordance with the implementation process defined in the blueprint for action [10] and real-world experiences in the participating countries. Activities were designed and implemented in different health care systems, in different contexts and were addressing different scopes in a variety of areas. All pilot actions developed and implemented their respective practices by following the same method, and QCR was used as a framework for practice design, development, implementation, monitoring and evaluation.

Based on the practical experience of the eight pilot actions, the guide outlines the suggested steps for a successful translation into practice of QCR. The full process is not completely linear but involves periodic evaluations and possibly the modification of the initially defined work plan and can be summarized in seven steps.

1. *Establishment of the core leadership group and the implementation working group.* Various aspects of governance and leadership have to be addressed prior to design practice and establish a wider group responsible for its implementation. A central leadership group has to be settled that plans, organizes, monitors, shares, reports and provides support during the pursuit of the objectives of the practice. The leadership group defines the implementation working group by identifying the stakeholders to be included and at what level: individuals and/or entities that are involved or influenced by the planned activity or are considered important for the sustainability or action implemented.
2. The second step is to define the *scope of the practice.* The implementation working group led by leadership group outlines, based on the available knowledge, the problem that the practice will address, defines the target populations, and selects the Recommendations and Criteria that are core to the successful implementation.
3. It is necessary to *identify the contextual factors* that could influence the implementation itself before the action plan is developed in detail. Baseline analysis of situation and context can be conducted using quantitative, qualitative, or mixed methodology [3].
4. Following step is to *define the action plan* that includes: definition of specific objectives and activities to be conducted per each objective; responsibilities, who does what, trying to create ownership among target population and other stakeholders; timing; key performance indicators, process and outcome measures.
5. It is necessary to perform *monitoring and evaluation*

of the implementation to encourage continuous learning and activity improvement. Intermediary as well as final evaluation of the activity can be performed using QCR, including assessment of key performance indicators. Intermediary evaluation can lead in an adaptation of the original plan, if needed. Results of the evaluations have to be shared among relevant stakeholders, showing the link to the defined goals and objectives.

6. *Preparation of a final report*, at the end of the planned activities, is essential to transmit key information and messages to the scientific, professional, and civil community, as well as to decision makers, and is a fundamental element for the sustainability and scalability of the practice. The report should be structured, partners in JA CHRODIS PLUS were using SQUIRE 2.0 Guidelines [17].
7. *Planning for sustainability of the practice and to increase potential the scale-up* should be considered from the first day of activity. A sustainability strategy should be defined that considers contextual factors and potential impact on the target population. The sustainability of the practice can be ensured through institutional anchoring and support from stakeholders or the community.

CONCLUSIONS

The process followed for translating recommendations to practice was based on the assessment of the applicability and transferability of QCR tool in different countries and settings, on the identification of predisposing factors and barriers and, above all, on collaboration amongst partners/countries which led to the definition of the guide for the implementation of QCR.

It is important to highlight that even though most of the studied activities were tackling diabetes and diabetes-related complications, each partner had different objectives facing different challenges, operating in various contexts and with target populations that varied from Country to Country.

Intervention methods were discussed and agreed with partners in a participatory process. Intermediary evaluation with multi-stakeholder participation allowed to re-define, if needed, the action plan through an iterative process also contributing to achieve a long-term, even if difficult to be measured, community benefit through research [3, 18].

Activities were conducted, in each participating Country, by a leadership and an implementation working group composed by the local relevant stakeholders, individuals, institutions or organizations in any way interested by the intervention or policy to be promoted. Population's target of the intervention (citizens, people with chronic diseases, health professionals, etc.) were also actively involved in the planning process and decision making. These characteristics are key elements to increase the likelihood of success and maximizes the benefits for the community [3, 5, 7, 8].

The partners were reflecting on essential elements of the QCR while establishing the leadership group and implementation working group, defining the scope of the pilot action in performing situation and context

analysis and in designing the pilot action plan. Involvement of target population and of decision makers in the process was seen as an important facilitator in developing and implementing complex interventions. These were studied by qualitative and quantitative methods and focused on meaningful involvement of target population representatives to achieve sustainable and scalable results [3].

QCR implementation presents a very ambitious objective because it is aimed at reshaping health care systems by facilitating the transition from fragmentation to integration of care, including prevention efforts, and incorporation of community resources, to ensure a seamless care coordinated with and around the needs of people with chronic diseases.

The aims of the overall experience were to build, using a blend of participatory approaches, a common methodology helping fostering group work and creating a sort of community of practice through the organization of seminars, workshops, and stakeholder events [3, 5]. It helped to build a platform for the exchange of ideas, experiences, and materials and for the organization of study visits with the local working group, national and local stakeholders, decision makers and external experts. The implicit idea was that a participatory approach amongst all relevant stakeholders had the potential to create that essential sense of ownership to achieve concrete outcomes and maximum health impact. The added value of this method is reflected in the creation of a network, a community, a transnational human capital contributing to a generalizable knowledge.

In conclusion, practical experiences from the pilot actions show the potential value of using the QCR in designing and implementing practices in the field of chronic diseases, improving quality and integration of care, thus contributing to the reduction of health inequalities. The guide for the implementation of QCR provides additional practical support to all of those who want to develop, implement, monitor, and evaluate good practices in the field of health promotion, prevention, and care for people with chronic diseases.

Author contributions

Conceptualization, JZ, MM; methodology, JZ, MM, AG, VS; original draft preparation JZ, DO, LN, DS, MM; writing review and editing MM, JZ, DO, LN, DS, VS, DB, BC, AG, FP, ES, MV.

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Conflicts of interest statement

The Authors declare no conflict of interest.

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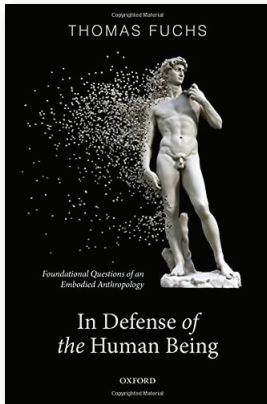
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BOOK REVIEWS, NOTES AND COMMENTS

Edited by
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IN DEFENSE OF THE HUMAN BEING

Foundational questions of an embodied anthropology

Thomas Fuchs
Oxford: Oxford University Press; 2021
272 p.
ISBN-13: 9780192898197
€ 43,70

In the year in which the CEO of one of the largest technology conglomerates in the world announced the development of the first “metaverse ecosystem” in the history of mankind, the reflection on what it means to be a human being and whether it is worth investing resources to try to overcome our human condition seems to become increasingly urgent. The philosophical debate that has sparked out of similar issues (sometimes even referred to as technophilosophies) includes contrasting views. The recent book by philosopher David Chalmers (2022), for example, proposes to think of virtual reality as a genuine reality in which we can live a meaningful life. On the other hand, the new captivating book by the psychiatrist and philosopher Thomas Fuchs brilliantly raises objections and challenges both to enthusiastic technophiles, to supporters of post- or trans-humanist theories, and to the scientific and philosophical assumptions upon which these visions of the human future are built: namely the various forms of cerebrocentrism and reductionist, biological psychiatric orientations.

The author, who is Karl Jaspers Professor of philosophy and psychiatry at Heidelberg University, sharply deals with the most topical and burning debates of our time. The phenomenological cut and the constant reference to phenomenological psychopathology allow to focus on known problems in an original perspective. The general inspiration of this work consists in critically considering those contemporary trends that seriously *question* our conception of the human being: from artificial intelligence to neurobiological reductionism, from neuroconstructivist positions on perception to the new temporality inaugurated by capitalist modernity and the impact of virtual reality on our ability to feel empathy.

The basic thesis, which Thomas Fuchs declines in ever different versions within the book, is that both philo-

sophical thought and psychiatric practice are not going to reach a sufficient understanding of human nature as long as they aspire to reduce embodied subjectivity (both normal and pathological) to lower levels of analysis (i.e., neural activations, disembodied higher-order cognitive processes, brain disorders, etc.). What are the theoretical assumptions from which the author wants to “defend” the human being? In a nutshell, they are identifiable with (1) the scientific naturalistic view in which there is no place for reflexive subjectivity, as well as (2) biological mechanicism, according to which living beings are better understood as “biological machines controlled by genetic programs” (p. 4) and (3) computational functionalism according to which our mental states are understood in terms of information processing, implementable on different types of hardware, and therefore simulable by AI programs. Fuchs’ “defense” could be summarized in the formula that constitutes the subtitle of the book: “Embodied Anthropology”. In other words, experience is not multiply realizable; the person’s embodied existence is the only plausible image of the human being, and the only one that philosophy as well as psychiatry should depict.

After a programmatic introduction, the first section of the book is devoted to the challenges posed by artificial intelligence, transhumanism, and digital virtualization processes. Chapter 1 contains a critique of the notion of intelligence as it is understood by AI research programs. Chapter 2 shows how transhumanist utopias, aimed at perfecting the deficits deriving from our corporeality, are essentially based on the refusal of the contradictions deriving from our embodied existence. In chapter 3 we find an examination of the effects that virtual interaction has on our capacity of intersubjective attunement with others. The second section of the book is devoted to an extended critique of cerebrocentrism. The reductionist positions coming from neuroscience are taken into consideration (chapter 4), determinism based on natural science is harshly criticized (chapter 5), and an enactivist refutation of constructivist theories of perception is put forward (chapter 6). The last section is dedicated to psychiatry and its role in society. In chapter 8 the author stresses the importance of a subject-oriented psychopathology. The diagnostic process and the treatment of psychiatric disorders should encompass patients’ subjectivity and interpersonal relationships: “the research efforts of the discipline must be equally focused on biological processes, psychopathological experiences, psychological-biographical connections, and social interactions, instead of being reduced to analyzing processes inside the brain” (pp. 190-191). Chapter 9 points out a possible change in the conception of dementia based on a phenomenological notion

of the self and personal identity; a concept of personhood grounded in embodiment and intercorporeal interactions allows to consider more fully the identity of the patient even when most cognitive abilities are impaired. Finally, the last chapter deals with the process of derythmitization of social and individual temporality that emerges in globalized capitalist societies. Here a concept of psychiatric treatment as “resynchronization therapy” is proposed.

In sum, the book offers an illuminating examination

of the factors that bring the human condition into question. The wide range of topics and a clear and accessible style make it of extreme interest both to readers with a philosophical background and to clinicians, as well as to students in the humanities and sciences.

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PUBLICATIONS FROM INTERNATIONAL ORGANIZATIONS ON PUBLIC HEALTH

Edited by
Annarita Barbaro

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS (FAO)

The State of Food and Agriculture 2021. Making agrifood systems more resilient to shocks and stresses. Rome: Food and Agriculture Organization of the United Nations 2021; 182 p. ISBN 978-92-5-134329-6. The State of Food and Agriculture 2021 presents country-level indicators of the resilience of agrifood systems. The indicators measure the robustness of primary production and food availability, as well as physical and economic access to food. They can thus help assess the capacity of national agrifood systems to absorb shocks and stresses, a key aspect of resilience. The report analyses the vulnerabilities of food supply chains and how rural households cope with risks and shocks. It discusses options to minimize trade-offs that building resilience may have with efficiency and inclusivity. The aim is to offer guidance on policies to enhance food supply chain resilience, support livelihoods in the agrifood system and, in the face of disruption, ensure sustainable access to sufficient, safe and nutritious food to all.

The FAO Action Plan on Antimicrobial Resistance 2021–2025. Supporting innovation and resilience in food and agriculture sectors. Rome: Food and Agriculture Organization of the United Nations 2021; 46 p. ISBN 978-92-5-134673-0. Due to antimicrobial resistance (AMR), drug-resistant infections are placing an ever-increasing burden on human, animal, plant, and environmental health. This document outlines the FAO Action Plan on Antimicrobial Resistance 2021–2025 which serves as a roadmap for focusing global efforts to address AMR in the food and agriculture sectors. The aim of this plan is to help accelerate progress in developing and implementing multi-sectoral National Action Plans to tackle AMR by calling attention to strategic priorities and areas of expertise for FAO support. The action plan was developed by a multidisciplinary FAO team to ensure that all relevant dimensions – including terrestrial and aquatic animal health and production, crop production, food and feed safety, genetic resources, natural resource management, risk communication, and behaviour change – are considered, with attention to regulatory frameworks, standards, norm-setting and bottom-up processes of collective action. By working together, food systems, livelihoods, and economies will be better protected from the destabilizing forces of untreatable illness.

Gomez San Juan M, Bogdanski A. **How to mainstream sustainability and circularity into the bi-**

oeconomy? A compendium of bioeconomy good practices and policies. Rome: Food and Agriculture Organization of the United Nations 2021; 132 p. ISBN 978-92-5-134726-3. This Compendium outlines 250 sources of good practices and policies to advance the global bioeconomy. It covers the entire continuum of economic sectors that have a stake in biological knowledge and resources. The Compendium, therefore, highlights the wide range of aspects that are included in the concept of the bioeconomy. Being an inherently multisectoral process that involves potential synergies and trade-offs among different sustainability objectives, the implementation of bioeconomy strategies presents greater challenges than activities that are focused on a single sector. The report also shows how good practices and policies contribute to the translation of bioeconomy strategies into coordinated actions for the achievement of local priorities and sustainability goals, while also addressing global issues. Overall, the review identifies a knowledge gap: Assessments do not always indicate if practices and policies have enough evidence of impact to be recommended as models that contribute to sustainability objectives of the bioeconomy. To address this, a context-specific approach described in Chapter 5, provides support for countries to make evidence-based decisions on policies and investments for the bioeconomy. The approach helps to identify good practices and policies ex-ante, which can help achieve common sustainability objectives of bioeconomy strategies that were presented in the 2019 FAO report, Towards sustainable bioeconomy - Lessons learned from case studies. Taken together, this Compendium and the 2019 report, provide practical guidelines and resources that can support decision-makers and stakeholders in bioeconomy systems to make progress towards reaching sustainable outcomes.

UNITED NATIONS EDUCATIONAL, SCIENTIFIC AND CULTURAL ORGANIZATION (UNESCO)

The United Nations World Water Development Report 2021. Valuing water. Paris: UNESCO Publishing 2021; 187 p. ISBN 978-92-3-100434-6. The 2021 World Water Development Report on Valuing Water assesses the current status of, and challenges to, the valuation of water across different sectors and perspectives, and identifies ways in which valuation can be promoted as a tool to help achieve sustainability. This report groups current methodologies and approaches to the valuation of water into five interrelated perspec-

tives: valuing water sources, in situ water resources and ecosystems; valuing water infrastructure for water storage, use, reuse or supply augmentation; valuing water services, mainly drinking water, sanitation and related human health aspects; valuing water as an input to production and socio-economic activity, such as food and agriculture, energy and industry, business and employment; and other sociocultural values of water, including recreational, cultural and spiritual attributes. These are complemented with experiences from different global regions, opportunities to reconcile multiple values of water through more integrated and holistic approaches to governance, approaches to financing, and methods to address knowledge, research and capacity needs.

JOINT UNITED NATIONS PROGRAMME ON HIV/AIDS (UNAIDS)

2021 Word AIDS Day report. Unequal, unprepared, under threat: why bold action against inequalities is needed to end AIDS, stop COVID-19 and prepare for future pandemics. Geneva: Joint United Nations Programme on HIV/AIDS 2021; 73 p. In this report the Joint United Nations Programme on HIV/AIDS (UNAIDS) issues a warning: progress against AIDS, which was already off track, is now under even greater strain as the COVID-19 crisis continues to rage, disrupting HIV prevention and treatment services, schooling, violence-prevention programmes and more. This report examines five critical elements from the Global AIDS Strategy that must urgently be universalized, and which are also critical but under-funded and under-prioritized for pandemic prevention, preparedness and response: community-led and community-based infrastructure, equitable access to medicines, vaccines and health technologies, supporting workers on the pandemic front lines, human rights at the centre of pandemic responses, and people-centred data systems that highlight inequalities.

ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT (OECD)

How Learning Continued during the COVID-19 Pandemic. Global Lessons from Initiatives to Support Learners and Teachers. Paris: OECD Publishing 2022; 384 p. ISBN 978-92-64-81909-2 (PDF) ISBN 978-92-64-53821-4 (print). This report brings together 45 of the education continuity stories that were jointly documented by the OECD, the World Bank, Harvard's Global Education Innovation Initiative and HundrED during the first wave of school closures related to the COVID-19 pandemic. It covers a variety of different examples on how governments and non-governmental organisations quickly responded to school closures to implement a strategy for learners around the world to continue to study. While often based on the use of digital solutions, those solutions target specific solutions

aimed at academic learning, socio-emotional support, teacher professional development, etc. The book covers examples from low, middle and high income countries on all continents and draws some lessons of these fast-paced responses to reimagine a post-pandemic education across the world.

INTERNATIONAL LABOUR ORGANIZATION (ILO)

Healthy and safe telework: technical brief. Geneva: World Health Organization and the International Labour Organization 2021; 32 p. ISBN (WHO) 978-92-4-004097-7 (electronic version) ISBN (WHO) 978-92-4-004098-4 (print version) ISBN (ILO) 978-92-2-036231-0 (print) ISBN (ILO) 978-92-2-036232-7 (web PDF). This report, jointly produced by the ILO and WHO, outlines the health benefits and risks of teleworking and the changes needed to accommodate the shift towards different forms of remote work arrangements brought on by the COVID-19 pandemic and the digital transformation of work. The report outlines the roles that governments, employers, workers and workplace health services should play in promoting and protecting health and safety while teleworking. Among the benefits, the report says, are improved work-life balance, opportunities for flexible working hours and physical activity, reduced traffic and commuting time, and a decrease in air pollution – all of which can improve physical and mental health and social wellbeing. Teleworking can also lead to higher productivity and lower operational costs for many companies. However, the report warns that without proper planning, organization and health and safety support the impact of teleworking on the physical and mental health and social wellbeing of workers can be significant. It can lead to isolation, burnout, depression, domestic violence, musculoskeletal and other injuries, eye strain, an increase in smoking and alcohol consumption, prolonged sitting and screen time and unhealthy weight gain. The report offers also practical recommendations for the organization of telework to meet the needs of both workers and organizations. These include discussing and developing individual teleworking work plans and clarifying priorities, being clear about timelines and expected results, agreeing on a common system to signal availability for work, and ensuring that managers and colleagues respect the system.

WORLD HEALTH ORGANIZATION (WHO)

HIV drug resistance report 2021. Geneva: World Health Organization 2021; 138 p. ISBN 978-92-4-003860-8 (electronic version) ISBN 978-92-4-003861-5 (print version). WHO's latest HIV Drug Resistance Report gives an in-depth picture of the extent to which drug resistance is growing, and the steps that countries are taking to ensure people will receive effective medicine to treat and prevent HIV. Antiretroviral therapy



(ART) has been scaled up: at the end of 2020, 27.5 million people were receiving ART globally. However, HIV drug resistance (HIVDR) can compromise the effectiveness of antiretroviral (ARV) drugs in reducing HIV incidence and HIV-associated morbidity and mortality. Minimizing the spread of HIVDR is a critical aspect of the broader global response to antimicrobial resistance. To minimize the emergence and transmission of drug resistant HIV, WHO recommends that ART and pre-exposure prophylaxis (PrEP) programmes be accompanied by measures to monitor the quality of ART and PrEP delivery and the routine surveillance of HIV drug resistance. The report also emphasizes the need for routine viral load monitoring and close follow-up of individuals with viral non-suppression, including regimen switch if indicated, to achieve favourable and sustained long term treatment outcomes. In addition, ensuring the continuous availability and accessibility to optimal medicines to treat HIV infections is essential to prevent HIV drug resistance. These findings emphasize the need to support countries in proactively finding sustainable solutions that are appropriate to local contexts and can involve community members and civil society. As the current Global Action Plan on HIV Drug Resistance 2017–2021 draws to a close, the report recommends future global, national and country efforts to identify ongoing opportunities to prevent, monitor and respond to HIV drug resistance including adapting to the rapidly evolving treatment landscape and new service delivery models.

World malaria report 2021. Geneva: World Health Organization 2022; 322 p. ISBN 978-92-4-004049-6 (electronic version) ISBN 978-92-4-004050-2 (print version). Each year, WHO's World malaria report provides a comprehensive and up-to-date assessment of trends in malaria control and elimination across the globe. It tracks investments in malaria programmes and research as well as progress across all intervention areas: prevention, diagnosis, treatment, elimination and surveillance. The 2021 report is based on information received from malaria-endemic countries in all WHO regions and took a closer look at the impact of disruptions to malaria prevention, diagnosis and treatment during the COVID-19 pandemic outlining what is needed to get back on track and accelerate progress in the fight against one of our oldest and most deadly diseases. The latest data show that the worst-case scenario projected by WHO – a doubling of malaria deaths in sub-Saharan Africa – did not come to pass. However, moderate disruptions to malaria services led to a marked increase in cases and deaths in 2020 over the previous year.

State of inequality: HIV, tuberculosis and malaria. Geneva: World Health Organization 2021; 231 p. ISBN 978-92-4-003944-5 (electronic version) ISBN

978-92-4-003945-2 (print version). HIV, tuberculosis (TB) and malaria are diseases of poverty and marginalization, with a heavy toll among populations that are chronically disadvantaged. Although remarkable progress has been made in reducing the overall burden of each disease over the past decade, certain population groups have persistently higher disease mortality and morbidity and lower access to life-saving interventions. Existing inequities have been widely acknowledged as barriers to achieving global and national goals and targets in HIV, TB and malaria programmes. These inequities have become even more pressing amidst the uncertainty of the COVID-19 pandemic. Yet, the magnitude and extent of health inequalities remain poorly documented and understood. This is the first monitoring report devoted to systematically assessing the global state of inequality in the three diseases, quantifying the latest situation of inequalities within countries and change over time. The report is timely due to the renewed emphasis on equity in prominent global initiatives and plans, including the United Nations 2030 Agenda for Sustainable Development, and global strategies to end AIDS, TB and malaria. The novelty of this report lies in its comprehensive and systematic approach to presenting the state of inequality across the three diseases. Using the latest available global data for 32 health indicators (addressing the burden of disease; knowledge, attitudes and practices; detection; prevention; testing and treatment; and social protection) and up to 186 countries, the report quantifies within-country inequalities by sex, economic status, education, place of residence and age.

Global analysis of healthcare waste in the context of COVID-19: status, impacts and recommendations. Geneva: World Health Organization 2022; 71 p. ISBN 978-92-4-003961-2 (electronic version) ISBN 978-92-4-003962-9 (print version). The COVID-19 pandemic has led to large increases in healthcare waste, straining under-resourced healthcare facilities and exacerbating environmental impacts from solid waste. This report quantifies the additional COVID-19 healthcare waste generated, describes current healthcare waste management systems and their deficiencies, and summarizes emerging best practices and solutions to reduce the impact of waste on human and environmental health. Scalable and environmentally sustainable solutions exist and are drawn, in part, from country case studies. Case studies are drawn from Colombia, the United Kingdom, Ghana, India, Lao People's Democratic Republic, Liberia, Madagascar, Malawi, Nepal and the Philippines. These include manufacture and use of safe, reusable PPE items; reduced and more sustainable packaging; centralized treatment and use of non-burn waste treatment technologies; and local production and just in-time shipments.

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Results, Discussion, Conclusions). In the Methods section a specific paragraph on the adopted statistical analysis should necessarily be included.

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

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