ISSN 0021-2571 (print) · 2384-8553 (online) | Coden: AISSAW 61 (No. 1) | 1-94 (2025)

ANNALI
DELL'ISTITUTO SUPERIORE DI SANITÀ

Volume **61** No. **1**
2025

A SCIENCE JOURNAL *for* PUBLIC HEALTH

ISTITVTO SVPERIORE DI SANITÀ
www.iss.it

Ann Ist Super Sanità 2025 | Vol. 61, No. 1

Annali
dell'Istituto Superiore di Sanità
A SCIENCE JOURNAL FOR PUBLIC HEALTH

Publication
Annali dell'Istituto Superiore di Sanità is published quarterly and in special issues.
Freely available online at www.iss.it/annali - https://annali.iss.it

Annali dell'Istituto Superiore di Sanità is indexed in
- CAB
- CHEMABS
- EMBASE/Excerpta Medica
- FSTA
- MEDLINE
- ProQuest
- SCOPUS
- WEB OF SCIENCE

The Journal Impact Factor is 1.1

Annali Editorial Office
Scientific Communication Service
Istituto Superiore di Sanità
Viale Regina Elena 299, 00161 Rome, Italy
Tel.: +39 06 49902945 Fax: +39 06 49902253
E-mail: annali@iss.it
www.iss.it/annali - https://annali.iss.it

Papers to be presented for publication should be submitted online to https://annali.iss.it

Instructions to Authors are available online at https://annali.iss.it

Publishing support
Il Pensiero Scientifico Editore, Rome
Via San Giovanni Valdarno 8, 00138 Rome, Italy
www.pensiero.it

Subscription information & terms
Il Pensiero Scientifico Editore
Tel.: +39 06 86282324 Fax: 06 86282250
E-mail: abbonamenti@pensiero.it

Year 2025
Italy individual subscription € 57,00 | Italy institutional subscription € 67,00.
Other countries € 67,00
Each quarterly issue € 21,00

Responsibility for the contents and opinions expressed on this journal rests solely with the Author(s).

ISSN 0021-2571 (print), 2384-8553 (online)
Coden: AISSAW 61 (No. 1)

Reg. Stampa - Tribunale di Roma, n. 482 del 29 ottobre 1985 (cartaceo); n. 121 del 16 maggio 2014 (online)

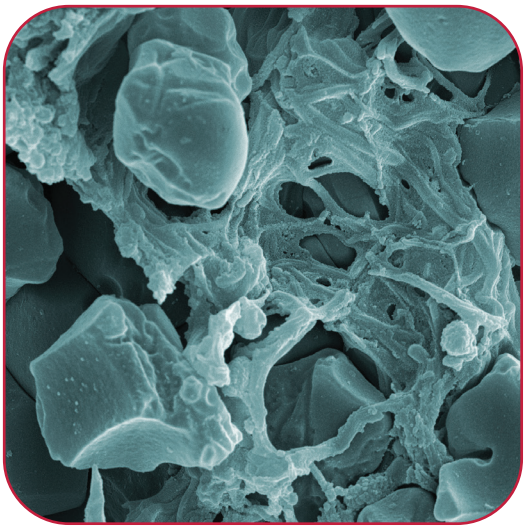
MISTO
Carta da fonti gestite in maniera responsabile
FSC® C017635

Printed in March 2025 by Ti Printing s.r.l.
Via Case Rosse 23, 00131 Rome, Italy

Ann Ist Super Sanità 2025 | Vol. 61, No. 1

Annali
dell'Istituto Superiore di Sanità
A SCIENCE JOURNAL FOR PUBLIC HEALTH

The cover image shows polyhedric erythrocytes compressed by the contraction of fibrin fibers, a detail of a human arterious stroke obtained by high resolution scanning electron microscopy. The image is provided by the Microscopy Area, Core Facilities, Istituto Superiore di Sanità, Rome, Italy.



ANNALI
dell'Istituto Superiore di Sanità

Vol. 61, No. 1 2025

Contents

Ann Ist Super Sanità 2025 | Vol. 61, No. 1: 1-2
DOI: 10.4415/ANN_25_01_01

LETTER
Visual responses in a transplanted eye: reality or chimera?

Key words
- eye diseases
- transplants
- retinal neurons

Dear Editor,

We read with interest the recent paper on JAMA by Ceradini *et al*. [1], reporting the clinical ophthalmological findings in a patient who received, for the first time, a whole-eye transplant. This patient underwent a detailed and state-of-the-art reconstruction of the hemiface and orbit with an excellent and important aesthetic postop result. The procedure was performed with great care also with respect to ethical issues [2] and, prospectively, could be an important step towards a therapeutic resource to treat patients with no viable alternatives. However, the transplanted eye resulted completely blind throughout the follow-up. Interestingly, the Authors evaluated both the structure and function of the retina and optic nerve in the transplanted eye, showing signs of atrophy at both retinal and optic nerve level; on the functional side, the Authors claimed some evidence of postop photoreceptor/bipolar cell function assessed by flicker electroretinograms. The Authors also claimed the presence of some electric signals of neural activity originating at the level of visual cortex, in response to flash stimulation (flash visual evoked potentials, VEPs) of the blind, transplanted eye. The recorded flash VEPs waveforms reportedly were blunted and delayed but within the range of International Society for Clinical Electrophysiology of Vision (ISCEV) standards for VEPs. This surprising finding raises several questions about the most effective VEP recording and analysis methodology to use, when recording VEP responses from severely visually impaired eyes. Transient VEP responses have the limitation of ambiguity of interpretation, or significance, when the amplitude response is reduced close to noise level, as in severely impaired eyes. Noise estimates should be considered in such contexts given their potential influence on the recorded signal. This can be done in different ways. The simplest way is to record the same VEPs with the stimulus completely occluded. Another useful way would be to digitally subtract odd from even (or *vice versa*) events in the averaging procedure. The difference may provide a signal reflecting the background noise-independent activity. Additional methods which proved to be efficient and well exploited in detecting very low-amplitude VEP signals are based on steady-state VEP recordings and application of sub microvolt methods based on the Fourier analysis and estimate of noise and signal-to-noise ratio [3, 4]. These methodologies, which are more advanced and sophisticated compared to the ISCEV standard clinically recommended procedures, increase the precision and confidence of measurements in blind or severely visually impaired eyes. The VEP signals reported in the study by Ceradini *et al*. [1], suffer from ambiguity and uncertainty, limiting an adequate interpretation of a finding (presence of a visual signal to visual cortex from the transplanted eye, presence of real, noise-free retinal signal) of the utmost importance when evaluating the results of whole eye transplantation. Digital methods of signal-to-noise ratio estimates may certainly improve the accuracy of functional results unlocking the doors to a better understanding of optic nerve graft to host integration.

Francesco Martelli[1]*, Benedetto Falsini[2] and Andrea Cusumano[2]

[1]*Dipartimento di Malattie Cardiovascolari, Endocrino-Metaboliche e Invecchiamento, Istituto Superiore di Sanità, Rome, Italy*
[2]*Macula and Genoma Foundation, Rome, Italy*

**Corresponding author*: francesco.martelli@iss.it

The Authors declare no conflict of interests

REFERENCES

1. Ceradini DJ, Tran DL, Dedania VS, et al. Combined whole eye and face transplant: Microsurgical strategy and 1-year clinical course. JAMA. 2024;332(18):1551. doi: 10.1001/jama.2024.12601
2. Petrini C, Nanni Costa A. Facial transplantation: From the early trials to ethical and clinical guidelines. Commentary. Ann Ist Super Sanità. 2019;55(2):105-7. doi: 10.4415/ANN_19_02_01
3. Trisciuzzi MTS, Riccardi R, Piccardi M, et al. A fast visual evoked potential method for functional assessment and follow-up of childhood optic gliomas. Clin Neurophysiol. 2004;115(1):217-26. doi: 10.1016/S1388-2457(03)00282-7
4. Fadda A, Martelli F, Zein WM, et al. Statistical evaluation of ERG responses: A new method to validate cycle-by-cycle recordings in advanced retinal degenerations. Invest Ophthalmol Vis Sci. 2024;65(4):3. doi: 10.1167/iovs.65.4.3

Ann Ist Super Sanità 2025 | Vol. 61, No. 1: 3-12
DOI: 10.4415/ANN_25_01_02

Monitoring prevalence of breastfeeding and associated factors: results of the 2022 data collection of the Italian surveillance of children aged 0-2 years

Enrica Pizzi[1]*, Michele Antonio Salvatore[2]*, Angela Giusti[1], Francesca Zambri[1], Leonardo Speri[3], Elise M. Chapin[4] and Serena Donati[1], on behalf of the 2022 SURVEILLANCE OF CHILDREN AGED 0-2 YEARS Group**

[1]Centro Nazionale per la Prevenzione delle Malattie e la Promozione della Salute, Istituto Superiore di Sanità, Rome, Italy
[2]Servizio Censimento della Popolazione e Integrazione delle Indagini Sociali, Istituto Nazionale di Statistica, Rome, Italy
[3]Formerly Dipartimento di Prevenzione, Azienda ULSS 9 Scaligera, Verona, Italy
[4]UNICEF Italia, Fondazione ETS, Rome, Italy
**These Authors share first authorship*
***The members of the 2022 SURVEILLANCE OF CHILDREN AGED 0-2 YEARS Group are listed before the References*

Abstract

Objective. To describe breastfeeding and associated factors in a large representative sample of children aged 0-2 years in Italy.

Materials and methods. Data from the 2022 Italian surveillance of children aged 0-2 years, comprised of 35,550 mothers, were analysed to estimate rates of EBF (exclusive breastfeeding), any breastfeeding (BF) and never breastfed (NBF). Logistic regression was used to investigate the association of EBF, BF and NBF with potential predictors.

Results. EBF among children aged 2-3 months varied from 36.4% in the South Italy to 54.0% in the North, decreasing respectively to 19.6% and 35.8% at 4-5 months. At 12-15 months BF ranged between 29.2% (South) and about 40% (Centre and North). Women with Italian citizenship, having a lower educational level, those who never attended antenatal classes (AC), and those residing in the South were significantly less likely to exclusively breastfeed or to breastfeed after the first year of life of the child.

Conclusions. The data underscore the gap between recommendations and actual breastfeeding practices, offering the first national perspective that highlights territorial disparities. The findings emphasize the need for targeted interventions, particularly in light of identified regional and socio-economic differences.

Key words

- surveillance
- breastfeeding
- exclusive breastfeeding
- health promotion

INTRODUCTION

Breastfeeding (BF) is the normal way to feed the newborn and offers positive implications for both the baby's and the mother's health [1-3]. It is the biological norm, the most sustainable practice [4], and is a right of both mother and child [5].

Based on consolidated evidence, the World Health Organization (WHO) and the United Nations International Children's Emergency Fund (UNICEF) recommend exclusive breastfeeding (EBF) for the first 6 months of life and, after introducing nutritionally adequate and safe complementary food, continuing BF up to 2 years of life or beyond. In 2003, the World Health Assembly and the UNICEF Executive Board unanimously endorsed the "global strategy for infant and young child feeding" [6]. Subsequently, the "global strategy for women's, children's and adolescents' health" was confirmed, urging member states to adopt and implement national policies and comprehensive, large-scale programs to protect, promote, and support adequate infant and young child feeding, as well as maternal nutrition practices [7].

Address for correspondence: Francesca Zambri, Centro Nazionale per la Prevenzione delle Malattie e la Promozione della Salute, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy. Email: francesca.zambri@iss.it.

Enhancing breastfeeding is a key factor for the achievement of the United Nations' Sustainable Development Goals [8] and constitutes a fundamental component of the nurturing care framework [9]. In 2012, WHO identified six global nutrition targets to be achieved by 2025. One of these objectives is to increase the rate of EBF during the first 6 months to a minimum of 50% [10]. In 2021, a more ambitious target of at least 70% was proposed by WHO and UNICEF [11]. These goals represent a priority for the national health systems, recognizing that BF is one of the most impactful interventions, "providing short-term and long-term health and economic and environmental advantages to children, women, and society" [12].

Despite being a public health and early childhood development (ECD) priority, in 2022, only 46% of infants started breastfeeding within the first hour after birth globally, and 48% of all babies under 6 months of age were exclusively breastfed. At 2 years, 59% of children were still breastfed [13].

The WHO European Region has the lowest prevalence of EBF. In 2006-2012, it was estimated that only 25% of infants were exclusively breastfed for 6 months [14]. This low prevalence is confirmed in other high-income countries [15].

International organizations and communities have undertaken various initiatives to protect, promote and support BF [16]. However, the lack of updated and standardized data, both between and within countries, does not permit appropriate monitoring and comparison of BF practices, nor does it allow for the evaluation of the effectiveness of interventions [17]. Standard indicators to monitor breastfeeding have existed since the 1990s, and the WHO has provided guidance for monitoring BF practices since 2008. In 2021, WHO/UNICEF published an updated guidance providing a set of revised indicators for assessing infant and young child feeding practices, with their definitions and measurement methods [18]. Despite this, full adherence to these standards has not yet been achieved [19]. The need to improve the standard methodology for monitoring and collecting BF data has been recognized as a critical issue [15]. More recently, considering the high number of countries (mostly high-income countries) which have no data on EBF collected according to international standards, WHO/UNICEF, in collaboration with the global breastfeeding collective, have set a target for 75% of countries to report on EBF at least every five years by 2030 [20]. They also call on civil society to take seven actions, one of which is to "strengthen monitoring systems that track the progress of policies, programs, and funding towards achieving both national and global breastfeeding targets" [21]. The World Breastfeeding Trend Initiative (WBTi) process advocates repeat assessment every 3-5 years [22].

In Italy, the protection, promotion, and support of BF is a goal that has been part of the national policies for over 25 years [23, 24]. The Italian National Institute of Statistics collected data in 2000 and 2013 through telephone interviews with women who had given birth during the previous 5 years. The percentage of women who had breastfed, regardless of duration, increased from 81.1% to 85.5% and the average duration of any breastfeeding increased from 6.2 to 8.3 months [25]. From two follow-up studies conducted during 2008-2011 [26] in selected populations, BF and EBF rates were estimated respectively at discharge, at 3 and 6 months (BF rates: 91.6%, 71.6%, 57.7%; EBF rates: 57.2%, 48.6%, 5.5%). Since then, the available estimates of BF seem to be far from WHO/UNICEF goals and show important differences in geographical and social determinants, which need to be addressed to reduce social and health inequalities [27].

In recent years, a national "surveillance system for the main determinants of health in children aged 0-2 years" (surveillance of children aged 0-2 years), promoted by the Ministry of Health and coordinated by the Italian National Institute of Health, (Istituto Superiore di Sanità, ISS) has been implemented.

The surveillance enabled collection of information on breastfeeding according to WHO/UNICEF criteria through sample surveys conducted in the vaccination centers (VCs) in Italian regions.

The previous pilot study, conducted in 13 local health districts (Distretti Sanitari) across six Italian regions between February and November 2015, revealed EBF prevalence rates of 44.4% among infants aged 2-3 months and 25.8% among those aged 4-5 months. In 2015, BF prevalence in the 11-12 months and 13-15 months age groups was 34.2% and 24.9% respectively, while 10.4% of children were never breastfed. Relevant geographical and socio-economic differences were found [28]. The first round of surveillance conducted in 2018-19 across 11 regions showed that the percentage of EBF among children aged 4-5 months was 23.7%, and at 12-15 months BF was 31.3%. The proportion of children who had never been breastfed was 11.7% [29].

The aim of this paper was to measure the prevalence of EBF, BF and never breastfed (NBF) according to WHO/UNICEF criteria using data from the 2022 surveillance of children aged 0-2 years. The paper also aims to assess factors associated with EBF, BF and NBF.

MATERIALS AND METHODS

The population-based surveillance of children aged 0-2 years was based on cross-sectional sample surveys repeated at regular intervals among mother-child pairs recruited during compulsory vaccination appointments in the Italian regions. The target population was mothers of children up to 2 years of age taken to VCs to receive immunizations. Mothers were enrolled in all the VCs of the regions when one of the following vaccine doses was administered to their children: first, second, third dose of mandatory vaccine against Diphtheria, Tetanus and Pertussis (DTP) or hexavalent vaccine (against Diphtheria, Tetanus, Pertussis, Poliomyelitis, *Haemophilus influenzae* type B, and Hepatitis B), and first dose of the vaccine against Measles, Mumps, Rubella, Varicella (MMRV). Four independent samples were selected within each region in correspondence of the four doses administered at approximately ages 2-3 months, 4-5 months, 11-12 months, and 13-15 months according to the Italian vaccination schedule. Data were collected through an anonymous questionnaire

compiled by mothers with the assistance of trained health professionals involved in the administration of the vaccines. The questionnaire collected information on several important determinants of children's health, including breastfeeding. Demographic and socio-economic characteristics of participants were also collected. A more detailed description of the surveillance methodology is reported in *Appendix 1*.

APPENDIX 1

SURVEILLANCE OF CHILDREN AGED 0-2 YEARS

BACKGROUND

The "surveillance system for the main determinants of health in children aged 0-2 years" – surveillance of children aged 0-2 years – is promoted by the Ministry of Health and coordinated by the Italian National Institute of Health (Istituto Superiore di Sanità, ISS, Rome, Italy) in collaboration with the Italian regions. The population-based surveillance was included among those of national and regional relevance identified by the Prime Minister's Decree of 2017 on "registers and surveillance" [1]. The implementation of the surveillance was preceded by a pilot study, promoted and financed by the National Centre for Disease Prevention and Control – Centro Nazionale per la Prevenzione e il Controllo delle Malattie (CCM) – of the Italian Ministry of Health, conducted in 13 selected local health districts of 6 Italian regions in 2014 [2] to test a surveillance system of the main determinants of health in children aged 0-2 years included in the National Programme "GenitoriPiù" [3].

The first round, carried out in 2018-19, involved 11 regions mainly from the South Italy [4]. The second round was conducted in 2022 and involved all of Italy's 21 regions with the exception for the Region of Molise and the autonomous province of Bolzano (the Molise Region had difficulty starting the data collection while the autonomous province of Bolzano was unable to complete it). The Region of Tuscany participated by sharing results of its ongoing maternity care survey.

METHOD

Sample

The surveillance is based on cross-sectional sample surveys repeated at regular intervals among mother-child pairs recruited during compulsory vaccination appointments in the Italian regions. The target population is mothers of children up to 2 years of age taken to vaccination centers (VCs) to receive immunizations. Mothers are enrolled at all the VCs of the regions when one of the following vaccine doses is administered to their children: first, second, third dose of mandatory vaccine against Diphtheria, Tetanus and Pertussis (DTP) or hexavalent vaccine (against Diphtheria, Tetanus, Pertussis, Poliomyelitis, *Haemophilus influenzae* type B, and Hepatitis B), and first dose of the vaccine against Measles, Mumps, Rubella, Varicella (MMRV). Four independent samples are selected within each region in correspondence of the four doses that are administered, according to the Italian vaccination schedule, at approximately ages 2-3 months, 4-5 months, 11-12 months and 13-15 months. A pseudo-random procedure is used to select children: starting at the beginning of the survey period, all eligible children are selected until the desired sample size is reached. Only children accompanied by their mothers are included in the survey. In the case of twins, mothers are requested to provide information only for the first child vaccinated. No other exclusion criteria are applied. The sample sizes are calculated based on an assumed maximum variability of the phenomenon being investigated, with a population proportion set at 50%, a margin of error of either 5% or 3% (depending on the choice of the region) and a confidence level of 95%. Finite population correction is applied because the sample size is relatively large compared to the population size, which is represented by the number of births in the year preceding the survey. The samples are representative of either the region or – with an expanded sample size – of local health units (depending on the choice of the region).

Data collection

Data are collected through an anonymous questionnaire compiled by the mothers with the assistance of trained health professionals involved in administering vaccines. The surveillance collects information on the following health determinants of children starting before conception through the first years of life: folic acid intake before and during pregnancy, tobacco and alcohol consumption during pregnancy and lactation, breastfeeding practices, infant sleep positions, family reading habits, exposure of children to screens (tablet, mobile phone, TV, computer), home and car safety measures, and mother's attitudes towards vaccination. Demographic and socio-economic characteristics of the participants are also collected. The questionnaire undergoes review at each data collection phase, allowing for the inclusion of new survey areas.

The questionnaire, available in multiple languages, can be completed either as a paper survey or online using personal devices such as mobile phones or tablets, or on devices provided by the VC during the waiting periods before or after vaccination sessions. Each mother is interviewed only once; therefore, those who have already participated in a previous vaccination appointment for the same child or another child are excluded. After the interview, all participating or non-participating mothers receive an information leaflet detailing the health determinants in children 0-2 years and their families. Responses to the questionnaires are

acquired through a dedicated platform. The construction of the database, the cleaning of the records, and the subsequent data analysis are carried out centrally by the coordination group.

ETHICS AND PRIVACY

Before data collection, mothers receive an information note with a description of the purpose of the survey. They can decline participation, with operators recording refusal on a designated sheet. After providing verbal consent to participate in the study, mothers receive information about privacy regulations including the processing of their personal data before completing either the digital or paper questionnaire. In accordance with principles of anonymity and privacy, respondents' identity is never disclosed. The surveillance system study protocol and questionnaire were formally approved by the National Ethics Committee for clinical trials of public research bodies of the Italian National Institute of Health (Istituto Superiore di Sanità, ISS) (Prot. n. PRE-4255 - 20/10/2014; Prot. n. PRE-BIO-CE 10939 - 06/04/2018; Prot. n. 0015067 PRE BIO – 19/04/2022).

REFERENCES

1. Italia. Decreto del Presidente del Consiglio dei Ministri (DPCM) 3 marzo 2017. Identificazione dei sistemi di sorveglianza e dei registri di mortalità, di tumori e di altre patologie. Gazzetta Ufficiale – Serie Generale n. 109, 12 maggio 2017.
2. Pizzi E, Spinelli A, Battilomo S, Azzarito C, Balducci MT, Bettinelli ME, Campostrini S, Germinario C, Mazzarella G, Mignuoli AD, Morbidoni M, Porchia S, Simeoni L, Speri L; Gruppo sorveglianza bambini 0-2 anni. I determinanti di salute nella prima infanzia: la sperimentazione di un nuovo sistema di sorveglianza in Italia. Epidemiol Prev. 2019;43(1):66-70.
3. Speri L, Gangemi M. GenitoriPiù compie 10 anni. Quaderni ACP. 2016;23(2):50.
4. Pizzi E, Salvatore AM, Donati S, Andreozzi S, Battilomo S, Privitera MG (Eds). Il sistema di sorveglianza bambini 0-2 anni finalità, metodologia e risultati della raccolta dati 2018-2019. Roma: Istituto Superiore di Sanità; 2022.

The present study used data from the second round of the surveillance, conducted between June and October 2022, involving 35,550 mothers enrolled in all of the 21 Italian regions, except for the Region of Molise and the autonomous province of Bolzano, who did not participate in the surveillance (the Molise Region had difficulty starting the data collection while the autonomous province of Bolzano was unable to complete it), and Region of Tuscany, who shared results of its ongoing maternity care survey. This ensured an adequate representation of the three areas of the country – North, Centre, and South – notoriously characterized by different maternal care outcomes. The response rate was 95.7%, ranging between 89.2% and 98.6% at the regional level. From the overall sample, specific age groups were selected for the analysis of breastfeeding irrespective of the administered vaccine dose (*Table S1, available online as Supplementary Material)*.

Outcome

EBF, BF and NBF were included in the analysis as outcome variables. According to WHO/UNICEF criteria, information on breastfeeding was collected for the previous 24 hours [18]. Children under six months who had only consumed breastmilk were classified as exclusively breastfed (EBF), children who had received breastmilk with other food or liquids, including formula, were classified as breastfed (BF). Participants who had not breastfed in the previous day were asked if they had ever breastfed to identify cases that had never received breastmilk (NBF). EBF under six months was analysed in the 2-3 month and 4-5 month age groups. BF was analysed in the same age groups and, to evaluate continued breastfeeding after the first year of life, among children aged 12-15 months. Age groups were considered as intervals of months completed and corresponded to or approximated those suggested by WHO/UNICEF.

Covariates

The following socio-economic characteristics were included as potential risk factors in accordance with previous studies [21]: mother's age (<30, 30-34, ≥35 years), citizenship (Italian, not Italian), educational level (low, middle school or lower; medium, high school; high, bachelor's degree or higher), perceived economic difficulties (no, some/many), parity (primiparous, multiparous), attendance at an antenatal class (AC) (yes, never), and geographical area of residence (North, Central, and South Italy).

Statistical analysis

Frequency distributions, prevalence rates and odds ratios (ORs) with 95% confidence intervals (CIs) were used to describe data. Percentages were calculated based on cases with available information, excluding missing values.

Frequency distributions by socio-economic characteristics of mothers participating in the study were computed by geographical area of residence. The prevalence rates of EBF and BF stratified by geographical area were calculated at different children's ages while NBF was considered across all age groups 2-15 months.

To show the effect on the estimates of different age distributions of children in the three areas, directed age standardization was applied to EBF and BF prevalence rates based on 10 days' age groups, by using the overall population sampled as a standard. The children's age in the questionnaire was reported in completed months plus days. However, due to a high percentage of missing values regarding the number of days, standardization

could only be conducted for cases where complete age information was available.

Adjusted ORs were estimated through multiple logistic regression models to explore factors associated with the occurrence of EBF at 4-5 months of age, BF at 12-15 months and NBF. Statistical analyses were performed using STATA/SE version 18.0 statistical software.

RESULTS

The socio-economic characteristics of women participating in the study are reported in *Table 1*. Overall, 43.5% of them were aged ≥35 years with no relevant differences across the different geographical areas. Similar to the general population in Italy, the percentage of women with foreign citizenship, as well as that of more-educated women, were higher in the North and the Centre compared to the South. Conversely, women reporting economic difficulties and those who never attended an AC were more prevalent in the South.

The percentage of EBF among children aged 2-3 months varied from 36.4% in the Southern regions to 54.0% in the North (*Table 2*). The percentages decreased at 4-5 months: ranging between 19.6% (South) and 35.8% (North). When considering any BF, the percentage ranged between 63.9% (South) and 77.6% (North) in the 2-3 month age group, and between 52.3% (South) and 67.6% (North) in the 4-5 month age group. Age standardization applied to prevalence calculated among cases where age information was available in completed months plus days had negligible effects as shown by comparing standardized estimates of EBF and BF with unstandardized estimates calculated for the same cases (*Table S2, available online as Supplementary Material*).

Regarding BF over one year of age, about 3 out of 10 children aged 12-15 months in the Southern regions were reported as still receiving breastmilk, whereas in the Centre and the North the figure was about 4 out of 10 (*Table 2*). The percentage of NBF, estimated among children aged 2-15 months, ranged from 10.3% in the Centre to 14.4% in the South. Even for these indicators, standardization had minimal impact on the estimates (*Table S2, available online as Supplementary Material*).

Table 1
Women's characteristics grouped by geographical area of residence

Variables	Geographical area of residence			
	North (N=16,318)	Centre (N=5,820)	South (N=13,412)	Total (N=35,550)
Age				
≤29 years	20.9	19.4	23.3	21.5
30-34 years	36.4	33.8	33.8	35.0
≥35 years	42.8	46.8	42.9	43.5
Missing	*5.9*	*4.8*	*5.3*	*5.5*
Citizenship				
Italian	82.7	84.6	95.3	87.8
Not Italian	17.3	15.4	4.7	12.2
Missing	*5.7*	*4.3*	*4.7*	*5.1*
Educational level*				
Low	13.9	11.6	17.1	14.8
Medium	43.0	42.0	49.7	45.4
High	43.1	46.4	33.2	39.9
Missing	*5.9*	*4.4*	*3.9*	*4.9*
Economic difficulties				
None	70.1	64.4	60.4	65.5
Some/many	29.9	35.6	39.6	34.5
Missing	*5.5*	*4.3*	*3.7*	*4.6*
Parity				
Primiparous	53.9	56.4	53.6	54.2
Multiparous	46.1	43.6	46.4	45.8
Missing	*7.1*	*6.7*	*9.2*	*7.8*
Attendance of an AC				
Never	28.2	33.5	54.1	38.8
Yes	71.8	66.5	45.9	61.2
Missing	*4.6*	*3.6*	*4.0*	*4.2*

AC: antenatal class; *low: middle school or lower; medium: high school; high: bachelor's degree or higher.

Table 2
Prevalence rates of exclusive breastfeeding (EBF), any breastfeeding (BF) and never breastfed (NBF) at different ages by geographical area of residence

Geographical area of residence	Children aged 2-3 months			Children aged 4-5 months			Children aged 12-15 months		Children aged 2-15 months	
		EBF	BF		EBF	BF		BF		NBF
	n	%	%	n	%	%	n	%	n	%
North	3,173	54.0	77.6	5,308	35.8	67.6	4,011	39.6	12,492	11.5
Centre	1,402	48.9	75.1	1,128	32.7	65.1	1,537	40.8	4,067	10.3
South	3,847	36.4	63.9	2,378	19.6	52.3	3,342	29.2	9,567	14.4
Total	8,422	46.7	72.2	8,814	30.0	62.2	8,890	36.2	26,126	12.3

Table 3 shows prevalence rates stratified by socio-economic characteristics and adjusted ORs for three indicators: EBF at 4-5 months, BF at 12-15 months and NBF. Women who were significantly less likely to exclusively breastfeed their children at 4-5 months included those aged ≥35 years (OR=0.73; 95% CI: 0.61-0.86), with Italian citizenship (OR=0.72; 95% CI: 0.59-0.87), having a lower educational level (medium: OR=0.60; 95% CI: 0.52-0.68; low: OR=0.42; 95% CI: 0.34-0.52), reporting economic difficulties (OR=0.79;

Table 3
Prevalences and mutually adjusted odds ratios for the reported variables. Logistic regression models

Variables	Model 1 Exclusive breastfeeding at 4-5 months (Yes *vs* No)				Model 2 Any breastfeeding at 12-15 months (Yes *vs* No)				Model 3 Never breastfed at 2-15 months (Yes *vs* No)			
	N=8,074				N=8,090				N=23,900			
	% EBF	OR	95% CI		% BF	OR	95% CI		% NBF	OR	95% CI	
Age												
≤29 years	27.8	1			32.3	0.84	0.71	0.99	11.7	1		
30-34 years	32.6	0.98	0.83	1.16	37.9	1.08	0.95	1.22	10.8	1.06	0.91	1.22
≥35 years	29.3	0.73	0.61	0.86	36.6	1			13.9	1.52	1.32	1.75
Citizenship												
Not Italian	32.9	1			56.9	1			7.6	1		
Italian	29.7	0.72	0.59	0.87	33.5	0.32	0.27	0.39	13.0	2.28	1.87	2.80
Educational level*												
Low	19.0	0.42	0.34	0.52	35.9	0.85	0.70	1.03	16.8	2.07	1.76	2.43
Medium	25.7	0.60	0.52	0.68	33.0	0.79	0.70	0.90	13.6	1.55	1.37	1.75
High	39.1	1			39.9	1			9.5	1		
Economic difficulties												
None	32.9	1			37.1	1			12.0	1		
Some/many	24.4	0.79	0.69	0.91	34.2	0.91	0.81	1.03	13.1	0.99	0.89	1.10
Parity												
Multiparous	32.9	1			36.9	1			12.6	1		
Primiparous	28.8	0.72	0.64	0.82	35.8	1.00	0.89	1.12	12.1	1.06	0.96	1.18
Attendance of an AC												
Yes	36.0	1			39.0	1			10.4	1		
Never	20.5	0.58	0.51	0.67	31.5	0.70	0.62	0.80	15.5	1.52	1.36	1.71
Geographical area of residence												
North	35.8	1			39.6	1			11.5	1		
Centre	32.7	0.93	0.78	1.12	40.8	1.10	0.95	1.29	10.3	0.82	0.70	0.96
South	19.6	0.57	0.49	0.65	29.2	0.78	0.68	0.88	14.4	0.99	0.89	1.12

AC: antenatal class; EBF: exclusive breastfeeding; BF: any breastfeeding; NBF: never breastfed; *low: middle school or lower; medium: high school; high: bachelor's degree or higher.

95% CI: 0.69-0.91), primiparous women (OR=0.72; 95% CI: 0.64-0.82), those who never attended an AC (OR=0.58; 95% CI: 0.51-0.67), and those residing in Southern Italy (OR=0.57; 95% CI: 0.49-0.65).

Italians (OR=0.32; 95% CI: 0.27-0.39), women who never attended an AC (OR=0.70; 95% CI: 0.62-0.80) and those residing in the South (OR=0.78; 95% CI: 0.68-0.88), along with younger women (OR=0.84; 95% CI: 0.71-0.99), were also significantly less likely to breastfeed at 12-15 months.

Women who were significantly more likely to have never breastfed their children were those aged ≥35 years, with Italian citizenship, having a lower level of education, and those who never attended an AC.

DISCUSSION

This manuscript has introduced, for the first time, breastfeeding prevalence rates calculated on a representative sample of mothers covering almost the entire country in Italy. The surveillance of children aged 0-2 years also provided a comprehensive overview of factors associated with breastfeeding practices.

Collecting data on breastfeeding prevalence through a national system shows multiple strengths. The surveillance data were collected during vaccination appointments, which are scheduled according to the Italian National Vaccination Plan [30]. In 2021, vaccination coverage was 94% for the first dose and 92-94% [31] for the second, making vaccination appointments a strategic, consolidated, and efficient opportunity for collecting data, especially since the proportion of mothers who either do not vaccinate their children or choose to vaccinate with their pediatrician instead a VC, remains low. Moreover, adherence to vaccinations is homogeneous, and less affected by regional variability or the north-south gradient that characterizes other health indicators in pregnancy, childbirth, and early childhood. Utilizing vaccination appointments for data collection emphasizes the integration of health determinants, of which breastfeeding is a part, and highlights the efficiency of leveraging existing healthcare infrastructures for surveillance as a means of sustainability.

Despite recommendations from WHO and other international agencies, exclusive breastfeeding rates in Italy remain below target levels, highlighting regional and socioeconomic disparities. The average prevalence of EBF at 2-3 months in the pool of regions participating in the surveillance is 46.7%, dropping to 30.0% at 4-5 months. This rate appears to align Italy with the levels observed in other European countries, although direct comparisons are challenging due to variations in the timing and methods of data collection [13]. The observed prevalence and duration of exclusive breastfeeding reflect a broader trend of increased adherence to early childhood best practices (such as reading out loud to infants and children, proper sleep positioning, car safety, and protection from alcohol and tobacco) in northern regions compared to southern regions [27]. There is also an issue of missed or denied opportunities for a significant number of mothers, children and fathers/partners, that go beyond mothers' informed choices about breastfeeding.

The profile of mothers – and babies – who breastfeed sub-optimally or do not breastfeed highlights some classic drivers of inequality, such as educational and economic levels and geographic location. Overall, non-Italian mothers are more likely to breastfeed compared with native Italians. As reported by Marchetti *et al.*, this might confirm that the "healthy migrant effect" also applies to breastfeeding practices in Italy and that, "in the absence of substantial policies for the protection, promotion and support of breastfeeding, the "exhausted migrant" effect is to be expected in the coming years" [32].

To improve maternal and child health, targeted interventions are needed at multiple levels. It is essential to implement and expand national breastfeeding protection, promotion and support policies, particularly in regions with lower EBF rates. These policies should include evidence-based awareness programs aimed at mothers, fathers/partner and healthcare providers, with a focus on reducing inequalities. Improving access to antenatal classes which have been confirmed as a positive determinant of breastfeeding [33], along with postnatal support groups (such as peer support groups) and community family services, can help sustain breastfeeding, as can expanding coverage of the Baby-Friendly Hospital and Community Initiatives. Another crucial aspect is enhancing parental leave policies, aligning the length of maternity leave with WHO recommendations to support exclusive breastfeeding for six months. Extending paternity leave – which in Italy currently provides only 10 days – would further encourage fathers' involvement in supporting breastfeeding. The neonatal discharge summaries (NCDs) are another important tool for supporting mothers during breastfeeding. Several studies in the Region of Lazio found that some neonatal discharge summaries (NDSs) reported information on infant feeding practices, but in most cases the prescription of formula for breastfeeding mothers was recommended even with no medical indication [34]. The NDSs are a tool, but not the only one, for supporting mothers during breastfeeding and, for this reason, further efforts to reduce their prescriptive attitudes and level of medicalization is required. Prioritizing these interventions in southern regions, where EBF rates are particularly low, should be a key focus.

The role, whether positive or negative, that the healthcare system can play in influencing the decision to start and continue breastfeeding is well-documented [35]. A study conducted in Italy on the Baby-Friendly Hospital network has demonstrated that a highly-structured, evidence-based care model, performed better in some of the WHO/UNICEF standards during the COVID-19 emergency [36]. Nevertheless the geographical distribution of the Baby-Friendly Initiative in Italy is uneven and predominantly concentrated in the northern regions (https://www.unicef.it/italia-amica-dei-bambini/mappa-italia-amica/), as is the provision of community maternity services (e.g., family care centres) offering AC, post-natal support, and mother-to-mother/parents support groups. In addition, and, considering the crucial role of fathers in supporting and bonding with their child, the 10 days currently allotted at birth are clearly inadequate.

Among the limitations of the surveillance of children aged 0-2 years is the lack of data on breastfeeding initiation. This absence makes it more challenging to speculate on and identify the structural factors that affect the initiation, exclusivity, and duration of breastfeeding. In Italy, a data collection system at birth is mandatory, and the birth register (CeDAP, *certificato di assistenza al parto*) provides population-based routine data [37]. It represents data readily available to assess the implementation of best practices in pregnancy and childbirth. However, while this could be the most efficient and sustainable method to measure the "initiation of breastfeeding" indicator, it presents several significant challenges, as described in previous studies [38]. The first concerns the heterogeneity of the data collection tool, as not all regions have included information on breastfeeding at birth. Additionally, not all regions use WHO/UNICEF standard questions, and, as for the timing of data collection, the information is insufficient for the "early initiation of breastfeeding" and "exclusive breastfeeding for the first 2 days after birth" indicators. Finally, the current CeDAP data collection system at birth does not allow for the construction of a comprehensive indicator of neonatal feeding throughout the entire hospital stay, an indicator used in the accreditation of Baby-Friendly Hospitals, which is coordinated by the Italian National Committee for UNICEF in Italy. As a general recommendation, enhancing the timing of data collection at the point of discharge to capture comprehensive and accurate breastfeeding data, training healthcare personnel to accurately define and report different modes of infant feeding (exclusive breastfeeding, predominant breastfeeding, complementary feeding, and formula feeding), and implementing a procedure for record linkage between different routine data could provide more comprehensive information on breastfeeding indicators and underlying drivers.

The surveillance of children aged 0-2 years is a robust, reliable, and sustainable tool for the estimation of breastfeeding prevalence, however some indicators are not yet being adequately measurable according to standard international time frames [13]. While it respects WHO/UNICEF methodology that involve a 24-hour recall period, because the data collection occurs following the vaccination schedule, the surveillance does not allow for the proper alignment of indicators with all those defined by the WHO/UNICEF [19]. Nevertheless, the availability of breastfeeding data provided by the surveillance – the only source of robust national data – has enabled the inclusion of the exclusive breastfeeding indicator at 4-5 months within the set of perinatal indicators used by the National Observatory of Good Practices on Safety in Healthcare of Italian National Agency for Regional Healthcare Services (AGENAS, *Agenzia Nazionale per i Servizi Sanitari Regionali*) [39].

CONCLUSIONS

The data underscore the gap between recommendations and actual breastfeeding practices, offering the first-ever national perspective, and highlighting territorial disparities. Despite a long-standing commitment to breastfeeding promotion and the implementation of several national policies, breastfeeding prevalence rates remain low, associated with socio-economic and geographical determinants, perpetuating inequalities in future generations [1]. The findings highlight the necessity for targeted, evidence-based interventions, particularly in light of identified regional and socio-economic variations.

While the Italian surveillance system provides valuable insights into breastfeeding practices, there is a clear need for enhancements in data collection and policy support to bridge the gap between recommendations and actual practices. Addressing these gaps, requires a concerted effort from policymakers, healthcare providers, and community support systems to create an environment that fosters breastfeeding, recognizing its foundational role in public health and social equity.

Funding

The surveillance of children aged 0-2 years is funded by the Italian National Institute of Health (Istituto Superiore di Sanità – ISS).

Acknowledgments

We thank all the mothers who were willing to complete the questionnaire. We thank all the Regional and local health unit coordinators and all the professionals involved in the survey for their valuable work. Our sincere gratitude to the surveillance of children aged 0-2 years Scientific Technical Committee for their contribution to the definition of methodological aspects and critical reading of the results.

Surveillance of children aged 0-2 years information

All information on surveillance of children aged 0-2 years can be requested to the principal investigator, Dr. Enrica Pizzi enrica.pizzi@iss.it. For further information, please see https://www.epicentro.iss.it/sorveglianza02anni/.

Ethical approval

The surveillance of children aged 0-2 years study protocol and questionnaire were formally approved by the National Ethics Committee for clinical trials of public research bodies of the Italian National Institute of Health (Istituto Superiore di Sanità – ISS) (Prot. n. PRE-4255 - 20/10/2014; Prot. n. PRE-BIOCE 10939 - 06/04/2018; Prot. n. 0015067 PRE BIO – 19/04/2022).

Authors' contributions

EP, MAS conceptualized and designed the study. MAS analysed the data. EP, MAS, AG, FZ wrote the first draft. SD, LS, EMC critically re-viewed the manuscript. All Authors have revised the manuscript and approved its final version.

Conflicts of interest statement

None of Authors declare competing financial interests.

Members of the 2022 SURVEILLANCE OF CHILDREN AGED 0-2 YEARS Group

Enrica Pizzi, Serena Donati, Michele Antonio Salvatore, Laura Lauria, Mauro Bucciarelli, Silvia Andreozzi, Claudia Ferraro, Monica Pirri (Istituto Superiore di Sanità, Rome, Italy), Maria Grazia Privitera, Renata Bortolus (Ministero della Salute, Rome, Italy), Manuela Di Giacomo (Regione Abruzzo), Maria Angela Mininni (Regione Basilicata), Anna Domenica Mignuoli, Dario Macchioni (Regione Calabria), Gianfranco Mazzarella (Regione Campania), Simona Di Mario (Regione Emilia Romagna), Luca Ronfani, Luisella Giglio, Claudia Carletti, Federica Concina, Alessandra Knowles, Paola Pani (Regione Friuli Venezia Giulia), Lilia Biscaglia, Maria Gabriella Calenda, Patrizia Proietti, Daniela Porta (Regione Lazio), Camilla Sticchi, Laura Pozzo (Regione Liguria), Corrado Celata, Fabio Mosca, Edda Pellegrini (Regione Lombardia), Marco Morbidoni, Annalisa Cardone, Antonella Guidi, Cristina Mancini (Regione Marche), Michele Colitti (Regione Molise), Marcello Caputo, Vittorina Buttafuoco (Regione Piemonte), Anna Pedrotti, Maria Grazia Zuccali, Laura Battisti (Provincia Autonoma di Trento), Sabine Weiss (Provincia Autonoma di Bolzano), Maria Teresa Balducci, Nehludoff Albano, Mariangela Dafne Vincenti (Regione Puglia), Maria Antonietta Palmas, Noemi Mereu (Regione Sardegna), Maria Paola Ferro, Patrizia Miceli (Regione Sicilia), Anna Ajello (Regione Toscana), Manila Bonciani (Scuola S. Anna, Pisa), Anna Maria Covarino, Enrico Ventrella (Regione Valle d'Aosta), Federica Michieletto, Anna Sabbadin, Diana Gazzani (Regione del Veneto).

Received on 20 June 2024.
Accepted on 12 November 2024.

REFERENCES

1. Victora CG, Bahl R, Barros AJ, França GV, Horton S, Krasevec J, Murch S, Sankar MJ, Walker N, Rollins NC. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. The Lancet. 2016;30;387(10017):475-90. doi: 10.1016/S0140-6736(15)01024-7
2. Ip S, Chung M, Raman G, Chew P, Magula N, DeVine D, Trikalinos T, Lau J. Breastfeeding and maternal and infant health outcomes in developed countries. Evid Rep Technol Assess (Full Rep). 2007;(153):1-186.
3. Rito AI, Buoncristiano M, Spinelli A, Salanave B, Kunešová M, Hejgaard T, García Solano M, Fijałkowska A, Sturua L, Hyska J, Kelleher C, Duleva V, Musić Milanović S, Farrugia Sant'Angelo V, Abdrakhmanova S, Kujundzic E, Peterkova V, Gualtieri A, Pudule I, Petrauskienė A, Tanrygulyyeva M, Sherali R, Huidumac-Petrescu C, Williams J, Ahrens W, Breda J. Association between characteristics at birth, breastfeeding and obesity in 22 countries: The WHO European childhood obesity surveillance initiative – COSI 2015/2017. Obesity Facts. 2019;12(2):226-43. doi: 10.1159/000500425
4. Long A, Mintz-Woo K, Daly H, O'Connell M, Smyth B, Murphy JD. Infant feeding and the energy transition: A comparison between decarbonising breastmilk substitutes with renewable gas and achieving the global nutrition target for breastfeeding. Journal of Cleaner Production. 2021;324:129280. doi: 10.1016/j.jclepro.2021.129280
5. Del Ciampo LA, del Ciampo IRL. Breastfeeding and the benefits of lactation for women's health. Rev Bras Ginecol and Obstet. 2018;40(6):354-9. doi: 10.1055/s-0038-1657766
6. World Health Organization, UNICEF. Global strategy for infant and young child feeding. Geneva: WHO; 2003. Available from: https://www.who.int/publications/i/item/9241562218.
7. World Health Organization. The global strategy for women's, children's and adolescents' health (2016-2030). Geneva: WHO; 2015. Available from: https://platform.who.int/data/maternal-newborn-child-adolescent-ageing/global-strategy-data.
8. United Nations. Transforming our World: the 2030 Agenda for Sustainable Development. New York: United Nations; 2015. Available from: https://www.un.org/sustainabledevelopment/sustainable development-goals.
9. World Health Organization, United Nations Children's Fund, World Bank Group. Nurturing care for early childhood development: a framework for helping children survive and thrive to transform health and human potential. Geneva: WHO; 2018.
10. World Health Organization. Global nutrition targets 2025: policy brief series (WHO/NMH/NHD/14.2). Geneva: World Health Organization; 2014. Available from: https://www.who.int/publications/i/item/WHO-NMH-NHD-14.2.
11. World Health Organization, UNICEF. The extension of the 2025 maternal, infant and young child nutrition targets to 2030: WHO/UNICEF discussion paper. Geneva: WHO; 2021. Available from: https://data.unicef.org/resources/extension-of-2025-maternal-infant-young-child-nutrition-targets-2030/.
12. Rollins NC, Bhandari N, Hajeebhoy N, Horton S, Lutter CK, Martines JC, Piwoz EG, Richter LM, Victora CG; Lancet breastfeeding series Group. Why invest, and what it will take to improve breastfeeding practices? Lancet. 2016;387(10017):491-504. doi: 10.1016/S0140-6736(15)01044-2
13. United Nations Children's Fund (UNICEF). Breastfeeding. Too few children benefit from recommended breastfeeding practices. New York: UNICEF; 2023. Available from: https://data.unicef.org/topic/nutrition/breastfeeding/.
14. Bagci Bosi AT, Eriksen KG, Sobko T, Wijnhoven TM, Breda J. Breastfeeding practices and policies in WHO European region member states. Public Health Nutr. 2015;22:1-12. doi: 10.1017/S1368980015001767
15. Vaz JS, Maia MFS, Neves PAR, Santos TM, Vidaletti LP, Victora C. Monitoring breastfeeding indicators in high-income countries: Levels, trends and challenges. Matern Child Nutr. 2021;17(3):e13137. doi: 10.1111/mcn.13137
16. United Nations Children's Fund (UNICEF). The Baby Friendly Initiative. New York: UNICEF; 2022. Available from: https://www.unicef.org/documents/baby-friendly-hospital-initiative.
17. Gupta PM, Perrine CG, Chen J, Elam-Evans LD, Flores-Ayala R. Monitoring the world health organization global target 2025 for exclusive breastfeed-

ing. J Hum Lact. 2017;1:890334417693210. doi: 10.1177/0890334417693210

18. World Health Organization, United Nations Children's Fund (UNICEF). Indicators for assessing infant and young child feeding practices: definitions and measurement methods. Geneva: WHO and the UNICEF; 2021.
19. Khanal V, Lee AH, Scott JA, Karkee R, Binns CW. Implications of methodological differences in measuring the rates of exclusive breastfeeding in Nepal: findings from literature review and cohort study. BMC Pregnancy Childbirth. 2016;16(1):389. doi: 10.1186/s12884-016-1180-9
20. World Health Organization, United Nations Children's Fund (UNICEF). Tracking progress for breastfeeding policies and programmes. Geneva: WHO; 2017. Available from: https://www.who.int/publications/m/item/global-breastfeeding-scorecard-2017-tracking-progress-for-breastfeeding-policies-and-programmes.
21. World Health Organization, United Nations Children's Fund (UNICEF). A global breastfeeding call to action. Geneva: WHO; 2017. Available from: https://www.who.int/publications/m/item/global-breastfeeding-collective--a-call-to-action.
22. Gupta A, Nalubanga B, Trejos M, Dadhich JP, Bidla N. Making a difference - An evaluation report of the World Breastfeeding Trends Initiative (WBTi) in mobilising national actions on breastfeeding and IYCF. Breastfeeding Promotion Network of India and IBFAN South Asia. Pitampura: WBTi; 2020.
23. Direzione Generale Prevenzione Sanitaria. Piano Nazionale della Prevenzione 2020-2025. Roma: Ministero della Salute; 2020. Available from: https://www.salute.gov.it/imgs/C_17_pubblicazioni_2955_allegato.pdf.
24. Direzione Generale Prevenzione Sanitaria. Investire precocemente in salute: azioni e strategie nei primi mille giorni di vita. Documento di indirizzo per genitori, operatori sanitari e policy maker, per la protezione e promozione della salute dei bambini e delle generazioni future. Roma: Ministero della Salute; 2019. Available from: https://www.salute.gov.it/portale/documentazione/p6_2_2_1.jsp?lingua=italiano&id=3120.
25. Italian National Institute of Statistics (ISTAT). Pregnancy, childbirth and breastfeeding in Italy. Rome: ISTAT; 2013. Available from: http://www.istat.it/en/archive/141520.
26. Lauria L, Spinelli A, Grandolfo M. Prevalence of breastfeeding in Italy: a population based follow-up study. Ann Ist Super Sanità. 2016;52(3):457-61. doi: 10.4415/ANN_16_03_18
27. Simpson DA, Carson C, Kurinczuk JJ, Quigley MA. Trends and inequalities in breastfeeding continuation from 1 to 6 weeks: findings from six population-based British cohorts, 1985-2010. European Journal of Clinical Nutrition. 2022;76(5):671-9. doi: 10.1038/s41430-021-01031-z
28. Lauria L, Spinelli A, Buoncristiano M, Bucciarelli M, Pizzi E. Breastfeeding prevalence at time of vaccination: results of a pilot study in 6 Italian regions. J Hum Lact. 2019;35(4):774-81. doi: 10.1177/0890334418823539
29. Pizzi E, Salvatore AM, Donati S, Andreozzi S, Battilomo S, Privitera MG (Eds). Il sistema di sorveglianza bambini 0-2 anni finalità, metodologia e risultati della raccolta dati 2018-2019. Roma: Istituto Superiore di Sanità; 2022.
30. Ministero della Salute. Piano Nazionale Prevenzione Vaccinale (PNPV) 2023-2025. Roma: Ministero della Salute; 2023. Available from: https://www.trovanorme.salute.gov.it/norme/dettaglioAtto.spring?id=95963&page=newsett.
31. Direzione Generale Prevenzione Sanitaria. Vaccinazioni dell'età pediatrica. Anno 2021 (coorte 2019). Coperture vaccinali a 24 mesi (per 100 abitanti), calcolate sui riepiloghi inviati dalle regioni e PP.AA. (per singolo antigene). Dati comunicati dalle regioni. Roma: Ministero della Salute; 2022.
32. Marchetti F, Preziosi J, Zambri F, Tambascia G, Di Nolfi A, Scardetta P, Splendore F, Colaceci S, Coia M, Caredda E, Masi L, De Luca V, Perra A, Giusti A. Health needs and perception of health care quality among asylum seekers and refugees in an Italian Local Health Authority: A qualitative study. Frontiers in Public Health. 2023;11:1125125. doi: 10.3389/fpubh.2023.1125125
33. Lauria L, Spinelli A, Grandolfo M. Prevalence of breastfeeding in Italy: a population based follow-up study. Ann Ist Super Sanità 2016;52(3):457-61. doi: 10.4415/ANN_16_03_18
34. Colaceci S, Chapin EM, Zambri F, Reali L, Cedrone L, Del Brocco A, Masi M, Mohamed A, Dellafiore F, Nichinonni S, Giusti A. "Verba volant, scripta manent": breastfeeding information and health messages provided to parents in the neonatal discharge summary in the Lazio Region, Italy. Ann Ist Super Sanità. 2020;56(2):142-9. doi: 10.4415/ANN_20_02_03
35. World Health Organization. Guideline: protecting, promoting and supporting breastfeeding in facilities providing maternity and newborn services. Geneva: WHO; 2017. Available from: https://www.who.int/publications/i/item/9789241550086.
36. Giusti A, Chapin EM, Spila Alegiani S, Marchetti F, Sani S, Preziosi J, Colaceci S, Zambri F. Prevalence of breastfeeding and birth practices during the first wave of the COVID-19 pandemic within the Italian Baby-Friendly Hospital network. What have we learned? Ann Ist Super Sanità. 2022;58(2):100-8. doi: 10.4415/ANN_22_02_05
37. Italia. Decreto 16 luglio 2001, n. 349. Modificazioni al certificato di assistenza al parto, per la rilevazione dei dati di sanità pubblica e statistici di base relativi agli eventi di nascita, alla nati-mortalità ed ai nati affetti da malformazioni. Gazzetta Ufficiale – Serie Generale n. 218, 19 settembre 2001. Available from: https://www.gazzettaufficiale.it/eli/id/2001/09/19/001G0405/sg.
38. Zambri F, Nannavecchia AM, Brescianini S, Rusconi F, Corsi Decenti E, Puglia M, Pacifici M, Buono P, Cantoira S, Gagliardi L, Visonà Dalla Pozza L, Giusti A. Breastfeeding and presence of the companion of woman's choice during COVID-19 pandemic in Italy: regional population-based routine data and best practices at birth. Epidemiol Prev. 2023;47(4-5):263-72. doi: 10.19191/EP23.4-5.A587.066
39. Agenzia Nazionale per i Servizi Sanitari Regionali (AGENAS) – Osservatorio nazionale delle buone pratiche sulla sicurezza in sanità. Roma: AGENAS; 2024. Available from: https://www.buonepratichesicurezzasanita.it/.

Ann Ist Super Sanità 2025 | Vol. 61, No. 1: 13-19
DOI: 10.4415/ANN_25_01_03

Awareness of digital tomosynthesis and attitudes towards breast cancer early diagnosis in women at first screening: findings from the IMPETO trial survey

Elisa Betti[1], Francesca Battisti[1], Anna Iossa[1], Noemi Auzzi[1], Francesca Peruzzi[1], Erika Del Prete[2], Paolo Giorgi Rossi[3] and Paola Mantellini[1], on behalf of the IMPETO Working Group*

[1]Istituto per lo Studio, la Prevenzione e la Rete Oncologica (ISPRO), Florence, Italy
[2]Dipartimento di Scienze della Salute, Università degli Studi di Firenze, Florence, Italy
[3]Azienda Unità Sanitaria Locale - IRCCS di Reggio Emilia, Reggio Emilia, Italy
**The members of the IMPETO Working Group are listed before the References*

Abstract

Background. The European guidelines on breast cancer and diagnosis recommend digital mammography (DM) or digital breast tomosynthesis (DBT) for screening asymptomatic women with an average risk of breast cancer. The research project innovation in mammography: tomosynthesis pathways (IMPETO) includes an interventional randomised trial conducted in Tuscany, Italy, aiming to assess the feasibility and impact of DBT in screening. Limited evidence exists on women's preferences and acceptability of this new technology. To address this gap, as part of the IMPETO trial, a questionnaire was administered to 441 women aged 45 at their first inclusion in the screening programme, to investigate women's awareness of tomosynthesis and their attitudes toward early diagnosis.

Methods. This cross-sectional study was nested within the IMPETO trial, whose participants were randomly sampled. From October 2021 to February 2022 all women who participated in the face-to-face enrolment for the IMPETO trial were asked to fill out a structured questionnaire collecting socio-demographic information and assessing awareness of tomosynthesis, breast density, attitudes toward breast cancer early diagnosis, and sources of information on breast health. Multiple logistic regression was performed to identify predictors of tomosynthesis awareness and attitudes toward early diagnosis.

Results. Out of the 441 women surveyed, only 12% knew what tomosynthesis was and this awareness was positively associated with prior mammography experience (OR=2.092; 95% CI: 1.036-4.11). More than half of the participants (56.7%) had undergone mammography before joining the screening programme. Education attainment emerged as a significant predictor, with women holding a secondary degree being more likely to undergo mammography before age 45 (OR=2.18; 95% CI: 1.04-4.56). Among those who had undergone mammography before 45, 38.8% were advised by their gynaecologist, 27.6% made the decision independently, and 13.6% followed the advice of their general practitioner.

Conclusion. This study highlights the need for improved education on screening appropriateness and associated risks and the importance of tailored communication to reduce knowledge differences across educational levels without increasing inappropriate use.

Key words

- cancer screening
- early detection of cancer
- digital breast tomosynthesis
- risk perception
- Italy

INTRODUCTION

Breast cancer is the most common cancer affecting women in the European Union, with 374,800 women estimated to be diagnosed with breast cancer and 95,800 women estimated to die of breast cancer in 2023, according to the European Cancer Information

Address for correspondence: Noemi Auzzi, Istituto per lo Studio, la Prevenzione e la Rete Oncologica (ISPRO), Via Cosimo il Vecchio 2, 50139 Florence, Italy. E-mail: noe.auzzi@gmail.com.

System [1]. Advancements in organised population-based screening programmes have contributed to reduced mortality rates in most European countries [2-4]. Early detection through breast cancer screening is pivotal in identifying treatable cases, significantly reducing mortality [5, 6].

The European guidelines on breast cancer screening and diagnosis, established under the European Commission Initiative on Breast Cancer (ECIBC) 2021 (https://healthcare-quality.jrc.ec.europa.eu/en/ecibc/european-breast-cancer-guidelines?topic=65&usertype=60&updatef2=0), provide guidance on the implementation of breast cancer screening. These guidelines suggest using either digital mammography (DM) or digital breast tomosynthesis (DBT) for asymptomatic women with an average risk of breast cancer. Women with high mammographic breast density are likely to benefit most from the increased detection capability of DBT. However, the guidelines underline the limited certainty of evidence and the absence of data on the downstream impact of DBT, such as its effect on reducing advanced cancer and mortality. Moreover, the guidelines reveal a lack of data regarding women's preferences, acceptability, and the value they attribute to the routine use of DBT.

In the Florence local health unit, the breast cancer screening programme was fully implemented in the first 1990s for women aged 50-69, with biennial invitations to mammography. In 2016 the programme was expanded to include women aged 45-49, receiving annual invitations.

In 2018, the Institute for Cancer Research, Prevention and Clinical Network (Istituto per lo Studio, la Prevenzione e la Rete Oncologica, ISPRO) initiated an interventional randomised trial to assess the impact of the introduction of tomosynthesis in mammography screening, analysing the benefits, disadvantages, and feasibility in current practice.

As part of this study, a questionnaire was developed to investigate women's awareness of tomosynthesis and their attitudes toward early diagnosis upon their initial inclusion in the screening programme. The questionnaire was administered to participants from October 2021 until the study concluded in February 2022. As new evidence emerged in the Italian context, we recognised the importance of conducting this questionnaire to analyse our specific circumstances [7].

METHODS

Participant selection and recruitment

The research project *Innovation in mammography: tomosynthesis pathway* (IMPETO - *Innovazione in Mammografia: PErcorsi di TOmosintesi)* involved in a randomise controlled trial women aged 45 who were participating in the Florence screening programme for the first time. Women in this age group were randomly assigned to either the control arm (2D DM) or the intervention arm (DBT plus 2D synthetic reconstruction). This study joined the Mammography screening ITAlian (MAITA) Consortium (a consortium of four Italian trials, REtomo, Proteus, Impeto, and MAITA trial). [8].

The cross-sectional study reported here was nested in the IMPETO trial. Women were invited to join the IMPETO study through a randomised selection process. The randomization of invitees (rather than enrolees) followed a simple random sampling method at a 1:1 ratio. All women who accepted to participate in the face-to-face enrolment were asked to fill out a self-administered questionnaire on their awareness of tomosynthesis and their attitudes toward early diagnosis. Neither the study recruiter nor the woman knew the study arm assignment before signing the consent form.

Data collection

The questionnaire is reported in *Appendix 1 available online as Supplementary Material*. It was structured into three sections aimed at assessing: (i) general attitudes toward breast cancer early diagnosis; (ii) awareness of breast density, tomosynthesis, and sources where women seek information related to breast cancer prevention (iii) socio-demographic information. The questions were designed drawing on insights from previous research [9, 10] and the Centers for Disease Control and Prevention (CDC) Q-Bank (https://wwwn.cdc.gov/qbank/).

A panel of experts in cancer screening reviewed the questionnaire incorporating all relevant observations. Administered on a self-reported and anonymous basis, the questionnaire aimed to mitigate response order bias by randomising the sequence of answers (questions 3, 4, 8, 10) after the first 200 responses using the Excel function Random.

Analysis

Data was processed using Stata/SE version 16.1 (StataCorp LP, College Station, TX). Descriptive statistics, including frequency distribution, were used to summarise participants' demographics and questionnaire responses. Multiple logistic regression analysis was performed to identify significant predictors of tomosynthesis awareness and attitudes toward early diagnosis. All statistical tests were two-sided and statistical significance was set at 0.05 ($p<0.05$). In the multiple logistic regression analysis to investigate the association between socio-demographic factors and the likelihood of having undergone mammography as a preventive measure before turning 45, women who had mammography due to symptoms (such as pain, skin changes, palpable nodules, nipple discharge) or benign lesions (fibroadenomas or cysts) control were excluded, as they were not undergoing the mammography for preventive reasons.

RESULTS

Socio-demographic characteristics

The study sample (*Table 1*) included women aged 45 years, following the IMPETO cohort inclusion criteria. Of the 441 women who completed the questionnaire, not all participants responded to every item. The number of non-responders is reported as missing values in the tables. The majority of participants (77.1%, n. 340) were either Italian or from highly developed countries (HDC), while 19.1% (84) were from high migratory pressure countries (HMPC) [11]. Educational backgrounds varied, with 44.7% (197) holding a high school

Table 1
Socio-demographic characteristics

	N.	%
Country of birth		
HDC[1]	340	77.1
HMPC[2]	84	19.1
Missing	17	3.9
Level of education		
None	2	0.5
Primary school	43	9.8
Secondary school	197	44.7
University graduate	189	42.9
Other	5	1.1
Missing	5	1.1
Residence[3]		
Florence	169	38.3
Piana municipalities	92	20.9
Rural areas	118	26.8
Missing	62	14.1
Occupational status		
Full-time employed	274	62.1
Part-time employed	93	21.1
Unemployed	28	6.4
Housewife	20	4.5
Private job	20	4.5
Missing	6	1.4
Had mammography before		
No	191	43.3
Yes	250	56.7
N. of mammography in lifetime		
1	144	32.7
2	40	9.1
3	34	7.7
4+	26	5.9
Missing	6	1.4

[1]Highly developed countries; [2]high migratory pressure countries; [3]piana municipalities: Calenzano, Sesto F.no, Campi, Prato; rural areas: Vicchio, Reggello, Incisa, Greve, Figline, Bagno a Ripoli.

diploma, 42.9% (189) being graduates, 9.8% (43) having completed the primary education cycle, and only 0.5% (2) lacking an education certificate. 38.3% (169) of participants resided in the city of Florence, 26.8% (118) in rural areas, and 20.9% (92) in the industrial area around Florence. The majority of participants were full-time employed (62.1%, n. 274), followed by 21.1% (93) part-time employed individuals. The remaining participants were either unemployed (6.4%, n. 28), housewives (4.5%, n. 20), or engaged in private jobs (4.5%, n. 20). In terms of mammography history, 43.3% (191) had never undergone mammography, while 56.7% (250) had at least one mammography session in their lifetime. Among these women 32.7% (144) had one, 9.1% (40) had two, 7.7% (34) had three, and 5.9% (26) had more than four.

Breast density and DBT awareness and source of information

While 51.0% (225) women have heard about breast density, only 12.0% (53) were aware of DBT. However, 91.2% (402) women had never undergone DBT, 1.6% (7) did not know and only 3.9% (17) experienced this test (15 missing). Among those who already had a mammography, 7.6% experienced this test. The 53 women aware of DBT were asked about the source of their knowledge through a multiple-select item: none cited a general practitioner (GP) or media channels, 43.4% (23) learned about DBT at the facilities where they underwent mammography, 16.9% (9) through specialist doctors, and 15.1% (8) via friends and family. Additionally, 15.1% (8) were informed through the Internet and Social Networks, and 13.2% (7) through specialised and non-specialised magazines/newspapers.

Attitudes towards early diagnosis

The 441 participants were asked where they would seek information about mammography in case of doubts or questions. Responders indicated as main points of reference general practitioners (41.5%, n. 183) and specialist doctors (43.8%, n. 193), followed by screening facilities (20.2%, n. 89) and the Internet (6.1%, n. 27). Family and friends (3.4%, n. 15) and specialised information sources (2.5%, n. 11) were cited less frequently.

Among the responders, 43.3% (191) had never undergone mammography, while 56.7% (250) had at least one mammography session (*Table 2*). Among those who had mammography, 51.2% (128) opted for private facilities, and 37.6% (94) chose public facilities. The primary motivation for mammography was secondary prevention in the absence of family history 52.8% (132), followed by prevention due to the presence of a family history 18.8% (47), and symptoms 18.4% (46). Among women who had undergone at least one mammogram, 38.8% (97) were advised by their gynaecologist, 27.6% (69) made the decision independently, and 13.6% (34) followed the advice of their GP.

Among women who underwent mammography for secondary prevention without a family history or symptoms (132), 50.0% (66) followed their gynaecologist's recommendation, 25.8% (34) made the decision independently, 7.6% (10) were influenced by family or friends, and 7.6% (10) followed a breast specialist's advice, and 5.3% (7) followed the GP advice (missing 5). For those with a family history (47), 31.9% (15) decided independently, 29.8% (14) were advised by their gynaecologists, 17.0% (8) by their GPs, 8.5% (4) by a breast specialist, and 8.5% (4) by their family or friends (missing n. 2). Among those who had mammography due to symptoms or for benign lesions control (64), 31.2% (20) made the decision independently, 29.7% (19) were advised by GPs, 25.0% (16) followed their gynaecologist's suggestion, 6.6% (4) followed a breast specialist recommendation, only one person was influenced by family or friends (missing n. 4).

Table 2
Attitudes towards early diagnosis

	N.	%
Where did you have mammography?		
Don't remember	1	0.4
Public health facility	94	37.6
Private facility	128	51.2
Abroad	5	2.0
Both in a private and public facility	15	6.0
Missing	7	2.8
Reason to undergo a mammography		
Symptoms[1]	46	18.4
Benign lesions[2] control	18	7.2
Family history	47	18.8
Prevention (no family history)	132	52.8
Missing	7	2.8
Who suggested undergoing mammography?		
Breast specialist	18	7.2
Gynaecologist	97	38.8
General practitioner	34	13.6
Family/friends	15	6.0
None, I decided on my own	69	27.6
Other	12	4.8
Missing	5	2.0

[1]Pain, skin changes, palpable nodules, nipple discharge; [2]fibroadenomas or cysts.

Predictors of DBT awareness

Table 3 column a shows the association between sociodemographic factors and DBT awareness. Participants who had previously undergone mammography showed a significant association with DBT awareness (OR=2.09; 95% CI: 1.04-4.11). Similarly, there was a correlation between knowledge about breast density and DBT awareness (OR=2.44; 95% CI: 1.20-4.93). Association with education and place of birth was weak, if any. Occupational status showed a non-significant association with being unemployed and an inverse association with being a housewife.

Predictors of attitudes towards early diagnosis by logistic regression

Table 3b presents the association between sociodemographic characteristics and having had screening mammography before the age of 45. As mentioned, symptomatic women and those who had benign lesions controls were excluded (N=64). Educational level emerged as a significant predictor, with women holding a secondary degree showing an increased likelihood of undergoing mammography before 45 (OR=4.00; 95% CI: 1.30-23.27). Moreover, university-educated women exhibited a stronger association, with a higher odds ratio for undergoing mammography before the age of 45 (OR=7.49; 95% CI: 2.43-23.07). In addition, the knowledge of breast density showed a positive association (OR=1.60; 95% CI: 1.02-2.54). Place of birth and occupational status showed small, if any association.

DISCUSSION

This study examined women's awareness of tomosynthesis and their attitudes towards early diagnosis within the context of the IMPETO study nested in the breast cancer screening programme of the Florence local health unit.

The findings of this study lie in two main themes. Firstly, there is a notable lack of awareness regarding tomosynthesis, despite the relatively high educational levels of the participants. To our knowledge, no prior studies have explored perceptions of tomosynthesis among women undergoing breast cancer screening. Awareness of breast density is higher but still around 50%, consistent with findings from similar studies [12, 13]. In this study, knowledge of tomosynthesis correlated more strongly with having undergone a mammogram than with educational attainment. Indeed, the primary source of information was the facility where participants had prior mammograms, with minimal influence by general practitioners or media channels.

Secondly, a significant number of women had a mammography before 45, aligning with previous studies [14], despite European guidelines on breast cancer screening and diagnosis (European Commission Initiative on Breast Cancer, ECIBC, 2021) not recommending routine mammography before the age of 45. Women with higher educational levels were more likely to undergo mammograms, often in private clinics and without a family history of breast cancer, consistent with other studies [15, 12]. Gynaecologists played a significant role in directing women to mammography, but a substantial percentage make the decision independently.

The phenomenon of mammography overuse, previously observed in Italy [16], persists regardless of education level. Thus, there is a need to improve knowledge about appropriateness and associated risks, especially concerning unnecessary screenings, consistent with previous findings [7]. It is crucial to re-imagine a communication strategy to enhance women's awareness of screening and tomosynthesis, to avoid an uneven introduction of DBT in breast cancer secondary prevention. Without such measures inappropriate use of DBT may rise, undermining women's trust in public screening programs.

As DBT becomes more common in private clinics, public screening programmes must address the increased demand for radiologists dedicated to screening reading or adopt new technologies to reduce DBT reading time [17]. Failure to balance access risks creating inequities: private clinics offering paid DBT while public programs rely on free DM.

The strength of our study lies in its unique focus on women invited to the first round of organised screening, providing insights into initial awareness and information-seeking behaviours regarding breast cancer prevention. In addition, this study contributes

Table 3
Association between socio-demographic factors and DBT[1] awareness investigated through multiple logistic regression analysis (a) and between socio-demographics factors and the likelihood of having undergone mammography before turning 45 years old as preventive measure (symptomatic women and those who had benign lesions controls were excluded) (b)

	a		b	
	N=53	**OR (95% CI)**	**N=186**	**OR (95% CI)**
Had mammography before				
None	14	1*	-	-
Yes	39	**2.09[2] (1.04-4.11)**	-	-
Country of birth				
HDC[2]	41	1*	158	1*
HMPC[3]	9	1.31 (0.57-2.99)	16	0.41 (0.21-0.83)
Level of education				
Primary education	2	1*	6	1*
Secondary education	22	1.28 (0.34-4.74)	75	**4.00 (1.30-23.27)**
University graduated	28	1.38 (0.37-5.22)	98	**7.49 (2.43-23.07)**
Occupational status				
Full/Part-time/Private job	46	1*	162	1*
Unemployed	5	2.34 (0.79-6.95)	7	0.71 (0.25-2.07)
Housewife	1	0.52 (0.06-4.21)	9	1.05 (0.36-3.04)
Knowledge of breast density				
No	14	1*	66	1*
Yes	37	2.44 (1.20-4.93)	109	1.60 (1.01-2.54)

*Reference status; [1]DBT= digital breast tomosynthesis; [2]HDC = people from highly developed countries (or Italians); [3]HMPC = people from high migratory pressure countries; values in bold indicate statistical significance.

to exploring the scarcely investigated perceptions and knowledge of tomosynthesis. However, this study has some limitations such as a relatively small sample size, and the questionnaire was exploratory. Additionally, it is important to acknowledge that the demographic characteristics of our participants may be influenced by self-selection bias, as individuals with certain traits may be more likely to accept to participate in the face-to-face enrolment and screening programmes, potentially impacting the generalizability of our findings to the whole population. However, the questionnaire was completed before the experimenter introduced the IMPETO study to the participants, allowing for a reduced influence of self-selection bias and ensuring a more representative sample. As a result, the responders to the questionnaire had a higher educational level and employment rate compared to data from the local female population aged 25-49. Indeed, only 9.8% of the questionnaire participants had a primary education level, while 42.9% were university graduates, compared to 19.3% and 37.1% respectively, among Florence's female population aged 25-49, according to National Institute of Statistics (Istituto Nazionale di Statistica, ISTAT) [18]. Regarding respondents' employment rate, 87.7% were employed, 6.4% were unemployed and 4.5% were housewives, compared to Florence's female population aged 25-49, where 74.3% were employed, 6.8% unemployed, and 11.2% housewives [18].

Nonetheless, the proportion of eligible citizens from HMPC countries aligns with the percentage of participants in the questionnaire, adding validity to our study sample composition. Specifically, 19.8% of participants were from HMPC countries, compared to 19.4% of the eligible population in the Florence province in 2022 [19].

CONCLUSIONS

Our study provides valuable insights into breast cancer screening, highlighting the importance of raising awareness about screening appropriateness and potential risks, particularly concerning unnecessary screenings. In addition, a communication strategy should involve not only screening centres but also general practitioners and gynaecologists. Moreover, the influence of educational levels on screening attitudes un-

derscores the need for tailored interventions to address existing disparities.

Further investigations and interventions should focus on improving women's awareness and decision-making regarding breast cancer screening. Addressing these issues will contribute not only to individual healthcare decisions but also to the overall success and effectiveness of breast cancer screening programmes. Specifically, there is a need to enhance the training of general practitioners and gynaecologists, enabling them to enrich women's understanding and facilitate their well-informed decision-making processes.

Acknowledgments

The IMPETO trial conducted in Florence is part of a consortium of four Italian trials on DBT in screening, named MAITA project and funded by the Italian Ministry of Health (RF2016-02363686).

Furthermore, the IMPETO trial received funding from Tuscany Region (DGRT 875/2016 and DGRT 185/2019).

PGR, as principal investigator (PI) of an independent study, conducted negotiation with Hologic to obtain reagents at a reduced price or for free; as PI of another independent study, received non-financial support (one DBT gantry for loan) from General Electric (GE) Healthcare; for a study sponsored by the Karolinska Institutet received support (software in use for the study conduction) by iCAD.

Conflict of interest statement

All Authors have no relevant financial or non-financial interests to disclose.

Ethics approval

Before data collection, formal approval was obtained from the local Ethics Committee (Approval n. CEAVC Em. 2021-460 Studio 11784_spe 27/09/2021) to ensure compliance with ethical guidelines. Participants were provided with clear and comprehensive information about the study's purpose, and their voluntary participation was contingent upon obtaining informed consent. Confidentiality was strictly maintained, with all collected data anonymised and stored securely. Participants were assured that their responses would be used solely for research purposes, and personal identifiers were carefully protected to uphold privacy. The study design and execution adhered to the principles outlined in the Declaration of Helsinki, prioritising the welfare and rights of the participants.

The members of the IMPETO Working Group are:
Daniela Ambrogetti, Francesco Regini, Fiorella Ciuffi, Patrizia Falini, Giulia Maddaleni, Giuseppe Gorini, Eva Carnesciali, Vincenzo Mazzalupo (ISPRO, Florence, Italy).

Received on 15 October 2024.
Accepted on 5 December 2024.

REFERENCES

1. European Commission's Joint Research Centre (JRC). Breast cancer in the EU: October 2023. European Cancer Information System; 2023. Available from: https://ecis.jrc.ec.europa.eu/sites/default/files/2024-01/jrc_Breast_cancer_2022_Oct_2023.pdf.
2. Paci E, EUROSCREEN Working Group. Summary of the evidence of breast cancer service screening outcomes in Europe and first estimate of the benefit and harm balance sheet. J Med Screen. 2012;19(Suppl. 1):5-13. doi: 10.1258/jms.2012.012077
3. Zielonke N, Gini A, Jansen EEL, Anttila A, Segnan N, Ponti A, Veerus P, de Koning HJ, van Ravesteyn NT, Heijnsdijk EAM; EU-TOPIA Consortium. Evidence for reducing cancer-specific mortality due to screening for breast cancer in Europe: A systematic review. Eur J Cancer. 2020;127:191-206. doi: 10.1016/j.ejca.2019.12.010
4. Dyba T, Randi G, Bray F, Martos C, Giusti F, Nicholson N, Gavin A, Flego M, Neamtiu L, Dimitrova N, Negrão Carvalho R, Ferlay J, Bettio M. The European cancer burden in 2020: Incidence and mortality estimates for 40 countries and 25 major cancers. Eur J Cancer. 2021;157:308-47. doi: 10.1016/j.ejca.2021.07.039
5. Ponti A, Anttila A, Ronco G, Senore C. Cancer screening in the European Union. Report on the implementation of the Council Recommendation on cancer screening; 2017. Available from: https://health.ec.europa.eu/system/files/2017-05/2017_cancerscreening_2ndreportimplementation_en_0.pdf.
6. Wanders AJT, Mees W, Bun PAM, Janssen N, Rodríguez-Ruiz A, Dalmış, MU, Karssemeijer N, van Gils CH, Sechopoulos I, Mann RM, van Rooden CJ. Interval cancer detection using a neural network and breast density in women with negative screening mammograms. Radiology. 2022;303(2):269-75. doi: 10.1148/radiol.210832
7. De Nard F, Deandrea S, Bastiampillai AJ, Cavazzana L, Carnevali D, Principi N, Luconi E, Schulz PJ, Castaldi S, Silvestri AR. Women's perception, preconceptions, and information preferences for the limitations of breast cancer screening and overdiagnosis: A think-aloud study on the new information materials of the Agency for Health Protection of the metropolitan area of Milan. Epidemiol Prev. 2021;45(4):271-80. doi: 10.19191/EP21.4.P271.083
8. Giorgi Rossi P, Mancuso P, Pattacini P, Campari C, Nitrosi A, Iotti V, Ponti A, Frigerio A, Correale L, Riggi E, Giordano L, Segnan N, Di Leo G, Magni V, Sardanelli F, Fornasa F, Romanucci G, Montemezzi S, Falini P, Auzzi N, Zappa M, Ottone M, Mantellini P, Duffy SW, Armaroli P; MAITA Working Group. Comparing the accuracy of tomosynthesis plus digital mammography or synthetic 2D mammography in breast cancer screening: Baseline results of the MAITA RCT Consortium. Eur J Cancer. 2024;199:113553. doi: 10.1016/j.ejca.2024.113553
9. Schifferdecker KE, Tosteson ANA, Kaplan C, Kerlikowske K, Buist DSM, Henderson LM, Johnson D, Jaworski J, Jackson-Nefertiti G, Ehrlich K, Marsh MW, Vu L, Onega T, Wernli KJ. Knowledge and perception of breast density, screening mammography, and supplemental screening: In search of "Informed". J Gen Intern Med. 2020;35(6):1654-60. doi: 10.1007/s11606-019-05560-z
10. Kyanko KA, Hoag J, Busch SH, Aminawung JA, Xu X, Richman IB, Gross CP. Dense breast notification laws,

education, and women's awareness and knowledge of breast density: A nationally representative survey. J Gen Intern Med. 2020;35(7):1940-5. doi: 10.1007/s11606-019-05590-7
11. Morandi I, Pugliese A, Calamita ML, Brusco A, Gallieri D, Burgio A, Loghi M, Surace L, Latella A, Biocca M, Caranci N, Pacelli B, Casagrande S, Vicario G, Carletti P, Barbini N, Squadroni R, Mondo L, Rusciani R, Spadea T, Fortunato F, Martinelli D, Ballotari P, Bonvicini L, Candela S, Giorgi Rossi P, Palazzi M, Vitali P. La salute della popolazione immigrata: il monitoraggio da parte dei sistemi sanitari regionali. Roma: Ministero della Salute – Agenas; 2013. Available from: https://www2.immigrazione.regione.toscana.it/sites/default/files/La_salute_della_popolazione_immigrata_il_monitoraggio_da_parte_dei_Sistemi_Sanitari_Regionali.pdf.
12. Rhodes DJ, Breitkopf CR, Ziegenfuss JY, Jenkins SM, Vachon CM. Awareness of breast density and its impact on breast cancer detection and risk. J Clin Oncol. 2015;33(10):1143. doi: 10.1200/JCO.2014.57.0325
13. Tran ATN, Hwang JH, Choi E, Lee YY, Suh M, Lee CW, Kim Y, Choi KS. Impact of awareness of breast density on perceived risk, worry, and intentions for future breast cancer screening among Korean women. Cancer Res Treat. 2021;53(1):55-64. doi: 10.4143/crt.2020.495
14. Roberto A, Colombo C, Candiani G, Satolli R, Giordano L, Jaramillo L, Castagno R, Mantellini P, Falini P, Carnesciali E, Valenza M, Costa L, Campari C, Caroli S, Faggiano RC, Orione L, Belmessieri B, Marchiò V, Deandrea S, Silvestri A, Luciano D, Paci E, Mosconi P. A dynamic web-based decision aid to improve informed choice in organised breast cancer screening: A pragmatic randomised trial in Italy. Br J Cancer. 2020;123(5):714-21. doi: 10.1038/s41416-020-0935-2
15. Damiani G, Basso D, Acampora A, Bianchi CB, Silvestrini G, Frisicale EM, Sassi F, Ricciardi W. The impact of level of education on adherence to breast and cervical cancer screening: Evidence from a systematic review and meta-analysis. Prev Med. 2015;81:281-9. doi: 10.1016/j.ypmed.2015.09.011
16. Giorgi Rossi P, Petrelli A, Rossi A, Francovich L, Zappa M, Gargiulo LL. L'inappropriatezza nell'uso dei test di screening oncologici femminili in Italia: determinanti di sovra e sottoutilizzo. Epidemiol Prev. 2019;43(1):35-47. doi: 10.19191/EP19.1.P35.019
17. Djuric O, Deandrea S, Mantellini P, Sardanelli F, Venturelli F, Montemezzi S, Vecchio R, Bucchi L, Senore C, Giordano L, Paci E, Bonifacino A, Calabrese M, Caumo F, Degrassi F, Sassoli De' Bianchi P, Battisti F, Zappa M, Pattacini P, Campari C, Nitrosi A, Di Leo G, Frigerio A, Magni V, Fornasa F, Romanucci G, Falini P, Auzzi N, Armaroli P, Giorgi Rossi P; MAITA Working Group; Italian Breast Cancer Screening Guidelines Working Group. Organizational impact of systemic implementation of digital breast tomosynthesis as a primary test for breast cancer screening in Italy. Radiol Med. 2024;129(8):1156-72. doi: 10.1007/s11547-024-01849-0
18. Istituto Nazionale di Statistica (ISTAT). Dati dei censimenti permanenti. Roma: ISTAT; 2023. Available from http://dati-censimentipermanenti.istat.it.
19. Regional Reference Center for Cancer Prevention (CRRPO). I programmi di screening della Regione Toscana, ventiquattresimo rapporto annuale, risultati 2022. Firenze: Istituto per lo Studio, la Prevenzione e la Rete Oncologica (ISPRO); 2023. Available from: https://www.osservatorionazionalescreening.it/sites/default/files/allegati/Rapporto%20Screening%20Oncologici-Regione%20Toscana-2022.pdf.

Ann Ist Super Sanità 2025 | Vol. 61, No. 1: 20-29
DOI: 10.4415/ANN_25_01_04

Exploring perceptions of vaccine safety: an Italian national survey on different COVID-19 vaccine formulations

Sara Boccalini[1], Claudia Cosma[2], Pietro Monaci[2], Andrea Guida[2], Beatrice Velpini[2], Gabriele Cerini[2], Fabrizio Chiesi[3], Paolo Bonanni[1] and Angela Bechini[1]

[1]*Dipartimento di Scienze della Salute, Università degli Studi di Firenze, Florence, Italy*
[2]*Scuola di Specializzazione in Igiene e Medicina Preventiva, Università degli Studi di Firenze, Florence, Italy*
[3]*Azienda Sanitaria Locale Toscana Centro, Florence, Italy*

Abstract

Objectives. COVID-19 vaccines have proven effective and safe, enabling the resumption of normal life. However, misinformation has hindered vaccination efforts. This study aimed to investigate perceptions of vaccine safety among Italians through an anonymous online survey.

Study design. An anonymous online survey was conducted from April to July 2022 and disseminated through social platforms, among adult individuals living in Italy.

Results. A total of 1,329 individuals participated. Younger individuals and healthcare professionals showed greater trust in vaccines. Education level was significantly associated with perceived vaccine safety. Most respondents, including many healthcare workers and highly educated individuals, believed vaccines to be safe, with confidence levels of 39.5% for mRNA, 32.9% for viral vector, and 39% for protein subunit vaccines. Younger age and trust in institutions were linked to higher confidence in all vaccine types.

Conclusions. These findings may be useful to further investigate the drivers of vaccine safety perceptions and their relationship with vaccine hesitancy and may help to develop more effective communication campaigns in the future.

Key words

- vaccination
- SARS-CoV-2
- subunit vaccines
- viral-vector vaccines
- mRNA vaccines

INTRODUCTION

On March 11th, 2020, the World Health Organization (WHO) declared a pandemic due to the new SARS-CoV-2 virus (severe acute respiratory syndrome-coronavirus 2), first identified in December 2019 in Wuhan, China [1].

By March 2023, the world had surpassed 759 million documented cases of COVID-19 [2] and 6.8 million deaths [3]. The pandemic has not only had direct health consequences but has also threatened health system stability, disrupted routine services, and indirectly impacted community health [4]. In Italy, more than 25 million cases and over 188,000 deaths have been recorded due to COVID-19, mainly affecting the older segments of the population and the frailest individuals in the same period [5]. Unsurprisingly, these two categories of people were the first to receive the anti-COVID-19 vaccine. COVID-19 does, in fact, cause less severe disease in young people, but the risk of severe illness and death remains high in people aged 60 years and older and those with underlying health conditions [6]. The "Vaccine-day" (December 27, 2020) is the date that marked the official start of the vaccination campaign against COVID-19 all over Europe [7]. In Italy, the distribution of the vaccine began on 31 December 2020 [8]. Achieving high acceptance and uptake rates is crucial for the success of such campaigns [9]. Globally, as of February 2024, approximately 70.6% of the world population, including 86.3% of Italians, has received at least one dose of a COVID-19 vaccine while 64.1% of the global population, including 81.2% of Italians, was fully vaccinated [10].

Along with the global spread of vaccines, "no-vax" movements have arisen, consisting of people who don't trust vaccines, particularly the new mRNA technology, or are afraid of adverse reactions [11]. Determining factors include the loss of trust in institutions regarding pandemic management, the rapid development of available vaccines and the spread of misinformation [12, 13]. Indeed, what characterized the COVID-19 pandemic was the presence of a massive infodemic, which the WHO describes as an "overabundance of in-

Address for correspondence: Claudia Cosma, Scuola di Specializzazione in Igiene e Medicina Preventiva, Università degli Studi di Firenze, Viale GB Morgagni 48, 50134 Florence, Italy. E-mail: claudia.cosma@unifi.it.

formation – some accurate and some not – that occurs during an outbreak" [14]. Due to misinformation and infodemic, the risks of COVID-19 have been trivialized, or misinformation has been spread about alleged anti-COVID-19 treatments (e.g., hydroxychloroquine) whose efficacy has never been proven, as has the simultaneous and conflicting emergence of opinions of so many public health experts [15].

The WHO has recognized vaccine hesitancy as one of the top ten threats to global health [16]. Vaccine hesitancy refers to the delayed acceptance or refusal of vaccination despite the availability of vaccines and vaccination services. According to the WHO's 3 Cs model, the propensity for vaccine hesitancy is a function of three factors: confidence, complacency and convenience.

In particular, complacency corresponds to the perceived risk of getting sick versus the perceived risk of experiencing adverse events after vaccination and determines the belief that vaccines are unnecessary; instead, convenience concerns the individual's ease of access to vaccination. Confidence is defined as trust in the efficacy and safety of vaccines, trust in the system that provides them (competence of health workers and services), and trust in immunization policies adopted by institutions [17]. Trust issues constitute the predominant reason for vaccine hesitancy [18]. Other factors contributing to vaccine hesitancy are many and partly overlap with those of trust: misperceptions of vaccine-preventable disease risk (based on prior experience or lack of experience), access to information and misinformation, media and social media exposure and social norms [19].

In Italy, nearly one in five people has expressed beliefs that vaccines are harmful, often accompanied by a lack of trust in the scientific community and limited engagement in political or cultural activities [20]. During the COVID-19 pandemic, these concerns became even more pronounced, with the rapid development of vaccines fueling doubts about their safety and efficacy. A survey conducted across seven European countries at the end of 2020 revealed that in Italy, 66% of respondents were willing to accept a COVID-19 vaccine – a higher rate than in some countries but still indicative of significant hesitation. Factors such as trust in healthcare institutions and clear, accurate information emerged as critical in shaping public attitudes [21, 22]. These findings emphasize the need for targeted strategies to rebuild trust and counter misinformation, especially in the context of new vaccine technologies.

Hesitation towards vaccines represents a significant challenge in the fight against SARS-CoV-2 [23]. Indeed, infodemic and misinformation cause an increase in vaccine hesitancy and a decrease in vaccine confidence [24]. Strong confidence in COVID-19 vaccines leads to an increase in immunizations for all age groups and vaccine trust is considered to be the main factor affecting COVID-19 vaccine uptake [25].

For these reasons, several important issues were addressed, including vaccination safety, public trust in the government, and sources consulted for information [26].

More than a year after the beginning of the vaccine campaign, evidence of the public's willingness to accept COVID-19 vaccines still deserves further investigation, and the role that determinants may play in vaccine confidence needs to be better understood. In addition, according to the best information we have, different types of anti-COVID-19 vaccine might have different impacts relative to vaccine hesitancy [27].

For this reason, our research aims to assess perceptions of vaccine safety in different anti-COVID-19 vaccine formulations (mRNA, protein subunits and viral-vector vaccines) and factors associated in the context of the pandemic.

METHODS

This study was conducted in a convenience sample of the general adult population residing in Italy one year after the introduction of the anti-COVID-19 vaccine. An anonymous online survey was conducted among the general adult population from 20 April 2022, to 23 July 2022.

The survey was disseminated via social platforms (Facebook, Instagram, WhatsApp, Telegram) and was especially disseminated through commenting on online newspaper posts that were closely related to information about anti-COVID-19 vaccines and the vaccination campaign. The questionnaire was also posted on a regional website aimed at improving vaccination knowledge and awareness in the general population [28].

Participants aged 18 years and older and residing in Italy were considered eligible. All participants provided online informed consent to be included in the study. Only questionnaires completed by Italians residents in Italy were included. Participation in the study was voluntary.

Questionnaire

The anonymous questionnaire could be filled out only after viewing the information note on the purpose of the survey and agreeing to a statement of consent to participate. Most of the questions included dichotomous answers (YES/NO), while two questions included open-ended answers.

The first part of the questionnaire addressed general socio-demographic characteristics (age group, sex, geographic area, education, type of employment, employment status, type of healthcare professional, trust in institutions).

The second part examined trust in vaccines and anti-COVID-19 vaccines in their different formulations (mRNA, viral vector and protein subunit). Specifically, the confidence in the protein subunit vaccine was assessed with respect to the mRNA vaccine and the viral vector vaccine, as the protein vaccine was released later than the others.

The last section assessed possible determinants of trust in the COVID-19 vaccine, such as perceived risk related to vaccination versus infection and trust in institutions. In this scenario, respondents were asked whether they knew individuals who had experienced severe adverse reactions, defined as reactions that resulted in hospitalization.

The main source of information regarding vaccination was investigated using a closed question which allowed more than one answer.

The questionnaire underwent a thorough internal validation process. In particular, the questionnaire was reviewed and tested by approximately 50 residents in Hygiene and Preventive Medicine at the University of Florence (Italy) to ensure its relevance and clarity. Although we did not conduct further validation with an external population, we relied on the School's professional expertise and extensive experience to improve the robustness and applicability of the questionnaire.

The questionnaire is available in the *Supplementary File 1 available online as Supplementary Materials*.

Statistical analysis

Descriptive statistics were conducted to generate summary tables for study variables. Based on median values, the continuous variable "age" was transformed in two age groups.

In order to assess the predictors of the outcomes indicating vaccine confidence, we performed single and multivariate modified Poisson regression models. Poisson regression can be used for the analysis of cross-sectional studies with binary outcomes. When the outcome event is common [29], it is often more desirable to estimate a prevalence ratio since there is an increasing differential between the RR (relative risk) and OR (odds ratio) with an increasing incidence ratio. Anyway, for binary data Poisson regression model produces CIs (confidence intervals) that tend to be too wide. To correct this potential limitation, Zou *et al*. proposed a modified Poisson regression approach (Poisson regression with a robust error variance) [30]. The effect estimates are presented as relative risks (RRs) with their 95% confidence intervals (CIs).

For all the analyses, a p-value <0.05 was considered statistically significant. Statistical analyses were conducted using STATA 17 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC).

RESULTS

Out of the 1,350 completed questionnaires, 1.5% (n=21) were excluded because responders reported living abroad. Finally, a total of 1,329 questionnaires were included. Sociodemographic characteristics of the sample are shown in *Table 1*.

Women represent 65.5% (n=870) of the sample, while the median age was 47 years (95% CI: 46.7-48). Additionally, 34.1% (n=453) were healthcare professionals, and 76.5% (n=1,020) declared to be employed at the time of the administration of the survey administration. Half of the responders (n=665) reported living in Northern Italy, 38.2% (n=508) in Central Italy, and 11.8% (n=156) in Southern Italy. Regarding the level of education, the majority of respondents (65% n=864) held a bachelor's or master's degree. These characteristics highlight a sample that is not representative of the general population but rather skewed towards individuals with higher education and professional involvement in healthcare. A majority of the sample, specifically 62.6% (n=832) reported having sufficient trust in institutions (e.g., Ministry of Health, National Institute of Health, Italian Drug Agency, etc.).

Table 1
Sociodemographic features of Italian respondents in the COVID-19 vaccine safety study

	NA	N or median	% or IQR
Age (year)		47	46.7-48.1
Sex	19		
Male		440	33.1
Female		870	65.5
Geographic area	0		
North of Italy		665	50
Center of Italy		508	38.2
South of Italy		156	11.8
Education	0		
Primary school		2	0.2
Secondary school		52	3.9
High school		411	30.9
Bachelor's degree		549	41.3
Master's degree/PhD		315	23.7
Type of employment	309		
Employee		702	52.8
Self-employed		318	23.9
Employment status	45		
Currently employed		1,020	76.5
Currently unemployed/retired		264	19.8
Healthcare professional	0		
Yes		453	34.1
No		876	65.9
Trust in institutions	0		
Yes		832	62.6
No		497	37.4

NA: not available; N: number of valid responses; IQR: inter quartile range.

Personal beliefs about vaccination and perceived safety of different COVID-19 vaccine formulations are shown in *Table 2*.

The majority of respondents, 63.9% (n=849), think vaccines are safe, while 39.5% (n=525), 32.9% (n=437), and 39% (n=518) consider vaccines with mRNA technology, viral vectors, and protein subunits safe, respectively. About 10.6% (n=142) and 9.1% (n=122) of the respondents reported higher confidence in the protein-subunit vaccine compared to the mRNA vaccine and the viral-vector vaccine, respectively.

Among the preferred sources of information on vaccines, scientific books or journals (59%), attending physicians, medical officers and health professionals (52%), and institutional sites (e.g., Ministry of Health, National Institute of Health, Italian Medicines Agency) (35%) were the most selected options. The local health unit (LHU) is a reference for 30% of the participants: 17% and 13% through the vaccination service and region's

Table 2
Personal beliefs about vaccinations and perceived safety of different COVID-19 vaccines formulations

	NA	N	%
Do you think vaccines are safe?	0		
Yes		849	63.9
No		480	36.2
Do you think that mRNA vaccines against COVID-19 are safe?	0		
Yes		525	39.5
No		804	60.5
Do you think that protein subunit vaccines against COVID-19 are safe?	0		
Yes		518	39
No		811	61
Do you think that viral-vector vaccines against COVID-19 are safe?	0		
Yes		437	32.9
No		892	67.2
Do you know anyone who have suffered from severe reactions to the mRNA technology COVID-19 vaccines?	0		
Ye		753	43.4
No		576	56.6
Do you know anyone who have suffered from severe reactions to the viral vector COVID-19 vaccines?	0		
Yes		620	46.6
No		709	53.4
Do you think that the risk you are exposed by being vaccinated against COVID-19 is greater than the risk caused by the disease itself?	0		
Yes		738	55.5
No		591	44.5
Do you think that the protein subunits vaccine is safer than mRNA vaccine?			
Yes		122	9.1
No		35	2.6
Do you think that the protein subunits vaccine is safer than viral vector vaccine?			
Yes		142	10.5
No		33	2.4

NA: not available; N: number of valid responses.

website or LHU respectively. In our sample, 16% of participants reported using sites/blogs/forums that are against vaccinations in case of doubt about a vaccine's risks or actual benefits.

Knowing someone who suffered from a serious adverse reaction to vaccines was reported by 43.4% (n=753) of subjects in the case of the mRNA vaccine and by 46.6% (n=620) in the case of the viral-vector vaccine. In this study, a serious adverse reaction is defined as an event that causes death, is life-threatening, requires hospitalisation or results in significant disability [31]. The exploration of personal beliefs about COVID-19 revealed that 55.5% (n=738) of respondents reported a higher perceived risk related to vaccination than to contracting COVID-19 disease.

The results of the single regression analysis are reported in *Table 3*.

Perceived vaccine safety is associated with being younger than 47 years (RR 1.34; 95% CI: 1.24-1.45; p<0.001), working as a healthcare professional (RR 1.18; 95% CI: 1.09-1.28; p<0.001), having a bachelor's degree or higher (RR 1.13; 95% CI: 1.03-1.24; p<0,008), geographical area of residence in Central Italy (RR 1.34 95%; CI: 1.22-1.46; p<0.001) or Southern Italy (RR 1.36; 95% CI: 1.21-1.53; p<0.002) and trust in institutions (RR 2.25; 95% CI: 2.08-2.43; p<0.001).

According to the multivariate analysis (*Table 4*), factors independently associated with higher vaccine confidence were age lower than 47 years (RR 1.12; 95% CI: 1.02-1.23), residing in Central Italy (RR 1.10; 95% CI: 1.01-1.20), and having trust in institutions (RR 2.16; 95% CI: 1.96-2.37).

Analysis of opinions about the different COVID-19 vaccine technologies produced interesting results. Trust in institutions remained the strongest predictor of vaccine confidence for both the mRNA vaccine (RR 6.66; 95% CI: 4.13-10.74) and the viral vector vaccine (RR 9.22; 95% CI: 6.10-13.99), as well as the protein subunit vaccine (RR 6.92; 95% CI: 5.44-8.81). Being younger than 47 years was specifically associated with higher confidence in the protein subunit vaccine (RR 1.15; 95% CI: 1.01-1.31). On the other hand, knowing someone who suffered a serious adverse reaction was a predictor of lower vaccine confidence in both mRNA vaccines (RR 0.31; 95% CI: 0.19-0.48) and viral vector vaccines (RR 0.35; 95% CI: 0.24-0.52).

Finally, being younger than 47 years (RR 0.92; 95% CI: 0.86-0.98), being an employee (RR 0.92; 95% CI: 0.86-0.98), living in Central Italy (RR 0.88; 95% CI: 0.82-0.96) or Southern Italy (RR 0.86; 95% CI: 0.76-0.98) and having trust in institutions (RR 0.05; 95% CI: 0.03-0.08) were predictors that reduce the possibility of a higher perceived risk associated to vaccination compared to COVID-19 disease.

DISCUSSION

This study was conducted more than a year after the start of the anti-COVID-19 vaccination campaign in Italy. The objective was to assess confidence in vaccination in general, confidence in anti-COVID-19 vaccination in particular, confidence in different vaccine formulations, and the factors influencing it.

The importance of anti-COVID-19 vaccination is demonstrated by numerous studies testifying to the effectiveness of vaccines, especially in protecting against severe illness, hospitalization, and death, despite the spread of the latest variants known to be more contagious [32]. At least five different vaccine technology platforms have been licensed and used for anti-COVID-19 vaccines in Italy: two mRNA vaccines (Comirnaty BNT162b2, Pfizer-BioNTech; Spikevax mRNA-1273, Moderna)

Table 3
Single regression analysis of variables associated with personal beliefs about the safeness of COVID-19 vaccines

Variables		Perceived vaccines safety				Perceived mRNA COVID-19 vaccines safety				Perceived protein subunit COVID-19 vaccines safety			
	n	RR	Lower	Upper	p value	RR	Lower	Upper	p value	RR	Lower	Upper	p value
			95% CI				95% CI				95% CI		
Sex	1,310	0.98	0.89	1.06	0.6	0.92	0.8	1.06	0.25	0.99	0.86	1.14	0.97
Age													
Younger than 47		1.34	1.24	1.45	**<0.001**	1.8	1.56	2.1	**<0.001**	1.76	1.53	2.02	**<0.001**
Geographic area	1,329												
Center of Italy		1.34	1.22	1.46	**<0.001**	2.07	1.77	2.42	**<0.001**	1.96	1.68	2.29	**<0.001**
South of Italy		1.36	1.21	1.53	**<0.002**	2.37	1.97	2.85	**<0.001**	2.18	1.8	2.63	**<0.001**
Education level	1,329												
Bachelor's degree or higher		1.13	1.03	1.24	**0.008**	1.17	1.01	1.36	**0.03**	1.34	1.15	1.56	**<0.001**
Type of employment	1,020												
Employee		0.98	0.89	1.08	0.78	0.99	0.83	1.17	0.913	0.97	0.81	1.14	<0.71
Working as healthcare professional	1,329	1.18	1.09	1.28	**<0.001**	1.39	1.22	1.59	**<0.001**	1.5	1.32	1.72	**<0.001**
Knowing someone who had suffered from severe reaction after mRNA COVID-19 vaccination						0.08	0.06	0.1	**<0.001**				
Knowing someone who had suffered from severe reaction after viral vector COVID-19 vaccination													
Having trust in institution	1,329	2.25	2.08	2.43	**<0.001**	14.6	11.02	18.3	**<0.001**	7.2	6	8.7	**<0.001**

Variables		Perceived viral-vector COVID-19 vaccines safety				Perceived COVID-19 vaccination as a higher risk than the disease itself			
	n	RR	Lower	Upper	p value	RR	Lower	Upper	p value
			95% CI				95% CI		
Sex	1,310	1.08	0.92	1.26	0.34	1.1	0.99	1.21	0.08
Age									
Younger than 47		1.91	1.62	2.23	**<0.001**	0.67	0.6	0.74	**<0.001**
Geographic area	1,329								
Center of Italy		2.2	1.84	2.63	**<0.001**	0.61	0.55	0.68	**<0.001**
South of Italy		2.25	1.8	2.82	**<0.001**	0.51	0.42	0.64	**<0.001**
Education level	1,329								
Bachelor's degree or higher		1.31	1.1	1.6	**0.002**	0.91	0.82	1	0.06
Type of employment	1,020								
Employee		0.97	0.8	1.18	0.801	0.95	0.84	1.06	0.365
Working as healthcare professional	1,329	1.55	1.34	1.8	**<0.001**	0.8	0.72	0.9	**<0.001**
Knowing someone who had suffered from severe reaction after mRNA COVID-19 vaccination									
Knowing someone who had suffered from severe reaction after viral vector COVID-19 vaccination		0.1	0.076	0.14	**<0.001**				
Having trust in institution	1,329	16.6	12.24	22.52	**<0.001**	0.04	0.03	0.07	**<0.001**

n: number; RR: relative risk; CI: confidence interval.

[33, 34], two viral vector vaccines (Vaxzevria ChAdOx1 nCoV-19, Oxford-AstraZeneca; Janssen Ad26.COV2-S recombinant, Janssen-Cilag International NV) [35], and one protein subunit vaccine (Nuvaxovid NVX-CoV2373, Novavax) [36]. Overall, mRNA vaccines were the most widely used in the vaccination campaign in Italy [37]. Randomized and observational studies have demonstrated the high efficacy of mRNA vaccines in reducing morbidity and mortality from SARS-CoV-2 infection [38-40]. In addition, a systematic review evaluated the efficacy and safety of vaccines against SARS-CoV-2 in general, showing high certainty evidence for mRNA vaccines and moderate certainty evidence for the protein subunit vaccine in reducing the incidence of symptomatic COVID-19 compared to placebo [41].

Regarding the three different anti-COVID-19 vaccine technology platforms available in Italy, 39.5% of participants had confidence in the mRNA vaccine, 32.9% in the viral vector vaccine, and 39% had confidence in the protein subunit vaccine. The protein subunit vac-

Table 4
Multiple regression analysis of variables associated with personal beliefs about the safeness of COVID-19 vaccines

Variables	Perceived vaccines safety				Perceived mRNA COVID-19 vaccines safety				Perceived protein subunit COVID-19 vaccines safety			
	RR	Lower	Upper	p value	RR	Lower	Upper	p value	RR	Lower	Upper	p value
		95% CI				95% CI				95% CI		
Age												
Younger than 47	1.12	1.02	1.23	**0.009**	1.08	0.99	1.18	0.074	1.16	1.03	1.33	**0.019**
Geographic area												
Center of Italy	1.1	1	1.2	**0.039**	1.16	1.05	1.28	**0.001**	1.29	1.11	1.49	**0.001**
South of Italy	0.98	0.87	1.11	0.833	1.13	1.1	1.27	**0.034**	1.26	1.06	1.48	**0.006**
Education level												
Bachelor's degree or higher	1	0.91	1.11	0.862	0.99	0.91	1.09	0.976	1.09	1.12	1.26	0.195
Type of employment												
Employee	0.99	0.9	1.08	0.953	1.01	0.94	1.1	0.756	0.98	0.87	1.1	0.788
Knowing someone who had suffered from severe reaction after mRNA COVID-19 vaccination					0.31	0.19	0.48	**<0.001**				
Knowing someone who had suffered from severe reaction after viral vector COVID-19 vaccination												
Working as healthcare professional	1	0.93	1.09	0.891	1.04	0.96	1.11	0.334	1.07	0.94	1.17	0.359
Having trust in institution	2.16	1.96	2.37	**<0.001**	6.66	4.13	10.69	**<0.001**	6.7	5.39	8.74	**<0.001**

Variables	Perceived viral-vector COVID-19 vaccines safety				Perceived COVID-19 vaccination as a higher risk than the disease itself			
	RR	Lower	Upper	p value	RR	Lower	Upper	p value
		95% CI				95% CI		
Age								
Younger than 47	1.13	0.99	1.29	**0.065**	0.91	0.85	0.98	**0.009**
Geographic area								
Center of Italy	1.2	1.05	1.4	**0.01**	0.88	0.82	0.96	**0.04**
South of Italy	1.13	0.93	1.35	0.187	0.86	0.76	0.98	**0.035**
Education level								
Bachelor's degree or higher	1.07	0.91	1.22	0.356	1.02	0.94	1.08	0.694
Type of employment								
Employee	0.97	0.8	1.18	0.801	0.91	0.76	0.98	**0.012**
Knowing someone who had suffered from severe reaction after mRNA COVID-19 vaccination								
Knowing someone who had suffered from severe reaction after viral vector COVID-19 vaccination	0.35	0.24	0.52	**<0.001**				
Working as healthcare professional	1.09	0.98	1.2	0.166	0.99	0.92	1.06	0.774
Having trust in institution	9.2	6.01	13.8	**<0.001**	0.05	0.03	0.08	**<0.001**

RR: relative risk; CI: confidence interval. Bold values indicate statistically significant results, with p-values less than 0.05 considered significant.

cine was licensed and used about a year after the others. In our sample, 10.6% and 9.1% reported greater confidence in the protein subunit vaccine than in the mRNA vaccine and the viral vector vaccine, respectively. This could be explained since it uses a traditional vaccine technology platform.

Our study showed that 63.9% of respondents had confidence in vaccines in general, but less than half reported confidence in COVID-19 vaccines. This may be due to the rapid development and approval of COVID-19 vaccines [42] which may have reduced the population's trust in their safety and efficacy. Indeed, trust is the main factor that contrasts vaccine hesitancy and influences vaccine acceptance [43]. Although the survey found a high percentage of people who do not believe in the safety of the anti-COVID-19 vaccination, Italy is one of the European countries with the highest percentage of the population that has received a full cycle (two doses of vaccine). A possible explanation for this discrepancy could be attributed to the mandatory vaccination that was introduced by the Italian government [44]. Furthermore, the way the benefits of vaccination were communicated, particularly to those who were undecided, may have played a role in shaping public

confidence. Research conducted in Italy indicates that clear communication can significantly improve perceptions of vaccine safety and efficacy, addressing concerns and uncertainties that may arise [21, 45].

Predictors of higher perceived safety for vaccines in general and anti-COVID-19 vaccine, in particular, include living in Central Italy compared to Northern Italy. This is consistent with the exceptionally low vaccination coverage in some regions, most notably Friuli Venezia Giulia or the province of South Tyrol [46], although it should be noted that these two regions collectively have a small population compared to the total population of Northern Italy (1,800,000 compared to 27,500,000 inhabitants).

Individuals in Central and Southern Italy reporting higher vaccine confidence may be influenced by various factors, such as cultural attitudes, local public health campaigns, or differences in healthcare infrastructure. Historically, these regions might have experienced more targeted outreach or communication strategies emphasizing vaccine benefits, particularly during recent public health emergencies. Additionally, sociopolitical dynamics or trust in local healthcare authorities might vary, contributing to these regional disparities.

Other predictors of greater perceived safety regarding vaccines in general and anti-COVID-19 in particular relate to young age (under 47 years) and having trust in institutions. In particular, in our survey, trust in institutions appears to be the most important factor positively associated with vaccine acceptance and with the belief that contracting the disease represents a greater risk than getting vaccinated. Indeed, in line with the WHO's 3 Cs model, vaccine confidence affects not only vaccines as drugs (vaccine safety) but also trust in vaccinators and health professionals (health worker competence) and politicians responsible for public health decisions and is intimately related to vaccine hesitancy (adequacy of the delivery system) [17, 47].

Lack of confidence is related to the level of importance and effectiveness attributed to vaccines; on the other hand, perceived risk relates to a lack of confidence in vaccine safety and concern about adverse events following immunization, which plays a role in vaccine hesitancy and uptake [48, 49].

Indeed, a significant finding concerns the negative association between those who have personally known individuals who have developed serious adverse reactions following the administration of one of the anti-COVID-19 vaccines and their feeling of trust in the same vaccine. In our survey, many people apparently know people who have had a serious reaction to the vaccination; however, this perception is not confirmed by the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA) pharmacovigilance data. According to the report on the surveillance of anti-COVID-19 vaccines produced by AIFA in 2022, most of the reported adverse events are classified as non-serious (about 81.3%) and to a lesser extent serious (18.7%). The finding that a significant proportion of respondents know someone who has suffered a serious adverse reaction underscores a critical aspect of vaccine perception. Personal connections to such events can amplify fears about vaccination, fostering increased hesitation. Social networks further exacerbate this phenomenon, as awareness of adverse reactions within one's social circle often decreases trust in vaccines and health authorities. This highlights the importance of addressing personal narratives in public health communication to mitigate fear and misinformation effectively. Understanding how these dynamics influence vaccine perception is crucial for developing targeted communication strategies [50].

The distribution of reports by vaccine type follows the distribution of administrations: 81.3% for mRNA vaccines, 18.6% for viral vector vaccines, and 0.1% for protein subunit vaccines [51].

Vaccine hesitancy among health workers can be harmful for several reasons. In our survey, being a healthcare worker in univariate analyses showed an association with a positive perception towards vaccine safety. However, this same association fails in multivariate analysis. Action to improve health workers' trust in institutions and in the safety of vaccines could lead to a higher acceptance rate [52]. Our study showed that people hesitant about vaccination seem to have certain characteristic traits, among which we found, in addition to distrust of institutions, a low perception of danger towards the disease and an extreme fear of adverse events. These aspects have also emerged in other studies [47, 53]. Factors contributing to vaccine trust are multiple: trust in health systems, manufacturers, institutions, information, and perceptions of the importance, safety, and efficacy of vaccines [54]. Analyzing factors related to vaccine acceptance is crucial to guide public health activities, which is the reason we decided to conduct a study based on an online questionnaire to assess in an adult population sample vaccine hesitancy and confidence.

WHO recently stated how infodemic and misinformation are able to negatively influence people's health behaviors [55]. It is a fact that those who did not vaccinate were those who suffered the most severe consequences of COVID-19 disease, constituting the majority of hospitalized cases [56]. Those who filled out this online survey are the same people who seek information through websites, social networks, and online search engines. Therefore, it is hoped that the effects of the infodemic and online health misinformation can be countered by improving awareness campaigns and, above all, by enhancing people's digital and health literacy. This task is precisely fulfilled by institutions, although the population does not always have full trust in them. Those who do not trust institutions probably do not trust the health authorities' decisions regarding health either. Primary prevention, particularly vaccination, represents the most powerful tool available to local and global health decision-makers for preventing the spread of disease and improving the outcome of those infected. The promotion and dissemination of reliable health information are of paramount importance for governments and health authorities to counter false or misleading health information spread on social media. It is critical to counter false or misleading information.

Our study has several limitations. It is necessary to consider the possibility of selection bias. Our ques-

tionnaire was distributed predominantly online, using social platforms and comments on posts regarding anti-COVID-19 vaccination. This approach may have attracted a sample that was not representative of the general population, favoring the participation of individuals with a particular interest, opinion or emotional involvement regarding vaccines. Consequently, the level of trust expressed in our sample, especially towards anti-COVID-19 vaccines, may not accurately reflect the perception of the entire Italian population. It is therefore plausible that this bias influenced our results, underlining the need to conduct further research with more representative samples and different data collection methods to verify our conclusions. Finally, ours is a cross-sectional study, which takes a snapshot of the community response at a specific time in the SARS-CoV-2 pandemic. The feelings and beliefs about COVID-19 vaccines might change over time. A further limitation of the study is that the survey focused on perceptions of vaccine safety and did not include comprehensive measures of vaccine hesitancy, such as complacency and convenience. Still, we evaluated vaccine safety perception as a proxy for vaccine hesitancy. Further studies are needed and should incorporate validated multi-item scales to assess these additional dimensions. The questionnaire was administered one year after the start of the vaccination campaign in Italy, so news about vaccination, alleged adverse reactions, and the evolution of the pandemic may have influenced perceptions toward vaccines.

Despite these limitations, including the non-representativeness of the sample due to the high percentage of healthcare workers and highly educated individuals, our findings are novel and interesting. By exploring the level of confidence in vaccine formulations, we incorporated the concept of an individual's experience, which is related to the feeling of trusting in the good qualities of vaccines. While our data do not represent the general population, they highlight an important phenomenon that deserves further research and attention. In this way, our findings can contribute to a better understanding of people's attitudes towards different vaccine technologies and inform future studies. However, it is essential to balance this individualised perspective with a broader public health approach. While recognition of individual concerns and preferences can improve vaccine uptake at the micro level, public health strategies must emphasise equity of access, consistency of communication and evidence-based guidelines for vaccine safety and efficacy. This dual perspective ensures that individual confidence in vaccines is strengthened without compromising the collective goal of achieving widespread immunity by balancing public health resources and priorities. With the evolution of the epidemic, it will be increasingly important to understand people's attitudes toward vaccinations and their level of confidence in order to construct well-designed communication campaigns.

CONCLUSIONS

Factors related to vaccine confidence and vaccine hesitancy indicate that among people who generally consider vaccines safe, there is a proportion who do not place the same trust in anti-COVID-19 vaccines. These findings underscore the need for further research into the drivers of vaccine perceptions, especially regarding different vaccine technologies, and should be considered primarily as an indicator of a phenomenon rather than a comprehensive representation of the general population.

There are factors, especially trust in institutions, associated with perceptions of safety toward anti-COVID-19 vaccines; therefore, it will also be important to take these aspects into account to guide future communication activities aimed at achieving SARS-CoV-2 pandemic control and public health goals.

It is important for policymakers to understand the factors related to vaccine confidence and hesitancy. Although our data are not representative of the general population, they provide an initial exploration of a critical phenomenon and stress the need for more extensive research. This study can help in understanding how to target vaccination and communication campaigns more effectively to counter the circulating infodemic and ensure the highest possible vaccination coverage.

Funding

This research received no external funding.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethics Committee of the University of Florence, Italy (Protocol code 0081791, 13/04/2022). The acronym of the questionnaire disseminated online is: PERSIC-VACCINICOVID-19.

Conflict of interest statement

The Authors declare no conflict of interest.

Received on 24 September 2024.
Accepted on 5 December 2024.

REFERENCES

1. Hui DS, I Azhar E, Madani TA, Ntoumi F, Kock R, Dar O, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health – The latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Dis. 2020;91:264-6. doi: 10.1016/j.ijid.2020.01.009
2. Edouard Mathieu, Hannah Ritchie, Lucas Rodés-Guirao, Cameron Appel, Daniel Gavrilov, Charlie Giattino, Joe Hasell, Bobbie Macdonald, Saloni Dattani, Diana Beltekian, Esteban Ortiz-Ospina, Max Roser. Coronavirus (COVID-19) Cases. Our World in Data; 2020, rev. 2024. Available from: https://ourworldindata.org/covid-cases#what-is-the-cumulative-number-of-confirmed-cases.
3. Mathieu E, Ritchie H, Rodés-Guirao L, Appel C,

Gavrilov D, Giattino C, Hasell J, Macdonald B, Dattani S, Beltekian D, Ortiz-Ospina E, Roser M. Coronavirus (COVID-19) Deaths. Our World in Data; 2020, rev. 2024. Available from: https://ourworldindata.org/covid-deaths#what-is-the-cumulative-number-of-confirmed-deaths.

4. Roy CM, Bollman EB, Carson LM, Northrop AJ, Jackson EF, Moresky RT. Assessing the indirect effects of COVID-19 on healthcare delivery, utilization and health outcomes: a scoping review. Eur J Public Health. 2021;31(3):634-40. doi: 10.1093/eurpub/ckab047
5. Mathieu E, Ritchie H, Rodés-Guirao L, Appel C, Gavrilov D, Giattino C, Hasell J, Macdonald B, Dattani S, Beltekian D, Ortiz-Ospina E, Roser M. Italy: Coronavirus pandemic country profile. Our World in Data; 2024. Available from: https://ourworldindata.org/coronavirus/country/italy.
6. Zheng H, Chen W. COVID-19 vaccines for the older population: Safety and efficacy go hand in hand. Lancet Healthy Longev. 2022;3(7):e455-6. doi: 10.1016/S2666-7568(22)00152-0
7. Mateo-Urdiales A, Spila Alegiani S, Fabiani M, Pezzotti P, Filia A, Massari M, et al. Risk of SARS-CoV-2 infection and subsequent hospital admission and death at different time intervals since first dose of COVID-19 vaccine administration, Italy, 27 December 2020 to mid-April 2021. Eurosurveillance [Internet]. 2021;26(25). Available from: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2021.26.25.2100507.
8. Istituto Superiore di Sanità (ISS). Piano strategico nazionale di vaccinazione COVID-19. Roma: ISS; 2021, rev 2024. Available from: https://www.epicentro.iss.it/vaccini/covid-19-piano-vaccinazione#:~:text=Il%2027%20dicembre%202020%2C%20il,iniziata%20il%2031%20dicembre%202020.
9. Del Riccio M, Boccalini S, Rigon L, Biamonte MA, Alborа G, Giorgetti D, et al. Factors influencing SARS-CoV-2 vaccine acceptance and hesitancy in a population-based sample in Italy. Vaccines (Basel). 2021;9(6):633. doi: 10.3390/vaccines9060633
10. Our World in Data. Coronavirus (COVID-19) vaccinations. Our World in Data; 2024. Available from: https://ourworldindata.org/covid-vaccinations.
11. Dubé E, Vivion M, MacDonald NE. Vaccine hesitancy, vaccine refusal and the anti-vaccine movement: influence, impact and implications. Expert Rev Vaccines. 2015 J;14(1):99-117.
12. Troiano G, Nardi A. Vaccine hesitancy in the era of COVID-19. Public Health. 2021;194:245-51. doi: 10.1586/14760584.2015.964212
13. Ahmed S, Rasul ME, Cho J. Social media news use induces COVID-19 vaccine hesitancy through skepticism regarding its efficacy: A longitudinal study from the United States. Front Psychol. 2022;13:900386. doi: 10.3389/fpsyg.2022.900386
14. World Health Organization (WHO). Infodemic management. Geneva: WHO; 2023. Available from: https://www.who.int/teams/risk-communication/infodemic-management.
15. Galvão J. COVID-19: The deadly threat of misinformation. Lancet Infect Dis. 2021;21(5):e114. doi: 10.1016/S1473-3099(20)30721-0
16. World Health Organization (WHO). Ten threats to global health in 2019. Geneva: WHO; 2024. Available from: https://www.who.int/news-room/spotlight/ten-threats-to-global-health-in-2019.
17. MacDonald NE. Vaccine hesitancy: Definition, scope and determinants. Vaccine. 2015;33(34):4161-4. doi: 10.1016/j.vaccine.2015.04.036
18. Fan J, Wang X, Du S, Mao A, Du H, Qiu W. Discussion of the trust in vaccination against COVID-19. Vaccines. 2022;10(8):1214. doi: 10.3390/vaccines10081214
19. Boccalini S, Bonanni P, Chiesi F, Pisa GD, Furlan F, Giammarco B, et al. The experience of VaccinarSinToscana website and the role of new media in promoting vaccination. Vaccines (Basel). 2020;8(4):644. doi: 10.3390/vaccines8040644
20. Cadeddu C, Daugbjerg S, Ricciardi W, Rosano A. Beliefs towards vaccination and trust in the scientific community in Italy. Vaccine. 2020;38(42):6609-17. doi: 10.1016/j.vaccine.2020.07.076
21. Zarbo C, Candini V, Ferrari C, d'Addazio M, Calamandrei G, Starace F, et al. COVID-19 vaccine hesitancy in Italy: Predictors of acceptance, fence sitting and refusal of the COVID-19 vaccination. Front Public Health. 2022;10:873098. doi: 10.3389/fpubh.2022.873098
22. Heyerdahl LW, Vray M, Lana B, Tvardik N, Gobat N, Wanat M, et al. Conditionality of COVID-19 vaccine acceptance in European countries. Vaccine. 2022;40(9):1191-7. doi: 10.1016/j.vaccine.2022.01.054
23. Rasul ME, Ahmed S. Not all conservatives are vaccine hesitant: Examining the influence of misinformation exposure, political ideology, and flu vaccine acceptance on COVID-19 vaccine hesitancy. Vaccines (Basel). 2023;11(3):586. doi: 10.3390/vaccines11030586
24. Lazarus JV, Wyka K, White TM, Picchio CA, Gostin LO, Larson HJ, et al. A survey of COVID-19 vaccine acceptance across 23 countries in 2022. Nat Med. 2023;29(2):366-75. doi: 10.1038/s41591-022-02185-4
25. Larson HJ, Cooper LZ, Eskola J, Katz SL, Ratzan S. Addressing the vaccine confidence gap. Lancet. 2011;378(9790):526-35. doi: 10.1016/S0140-6736(11)60678-8
26. Schaffer DeRoo S, Pudalov NJ, Fu LY. Planning for a COVID-19 vaccination program. JAMA. 2020;323(24):2458. doi: 10.1001/jama.2020.8711
27. Salerno L, Craxì L, Amodio E, Lo Coco G. Factors affecting hesitancy to mRNA and viral vector COVID-19 vaccines among college students in Italy. Vaccines. 2021;9(8):927. doi: 10.3390/vaccines9080927
28. Gruppo di Redazione Vaccinarsintoscana.org (Ed). Quanto ne sai di vaccini anti-COVID19? Partecipa al nostro questionario! Firenze: Università degli Studi di Firenze; 2022. Available from: https://www.vaccinarsintoscana.org/notizie/2022/04/quanto-ne-sai-di-vaccini-anti-covid19-partecipa-al-nostro-questionario!
29. McNutt LA. Estimating the relative risk in cohort studies and clinical trials of common outcomes. Am J Epidemiol. 2003;157(10):940-3. doi: 10.1093/aje/kwg074
30. Zou G. A modified Poisson regression approach to prospective studies with binary data. Am J Epidemiol. 2004;159(7):702-6. doi: 10.1093/aje/kwh090
31. World Health Organization (WHO). Monitoring and responding to adverse events following immunization (AEFIs). Geneva: WHO; 2021. Available from: https://www.who.int/docs/default-source/covid-19-vaccines-safety-surveillance-manual/training-slides_covid-19_vs_aefi.pdf?Status=Master&sfvrsn=c81f2d76_8.
32. Wu N, Joyal-Desmarais K, Ribeiro PAB, Vieira AM, Stojanovic J, Sanuade C, et al. Long-term effectiveness of COVID-19 vaccines against infections, hospitalisations, and mortality in adults: Findings from a rapid living systematic evidence synthesis and meta-analysis up to December, 2022. Lancet Respir Med. 2023;11(5):439-52. doi: 10.1016/S2213-2600(23)00015-2
33. European Medicines Agency (EMA). Comirnaty. Am-

sterdam, The Netherlands: EMA; 2024. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/comirnaty.
34. European Medicines Agency (EMA). Spikevax (previously COVID-19 Vaccine Moderna). Amsterdam, The Netherlands: EMA; 2024. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/spikevax-previously-covid-19-vaccine-moderna.
35. European Medicines Agency (EMA). Vaxzevria (previously COVID-19 Vaccine AstraZeneca). Amsterdam, The Netherlands: EMA; 2024. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/vaxzevria-previously-covid-19-vaccine-astrazeneca.
36. Commissione Europea. Allegato 1. Riassunto delle caratteristiche del prodotto. 2022. Available from: https://ec.europa.eu/health/documents/community-register/2021/20211220154520/anx_154520_it.pdf.
37. Fabiani M, Puopolo M, Morciano C, Spuri M, Spila Alegiani S, Filia A, et al. Effectiveness of mRNA vaccines and waning of protection against SARS-CoV-2 infection and severe covid-19 during predominant circulation of the delta variant in Italy: Retrospective cohort study. BMJ. 2022;376:e069052. doi: 10.1136/bmj-2021-069052
38. Thomas SJ, Moreira ED, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine through 6 months. N Engl J Med. 2021;385(19):1761-73. doi: 10.1056/NEJMoa2110345
39. Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. N Engl J Med. 2021;384(15):1412-23. doi: 10.1056/NEJMoa2101765
40. Lopez Bernal J, Andrews N, Gower C, Robertson C, Stowe J, Tessier E, et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on Covid-19 related symptoms, hospital admissions, and mortality in older adults in England: Test negative case-control study. BMJ. 2021;373:n1088. doi: 10.1136/bmj.n1088
41. Graña C, Ghosn L, Evrenoglou T, Jarde A, Minozzi S, Bergman H, et al. Efficacy and safety of COVID-19 vaccines. Cochrane Database Syst Rev. 2022;12(12):CD015477. doi: 10.1002/14651858.CD015477
42. Beretta G, Marelli L. Fast-tracking development and regulatory approval of COVID-19 vaccines in the EU: A review of ethical implications. Bioethics. 2023;37(5):498-507. doi: 10.1111/bioe.13151
43. Rozek LS, Jones P, Menon A, Hicken A, Apsley S, King EJ. Understanding vaccine hesitancy in the context of COVID-19: The role of trust and confidence in a seventeen-country survey. Int J Public Health. 2021;66:636255. doi: 10.3389/ijph.2021.636255
44. Paterlini M. Covid-19: Italy makes vaccination mandatory for healthcare workers. BMJ. 2021;373:n905. doi: 10.1136/bmj.n905
45. Primieri C, Bietta C, Giacchetta I, Chiavarini M, de Waure C. Determinants of COVID-19 vaccination acceptance or hesitancy in Italy: An overview of the current evidence. Ann Ist Super Sanità. 2023;59(1):10-25. doi: 10.4415/ANN_23_01_03
46. Ministero della Salute. Report vaccini anti-COVID-19. Roma: Ministero delle Salute; 2024. Available from: https://www.governo.it/it/cscovid19/report-vaccini/.
47. Bajos N, Spire A, Silberzan L, Sireyjol A, Jusot F, Meyer L, et al. When lack of trust in the government and in scientists reinforces social inequalities in vaccination against COVID-19. Front Public Health. 2022;10:908152. doi: 10.3389/fpubh.2022.908152
48. Quinn SC, Jamison AM, An J, Hancock GR, Freimuth VS. Measuring vaccine hesitancy, confidence, trust and flu vaccine uptake: Results of a national survey of White and African American adults. Vaccine. 2019;37(9):1168-73. doi: 10.1016/j.vaccine.2019.01.033
49. Larson HJ, Schulz WS, Tucker JD, Smith DM. Measuring vaccine confidence: Introducing a global vaccine confidence index. PLoS Curr. 2015;7:ecurrents.outbreaks.ce0f6177bc97332602a8e3fe7d7f7cc4. doi: 10.1371/currents.outbreaks.ce0f6177bc97332602a8e3fe7d7f7cc4
50. Roy DN, Biswas M, Islam E, Azam MdS. Potential factors influencing COVID-19 vaccine acceptance and hesitancy: A systematic review. PLoS ONE. 2022;17(3):e0265496. doi: 10.1093/eurpub/ckab047
51. Agenzia Italiana del Farmaco (AIFA). Rapporto sulla Sorveglianza dei vaccini anti-COVID-19. Roma: AIFA; 2024. Available from: https://www.aifa.gov.it/documents/20142/1315190/Rapporto_sorveglianza_vaccini_COVID-19_14.pdf.
52. Trabucco Aurilio M, Mennini FS, Ferrari C, Somma G, Di Giampaolo L, Bolcato M, et al. Main predictors of COVID-19 vaccination uptake among Italian healthcare workers in relation to variable degrees of hesitancy: Result from a cross-sectional online survey. TropicalMed. 2022;7(12):419. doi: 10.3390/tropicalmed7120419
53. Rief W. Fear of adverse effects and COVID-19 vaccine hesitancy: Recommendations of the Treatment Expectation Expert Group. JAMA Health Forum. 2021;2(4):e210804. doi: 10.1001/jamahealthforum.2021.0804
54. de Figueiredo A, Simas C, Karafillakis E, Paterson P, Larson HJ. Mapping global trends in vaccine confidence and investigating barriers to vaccine uptake: A large-scale retrospective temporal modelling study. Lancet. 2020;396(10255):898-908. doi: 10.1016/S0140-6736(20)31558-0
55. World Health Organization (WHO). Infodemics and misinformation negatively affect people's health behaviours, new WHO review finds. Geneva: WHO; 2022. Available from: https://www.who.int/europe/news/item/01-09-2022-infodemics-and-misinformation-negatively-affect-people-s-health-behaviours--new-who-review-finds.
56. Mendoza-Cano O, Trujillo X, Ríos-Silva M, Lugo-Radillo A, Benites-Godínez V, Bricio-Barrios JA, et al. Association between vaccination status for COVID-19 and the risk of severe symptoms during the endemic phase of the disease. Vaccines (Basel). 2023;11(10):1512. doi: 10.3390/vaccines11101512

Ann Ist Super Sanità 2025 | Vol. 61, No. 1: 30-41
DOI: 10.4415/ANN_25_01_05

Life project: a scoping review of assessment tools for persons with autism spectrum disorder

Giulia Ferrazzi[1], Mattia Marchi[1], Virginia Giuberti[2], Virginia Politi[2], Luca Pingani[1], Silvia Ferrari[1], and Gian Maria Galeazzi[2]

[1]*Dipartimento di Scienze Biomediche, Metaboliche e Neuroscienze, Università degli Studi di Modena e Reggio Emilia, Modena, Italy*
[2]*Dipartimento ad Attività Integrata di Salute Mentale e Dipendenze Patologiche, Azienda USL - IRCCS di Reggio Emilia, Reggio Emilia, Italy*

Key words
- life project
- autism spectrum disorder
- transition
- coping review
- person-centered plan

Abstract

Background. Persons with autism spectrum disorder (ASD) may face significant challenges during transition from adolescence to adulthood. This phase necessitates tailored support to address all needs, underscoring the importance of a comprehensive life project (LP) planning. This scoping review aims to identify methods and tools used in the development of LP for persons with ASD.

Methods. The preferred reporting items for systematic reviews and meta-analyses (PRISMA) extension for scoping reviews was used. The literature search was performed across Embase, Scopus, Web of Science, PubMed, CINAHL, and PsycINFO. The selection process involved screening titles and abstracts, followed by full-text reading, data extraction, and narrative synthesis of findings.

Results. A total of 899 records were identified, and 8 studies were included in the review. Preference assessment and ecological balance emerged as crucial elements in developing LP.

Conclusions. This review highlights the importance of tools that accurately capture individual preferences and support needs for persons with ASD but also reveals a gap in the literature concerning the development of tailored LP for this population.

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by persistent and pervasive difficulties in social communication and by restricted and/or repetitive interests or behaviors which may be associated with different levels of disability [1]. Around the age of 18, in most European countries, a large proportion of people with ASD receiving mental health care have to cross the artificial boundary between child and adolescent mental health services (CAMHS) and adult mental health services (AMHS) [2]. The term "transition" specifically refers to the period when young individuals move from CAMHS to AMHS.

Transition from CAMHS to AMHS may represent a challenge for transitional age youth with ASD [3], in particular for those presenting additional mental and physical health challenges [4, 5]. Transition refers to the planned process that addresses the medical, psychosocial, educational, and vocational needs of adolescents and young adults with long term physical, neurodevelopmental and medical conditions as they move from child-centered to adult-oriented health-care systems [6]. Transition is crucial for adult life fulfillment, which may include: obtaining a job, post-secondary education, attending a day habilitation program or maybe living outside of the family home [7]. Transition necessitates planning to ensure that ASD individuals receive support and services they will need as adults [8]: for this purpose, transition plans (TP) and life projects (LPs) are needed [9, 10]. TP is the document that outlines how transition should be managed, detailing the steps and support required to facilitate this change. TP is a comprehensive strategy designed to ensure that adolescents and young adults with long term physical, neurodevelopmental, and medical conditions, like ASD, receive the necessary support and services as they enter adulthood [11]. While TP encompasses a broad spectrum of needs and considerations, focusing on the individual's person-

Address for correspondence: Gian Maria Galeazzi, Dipartimento di Salute Mentale e Dipendenze Patologiche, Azienda USL - IRCCS di Reggio Emilia, Via Giovanni Amendola 2, 42122 Reggio Emilia, Italy. E-mail: gianmaria.galeazzi@unimore.it.

al goals, preferences, and aspirations require additional planning, which in the Italian context is known as the LP. LP generally includes TP, referring to the broader process that goes beyond the immediate transition, encompassing all aspects of a person's life from adolescence onwards. The LP integrates educational, social, and professional goals, ensuring a comprehensive approach to an individual's development and well-being. It is a person-centered approach that considers the unique strengths and challenges of the person with ASD. LP is developed collaboratively, involving the individual, their family/caregivers, and relevant professionals. Despite referring to different concepts, an overlap exists between TP and LP, due to the timing of the transition and its integration within the broader design of the future LP. Both are crucial for ensuring a smooth and effective transition for ASD individuals as they navigate the challenging shift from child-oriented to adult-oriented mental health services. The seamless integration of the TP within the larger LP is essential for supporting these individuals through transition from adolescence to adulthood. LP aims to a comprehensive, personalized approach designed to support the individual's overall well-being, development, and integration into society across their lifespan. It encompasses various dimensions, aims and activities of life, including education, employment, health, social connections, leisure activities, and living arrangements [12]. The goal is to ensure that ASD individuals can achieve the highest quality of life (QoL) possible, according to their desires, strengths, challenges, and needs. The LP concerns the ASD population who, once they finish schooling (around age 18), find themselves having to reconsider and reorganize their daily lives, which the school institution previously contributed to manage and give structure to [13]. In doing so, LP emphasizes the individual's autonomy and personal definition of a fulfilling life [14].

Notably, in the Italian context, the concept of a LP has been particularly used during the transition from school to "adult life". This transition is not a simply chronological progression but a real transformation that necessitates a comprehensive reevaluation and adaptation of one's daily environment. The development of a personalized LP can help in overcoming the critical nature of this phase [15]. Although much literature on the transition to adulthood for ASD population is present [2, 6, 15-17], still little addresses issues around the concept, development and implementation of the LP [10]. In this context, Italian legislation has introduced specific measures to ensure greater autonomy and social integration for individuals, which further reinforced the concept of a LP. The Italian Law 112/2016, titled "Provisions on assistance for people with severe disabilities lacking family support", commonly known as the "after us law", introduced for the first time specific protections for individuals with severe disabilities in Italy. The law aims to ensure maximum autonomy and independence for people with disabilities, enabling them, for example, to continue living in environments as close as possible to their family home even when their parents are no longer able to care for them. The goal is to ensure a high QoL in the community, in line with the principles of the United Nations' Convention on the rights of persons with disabilities [18]. Thereafter the Italian State-Regions Unified Conference [19] on May 10, 2018, concerning the "Update of the guidelines for the promotion and improvement of the quality and appropriateness of care interventions in ASD" highlighted the need to train professionals to participate in the creation of individualized LP aimed at improving the QoL. The conference advocates for the incorporation of the LP into treatment strategies for ASD people, and to promote professional competencies for delivering therapeutic and habilitative/rehabilitative interventions based on the best available scientific evidence [20]. Moreover, in order to address social and healthcare needs of individuals with complex necessities, including ASD people, the personal health budget (PHB) has been implemented in various European countries [21]. The PHB is an integrated social-health tool designed to align the individualized therapeutic program with LP, promoting social inclusion and autonomy [22]. Guidelines have been established to support the development of LPs focused on improving QoL. Each Italian region and autonomous province, through regional centers and networks of community mental health services, rare disease programs, and adult disability services, promotes differentiated pathways tailored to individual needs. These pathways are based on varying levels of support required, adaptive functioning, and any associated diagnoses [23]. The guidelines (*linee di indirizzo*) for Italian regions and autonomous provinces for formulation of individualized LP, highlight the needs for its implementation [24, 25].

Overall the concept of a LP received increased attention, particularly following the release of the 2023 guidelines from the Italian National Institute of Health (Istituto Superiore di Sanità, ISS) [26]. At the moment there is an ongoing debate about the best assessments needed to support the development of LPs [23].

Recently the Italian government with the Legislative Decree 62 of May 3, 2024 introduced a comprehensive framework for defining disability conditions and establishing personalized LP for individuals with disabilities. This decree emphasizes a multidimensional assessment approach to create and implement individualized LP that focus on autonomy and social inclusion. Such legislative measures seem crucial for improving the QoL and promoting the independence of individuals with ASD [27].

The development and validation of assessment tools to accurately measure the needs, strengths, and goals of ASD individuals is urgent [28]. These tools should be adaptable to the diversity in the clinical presentation of ASD and flexible enough to accommodate changes over time. From that perspective, integrating LP with care programs through a unified, person-centered approach is essential. The aim of this scoping review is to identify evidence on the principal assessment tools in LP development for ASD individuals.

MATERIAL AND METHODS

We used the preferred reporting items for systematic reviews and meta-analyses (PRISMA) extension for scoping review [29]. A comprehensive literature search

was performed across Embase, Scopus, Web of Science, PubMed, CINAHL, and PsycINFO, up to 11th April 2024.

The search terms included key phrases related to ASD, assessment tools, LP and related concepts. Boolean operators (AND, OR) were utilized to refine the search queries. The search string was defined and approved by the chief librarian from the authors' institution, who supervised its adaptation across the various databases searched. Details on the search strategies are shown in *Table 1*.

The selection of studies was done by a single review Author (GF) using the web software Rayyan for the screening part of titles and abstracts. Rayyan's artificial intelligence (AI) tool aided in the screening process by learning from screening decisions made on a subset of articles. Once at least 50 studies have been manually reviewed, Rayyan's AI calculates the probability of inclusion or exclusion for each remaining undecided article [30, 31]. Rayyan assigns each record with one of the following ratings: 0.5 stars, 1.5 stars, 2.5 stars, 3.5 stars, or 4.5 stars. Records with a rating of 0.5 or 1.5 were considered ineligible according to the software guidelines available at the help center (https://help.rayyan.ai) as the optimal choice for records screening. Previous reports, suggested that at the threshold of <2.5 for exclusion, Rayyan showed 100% specificity compared to human decision, resulting in a reliable tool for excluding ineligible records in the screening process [32]. Selection by full-text reading and data extraction was performed by the same researcher (GF). An expert reviewer supervised the entire phase of study selection and data extraction. For each study, data were extracted regarding the study design, reported aims, country, LP, evaluation tool, and main results.

Table 1
Database search strategy

Database	Search strategy 11th April 2024
Embase	('life plan' OR 'personal development plan' OR 'life roadmap' OR 'person-centered plan*' OR 'support plan*' OR 'transition plan*' OR 'life project') AND 'autism'/exp
Web of Science	"Life Plan" OR "Personal Development Plan" OR "Life Roadmap" OR "Person-Centered Plan*" OR "Support Plan*" OR "Transition Plan*" OR "life project"
Scopus	"life plan" OR "personal development plan" OR "life roadmap" OR "person-centered plan*" OR "support plan*" OR "transition plan*" OR "life project" + "autism" OR "autism spectrum disorder"
CINAHL & PsycINFO	("Life Plan" OR "Personal Development Plan" OR "Life Roadmap" OR "Person-Centered Plan*" OR "Support Plan*" OR "Transition Plan*" OR "life project") AND ("Autism" OR "Autism Spectrum Disorder")
PubMed	("Life Plan" OR "Personal Development Plan" OR "Life Roadmap" OR "Person-Centered Plan*" OR "Support Plan*" OR "Transition Plan*" OR "life project") AND ("Autism" OR "Autism Spectrum Disorder")

Inclusion and exclusion criteria

Studies were included if they focused on developing LP for individuals of any age (both minor and adults) diagnosed with ASD according to diagnostic and statistical manual of mental disorders or international classification of diseases [33, 34], and explicitly discussing the assessment tools employed. All types of studies published in peer-reviewed journals were considered for inclusion. We excluded reviews and book chapters as these are not primary publications, conference abstracts and dissertations as these are not generally peer reviewed. Although no language or publication date restrictions were applied in the initial search, only English-language full texts were considered in the eligibility stage to ensure inclusion of studies accessible to an international audience. Studies that only addressed transition phases without mention to TP or LP and studies involving participants with different diagnoses than ASD (e.g., attention deficit hyperactivity disorder) were also excluded.

Data extraction

Data extraction was performed by one review Author (GF) using a predefined form which was verified by a second reviewer [35]. Extracted information included study design, participant characteristics, LP assessment tools, and key findings related to the effectiveness of the tools in the LP development, realization and ongoing adaptation. Any discrepancies or uncertainties during the extraction process were resolved through discussions with the second review Author (GMG). A narrative synthesis approach was then employed to summarize and analyze the identified assessment tools. This involved categorizing the tools based on their focus areas, such as educational goals, life skills, and community integration.

Quality assessment

The quality of the included studies was assessed using the Joanna Briggs Institute (JBI) critical appraisal tools [36]. One review Author (GF) conducted the initial assessment, and the results were checked by a second review Author (MM) to ensure accuracy and consistency in the evaluation.

RESULTS

The first search identified 899 records. After duplicate removal 640 were eligible for screening. Following a preliminary screening of 50 records performed by a researcher to train the software, the subsequent screening was automated in Rayyan. Records with a rating of 0.5 or 1.5 were considered ineligible [32]. A total of 312 records remained and were screened by a human researcher (GF) on the title and abstract. Following this, 57 full texts were assessed for eligibility, leading to the selection of 8 studies which were included as the foundational literature for this paper. Most of the excluded studies (n=30) primarily focused exclusively on the transition period but not on LP or were based on the experiences of individuals with ASD or their caregivers, were therefore because "out of topic". Additionally, many of the excluded studies were dissertations or book

chapters, leading to their exclusion based on publication type (n=18). The PRISMA flowchart summarizing the selection process is shown in *Figure 1*.

For each study included in the review, data on the aim of the study, type of study, tools used for the LP and the main results were extracted and summarized in *Table 2*. The included studies display a wide range of methodologies and objectives, emphasizing the complexity and individualized nature of planning LP for in the context of ASD.

All included studies were published after the year 2000. Four were published between 2000 and 2010, two between 2010 and 2020, and the remaining two after the 2020. Seven out of the eight studies focused on the descriptive analysis regarding the LP, with only one study including participant data. Three studies were purely descriptive, three were conceptual analyses, one was a commentary, and the remaining one used a mixed-method design. Four studies addressed the topic of LP only for adults, three for adult and adolescents of which two considered also children, and one exclusively focused on adolescents.

Five studies out of eight used "person-centered planning" (PCP) [37-41]. Two Italian studies used "life project" [10, 42] and the last one [43] used the individualized education program (IEP). IEP is a term often used to refer to school programs [44], but in that paper, it is used in reference to post-school programming.

All the studies emphasize the importance of personalized design, which should be tailored to the individual's characteristics, such as adaptive functioning and context, as well as the person's preferences. Ecological Balance, as an integrative tool for the assessment of the needs of an ASD individual, is mentioned in two studies out of eight [10, 37]. The "ecological life balance" serves as an integrative tool designed to harmonize various assessment systems and support methods for individuals with ASD and intellectual disabilities. The key components include: Assessment of Preferences and Values (procedures are tailored to accommodate the distinct characteristics of adaptive and communicative functioning in individuals with disabilities), Support Needs Assessment (tools for evaluating the support required by individuals to enhance their QoL promoting an "universal design" that accommodate different needs ensuring accessibility and inclusivity), Methods for defining life goals (providing positive behavior support as an example) and Monitoring and Verification (for continuously assessing and verifying the outcomes of the support plans). Indirect screening measures like the systematic psychopathological assessment for persons with intellectual and developmental disabilities-general screening (SPAIDD-G) [45] and the Italian version of the diagnostic assessment for the severely handicapped revised (DASH II) [46] were also implied to better understand support needs. Moreover, to achieve health and behavioral needs, has been recommended to complement these assessments with direct functional analysis tools for behavior, such the experimental functional analysis methods [47].

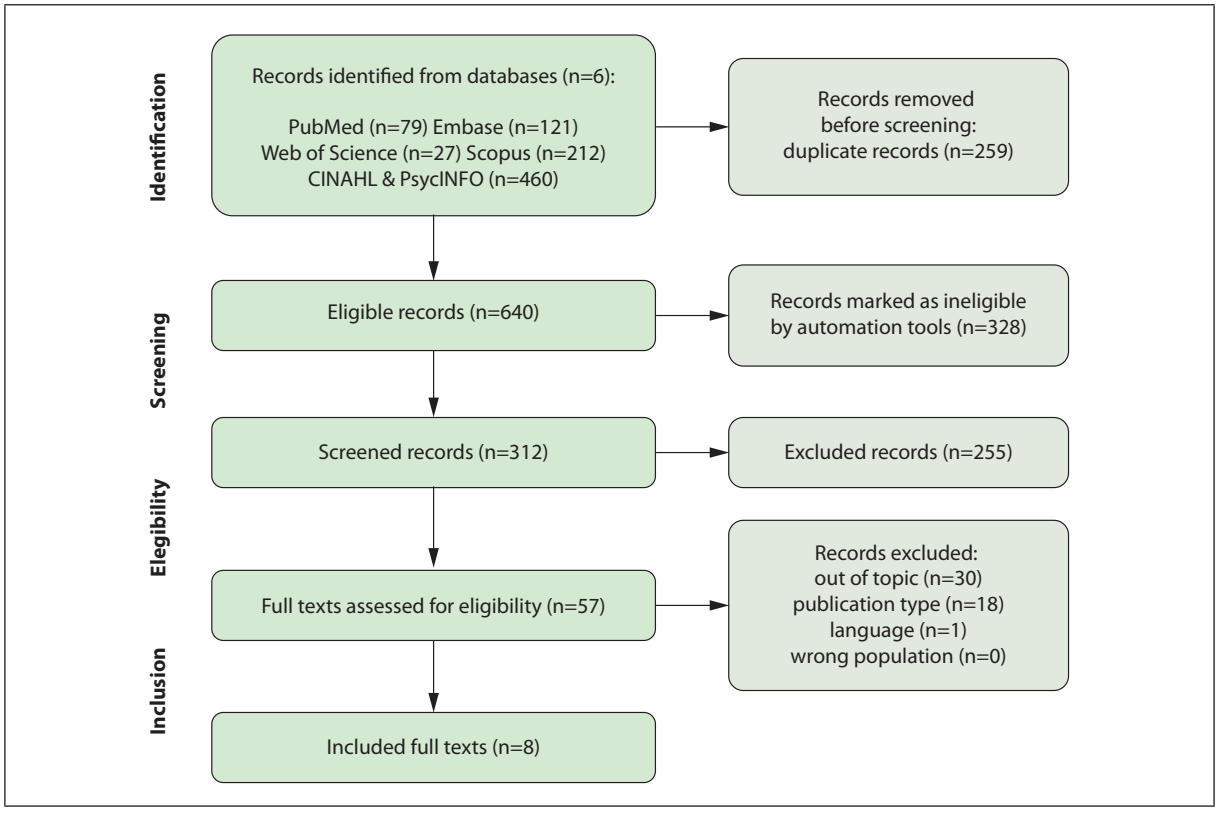


Figure 1
PRISMA flow diagram of study selection for this review.

Table 2
Synthesis of the main features of the studies included in the review

First Author, year	Title	Country	Focus of the study	Publication type	Participants	LP evaluation tool	Main conclusion	Quality assessed
Bui *et al.*, 2003 [40]	East meets West: analysis of PCP in the context of Asian American values	USA	Evaluate the extent to which core values of PCP are consistent	Conceptual analysis	Child, adolescent and adult	Specific approaches are used: Individual service design, person future planning, essential lifestyle planning, whole life planning, McGill action planning system, path, group action planning	This paper emphasizes the importance of a value, culture-based PCP and highlights a gap in the literature about PCP for Asian American families	Low
Callicott *et al.*, 2003 [41]	Culturally sensitive collaboration within PCP	USA	This article provides background, and a description of PCP based on process, components, and outcomes and examines each in relation to working with individuals and families of other cultures and languages	Descriptive study	Adult	The components necessary for PCP to be conducted smoothly involve organizing the logistics for the meeting, developing a personal profile for the individual on structuring a future vision, developing action sets, providing support, and evaluating ongoing implementation. Regardless of the steps or tools used, the essential components of PCP offer open communication for all participants involved in the focus person's life	The PCP effectively involves individuals with disabilities in planning their future by leveraging their strengths and needs and emphasizes the importance of cultural and linguistic sensitivity to enhance communication and support within families and communities	Low
Cappa *et al.*, 2020 [42]	Network of services facilitating and supporting job placement for people with autism spectrum disorders. The experience of the ASL Piacenza, Italy	Italy	Describe how to integrate job opportunity and LP for ASD individuals in ASL Piacenza, Italy	Descriptive study	Adult	Three different paths based on individual functioning: a) internship; b) social co-operative job fair and c) individual placement and support	Psychiatric services must be able to provide different types of job opportunities and the possibility to switch from one to another when the patient desires it	Low
Corti *et al.*, 2023 [10]	The life project of people with autism and intellectual disability: investigating personal preferences and values to enhance self-determination	Italy	Describe the six key phases and the corresponding evaluation to establish and implement the life project for people with ASD and intellectual disability, as conceptualized by the Italian Society of Neurodevelopmental Disorders	Descriptive study	Adult	1. PA; 2. assessment of necessary supports; 3. ecological life balance; 4. definition of existential goals; 5. implementation of the support plan; 6. monitoring and verification	The development of LP for individuals with ASD and intellectual disabilities is essential for enhancing their quality of life, considering their unique communication and adaptive challenges. The LP implementation involves a detailed process of assessing preferences, values, support needs, and utilizing tools like the ecological life balance to harmonize the project. Continuous monitoring and evaluation of outcomes are critical to ensure that the LP remain aligned with the individual's goals	Low

Continues

Table 2
Continued

First Author, year	Title	Country	Focus of the study	Publication type	Participants	LP evaluation tool	Main conclusion	Quality assessed
Hagner *et al.*, 2014 [39]	PCP for transition-aged youth with ASD	USA	Explore the effectiveness and adaptability of PCP for transition-aged youth with ASD	Mixed-method design	Adolescent 47 participants enrolled from high schools in New Hampshire and Maine	The study includes an observational checklist called "How person-centered was this planning?" to assess the fidelity of the planning process. This checklist is used to ensure that the planning meetings are substantially person-centered. The checklist involves assessing various aspects of the meeting, including the extent to which the individual's preferences and choices are prioritized, the participation of the individual in setting goals, and the inclusivity of the meeting atmosphere	PCP can be effectively utilized for transition planning with ASD people. The process allowed these individuals to actively participate in developing their transition goals. Evidence of accommodation strategies was found for 29 participants (62%). There was a tendency for participants with lower levels of adaptive behavior to use accommodations more frequently, although this difference was not statistically significant	Medium
Kim *et al.*, 2004 [38]	Shifting toward person-family interdependent planning	USA	Provide an overview of person-centered planning and family-centered planning approaches for young adults with severe ID linked to ASD, and propose a new, integrated approach called person-family interdependent planning	Conceptual analysis	Adolescent and adult	Person-family interdependent planning should use comprehensive policies and programs providing social, emotional, and financial supports for young adults focusing on values with severe ID linked to ASD and their families should be implemented	Person-family interdependent planning approaches emphasize thinking about transitions into adulthood from the perspectives of persons with disabilities and caregiver	Low
Renzaglia *et al.*, 2003 [37]	Promoting a lifetime of inclusion	USA	Assist parents and professionals in developing effective educational programs that promote a lifetime of successful inclusion for individuals with severe disabilities including ASD with ID	Conceptual analysis	Child, adolescent and adult	PCP tool includes an ecological inventory process, self-determination values (focusing on teaching individuals to engage in goal-directed, autonomous behavior through personalized instruction and supportive environments). Positive behavior support is incorporated, using thorough functional assessments regular reviews and adjustments, along with feedback from individual and their network	PCP and ecological assessment create an individualized picture of a person's goals and skills, and the supports needed to help reach meaningful goals	Low
Tullis *et al.*, 2019 [43]	Incorporating PA into transition planning for people with autism spectrum disorder	USA	Overview of the TP process, as well as how PA may enhance that process	Commentary	Adult	Systematic PA involve direct observation of learner behavior to determine preferred items or activities and are valuable tools to determine preferred stimuli for learners with ASD across a variety of environments (e.g., school, clinic, community)	PA and opportunities to express those preferences (i.e., choice) are one central component for the inclusion of people with ASD	Low

ASD: autism spectrum disorder; ASL: azienda sanitaria locale (local health unit); ID: intellectual disability; LP: life project; PA: preference assessment; PCP: person centered planning; TP: transition plan; USA: United States of America.

One article focused specifically on different paths to ensure employment [42]. The difference between three different ways of supporting employment in the Italian context based mainly on individual level of functioning was the specific framework discussed in the paper. These were: (1) internship which offers a practical work experience in a structured setting; (2) social co-operative jobs fair which provide opportunities for employment within cooperative social enterprises and (3) "Individual Placement and Support", a tailored job placement with ongoing support to ensure success in the free market workplace.

Hagner and colleagues showed that a PCP can be developed through a series of six meetings, guided by a specific checklist covering the following topics: introduction and personal history, career profile (skills, accomplishments, and personal qualities), career profile (preferences and aspirations), vision for the future, resources and barriers, transition and career goals, and career exploration and work experience action steps [39].

Three studies utilized personal values as an inner point to guide the PCP [38, 40, 41]. The first study presented the person-family interdependent approach, where both individual and family values contributed to shaping shared goals and enhancing overall QoL. The second emphasized culturally sensitive PCP, leveraging personal and cultural values to bridge communication gaps and foster inclusion. The third highlighted values within a cultural framework as a foundational element in developing effective PCP. Instead Tullis and colleagues more specifically focused on systematic preference assessments (SPAs) [43]. SPAs use direct observation of the behavior to identify preferred items or activities and serve for determining preferred stimuli for individuals with ASD across various environments (e.g., school, clinic, community).

PCP include different assessments helpful to highlight individuals needs and supports. Some examples are individual service design, person future planning, essential lifestyle planning, whole life planning, McGill action planning system, and group action planning. Although these are not direct or indirect measures, these can be used as a conceptual framework for developing a PCP by inspiring non-traditional strategies [40]. As such they ensure that PCP are focused on desires and preferences of the individual with higher needs and the collaborative efforts of those who care about them [48]. The individual is placed in the center of the planning process, with family members and close friends serving as key authorities in guiding the direction of their life [49].

One study also includes an observational checklist called "How person-centered was this planning?" to assess the fidelity of the planning process [39]. This criterion-referenced checklist ensures that planning meetings are substantially person-centered, with a score of 20 serving as the threshold to identify a PCP process. The checklist involves assessing multiple aspects of the meeting, including the extent to which the individual's preferences and choices are prioritized, the participation of the individual in setting goals, and the atmosphere of inclusivity of the meeting atmosphere.

The quality of the included studies was assessed using the JBI critical appraisal tool. Overall, the studies resulted of low, except one study which was rated as medium quality [39]. Notably, this study was the only one involving human participants and using a mixed-method design. The low quality across studies was primarily due to low scores in the items related to the alignment of methodology with objectives, researcher-research neutrality and inadequate participant representation.

DISCUSSIONS

The aim of this scoping review is to identify evidence concerning methods and assessment tools helpful in the development of LP for ASD individuals.

The transition into adulthood means to become ready for several changes [50]. Transitioning typically involves moving from the structured environment of school to the more self-directed world of adulthood [51, 52]. The transition includes several key areas, such as moving to the workplace, shifting from living with family to more independent living situations, transitioning from pediatric to adult healthcare services, and developing and maintaining social relationships outside the school environment [53]. This phase can be particularly challenging due to difficulties in social communication, sensory sensitivities, and the need for an organized routine [54]. Most of the excluded literature for this review focused exclusively on the transition to adulthood as the movement from CAMHS to AMHS [15, 55]. Indeed, according to the findings published by Appleton in 2019, only a quarter of these young individuals moved to AMHS, and another quarter continued to receive care from CAMHS despite exceeding the age limit [55]. The transition to adulthood is particularly challenging, due to both the continuing dependency of many young ASD adults on their caregivers and the frequent loss of the social support they received during their childhood and adolescence also by mental health and social services [56].

Accordingly, LP planning becomes an essential process in order to ensure the optimal TP [57]. Moreover, TP and LP for ASD often overlap in several areas. For example, both emphasize a person-centered approach, tailoring strategies to the individual's unique strengths, needs, and preferences [10, 16, 23]. TP often begin with goal setting, which is a core component of LP [58]. These goals might include further education, employment, or independent living [59]. Skills required for successful transition, such as self-advocacy, communication, and daily living skills, are also essential for achieving long-term life goals [60]. Building and maintaining a support network is crucial during the transition and throughout life, as these networks provide emotional, social, and practical support [61]. Both processes require ongoing assessment and flexibility to adjust plans as needed [62]. On the other side LP is a proactive approach that involves setting goals and creating strategies to achieve a desired QoL [14]. A LP is not just about addressing immediate needs but also about a long-term path that includes personal, social, and professional aspirations [63]. According to the literature, LP involves establishing personal milestones such as ed-

ucation, employment, hobbies, and skills development [64]. It also requires to identify and build a network of support that includes family, friends, mentors and professional services [12, 65]. Additionally the review support the inclusion, within the LP, of financial planning, maintaining physical and mental health through regular medical check-ups, pharmacological therapy, and a balanced lifestyle [10, 37]. Finally the understanding and advocating for personal rights, including accommodations and anti-discrimination measures, also plays a pivotal role in LP [40]. In fact, as is widely acknowledged, ASD presents significant lifetime social costs, including expenses for specialized education, adult care and productivity loss [66, 67]. Our review highlights a geographic imbalance on LP or PCP development in low- and middle-income countries. The prevalence of American studies may be due to an established research infrastructure and a substantial financial investment in autism research and support services [68, 69]. Resource allocation may partly explain why high-income countries place a greater emphasis on comprehensive PCP approaches [70]. In contrast, in low and middle-income countries ASD support primarily addresses basic care needs, with limited resources [71, 72]. Moreover, in low-to middle-income countries, using the same methods and strategies as high-income countries may not be advantageous, effective, or sustainable.

The studies included in the current review provide only an initial understanding of different approaches and methodologies to support the life planning of individuals with ASD. LP is the term used in Italy but PCP seems to be the term most used in literature [37-41]. PCP is defined as a process for selecting and organizing the services and supports that an older adult or a person with disability may need to live in the community [73]. Most important, it is a process that is directed by the person who receives the support. A PCP process aims to discover how an individual desires to live their life and what may be needed to make that possible, with the aim of influencing positive change in the person's life and supporting services [74]. Similarly, the concept of LP in the Italian context emphasizes planning and supporting an individual's life needs [10, 14, 42]. Both frameworks prioritize the individual's preferences, goals, and active involvement in the planning process. The LP, like PCP, seeks to empower individuals by focusing on their personal desires and ensuring that the necessary resources and supports are aligned to help them achieving their desired life. Thus, while the terminology may differ, the core principles of enhancing personal autonomy, ensuring tailored support, and fostering positive life changes are shared between the LP and PCP. The LP appeared particularly beneficial for individuals with intellectual disabilities associated with ASD, as they often require extensive support in various aspects of life [75], including educational, social, and professional needs. The current review emphasized the LP should ensure personalized assistance to enhance individual's QoL and integration into society. Purposely the concept of QoL emerges as a pivotal construct in defining and guiding the implementation of LP, offering a multidimensional lens through which individual well-being can be assessed and enhanced [10, 37-41, 43]. Defining that construct requires more than one explanation. Individual QoL is a multidimensional construct composed of core domains influenced by personal characteristics and environmental factors [76]. These core domains are the same for all people, although they may vary individually in relative value and importance [77]. Assessment of QoL domains is based on culturally sensitive indicators mostly related to perceptions, behaviors, and life conditions [78]. Adopting a QoL perspective may help services to understand what matters most to someone and how to make things better [79, 80]. From this review several key components emerged as crucial for developing a comprehensive LP:

1. *preference assessment:* systematic preference assessments involve direct observation of individual's behavior to determine preferred items or activities. These assessments are valuable tools for identifying preferred stimuli for individuals with ASD across various environments (e.g., school, clinic, community);
2. *assessment of necessary supports*: this involves identifying the specific supports required for an individual to enhance their QoL. Tools for evaluating support needs ensure that individuals receive the appropriate assistance to achieve their goals;
3. *ecological life balance*: this tool adds various assessment systems and support methods, focusing on achieving a balance that accommodates the distinct characteristics of adaptive and communicative functioning in individuals with disabilities;
4. *definition of existential goals*: this step involves defining life goals that are meaningful and personalized, ensuring that the planning process aligns with the individual's aspirations and desires;
5. *implementation of the support plan*: once goals are defined, a detailed support plan is implemented, incorporating strategies like Positive Behavior Support and other tailored interventions;
6. *monitoring and verification*: continuous assessment and verification of the support plan's outcomes are crucial to ensure that the individual's goals are met and adjustments are made as necessary.

Ecological balance was frequently reported among the selected studies [10, 37]. However, research would benefit from a better definition and agreement of the specific elements of this concept. For instance, personal values as discussed in three papers [10, 37, 38], can lead to understanding ecological balance. Values are crucial because they form the philosophical foundation of inclusion, which is essential for creating equitable, supportive, and empowering environments for ASD individuals [81]. These values emphasize equality, QoL and human rights, ensuring that ASD individuals can live lives similar to those without ASD, with access to the same opportunities and environments [82]. In a nutshell, LP could be defined by identifying supports, structures, and action plans suited to the individual's preferences. Moreover, the importance of preference assessment for the development of LP was also frequently discussed in the included studies [10, 43]. Preference assessment involved a multitude of procedures to determine preferred items or activities. Moreover, in

a therapeutic environment, a therapist might use these assessments to identify stimuli that can be used as positive reinforcement for clients working on behavior modification or skill development. Preference assessments can take various forms including direct observation, trial-based methods that involve the presentation of pairs [83], groups of stimuli [84], or survey methods [85].

Future studies should aim to develop and validate assessment tools that are capable of accurately capturing the complex and multifaceted nature of individual preferences and support needs through the LP process. Additionally, research should evaluate the long-term outcomes of LP implementation to determine their effectiveness and sustainability. This involves examining how LP plans influence clinical outcomes, QoL, independence, and community integration for ASD adults. By tracking these factors over an extended period, researchers could gain a deeper understanding of the true impact of LP and identify areas where improvements are needed. Assessing the cost-effectiveness of LP across diverse economic contexts and not only in high-income countries is essential. Given the global prevalence of ASD [86], future research should address this gap to provide a more comprehensive understanding of LP's benefits worldwide. Follow-up studies are crucial, not only for monitoring the progress and effectiveness of the work done but also for identifying limitations and shortcomings of the planning process. Through continuous assessment and adjustment, the LP process can be optimized to better support the long-term well-being and integration of ASD adults in the community. Future research should also aim to significantly improve articles quality. There should be a particular focus on improving methodological alignment, ethical rigor, and representation of participants' voices. Adopting mixed-methods approaches, as demonstrated in studies like Hagner *et al.*, could enhance methodological alignment by integrating quantitative data with qualitative insights [39]. To improve ethical value, studies might establish advisory boards that include stakeholders, such as ASD individuals and their families. Additionally, engaging individuals with ASD through participatory research methods, like focus groups or co-design sessions, would bring real-life perspectives, leading to findings relevant and applicable.

Several limitations of this review need to be acknowledged. First, due to the context specific nature of the LP, each country may refer to it differently, and there may not always be a direct English translation. This variation in terminology could have led to a significant loss of information in the review. The different names and conceptual frameworks used across various cultures and languages might have caused some relevant studies and approaches to be overlooked, potentially limiting the comprehensiveness of the findings. While the American PCP construct overlaps significantly with the Italian LP concept, integrating these diverse paradigms as we did in this paper may lead to inconsistencies and practical challenges. For example, the cultural contexts and theoretical foundations from which the PCP construct arose may affect the effectiveness of LPs tailored for individuals with ASD in Italy adopting the PCP approach. Second, in May 2024 in Italy, the release of Decree 62 [27] more clearly defines what an LP is within the context of national policy and practice. This decree provides a clearer framework for developing and implementing LPs, aiming to enhance the QoL for individuals with disabilities. However, this decree broadly refers to LP for people with intellectual disability. Third, the selection of studies and data extraction were not conducted independently by two reviewers, which could increase the risk of selection bias [87]. Fourth the inclusion of primarily conceptual studies and only one study involving ASD participants limited the applicability of the findings to real-world scenarios. Sixth, the review was restricted to studies published in English, potentially overlooking relevant research in other languages. Finally, the small number of studies included in the review limited the generalizability and robustness of the conclusions.

CONCLUSIONS

Our results pointed out that there were few studies focusing on the LP for people with ASD, on its definition and how to develop it. The lack of studies specifically addressing the development and implementation of LP for individuals with ASD underscores a critical gap in the current research landscape. Despite the recognized importance of tailored TP and LP development for enhancing the QoL and autonomy of individuals with ASD, there remained a significant need for more comprehensive, evidence-based approaches to guide these processes effectively.

Conflict of interest statement

The Authors declare no conflict of interest.

Received on 3 August 2024.
Accepted on 6 December 2024.

REFERENCES

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5. Washington DC: American Psychiatric Association; 2013.
2. Maurice V, Russet F, Scocco P, McNicholas F, Santosh P, Singh SP, Street C, Purper-Ouakil D. Transition from child and adolescent mental health care to adult services for young people with attention-deficit/hyperactivity disorder (ADHD) or autism spectrum disorder (ASD) in Europe: Barriers and recommendations. L'Encéphale. 2022;48(5):555-9. doi: 10.1016/j.encep.2022.01.012
3. Singh SP, Paul M, Ford T, Kramer T, Weaver T, McLaren S, Street C. Process, outcome and experience of transition from child to adult mental healthcare: multiperspective study. Br J Psychiatry. 2010;197(4):305-12. doi: 10.1192/bjp.bp.109.075135
4. Reis J, Marchini S, Delvenne V. The Transition from child and adolescent mental health services (CAMHS) to adult mental health services (AMHS): What about autism

spectrum disorder? Psychiatr Danub. 2021;33(1):52-7.
5. Howlin P, Magiati I. Autism spectrum disorder: outcomes in adulthood. Curr Opin Psychiatry. 2017;30(2):69-76. doi: 10.1097/YCO.0000000000000308
6. Fortune J, Murphy P, Merchant N, Kerr C, Kroll T, Walsh A, Kelly G. Transition from child-centred to adult-oriented healthcare systems for young people with neurodisability: a scoping review protocol. HRB Open Res. 2020;3:61. doi: 10.12688/hrbopenres.13095.1
7. Keller TE, Cusick GR, Courtney ME. Approaching the transition to adulthood: distinctive profiles of adolescents aging out of the child welfare system. Soc Serv Rev. 2007;81(4):453-84. doi: 10.1086/519536
8. Pillay Y, Brownlow C, March S. Transition approaches for autistic young adults: A case series study. PLoS One. 2022;17(5): 20267942. doi: 10.1371/journal.pone.0267942
9. Colver A, Rapley T, Parr JR, McConachie H, Dovey-Pearce G, Couteur AL, McDonagh JE, Bennett C, Maniatopoulos G, Pearce MS, Reape D, Chater N, Gleeson H, Vale L. Facilitating transition of young people with long-term health conditions from children' to adults' healthcare services – Implications of a 5-year research programme. Clin Med. 2020;20(1):74-80. doi: 10.7861/clinmed.2019-0077
10. Corti S, Cavagnola R, Carnevali D, Leoni M, Francesco F, Galli L, Alzani L, Michelini G, Miselli G, Chiodelli G. The life project of people with autism and intellectual disability: investigating personal preferences and values to enhance self-determination. Psychiatr Danub. 2023;35(Suppl. 3):17-23.
11. Mubanga N, Baumgardner DJ, Kram JJF. Health care transitions for adolescents and young adults with special health care needs: where are we now? J Patient-Centered Res Rev. 2017;4(2):90-5. doi: 10.17294/2330-0698.1406
12. Fulceri F, Gila L, Caruso A, Micai M, Romano G, Scattoni ML. Building bricks of integrated care pathway for autism spectrum disorder: A systematic review. Int J Mol Sci. 2023;24(7):6222. doi: 10.3390/ijms24076222
13. Laghi F, Trimarco B. Individual planning starts at school. Tools and practices promoting autonomy and supporting transition to work for adolescents with autism spectrum disorder. Ann Ist Super Sanità. 2020;56(2):222-9. doi: 10.4415/ANN_20_02_12
14. Perego C, Oberti I, Pavesi AS. "Progetto di Vita" and universal design for persons with disabilities. Stud Health Technol Inform. 2022;297:201-8. doi: 10.3233/SHTI220840.
15. Appleton R, Canaway A, Tuomainen H, Dieleman G, Gerritsen S, Overbeek M, Maras A, van Bodegom L, Franić T, de Girolamo G, Madan J, McNicholas F, Purper-Ouakil D, Schulze UME, Tremmery S, Singh SP. Predictors of transitioning to adult mental health services and associated costs: a cross-country comparison. BMJ Ment Health. 2023;26(1):e300814. doi: 10.1136/bmjment-2023-300814
16. Westbrook JD, Fong CJ, Nye C, Williams A, Wendt O, Cortopassi T. Transition services for youth with autism: a systematic review. Res Soc Work Pract. 2015;25(1):10-20. doi: 10.1177/1049731514524836
17. Hatfield M, Falkmer M, Falkmer T, Ciccarelli M. Evaluation of the effectiveness of an online transition planning program for adolescents on the autism spectrum: trial protocol. Child Adolesc Psychiatry Ment Health. 2016;10:48. doi: 10.1186/s13034-016-0137-0
18. McCusker P, Gillespie L, Davidson G, Vicary S, Stone K. The United Nations Convention on the rights of persons with disabilities and social work: evidence for impact? Int J Environ Res Public Health. 2023;20(12):6927. doi: 10.3390/ijerph20206927
19. Ceccherini E. Intergovernmental relations in Italy: the permanent state-regions-autonomous provinces conference. Intergovernmental relations in Italy: the permanent state-regions-autonomous provinces conference. Genova: Università di Genova; 2009. p. 216-38.
20. Presidenza del Consiglio dei Ministri (PCM). Aggiornamento delle linee di indirizzo per la promozione ed il miglioramento della qualità e dell'appropriatezza degli interventi assistenziali nei disturbi dello spettro autistico. Roma: PCM; 2018. Available from: https://www.trovanorme.salute.gov.it/norme/renderNormsanPdf?anno=2018&codLeg=66884&parte=1%20&serie=null.
21. Jones K, Forder J, Caiels J, Welch E, Glendinning C, Windle K. Personalization in the health care system: do personal health budgets have an impact on outcomes and cost? J Health Serv Res Policy. 2013;18(1):59-67. doi: 10.1177/1355819613503152
22. Presidenza del Consiglio dei Ministri (PCM). Linee programmatiche: progettare il budget di salute con la persona-proposta degli elementi qualificanti. Roma: PCM; 2022. Available from: https://siep.it/wp-content/uploads/2022/07/BdS-Intesa-sancita-il-6-luglio-2022-Rep.-Atti-n.-104CU.pdf.
23. Valenti M, Mazza M, Arduino GM, Keller R, Le Donne I, Masedu F, Romano G, Scattoni ML. Diagnostic assessment, therapeutic care and education pathways in persons with autism spectrum disorder in transition from childhood to adulthood: the Italian National Ev.A Longitudinal Project. Ann Ist Super Sanità. 2023;59(4):304-12. doi: 10.4415/ANN_23_04_10
24. Osservatorio Nazionale Autismo (OssNA). Linee di indirizzo per le regioni e province autonome finalizzate alla definizione e implementazione di percorsi differenziati per la formulazione del progetto di vita basato sui costrutti di "Quality of Life" e tenendo conto delle diverse necessità di supporto, livello di funzionamento adattivo e disturbi associati delle persone con ASD, con particolare attenzione alla fascia d'età dai 16 anni in su. Roma: OssNA; 2022. Available from: https://osservatorionazionaleautismo.iss.it/documents/20126/170236/Linee+di+Indirizzo_Progetto+di+vita_16_anni_in_su.pdf/fac22cca-7b9b-6011-f6b9-ed842754c0e5?t=1648042142393.
25. Osservatorio Nazionale Autismo (OssNA). Linee di indirizzo per le regioni e province autonome finalizzate alla definizione e implementazione di percorsi differenziati per la formulazione del progetto di vita basato sui costrutti di "Quality of Life" e tenendo conto delle diverse necessità di supporto, livello di funzionamento adattivo e disturbi associati delle persone con ASD, con particolare attenzione alla fascia d'età 7-21 anni. Roma: OssNA; 2022. Available from: https://osservatorionazionaleautismo.iss.it/documents/20126/170236/Linee+di+Indirizzo_Progetto+di+vita_7-21anni.pdf/2671fbdd-5a9b-0983-ec97-b33306739e82?t=1648042138144.
26. Istituto Superiore di Sanità (ISS). Linea guida sulla diagnosi e sul trattamento di adulti con disturbo dello spettro autistico. Roma: ISS; 2023. Available from: https://www.iss.it/documents/20126/8968214/Linea_Guida_ASD_adulti_dic2024.pdf/2f89bd78-d44b-f8da-5de7-f1e69b62974c?t=1734950813404.
27. Italia. Decreto legislativo 3 maggio 2024, n. 62. Definizione della condizione di disabilità, della valutazione di base, di accomodamento ragionevole, della valutazione multidimensionale per l'elaborazione e attuazione del progetto di vita individuale personalizzato e partecipato. Gazzetta Ufficiale – Serie Generale n. 111, 14 maggio 2024.

28. Ratto AB, Bascom J, daVanport S, Strang JF, Anthony LG, Verbalis A, Rosen W. Centering the inner experience of autism: development of the self-assessment of autistic traits. Autism in Adulthood. 2023;5(2):93-105. doi: 10.1089/aut.2021.0099
29. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, Morrison C. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med. 2018;169(7):467-73. doi: 10.7326/M18-0850
30. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A, Shafer D. Rayyan – a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):210. doi: 10.1186/s13643-016-0384-4
31. Hamel C, Hersi M, Kelly SE, Tricco AC, Straus S, Wells G, Goldstein J. Guidance for using artificial intelligence for title and abstract screening while conducting knowledge syntheses. BMC Med Res Methodol. 2021;21(1):285. doi: 10.1186/s12874-021-01451-2
32. Valizadeh A, Moassefi M, Nakhostin-Ansari A, Hosseini Asl SH, Saghab Torbati M, Aghajani R, Jafari K. Abstract screening using the automated tool Rayyan: results of effectiveness in three diagnostic test accuracy systematic reviews. BMC Med Res Methodol. 2022;22(1):160. doi: 10.1186/s12874-022-01631-8
33. Pompili E, Biondi M, Nicolò G, editors. DSM-5-TR: manuale diagnostico e statistico dei disturbi mentali. Milano: Raffaello Cortina; 2023.
34. World Health Organization (WHO). ICD-11: international classification of diseases (11th revision). Geneva: WHO; 2022.
35. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Kastner M, Straus SE. A scoping review on the conduct and reporting of scoping reviews. BMC Med Res Methodol. 2016;16(1):15. doi: 10.1186/s12874-016-0116-4
36. Lockwood C, Munn Z, Porritt K. Qualitative research synthesis: methodological guidance for systematic reviewers utilizing meta-aggregation. Int J Evid Based Healthc. 2015;13(3):179-87. doi: 10.1097/XEB.0000000000000062
37. Renzaglia A, Karvonen M, Drasgow E, Stoxen CC. Promoting a lifetime of inclusion. Focus Autism Other Dev Disabl. 2003;18(3):140-9. doi: 10.1177/10883576030180030201
38. Kim KH, Turnbull AP. Transition to adulthood for students with severe intellectual disabilities: Shifting toward person-family interdependent planning. Res Pract Pers Severe Disabil. 2004;29(1):53-7.
39. Hagner D, Kurtz A, May J, Cloutier H. Person-centered planning for transition-aged youth with autism spectrum disorders. J Rehabil. 2014;80(1):4-10.
40. Bui YN, Turnbull A. East meets West: Analysis of person-centered planning in the context of Asian American values. Educ Train Dev Disabil. 2003;38(1):18-31.
41. Callicott KJ. Sensitive collaboration with person-centered planning. Focus Autism Other Dev Disabl. 2003;18(1):60-8. doi: 10.1177/108835760301800108
42. Cappa C, Figoli M, Rossi P. Network of services facilitating and supporting job placement for people with autism spectrum disorders. The experience of the ASL Piacenza, Italy. Ann Ist Super Sanità. 2020;56(2):241-6. doi: 10.4415/ANN_20_02_14
43. Tullis CA, Seaman-Tullis RL. Incorporating preference assessment into transition planning for people with autism spectrum disorder. Behav Anal Pract. 2019;12(3):727-33. doi: 10.1007/s40617-019-00353-6
44. Woods AD, Ireland MC, Murphy KA, Lancaster HS. Go beyond compliance: use individualized education programs to answer strategic questions and improve programs. Lang Speech Hear Serv Sch. 2024;55(2):249-58. doi: 10.1044/2023_LSHSS-23-00084
45. Bertelli M. Systematic psychopathological assessment for persons with intellectual and developmental disabilities-general screening. Firenze: Private Edition; 2019.
46. Guaraldi G, Ruggerini C, Neviani V, Vicini S. La scala DASH-II (diagnostic assessment for the severely handicapped) per la valutazione dei disturbi mentali nei ritardati mentali gravi. Quaderni Italiani di Psichiatria. 2002;21(1):39-45.
47. Beavers GA, Iwata BA, Lerman DC. Thirty years of research on the functional analysis of problem behavior. J Appl Behav Anal. 2013;46(1):1-21. doi: 10.1002/jaba.30
48. Abery B, McBride M. Look and understand before you leap. Impact. 1998;11(2):2-26.
49. O'Brien J, Lovett H. Finding a way toward everyday lives: The contribution of person-centered planning. Ontario Independent Facilitation Network (OIFN); 1992. Available from: http://www.oifn.ca/wp-content/uploads/2016/10/everyday_lives.pdf.
50. White SW, Smith IC, Miyazaki Y, Conner CM, Elias R, Capriola-Hall NN. Improving transition to adulthood for students with autism: a randomized controlled trial of steps. J Clin Child Adolesc Psychol. 2021;50(2):187-201. doi: 10.1080/15374416.2019.1669157
51. Gerhardt PF. Effective transition planning for learners with ASD. Exceptional Parent. 2007;37(9):26-7.
52. Gabriels RL. Review of universal design for transition: A roadmap for planning and instruction. J Autism Dev Disord. 2010;40(5):651-2. doi: 10.1007/s10803-009-0838-9
53. Rehm RS, Fuentes-Afflick E, Fisher LT, Chesla CA. Parent and youth priorities during the transition to adulthood for youth with special health care needs and developmental disability. Adv Nurs Sci. 2012;35(3):e57-72. doi: 10.1097/ANS.0b013e3182626180
54. Stromberg M, Liman L, Bang P, Igelstrom K. Experiences of sensory overload and communication barriers by autistic adults in health care settings. Autism in Adulthood. 2022;4(2):66-75. doi: 10.1089/aut.2020.0074
55. Appleton R, Connell C, Fairclough E, Tuomainen H, Singh SP. Outcomes of young people who reach the transition boundary of child and adolescent mental health services: a systematic review. Eur Child Adolesc Psychiatry. 2019;28(11):1431-46. doi: 10.1007/s00787-019-01307-7
56. Marsack-Topolewski CN, Church HL. Impact of caregiver burden on quality of life for parents of adult children with autism spectrum disorder. Am J Intellect Dev Disabil. 2019;124(2):145-56. doi: 10.1352/1944-7558-124.2.145
57. Chancel R, Miot S, Dellapiazza F, Baghdadli A. Group-based educational interventions in adolescents and young adults with ASD without ID: a systematic review focusing on the transition to adulthood. Eur Child Adolesc Psychiatry. 2022;31:1-21. doi: 10.1007/s00787-020-01609-1
58. Hutchinson SL. Lifestyle planning in the transition to retirement. JAR Life. 2024;13:30-2. doi: 10.14283/jarlife.2024.4
59. Nell-Rood C, Ruble L, Kleinert H, McGrew JH, Adams M, Rodgers A, Goodman J. Stakeholder perspectives on transition planning, implementation, and outcomes for students with autism spectrum disorder. Autism. 2020;24(5):1164-76. doi: 10.1177/1362361319894827
60. Wehman P, Schall C, Carr S, Targett P, West M, Cifu G. Transition from school to adulthood for youth with autism spectrum disorder: what we know and what we need to know. J Disabil Policy Stud. 2014;25(1):30-40. doi: 10.1177/1044207313518071
61. Bauer A, Stevens M, Purtscheller D, Knapp M, Fonagy

P, Evans-Lacko S, Paul J. Mobilising social support to improve mental health for children and adolescents: A systematic review using principles of realist synthesis. PLoS ONE. 2021;16(5):e0251750. doi: 10.1371/journal.pone.0251750
62. Wehman PH, Schall CM, McDonough J, Kregel J, Brooke V, Molinelli A, Smith AC. Competitive employment for youth with autism spectrum disorders: Early results from a randomized clinical trial. J Autism Dev Disord. 2014;44(3):487-500. doi: 10.1007/s10803-013-1892-x
63. Bernhardt JB, Lam GYH, Thomas T, Cubells JF, Bohlke K, Reid M, Green W. Meaning in measurement: evaluating young autistic adults' active engagement and expressed interest in quality-of-life goals. Autism Adulthood. 2020;2(3):227-42. doi: 10.1089/aut.2019.0081
64. Benevides T, Watling R, Robertson SM. Person-centered interventions for autistic adults ages 18+ (2013-2021). Am J Occup Ther. 2023;77:1-8. doi: 10.5014/ajot.2023.77S10023
65. Edelson SM, Nicholas DB, Stoddart KP, Bauman MB, Mawlam L, Lawson WB, McCauley JB. Strategies for research, practice, and policy for autism in later life: a report from a think tank on aging and autism. J Autism Dev Disord. 2021;51(2):382-90. doi: 10.1007/s10803-020-04514-3
66. Cakir J, Frye RE, Walker SJ. The lifetime social cost of autism: 1990-2029. Res Autism Spectr Disord. 2020;72:101502. doi: 10.1016/j.rasd.2019.101502
67. Matin BK, Byford S, Soltani S, Kazemi-Karyani A, Atafar Z, Zereshki E, Mokhayeri Y, Vafaee R, Tabrizi R, Asadollahi M. Contributing factors to healthcare costs in individuals with autism spectrum disorder: a systematic review. BMC Health Serv Res. 2022;22(1):604. doi: 10.1186/s12913-022-07932-4
68. Cervantes PE, Matheis M, Estabillo J, Seag DEM, Nelson KL, Peth-Pierce R, Kantarovich K, Pulido N, Kelly M. Trends over a decade in NIH funding for autism spectrum disorder services research. J Autism Dev Disord. 2021;51(8):2751-63. doi: 10.1007/s10803-020-04746-3
69. Harris L, Gilmore D, Longo A, Hand BN. Short report: patterns of US federal autism research funding during 2017-2019. Autism. 2021;25(8):2135-9. doi: 10.1177/13623613211003430
70. Zablotsky B, Maenner MJ, Blumberg SJ. Geographic disparities in treatment for children with autism spectrum disorder. Acad Pediatr. 2019;19(7):740-7. doi: 10.1016/j.acap.2019.02.013
71. McConkey R. Responding to autism in low and middle income countries (Lmic): what to do and what not to do. Brain Sci. 2022;12(11):1475. doi: 10.3390/brainsci12111475
72. Zhou E, Kyeong Y, Cheung CS, Michalska KJ. Shared cultural values influence mental health help-seeking behaviors in asian and latinx college students. J Racial Ethn Health Disparities. 2022;9(3):1325-34. doi: 10.1007/s40615-021-01073-w
73. McCausland D, Murphy E, McCarron M, McCallion P. The potential for person-centred planning to support the community participation of adults with an intellectual disability. J Intellect Disabil. 2022;26(4):603-23. doi: 10.1177/17446295211022125
74. Sanderson H, Thompson J, Kilbane J. The emergence of person-centred planning as evidence-based practice. J Integr Care. 2006;14(1):18-25. doi: 10.1108/14769018200600014
75. Waizbard-Bartov E, Fein D, Lord C, Amaral DG. Autism severity and its relationship to disability. Autism Res. 2023;16(4):685-96. doi: 10.1002/aur.2898
76. Schalock RL, Verdugo MA, Gomez LE, Reinders HS. Moving us toward a theory of individual quality of life. Am J Intellect Dev Disabil. 2016;121(1):1-12. doi: 10.1352/1944-7558-121.1.1
77. Schalock RL, Verdugo MÁ. Handbook on quality of life for human service practitioners. Washington, DC: American Association on Mental Retardation; 2002.
78. Grabowska I, Antczak R, Zwierzchowski J, Panek T. How to measure multidimensional quality of life of persons with disabilities in public policies – a case of Poland. Arch Public Health. 2022;80(1):230. doi: 10.1186/s13690-022-00981-5
79. Bertelli M, Francescutti C, Brown I. Reframing QoL assessment in persons with neurodevelopmental disorders. Ann Ist Super Sanità. 2020;56(2):180-92. doi: 10.4415/ANN_20_02_08
80. Evers K, Maljaars J, Schepens H, Vanaken G, Noens I. Conceptualization of quality of life in autistic individuals. Dev Med Child Neurol. 2022;64(8):950-6. doi: 10.1111/dmcn.15205
81. Petersson-Bloom L. Equity in education for autistic students: professional learning to accommodate inclusive education; 2022. Available from: http://urn.kb.se/resolve?urn=urn:nbn:se:mau:diva-55508.
82. Hasson L, Keville S, Gallagher J, Onagbesan D, Ludlow AK. Inclusivity in education for autism spectrum disorders: Experiences of support from the perspective of parent/carers, school teaching staff and young people on the autism spectrum. Int J Dev Disabil. 2024;70(2):201-12. doi: 10.1080/20473869.2022.2070418
83. Fisher W, Piazza CC, Bowman LG, Hagopian LP, Owens JC, Slevin I. A comparison of two approaches for identifying reinforcers for persons with severe and profound disabilities. J Appl Behav Anal. 1992;25(3):491-8. doi: 10.1901/jaba.1992.25-491
84. DeLeon IG, Iwata BA. Evaluation of a multiple-stimulus presentation format for assessing reinforcer preferences. J Appl Behav Anal. 1996;29(4):519-32. doi: 10.1901/jaba.1996.29-519
85. Wine B, Reis M, Hantula DA. An Evaluation of stimulus preference assessment methodology in organizational behavior management. J Organ Behav Manag. 2014;34(1):7-15. doi: 10.1080/01608061.2013.873379
86. Zeidan J, Fombonne E, Scorah J, Ibrahim A, Durkin MS, Saxena S, Zhao Y, Brown C, Mucic D. Global prevalence of autism: A systematic review update. Autism Res. 2022;15(5):778-90. doi: 10.1002/aur.2696
87. Afifi M, Stryhn H, Sanchez J. Data extraction and comparison for complex systematic reviews: a step-by-step guideline and an implementation example using open-source software. Syst Rev. 2023;12(1):226. doi: 10.1186/s13643-023-02322-1

Ann Ist Super Sanità 2025 | Vol. 61, No. 1: 42-49
DOI: 10.4415/ANN_25_01_06

Assessing brain vascular impairment, white matter lesions and ApoE status as predictors of behavioral and psychological symptoms of dementia (BPSD) in a multicentre sample of patients with Alzheimer's disease: a multidisciplinary retrospective study

Luana Vaianella[1], Raffaele Bove[2], Alessandro Giuliani[3], Valentina Pavino[4], Valeria Guglielmi[5], Gianmarco Giacomini[6], Concettina Rossi[7], Maria Carla Massimetti[8], Cesare Iani[2] and Alessandra Bizzarro[9]

[1]*Dipartimento di Neuroscienze, Istituto Superiore di Sanità, Rome, Italy*
[2]*UOC Neurologia, Ospedale Sant'Eugenio, Rome, Italy*
[3]*Dipartimento Ambiente e Salute, Istituto Superiore di Sanità, Rome, Italy*
[4]*RSA San Michele Hospital, Aprilia, Latina, Italy*
[5]*Dipartimento di Neuroscienze, Organi di Senso e Torace, Fondazione Policlinico Universitario A. Gemelli IRCCS, UOC Neurologia, Rome, Italy*
[6]*Dipartimento di Scienze della Sanità Pubblica e Pediatriche Università di Torino, Turin, Italy*
[7]*Dipartimento di Neuroscienze, Università Cattolica del Sacro Cuore, Rome, Italy*
[8]*Azienda Sanitaria Locale di Rieti, Rieti, Italy*
[9]*Dipartimento di Geriatria, Ortopedia e Reumatologia, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy*

Abstract

Background. Understanding pathogenetic background and risk factors is the primary step to a better behavioral and psychological symptoms of dementia (BPSD) management. To this aim, this exploratory study is designed to sketch some indicative correlations between BPSD severity and vascular, genetic and cognitive variables.

Methods. A retrospective cross-sectional study conducted on medical reports of 135 Alzheimer Dementia (AD) patients from two memory clinics. Each subject underwent clinical examination and brain Magnetic Resonance Imaging (MRI), mini mental state examination (MMSE) and behavioral assessment using the neuropsychiatric inventory (NPI). This real-world cross-sectional study aimed to correlate the load of white matter lesions and global vascular compromise with clinical assessment. In addition, apolipoprotein E (ApoE) genotype was checked in 92 patients. Data were analysed performing Spearman correlation and principal component analysis (PCA).

Results. BPSD severity was independent from cognitive impairment, vascular impairment, white matter lesions and ApoE status.

Conclusions. Our results do not confirm the possible role for vascular impairment in BPSD severity as previously reported. Studies focusing on different biological features in relation to other structural, psychosocial and environmental factors are needed in order to get a more reliable model.

Key words

- behavioral symptoms
- dementia
- ApoE gene
- retrospective study
- vascular impairment

Address for correspondence: Gianmarco Giacomini, Dipartimento di Scienze della Sanità Pubblica e Pediatriche Università di Torino, Via Santena 5 bis, 10126 Turin, Italy. E-mail: gianmarco.giacomini@unito.it.

INTRODUCTION

Cognitive impairment in Alzheimer's disease (AD) has been extensively studied from a clinical, biological and anatomical point of view [1, 2]. In contrast, the causes of behavioral and psychological symptoms of dementia (BPSDs) in AD are not so well known, although BPSDs affect nearly all patients with AD during their disease history, and they increase the risk for institutionalization and caregiver burden [3, 4]. Agitation, aberrant motor behaviour, anxiety, euphoria, irritability, depression, apathy, disinhibition, delusions, hallucinations, and sleep or appetite disturbances are the most reported BPSDs [1], and their treatment is often problematic [1, 5]. Accurate knowledge of predictors of BPSDs could help clinicians identify patients at risk, use preventive strategies and provide patients with appropriate timely care.

Since the detection and assessment of BPSDs are often based on caregivers' reports, previous studies have tried to further examine the burden on caregivers in order to better assess the onset, severity and nature of BPSDs [6]. On the other hand, many studies have analysed the correlations between biological factors and BPSD (general genetic risk factors), comorbidities (general vascular damage) and burden of white matter lesions [7].

The genetic background has been considered one of the main factors responsible for the predisposition of patients with AD to BPSDs [8]. Indeed, AD is sporadic in most cases, but there are also familial forms due to specific genetic mutations. However, it has long emerged that the main genetic risk factor for sporadic AD is a precise allele in the apolipoprotein E (ApoE) genotype [9]. The gene is found in the chromosome 19 and has three different allelic forms: ApoE-epsilon 2(ε2), ApoE-epsilon 3(ε3) and ApoE-epsilon 4(ε4). As reported in a seminal meta-analysis, there is a clear association between the ApoE(ε4) and AD. The presence of the ApoE ε4 allele (ε2/ε4 or ε3/ε4) confers risk, and ApoE ε4 homozygotes (ε4/ε4) have an increased risk compared with heterozygotes, whereas ApoE2 (ε2/ε4 or ε2/ε3) is protective against AD [10-12]. Furthermore, according to some studies, the ε4 allele is associated with specific BPSDs in AD [8-12].

The contribution of vascular factors in the pathogenesis of BPSDs has also been studied. The risk of developing AD is known to be increased in patients with vascular diseases (such as high blood pressure, atherosclerosis), as well as in metabolic diseases such as type 2 diabetes or hyperlipidemia [13]. Cerebrovascular disease and the burden of white matter hyperintensities (WMH) on the development of BPSDs have been later associated with anxiety, psychomotor agitation, and other neuropsychiatric symptoms in AD [7, 8-14]. Although previous literature showed conflicting results [15], understanding pathogenetic background and risk factors is the primary step to reach a better BPSDs management [16].

The aim of this study is to identify predictors of BPSDs using a multidisciplinary approach, in order to analyse the relationship between BPSDs severity and vascular risk factors, neuroimaging alterations, genetic markers and cognitive variables.

MATERIALS AND METHODS

A multicentre retrospective real-word cross-sectional study based on outpatients' clinical data from year 2014 was conducted. The patients' medical records came from two different Alzheimer Units: the Memory Clinic of Catholic University of Rome, and the Clinic for Memory and Cognitive Behavioural disorders of Sant'Eugenio Hospital of Rome. The outpatients' medical records were analysed and selected according to the presence of specific inclusion criteria: diagnosis of probable AD, as according at least to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCS-ADRDA) criteria of 1984 (as they were a common and reliable diagnostic method widely used, and because it required patients to undergo neuropsychological tests for the AD clinical diagnosis) [17]; suffering from BPSDs; having undergone a baseline cerebral MRI. Age, sex, education (in years), and vascular risk factors, including smoking (presence/absence), alcoholism, cardiovascular disease (hypertension, stroke, diabetes, cerebral vascular disease, and thromboendarterectomy) were recorded for all patients. The scores of cognitive and behavioral tests, scales for the differential diagnosis between primary dementia and vascular dementia and scores to measure white matter lesions on MRI were recorded. The carriers of the apolipoprotein E ε4 allele were identified (*Table 1*). Due to the outpatients setting, criteria were based primarily on clinical indicators. Clinical data from 2014 were found to be collected according to these criteria in both centers, making it possible to conduct a study with a standardized and consistent dataset across centers.

Cognitive deficits were assessed using the mini mental state examination (MMSE), which is commonly used as part of the dementia diagnostic process. MMSE score ranges from 0 (maximum cognitive deficit) to 30 (no cognitive deficit). It is necessary to correct the raw score based on variables potentially able to influence the result: age and years of schooling of the subject. A score of 24/30 or above is considered normal. As one falls below the threshold value of 24, cognitive impairment is indicated, which can be severe if the score is ≤9 points, moderate between 10 and 18 points, or mild between 19 and 23 points. In this study, patients with a MMSE score <24 were included [18]. MMSE adjustment coefficients for age and education classes in the Italian population were used [19].

BPSDs were assessed using the neuropsychiatric inventory (NPI) in the original version [20]. This test, through questions to the caregiver, investigates the frequency (score from 0 to 4 points) and severity (score from 1 to 3 points) of psychotic, affective and behavioral syndromes in patients with dementia. The following items were evaluated: Delusions, Hallucinations, Agitation/Aggression, Dysphoria/Depression, Anxiety, Euphoria/Elation, Apathy/Indifference, Disinhibition, Irritability/Lability, Aberrant Motor, Nighttime Behavior, Appetite/Eating. The higher the score for each symptom, the greater the severity, and the higher the overall score represents a greater severity of the BPSD. It also allowed us to evaluate the burden on the caregiver, for

the care burden was measured from 0 to 5 points, with a higher total score indicating a higher caregiver burden.

For the differential diagnosis between primary dementia and vascular dementia the Hachinski Ischemic Score (HIS) was used. This is a 13-item clinical scale. Each item is assigned a score of 1 or 2, with the latter indicating a vascular form. A total score of 4 or lower indicates Alzheimer's disease or a degenerative form, while a score between 5 and 6 suggests mixed dementia or an uncertain outcome. A score of at least 7 indicates vascular dementia. The presence of focal neurological symptoms was an important indicator of vascular dementia in cases where there was doubt [21].

The white matter hyperintensity (WMH) burden was assessed using the Fazekas Score (FS). It classifies lesions according to their hyperintensity at the MRI examination. Lesions were characterized as 0 (absence of lesions), 1 (non-confluent lesions), 2 (confluent lesions) and 3 (widespread lesions) [22].

The MRI examinations were performed at different scanners (magnetic field range 1.0-3.0 Tesla), without contrast administration. To mitigate the possible confounding effect of using different scanners, axial T2- and T1-weighted MRI images were analysed separately and blindly by a neurologist from each memory clinic and only scans that both neurologists judged suitable for the application of the FS were used for the retrospective study.

In order to identify the carriers of the apolipoprotein E ε4 allele, we extracted DNA from peripheral blood samples of 92 patients who gave consent for the examination. Genomic DNA was extracted by a standard salt-chloroform procedure [23] and it was amplified by a PCR in a thermal-cycler with specific oligonucleotide primers. The following primers were used according to previous literature: [24] upstream 5'-TCCAAGGAGCTGCAGGCGGCGA-3' and downstream 5'-ACAGAATTCGCCCCGCCTGGTACACTGCCA-3'. PCR was performed as described in [25].

Patients were stratified according to the presence/absence of at least one ε4 allele, and therefore divided in ApoE4 carriers (genotypes ε2 ε4+ε3 ε4+ε4 ε4) and non carriers (genotypes ε2 ε3+ε3 ε3). No ε2 ε2 genotype carriers were present in our sample.

The pairwise correlations between variables were assessed using Spearman correlation analysis, and to understand the mutual relation among different variables, we operated a principal component analysis (PCA). PCA is used to reduce the dimensionality of multivariate data sets while retaining the most important information [26]. The analysis decomposes the total variance (information) of the dataset into mutually independent patterns of variation (components) that best capture the structure of the data. In other words, when variables are correlated, PCA allows us to represent one variable in terms of another, simplifying the data. This allows to save the relevant part of information originally residing in N variables into P components (with P<<N), discarding the noise while retaining relevant "signal-like" information [27].

The number of components was determined using Cattel's test, which identifies significant differences between informative components ("signal-like" information) and noise [28].

To interpret the meaning of the components, we used the "component loadings", which is the Pearson correlation coefficient between original variables and components. The original variables with a higher correlation allow the researchers to attach a meaning to a specific component.

PCA was applied to the subset of patients with no missing values. Components were extracted in decreasing order of explained variance using eigenvalues obtained from Cattel's test. An eigenvalue represents the overall variance explained by each component. Since we standardized the variables to have a mean of 0 and a standard deviation of 1, an eigenvalue close to 1 means the component explains about as much as an average original variable. The percentage of variance explained by each component is calculated by dividing its eigenvalue by the total sum of eigenvalues, which equals the number of original variables analysed. The cumulative explained variance shows how accurately the components represent the dataset, reaching 100% when the number of components matches the number of original variables (*Table 2a*).

The names of the components reported below stem from the analysis of component loading pattern reported in *Table 2b*.

Analyses were carried out using SAS software version 9.4M1.

RESULTS

135 patients (52.1% with mild, 45.8% with moderate and 2.1% with severe AD) were selected based on their outpatient medical records

Demographic and clinical characteristics of the whole sample are detailed in *Table 1*, together with vascular risk factors and comorbidities of the sample. ApoE genotype distribution, which was analysed in 92 patients, is also shown in *Table 1*.

Table 2a reports the distribution of explained variance across the principal components: considering the four most important components, 77% of total variance is explained, with the first component (PC1) accounting for 34% of variance. The name assigned to the different components stems from the loading pattern as we will discuss below.

The most relevant variables (higher absolute loading) for the component interpretation are bolded in *Table 2b*. PC1 is a "cardiovascular" component (high loading hypertension, Fazekas and HIS). The second component PC2 is a "metabolic" factor (hypercholesterolemia and diabetes as main drivers). PC3 demonstrates the NPI singularity: BPSD severity in AD has a near to unity (0.94) loading on PC3. Given components are each other mutually independent by construction; this result implies that BPSD severity in AD is totally independent from the rest of the descriptors (cognitive impairment, vascular impairment, white matter lesions and ApoE status). The fourth component has to do with diabetes pathological features independent from general metabolic pattern shaping PC2.

Table 1
Descriptive statistics of measured features

Variable	Mean (SD)	Median	Minimum	Maximum
Age (years) n=135	74.45 (7.17)	75.00	55.00	90.00
Females/Males ratio	1.14			
MMSE n=132	18.66 (4.81)	20.00	7.00	29.00
ApoE4 carriers n=92	0.48 (0.50)	0	0	1.00
HIS n=126	2.83 (2.08)	3.00	0	12.00
NPI n=135	21.47 (18.26)	16.00	0	94.00
Fazekas score n=135	1.14 (0.86)	1.00	0	3.00
Education (years) n=131	8.00 (4.15)	8.00	1.00	19.00
Rivastigmine n=131	0.82 (0.38)	1.00	0	1.00
Hypertension n=132	0.61 (0.49)	1.00	0	1.00
Antiplatelet therapy n=131	0.47 (0.52)	0	0	1.00
Oral hypoglycemic drugs n=131	0.12 (0.33)	0	0	1.00
Insulin n=131	0.01 (0.09)	0	0	1.00
Antiarrhythmic drugs n=131	0.07 (0.25)	0	0	1.00
Statins n=132	0.39 (0.49)	0	0	1.00
Anticoagulants n=132	0.08 (0.27)	0	0	1.00
Folic acid treatment n=133	0.07 (0.25)	0	0	1.00
Familiarity for vascular diseases n=131	0.33 (0.52)	0	0	2.00
Smoking n=134	0.25 (0.44)	0	0	1.00
Alcoholism n=132	0.01 (0.09)	0	0	1.00

The mean of binary (0/1) variables corresponds to the proportion of patients having a 1 (yes) score to the variable itself; SD: standard deviation; HIS: Hachinski Ischemic Score; MMSE: mini mental state examination; NPI: neuropsychiatric inventory.

Table 2
Descriptive characteristics and composition of principal components

a) Variance of the principal components

Component	Eigenvalue	Proportion	Cumulative
1	**2.35**	**0.34**	**0.34**
2	**1.27**	**0.18**	**0.52**
3	**1.00**	**0.14**	**0.66**
4	**0.79**	**0.11**	**0.77**
5	0.69	0.10	0.87
6	0.47	0.07	0.94
7	0.42	0.06	1.00

b) Loading pattern corresponding to the correlation coefficients between original variables and extracted principal components

Variables	PC1	PC2	PC3	PC4
Hypertension	**0.78**	-0.08	-0.08	-0.27
Fazekas	**0.80**	-0.02	0.23	-0.10
HIS	**0.82**	-0.10	0.075	-0.07
NPI	-0.17	0.25	**0.94**	0.07
Age (years)	**0.40**	**-0.60**	0.14	**0.49**
Hypercholesterolemia	0.34	**0.70**	-0.03	-0.19
Diabetes mellitus	0.35	**0.59**	-0.20	**0.65**

PC1: cardiovascular component (high loading hypertension, Fazekas and Hachinski scores); PC2: metabolic component (hypercholesterolemia and diabetes); PC3: BPSDs; PC4: diabetes; PC: principal component; NPI: neuropsychiatric inventory; BPSDs: behavioral and psychological symptoms; HIS: Hachinski Ischemic Score; significant results are bolded.

As it can be seen in *Table 2b*, age (mean: 74.45, standard deviation: 7.17) was significantly related to most of the components but the BPSDs one. The loading pattern of Age variable points (as expected) to a pervasive role of age as for different pathological features but not influencing the severity of Alzheimer. This result stems from the observation that the data set is made only by Alzheimer patients so ruling out the well-established correlation between the onset of dementia and aging. The cardiovascular component had a positive and statistically significant correlation with presence of hypertension, FS and HIS (correlation coefficients of 0.78; 0.80; 0.82 respectively). The metabolic component was significantly related with presence of hypercholesterolemia and diabetes mellitus (correlation coefficients of 0.70 and 0.59). The BPSDs component was significantly related only with the NPI score (0.94), while the fourth component was related to diabetes (0.65).

The negative relationship between NPI score and rivastigmine use (correlation coefficient -0.52, $p<0.0001$) was of particular interest, since its values were correlated with PC3 scores obtaining a Spearman correlation coefficient equal to $r=-0.52$ ($p<0.001$), identical to the direct correlation between NPI and rivastigmine.

DISCUSSION

We correlated the load of white matter lesions and global vascular impairment with cognitive clinical assessment and ApoE genotype in a sample of AD patients with BPSDs. According to our results, BPSD severity (estimated by NPI total score) seemed to be independent from cognitive impairment (MMSE), vascular impairment (HIS), white matter lesions (FS) and ApoE status.

When comparing our results with those of the literature (cited below), it must be considered that similar studies have used other assessment tools for both AD and BPSDs, and that BPSD expression can vary or fluctuate in the different stages of Alzheimer's and in different settings. Therefore, it is important to keep in mind that we based our study on outpatients mostly with mild and moderate AD, as described below.

According to our data, we were not able to confirm a role for vascular impairment in BPSDs expression in our sample. This is inconsistent with some previous literature, according to which mood and psychomotor symptoms are more prevalent in patients with greater vascular cognitive impairment (VCI) compared to AD patients. On the other hand, VCI patients tend to show more psychotic symptoms [7, 29]. Also, VCI has been associated with WMH, and it is thought that VCI could have a moderating effect between WMH and BPSDs [30]. Notwithstanding this, BPSDs pathogenesis has not yet been completely elucidated [31].

While discussing our results, it must be noted that our sample consisted mostly of outpatients with mild and moderate cognitive impairment. Previous studies concluded that WMH is particularly evident with BPSD in moderate to severe AD [7, 32]. This may have influenced our results, as some initial structural changes in the brain, more common in patients with mild cognitive impairment, may not yet be detectable on neuroimaging (i.e., abnormal connectivity and circuitry between various areas of the brain) [32]. Therefore, our findings must be taken with caution.

We did not find correlations between ApoE4 genotype and BPSDs in our sample. This is similar to previous literature, since both positive and negative correlations have been described over time [33, 34]. Although correlations of ApoE4 genotype with specific clusters of BPSD have been proposed [8, 12], this has not been always supported [35].

BPSDs are thought to be the result of complex interplay between biological (brain changes due to multiple causes), sociological (social network, living arrangements) and psychological factors (e.g., personality) [31]. Some researchers also point at specific conditions – such as chronic neuroinflammation – in which histaminergic neurotransmission could have a pivotal role in microglia inflammation [36]. Serotonergic and dopaminergic circuitry are known to be involved as well [37, 38]. Furthermore, grouping BPSDs into "clusters of symptoms" – as we also did – could distort relationships with different variables, because BPSDs are not grouped consistently across studies, with each "cluster" reflecting a different prevalence, timeline and bio-psychosocial correlates [31]. This often increases the difficulty in interpreting data [1]. For instance, previous research suggested that specific clusters of symptoms did not affect the progression of cognitive decline, while the greater the cognitive impairment, the more severe were the BPSDs.

An important aspect to note is that although the NPI is a largely diffused tool for studying BPSDs in dementia, our results – and some others as well [7, 39, 40] – underlie an emerging need to investigate bio-psychosocial and environmental factors in pathogenesis of BPSDs too. NPI is a useful measure to assess BPSD in people with dementia, but is a caregiver-dependent measure. The caregiver's personal characteristics (e.g., age, educational level, personality, psychological conditions, coping skills, etc) may modify levels of perceived stress and burden, impacting his/her reliability [1]. Moreover, it is known that the patient-caregiver emotional relationship and communication can have effects on BPSDs expression. Experience, emotional relationships, or familiarity could have a role in this process [41]. Therefore, it is essential to assess caregivers' burden including measures of objective and subjective caregiver stress and analysis of environmental conditions.

The association between the use of rivastigmine and less BPSDs we found is consistent with existing literature. It is widely known that cholinergic deficits cause cognitive impairment and are involved in BPSDs and delusional thinking [42,] and the positive clinical response to acetylcholinesterase inhibitors of patients with such symptoms (especially apathy, psychosis) are well known [43, 44].

Cardiovascular and metabolic components that came out from the PCA were consistent with previous literature [41]. Regarding the association of age with most of the PCA components: its role, even if statistically significant, is ambiguous. Indeed, it is important to remember that we analysed an aged population, imposing a range restriction to the age variable that is detrimental to the discovery of meaningful correlations with other variables [45].

Considering the high prevalence, and the often early occurrence of BPSDs – particularly of mood disorders – a rigorous assessment of psychiatric features in cognitively impaired patients should be part of the routine examination. Characterizing the behavioral profile of these patients may lead to a wholesome comprehension of their condition during the evolving of the disease, and may allow both caregivers and professionals to use more effective treatments for improving patients' and caregivers' quality of life [29].

LIMITATIONS

Our study has several limitations. Radiologic images were taken using different MRIs with different magnetic fields (range 1.0-3T) and different protocols by different centers. Independent confirmation of the FS from an external neuroradiologist was not taken. Since BPSDs symptoms fluctuate over time, estimating their prevalence using a cross-sectional approach may not be completely appropriate. Moreover, the cross-sectional design precludes causal inferences and reverse causality cannot be excluded. In future research, a longitudinal design could be accurate to study the causality of this study's topic. NPI is a broad-spectrum screening test: in future research, it may be useful to administer tests for specific symptoms of interest. The lack of a control group prevented us from conducting a case-control study. Limitations of our study include also its retrospective nature and the relatively small sample size.

CONCLUSIONS

In conclusion, we did not find in our sample and according to our study design the expected associations between vascular, genetic and imaging factors with expression of BPSDs. Our results could therefore underline the complex interactions between the above mentioned factors in the expression of BPSDs, being unable to identify a specific one. Conducting further studies in real-world contexts will be necessary to better understand other factors, aside from the biological ones, that may influence BPSD expression in AD patients, also through a more structured data collection on family members and patients. BPSDs are a very complex aspect of neurologic care, as they increase the risk of patients' hospitalization, death and caregiver exhaustion, and their pathogenesis is yet to be fully comprehended. The challenge for future studies may be to better understand this complex interaction of variables in the pathogenesis of BPSD by analysing the bio-psychosocial factors that are the least identified. Different methodological approaches could help deepening the knowledge on this topic. Also, further studies on brain circuitry could improve knowledge on this topic.

Conflicts of interest statement

The Authors have no conflit of interest to disclose.

Received on 6 August 2024.
Accepted on 6 December 2024.

REFERENCES

1. Cerejeira J, Lagarto L, Mukaetova-Ladinska EB. Behavioral and psychological symptoms of dementia. Front Neurol. 2012;3:73. doi: 10.3389/fneur.2012.00073
2. Breijyeh Z, Karaman R. Comprehensive review on Alzheimer's disease: causes and treatment. Molecules. 2020;25(24):5789. doi: 10.3390/molecules25245789
3. Li XL, Hu N, Tan MS, Yu JT, Tan L. Behavioral and psychological symptoms in Alzheimer's disease. BioMed Res Int. 2014;2014:927804. doi: 10.1155/2014/927804
4. Deardorff WJ, Grossberg GT. Behavioral and psychological symptoms in Alzheimer's dementia and vascular dementia. Handb Clin Neurol. 2019;165:5-32. doi: 10.1016/B978-0-444-64012-3.00002-2
5. Masopust J, Protopopová D, Vališ M, Pavelek Z, Klímová B. Treatment of behavioral and psychological symptoms of dementias with psychopharmaceuticals: a review. Neuropsychiatr Dis Treat. 2018;14:1211-20. doi: 10.2147/NDT.S163842
6. Stella F, Forlenza OV, Laks J, de Andrade LP, de Castilho Cação J, Govone JS, de Medeiros K, Lyketsos CG. Caregiver report versus clinician impression: disagreements in rating neuropsychiatric symptoms in Alzheimer's disease patients. Int J Geriatr Psychiatry. 2015;30(12):1230-7. doi: 10.1002/gps.4278
7. Kandiah N, Chander R, Zhang A, Yee CC. Cerebral white matter disease is independently associated with BPSD in Alzheimer's disease. J Neurol Sci. 2014;337(1-2):162-6. doi: 10.1016/j.jns.2013.11.042
8. Flirski M, Sobow T, Kloszewska I. Behavioural genetics of Alzheimer's disease: a comprehensive review. Arch Med Sci. 2011;2:195-210. doi: 10.5114/aoms.2011.22068
9. Saunders AM, Strittmatter WJ, Schmechel D, St George-Hyslop PH, Pericak-Vance MA, Joo SH, Rosi BL, Gusella JF, Crapper-MacLachlan DR, Alberts MJ, Hulette C, Crain B, Goldgaber D, Roses AD. Association of apolipoprotein E allele ε4 with late-onset familial and sporadic Alzheimer's disease. Neurology. 1993;43(8):1467. doi: 10.1212/WNL.43.8.1467
10. Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, Myers RH, Pericak-Vance MA, Risch N, van Duijn CM. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. ApoE and Alzheimer disease meta analysis Consortium. JAMA. 1997;278(16):1349-56.
11. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science. 1993;261(5123):921-3. doi: 10.1126/science.8346443
12. Michels A, Multhammer M, Zintl M, Mendoza MC, Klünemann HH. Association of apolipoprotein E ε4 (ApoE ε4) homozygosity with psychiatric behavioral symptoms. J Alzheimers Dis. 2012;28(1):25-32. doi: 10.3233/JAD-2011-110554
13. Armstrong RA. Risk factors for Alzheimer's disease. Folia Neuropathol. 2019;57(2):87-105. doi: 10.5114/fn.2019.85929
14. Misquitta K, Dadar M, Louis Collins D, Tartaglia MC. White matter hyperintensities and neuropsychiatric symptoms in mild cognitive impairment and Alzheim-

er's disease. NeuroImage Clin. 2020;28:102367. doi: 10.1016/j.nicl.2020.102367
15. Staekenborg SS, Gillissen F, Romkes R, Pijnenburg YA, Barkhof F, Scheltens P, van der Flier WM. Behavioural and psychological symptoms are not related to white matter hyperintensities and medial temporal lobe atrophy in Alzheimer's disease. Int J Geriatr Psychiatry. 2008;23(4):387-92. doi: 10.1002/gps.1891
16. Shin IS, Carter M, Masterman D, Fairbanks L, Cummings JL. Neuropsychiatric symptoms and quality of life in Alzheimer disease. Am J Geriatr Psychiatry. 2005;13(6):469-74. doi: 10.1097/00019442-200506000-00005
17. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology. 1984;34(7):939. doi: 10.1212/WNL.34.7.939
18. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". J Psychiatr Res. 1975;12(3):189-98. doi: 10.1016/0022-3956(75)90026-6
19. Magni E, Binetti G, Bianchetti A, Rozzini R, Trabucchi M. Mini-mental state examination: A normative study in Italian elderly population. Eur J Neurol. 1996;3(3):198-202. doi: 10.1111/j.1468-1331.1996.tb00423.x
20. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric inventory: comprehensive assessment of psychopathology in dementia. Neurology. 1994;44(12):2308. doi: 10.1212/WNL.44.12.2308
21. Hachinski VC, Iliff LD, Zilhka E, Du Boulay GH, McAllister VL, Marshall J, Russell RW, Symon L. Cerebral blood flow in dementia. Arch Neurol. 1975;32(9):632-7. doi: 10.1001/archneur.1975.00490510088009
22. Fazekas F, Kleinert R, Offenbacher H, Schmidt R, Kleinert G, Payer F, Radner H, Lechner H. Pathologic correlates of incidental MRI white matter signal hyperintensities. Neurology. 1993;43(9):1683. doi: 10.1212/WNL.43.9.1683
23. Müllenbach R, Lagoda PJ, Welter C. An efficient salt-chloroform extraction of DNA from blood and tissues. Trends Genet. 1989;5(12):391.
24. Wenham PR, Price WH, Blundell G. Apolipoprotein E genotyping by one-stage PCR. Lancet. 1991;337(8750):1158-9. doi: 10.1016/0140-6736(91)92823-K
25. Bizzarro A, Guglielmi V, Lomastro R, Valenza A, Lauria A, Marra C, Silveri MC, Tiziano FD, Brahe C, Masullo C. BuChE K variant is decreased in Alzheimer's disease not in fronto-temporal dementia. J Neural Transm. 2010;117(3):377-83. doi: 10.1007/s00702-009-0358-y
26. Giuliani A. The application of principal component analysis to drug discovery and biomedical data. Drug Discov Today. 2017;22(7):1069-76. doi: 10.1016/j.drudis.2017.01.005
27. Jolliffe IT. Principal component analysis: a beginner's guide. Weather. 1990. doi: 10.1002/j.1477-8696.1990.tb05558.x
28. Jackson DA. Stopping rules in principal components analysis: A comparison of heuristical and statistical approaches. Ecology. 1993;74(8):2204-14. doi: 10.2307/1939574
29. Tiel C, Sudo FK, Alves GS, Ericeira-Valente L, Moreira DM, Laks J, Engelhardt E. Neuropsychiatric symptoms in vascular cognitive impairment: A systematic review. Dement Neuropsychol. 2015;9(3):230-6. doi: 10.1590/1980-57642015dn93000004
30. Boublay N, Schott AM, Krolak-Salmon P. Neuroimaging correlates of neuropsychiatric symptoms in Alzheimer's disease: a review of 20 years of research. Eur J Neurol. 2016;23(10):1500-9. doi: 10.1111/ene.13076
31. Calsolaro V, Femminella GD, Rogani S, Esposito S, Franchi R, Okoye C, Rengo G, Monzani F. Behavioral and psychological symptoms in dementia (BPSD) and the use of antipsychotics. Pharmaceuticals. 2021;14(3):246. doi: 10.3390/ph14030246
32. Serra L, Bruschini M, Di Domenico C, Mancini M, Bechi Gabrielli G, Bonarota S, Caltagirone C, Cercignani M, Marra C, Bozzali M. Behavioral psychological symptoms of dementia and functional connectivity changes: a network-based study. Neurobiol Aging. 2020;94:196-206. doi: 10.1016/j.neurobiolaging.2020.06.009
33. Borroni B, Grassi M, Agosti C, Costanzi C, Archetti S, Franzoni S, Caltagirone C, Di Luca M, Caimi L, Padovani A. Genetic correlates of behavioral endophenotypes in Alzheimer disease: role of COMT, 5-HTTLPR and ApoE polymorphisms. Neurobiol Aging. 2006;27(11):1595-603. doi: 10.1016/j.neurobiolaging.2005.09.029
34. Mou C, Han T, Wang M, Jiang M, Liu B, Hu J. Correlation of polymorphism of ApoE and LRP genes to cognitive impairment and behavioral and psychological symptoms of dementia in Alzheimer's disease and vascular dementia. Int J Clin Exp Med. 2015;8(11):21679-83.
35. Panza F, Frisardi V, Seripa D, D'Onofrio G, Santamato A, Masullo C, Logroscino G, Solfrizzi V, Pilotto A. Apolipoprotein E genotypes and neuropsychiatric symptoms and syndromes in late-onset Alzheimer's disease. Ageing Res Rev. 2012;11(1):87-103. doi: 10.1016/j.arr.2011.06.005
36. Eissa N, Sadeq A, Sasse A, Sadek B. Role of neuroinflammation in autism spectrum disorder and the emergence of brain histaminergic system. Lessons also for BPSD? Front Pharmacol. 2020;11:886. doi: 10.3389/fphar.2020.00886
37. Nyberg L, Karalija N, Salami A, Andersson M, Wåhlin A, Kaboovand N, Köhncke Y, Axelsson J, Rieckmann A, Papenberg G, Garrett DD, Riklund K, Lövdén M, Lindenberger U, Bäckman L. Dopamine D2 receptor availability is linked to hippocampal-caudate functional connectivity and episodic memory. Proc Natl Acad Sci. 2016;113(28):7918-23. doi: 10.1073/pnas.1606309113
38. Chakraborty S, Lennon JC, Malkaram SA, Zeng Y, Fisher DW, Dong H. Serotonergic system, cognition, and BPSD in Alzheimer's disease. Neurosci Lett. 2019;704:36-44. doi: 10.1016/j.neulet.2019.03.050
39. Sink KM, Covinsky KE, Barnes DE, Newcomer RJ, Yaffe K. Caregiver characteristics are associated with neuropsychiatric symptoms of dementia. J Am Geriatr Soc. 2006;54(5):796-803. doi: 10.1111/j.1532-5415.2006.00697.x
40. Raccichini A, Spazzafumo L, Castellani S, Civerchia P, Pelliccioni G, Scarpino O. Living with mild to moderate Alzheimer patients increases the caregiver's burden at 6 months. Am J Alzheimers Dis Dement. 2015;30(5):463-7. doi: 10.1177/1533317514568339
41. Park S, Kim DK, Myung W, Yoo JH, Shin SJ, Na DL, Kim SY, Lee JH, Kim SY, Han SH, Choi SH, Shin J. Risk factors of behavioral and psychological symptoms in patients with Alzheimer disease: the clinical research of dementia of South Korea study. Korean J Fam Med. 2019;40(1):16-21. doi: 10.4082/kjfm.17.0061
42. Caton M, Ochoa ELM, Barrantes FJ. The role of nicotinic cholinergic neurotransmission in delusional thinking. Npj Schizophr. 2020;6(1):16. doi: 10.1038/s41537-020-0105-9
43. Pinto T, Lanctôt KL, Herrmann N. Revisiting the cholinergic hypothesis of behavioral and psychological symp-

toms in dementia of the Alzheimer's type. Ageing Res Rev. 2011;10(1):12-31. doi: 10.1016/j.arr.2011.01.003
44. Finkel SI. Effects of rivastigmine on behavioral and psychological symptoms of dementia in Alzheimer's disease. Clin Ther. 2004;26(7):980-90. doi: 10.1016/S0149-2918(04)90172-5
45. Zimmermann S, Klusmann D, Hampe W. Correcting the predictive validity of a selection test for the effect of indirect range restriction. BMC Med Educ. 2017;17(1):246. doi: 10.1186/s12909-017-1070-5

Ann Ist Super Sanità 2025 | Vol. 61, No. 1: 50-60
DOI: 10.4415/ANN_25_01_07

Monitoring of antibiotic residues in muscles, milk and eggs of food-producing animals in Umbria and Marche regions (Central Italy) during the period time 2012-2021

Cinzia Pagano[1]*, Matteo Puccetti[1]*, Luana Perioli[1], Anna Imbriano[1], Cristiano Carloni[2], Irene Diamanti[2], Ivan Pecorelli[2] and Laura Fioroni[2]

[1]*Dipartimento di Scienze Farmaceutiche, Università degli Studi di Perugia, Perugia, Italy*
[2]*Istituto Zooprofilattico Sperimentale dell'Umbria e delle Marche "Togo Rosati", Perugia, Italy*
**These Authors equally contributed to the study*

Abstract

Introduction. The use of antibiotics in food-producing animals for infections treatment, metafilaxis and, although not allowed in Europe, as growth enhancer is responsible for the presence of antibiotic residues in animal derived foodstuffs. For this reason, it is very important to perform a monitoring.

Methods and results. Muscle samples from bovine, pig, poultry, turkey and fish, as well as bovine milk and hen's egg samples, deriving from 444 farms of both Umbria and Marche regions (Italy) were analyzed by well-established and validated analytical methods in order to evaluate the presence or not of antibiotic residues (penicillins, quinolones, tetracycline and sulphonamides). The samples were collected during 2012-2021 period of time. In total, 15/2,354 samples resulted positive to the analyses. The amount of antibiotics found in the 15 samples resulted below the maximum residue limit fixed by EU Regulation 37/2010 and for this reason considered compliant.

Conclusions. Despite irregular samples were not found, the presence of antibiotic residues in foodstuff represents a risk for public health as they are responsible for the selection of resistant strains contributing to antimicrobial resistance problem spread. In the present work, this aspect was evaluated in relation to the results obtained from the analyzed samples coming from Umbria and Marche regions.

Key words

- antibiotics residues
- muscles
- eggs
- milk
- antibiotic-resistance
- One Health

INTRODUCTION

Food safety and control of antimicrobial resistance (AMR) are among the aims of the One Health concept that considers the health of humans, animals and environment strictly interconnected [1, 2].

In a recent study, referring to 2019, is reported that 1.27 million people worldwide died because of infections associated to bacterial AMR [3]. Without appropriate strategies aimed at limiting this phenomenon these numbers would rise. It is in fact estimated that the number of death would reach 10 million/year by 2050 due to infections associated with multi-resistant micro-organisms [4].

The main factors responsible for the AMR are: i) antibiotics overuse and misuse in both humans and animals; ii) absorption of antibiotic residues deriving both from the environment (contaminated water, air, soil, or manure) and food; iii) direct animal-to-human contact on farms and slaughterhouses [5].

In food producing animals, antibiotics are used for therapeutic purposes, for disease prevention or as growth promoters [6], the last practice was banned in Europe starting from 1st January 2006.

The massive use of antibiotics in food producing animals represents a serious health care problem as the foodstuff is a vehicle for AMR transmission. Through foodstuff consumption, antibiotic residues could be transmitted to humans and, once internalized, they could promote the selection of AMR microorganisms. The latter could also develop in the animal continuously

Address for correspondence: Luana Perioli, Dipartimento di Scienze Farmaceutiche, Università degli Studi di Perugia, Via del Liceo 1, 06123 Perugia, Italy. E-mail: luana.perioli@unipg.it.

exposed to antibiotics so that the animal derived foodstuff could also represent a vehicle for the transmission of resistant bacteria or genes [6].

Considering the European scenario, according to the data collected from the European Medicines Agency (EMA), the use of antibiotics in the livestock's changes in the different countries [7]. In Nordic-Baltic nations for example, the antibiotics consumption is very low due to the combination of national strategies (surveillance program as well as good practice veterinary guidelines) aiming to limit the use of antibiotics and thus to control the AMR phenomenon [8, 9].

The largest users of antibiotics are: i) Poland, Italy and Spain where the amount used per livestock unit is 10-20 times higher than the lowest users (Nordic-Baltic countries); ii) France and Germany where the usage levels are about 5-10 times higher per livestock unit than the lowest users [7].

It is well demonstrated that the use of antibiotics in food producing animals contributes to AMR problem with consequent impact on the global health [10].

For this reason, over the years it was considered necessary to elaborate projects aiming to perform a deep surveillance and collaboration among the countries in order to better control and monitor the antibiotics consumption and thus AMR.

In 2005 the European Centre for Disease Prevention and Control (ECDC) was established. It is an agency of the European Union (EU) born with the aim to control the infectious diseases. ECDC performs a surveillance of both antibiotics' consumption in humans as well as AMR. ECDC, together to the European Food Safety Authority (EFSA) and EMA, elaborates periodically a report about antimicrobial agent consumption and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals. The purpose of this is to furnish periodic reports useful to provide an integrated analysis of the relationships between the use of antibiotics both in human and animals and the incidence of AMR in bacteria from humans and food [10].

The European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) started in 2009. This is a project aimed at collecting information about the use of antimicrobial medicines in animals in the EU. These data are useful to create a database to correlate the consumption of antibiotics in veterinary field to AMR. The Decision 2013/652/EU has a very significant importance for the collection of data about AMR. This document reports the rules useful to perform the monitoring and reporting of antimicrobial resistance in zoonotic and commensal bacteria according to harmonized practices in all the EU member states.

On 30th June 2017 the European Commission adopted the "European One Health Action Plan against Antimicrobial Resistance (AMR)" aiming to limit the use of antimicrobials together to the improvement of the information about the problems related to AMR. The adoption of these measures has produced a positive impact as demonstrated in the thirteenth ESVAC report, which highlights that the sales of antibiotics in veterinary field (reported as milligrams per population correction unit mg/PCU) decreased of 53.0% from 2011 to 2022 [11]. In Italy Decision 2013/652/EU was adopted starting from 2014 and the Piano Nazionale di Contrasto dell'Antimicrobico-Resistenza (PNCAR) launched a monitoring program aimed at counteracting AMR through an integrated plan involving the human, veterinary, food, environmental and agricultural fields.

According to this plan in Italy the main pathogen species, representing the main risks of developing acquired antibiotic resistance, are *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Enterococcus faecalis*, *Enterococcus faecium*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter*.

This paper deals with the examination of the results obtained from the search of selected antibiotic residues (penicillins, quinolones, tetracyclines and sulphonamides) within a surveillance study conducted in Central Italy by Istituto Zooprofilattico Sperimentale dell'Umbria e delle Marche, under the auspices of the Italian Ministry of Health. Meat samples (bovine, pig, poultry, turkey and fish), bovine milk and hen's eggs were analyzed in the period 2012-2021 in Umbria and Marche regions.

MATERIALS AND METHODS

Sample collection

2,354 samples (bovine, pig, poultry, turkey, fish muscle, hen's eggs and bovine milk) were collected during a ten-year period (2012 to 2021) from 444 farms of both Umbria (217) and Marche (227) regions, within the framework of the official control and self-control plan of the Italian dairy industry. 287 samples were submitted to penicillins, 454 samples analyzed for tetracycline, 990 for sulphonamides and 623 for fluorofluoroquinolones detection. Sampling was performed according to Piano Nazionale Ricerca Residui (PNR) 2021 from the Italian Ministry of Health and the analyses were carried out by the Istituto Zooprofilattico Sperimentale of Umbria and Marche "Togo Rosati".

Standards and reagents

Milli-Q system Millipore (Bedford, MA, USA, 18.2 mΩ cm^{-1} resistivity) was used to obtain ultrapure water. SPE SCX (100 mg, 3 mL) cartridges were purchased from Phenomenex (Torrance, CA, USA). The standards of antibiotics sulfamerazine, sulfamonomethoxine, sulfadiazine, sulfathiazole, sulfamethoxazole, oxolinic acid, flumequine, marbofloxacin, chlortetracycline, doxycycline, benzylpenicillin, cloxacillin, dicloxacillin, nafcillin, oxacillin were purchased from Dr. Ehrenstorfer (Augsburg, Germany); sulfachloropyridazine, sulfametoxipiridazine, sulfadimethoxine, sulfachinoxaline, sulfamethazine, sulfapyridine, ciprofloxacin, danofloxacin, difloxacin, enrofloxacin, norfloxacin, sarafloxacin, tetracycline, amoxicillin, ampicillin, purity ≥95% (HPLC), were purchased from Sigma-Aldrich (St. Louis, MO, USA). All the other reagents and solvents used were of analytical grade and were supplied by Carlo Erba (Milan, Italy).

Analytical methods

The detection of penicillins (nafcillin, dicloxacillin, cloxacillin, oxacillin, ampicillin, amoxicillin, benzyl-

penicillin) in muscle samples (bovine, pig, poultry, turkey, fish) was performed by Premi®Test (DSM, DSM Food Specialities R&D, Delft, The Netherlands) while for bovine milk samples Delvotest® (DSM, DSM Food Specialities R&D, Delft, The Netherlands) was used. They are microbiological assays, in which the samples, are submitted to antibiogram analysis based on the evaluation of growth inhibition of the strain *Bacillus stearothermophillus*. The limit of antibiotic detection is ≥25 µg/kg for muscle samples while for milk samples concentrations ≥3 µg/L for ampicillin, amoxicillin, benzylpenicillin and ≥20 µg/L for nafcillin, dicloxacillin, cloxacillin, oxacillin are detectable.

Before the analysis, muscle samples were treated according to the following procedure: 4 g of minced muscle was placed in a 50 mL Falcon® tube and added by 10 mL of extraction solvent constituted by acetonitrile (ACN)-acetone 70:30 v/v. The sample was homogenized for 10 min and then centrifuged at 4,000 rpm for 10 min. The supernatant was placed in a 15 mL Falcon® tube and the solvent removed under nitrogen at 40-45 °C. The solid was then suspended in 500 µL di Lab Lemco broth (Thermo Scientific™, Roma, Italy) and vortexed. Premi®Test was performed for screening e post-screening using 100 µL (screening) and 230 µL (post-screening) of the extract (*Figure 1*).

Bovine milk samples were analyzed without preventive preparation procedures (*Figure 2*). The determinations were carried out following the kit manufacturer instructions [12, 13].

Tetracyclins (doxycycline, chlortetracycline, tetracycline, oxytetracycline) were detected by TetraSensor (Tissue) – KIT036 for both muscles (bovine, pig, poultry, turkey, fish) and hen's eggs and KIT014 for bovine milk (Unisensor, Seraing (Ougrée) – Belgium). The detection limit is ≥40 µg/kg for muscles and ≥25 µg/L for milk and ≥75 µg/kg for eggs. Before the analysis, the muscle samples were prepared as follows: the homogenized muscle (10 g) was put in a stomacher bag added by 30 mL of extraction buffer provided in the kit. The sample was then homogenized in stomacher for 2 min. One mL of extract was ultracentrifuged at 10,000 rpm for 3 min. Then 200 µL of the extract were seeded in the microplate well. The dipstick was put in the well and left for 10 min. Afterwards the dipstick was removed and performed the analysis by Readsensor reader (*Figure 1*). In the case of bovine milk samples, they were assayed without preliminary extraction procedures (*Figure 2*). Hen's egg samples were prepared as follows: the homogenized eggs (10 g) were put in a centrifuge tube (50 mL) then added by 30 mL of extraction buffer (prepared according to kit procedures). The sample was centrifuged (4,000 rpm, 20 min), then put in a centrifuge tube (15 mL), added by n-hexane (5 mL) vortexed, centrifuged (4,000 rpm, 10 min) and the hexane removed. The remaining aqueous phase (200 µL) was used for the assay (*Figure 1*). The determinations were carried out following the kit manufacturer instructions [14].

Fluoroquinolones (flumequine, difloxacin, ciprofloxacin, marbofloxacin, norfloxacin, sarafloxacin, danofloxacin, enrofloxacin, oxolinic acid) were detected by

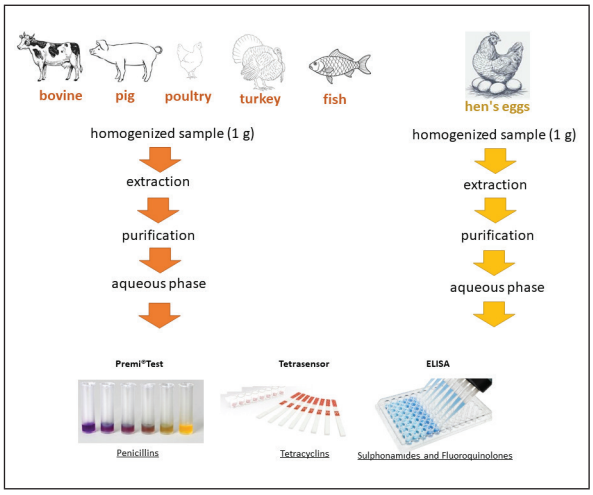


Figure 1
Scheme of the procedure followed for both muscles and eggs samples preparation before the analysis of the different antibiotics.

enzyme immunoassay using the immunoenzymatic kit chinolone ridascreen® cod. R3113 (r-Biopharm, Darmstadt, Germany). The detection limit is ≥25 µg/kg for both muscles and eggs and ≥15 µg/L for bovine milk. The samples (bovine, pig, poultry, turkey, fish) were prepared using the methods proposed by Scortichini *et al.* [15] starting from 1 g of homogenized muscle or eggs (*Figure 1*).

Extraction of fluoroquinolones was obtained by introducing 4 mL of extraction solution (m-phosphoric acid 0.45%/ACN 70/30 v/v). Then the tube was vortexed for 10 min. Afterward the tube was placed in a water-bath for 30 min at 45-50 °C in order to induce the precipitation of proteins. Then the sample was left to cool and centrifuged (4,500 rpm for 10 min), the supernatant was filtered in a 15 mL Falcon® tube by using a nylon syringe filter (30 mm, 0.45 µm). The obtained sample was resubmitted to another extraction cycle adding 4

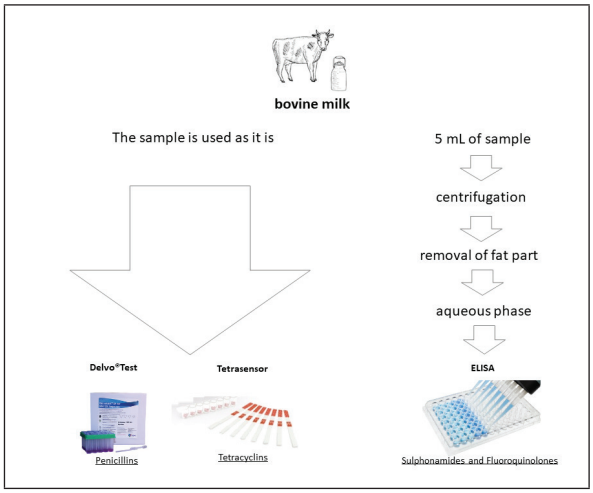


Figure 2
Scheme of the procedure followed for bovine milk samples preparation before the analysis of the different antibiotics.

mL of extraction solution (m-phosphoric acid 0.45%/ACN 70/30 v/v) and performing the steps described above. The extracts (~8 mL) were combined and an aliquot of 4 mL was evaporated under a nitrogen flux (40-50 °C) until the complete evaporation of ACN (until 2 mL). Then the concentrated extract was diluted with 4 mL of water. The extract purification was performed by loading on the OASIS HLB cartridge previously conditioned with 1 mL of MeOH and 1 mL of Milli-Q water. Subsequently, the cartridge was washed with 2 mL of phosphate buffer (0.025 M, pH 3)/MeOH 95:5 (v/v) and with 2 mL of water. The fluoroquinolones were eluted with 2 mL of MeOH/ammonia 95:5 (v/v). The solvent was removed under nitrogen (40-50 °C), just before application to the microtiter plates, the residue was dissolved in 2 mL of MeOH/water 35/65 (v/v). The determinations were carried out following the kit manufacturer instructions [16]. In case of the milk 5 mL of sample were centrifuged (4500×*g* for 10 min) in order to eliminate the fat fraction (*Figure 2*).

Sulfonamides (sulfamerazine, sulfamonomethoxine, sulfadiazine, sulfachloropyridazine, sulfametoxipiridazine, sulfadimethoxine, sulfachinoxaline, sulfathiazole, sulfamethazine, sulfamethoxazole, sulfapyridine) detection was performed by ELISA method using a sulphonamides ELISA KIT cod. SM390 (Tecna srl, Trieste, Italy), detection limit ≥20 µg/kg for muscle, egg and milk samples. The ELISA determinations were carried out following the manufacturer instructions. Muscle samples were prepared as described by Galarini *et al*. [17].

The samples (bovine, pig, poultry, turkey, fish) were prepared as follows: 1 g of homogenized muscle was placed in a 50 mL Falcon® tube. Then 5 mL of ethyl acetate were added and the sample was vortexed for 10 s and then stirred at 300 rpm for 15 min. Afterwards the sample was centrifuged for 10 min at 4,000 rpm. Three mL of supernatant (corresponding to 0.6 g of muscle) were taken and placed in a 15 mL Falcon® tube. The solvent was removed under nitrogen atmosphere at 50 °C. The obtained solid was then suspended in 0.6 mL of buffer provided in the kit and added by 1 mL of n-exane. The sample was vortexed for 30 s and centrifuged for 10 min at 4,000 rpm. The supernatant was removed and the aqueous phase submitted to the analysis. For the analysis 50 µL of sample were used for the seed in the microplate (*Figure 1*).

For bovine milk samples 5.0 g were centrifuged for 15 min at 4000 rpm and 4 °C in order to remove the fat fraction. Then the sample (2.5 g) was put in a centrifuge tube (50 mL), added by ethyl acetate (5 mL) and mixed for 1 min. The sample was then left in static conditions at room temperature for 10 min in order to obtain the phases separation. The supernatant (4 mL) was then dried under nitrogen at (50 °C). The obtained solid was then solubilized in 1 mL of buffer prepared according to kit procedures and 50 µL used for the assay (*Figure 2*).

For hen's egg samples 1.0 g of homogenized sample was added by ethyl acetate, vortexed for 10 min and put in a mechanical stirrer for 15 min at 300 rpm. The sample was then centrifuged, 10 min at 4,000 rpm. The supernatant (3 mL) was then dried under nitrogen at 50 °C and the obtained solid resuspended in 0.6 mL of buffer prepared according to kit procedures. The sample was then added by n-hexane (1 mL), vortexed for 30 sec, centrifuged for 5 min at 4,000 rpm. The supernatant was removed and the aqueous phase (50 µL) used for the analysis (*Figure 1*). The determinations were carried out following the kit manufacturer instructions [18].

Methods validation

The assays used for antibiotic residues identification are widely developed and implemented as routine laboratory tests for official analyses, due to the low costs and reduced working times allowing well-timed decisions. This is particularly important in the search of antibiotic residues in foodstuffs deriving from food-producing animals. The validation was performed according to the Commission Decision 2002/657/EC regulating the performances of analytical methods applied in EU official monitoring programs (*Table 1*). The main parameter considered in the validation is represented by the detection capability (CCβ) defined as "the smallest content of the substance that may be detected identified and/or quantified in a sample with an error probability of β". In the case of substances with an established permitted limit, the detection capability is the concentration at which the method is able to detect the allowed limit concentrations with a statistical certainty of 1 – β" (point 1.12 of the Annex to CD 2002/657/EC). β error represents the probability that the considered sample is truly non-compliant, even though a compliant measurement is obtained (false compliant decision). For screening tests the β error is fixed ≤5% [19].

RESULTS AND DISCUSSION

During 2012-2021 food samples (bovine, pig, poultry, turkey and fish muscles, as well as bovine milk and hen's eggs) deriving from farms of both Umbria and Marche regions were analyzed for the search of the following antibiotics residues: penicillins, tetracycline, sulphonamides and fluoroquinolones. The search was performed according to "Piano Nazionale Residui" (PNR) 2021 hat prescribes the search of antibiotics residues in the following samples: muscles (bovine, porcine, ovine, caprine, equine, poultry, turkey, fish, rabbits, farmed game), milk, eggs, honey [20]. In PNR the groups of chemical substances to be investigated in such samples, provided in the Annex I of the Legislative Decree 158/2006, are divided in category A (anabolic substances and non-authorised substances) and category B (veterinary medicinal products and contaminants). The latter category, is further divided in B1, B2 and B3 sub-category. B1 is the sub-category of interest in this study as it represents the antibacterial substances.

The results obtained from the analyses performed showed that non-compliant (irregular) samples were not detected (*Table 2*). No positive samples were detected in both hen's eggs and bovine milk while in the case of muscles some samples resulted positive for tetracycline, sulphonamides and fluoroquinolones. In 2012 one poultry muscle sample was positive to the fluoroquinolone flumequine (47.9 µg/kg). During 2013 one

Table 1
Methods used for antibiotics determination in the different food matrices considered: data obtained in validation *vs* corresponding requirements (Commission Decision 2002/657/EC)

Test	Detection method	Antibiotic class	Matrix	Parameters considered during the validation according to Decision 2002/657/EC	In-house validation
Premi®Test DSM	Microbiological technique	Penicillins	Muscles (bovine, pig, poultry, turkey, fish)	Detection capability (CCβ): is the smallest analyte content that can be detected or quantified in a sample with an error of β: the maximum error rate for authorized substances should not exceed 5%. The value of CCβ depends on the regulatory limit for each substance or class of them. Specificity: is the power of an analytical method to discriminate between the analyte and any closely related substance. Ruggedness: is the ability of an analytical method to withstand minor changes of experimental conditions.	Analyzing at least 20 fortified blanks for the concentration level chosen according to the MRL of each substance, the lack of any false negative result demonstrated method compliance (percentage of false compliant results or beta-error ≤5%). After fortifying of representative blank samples at a relevant concentration with substances that could be interferences, the lack of false identifications demonstrated the specificity of the analytical method. The ruggedness tests of the analytical method were conducted using the Youden approach.
Delvotest® DSM	Microbiological technique	Penicillins	Bovine milk		
TetraSensor (Tissue) – KIT036 Unisensor	Receptorial technique	Tetracyclins	Muscles (bovine, pig, poultry, turkey, fish) and hen's eggs		
TetraSensor (Milk) – KIT014 Unisensor	Receptorial technique	Tetracyclins	Bovine milk		
Immunoenzymatic Kit Chinolone Ridascreen®	ELISA	Quinolones	Muscles (bovine, pig, poultry, turkey, fish), bovine milk, hen's eggs		
Immunoenzymatic Kit Sulphonamides Tecna®	ELISA	Sulfonamides	Muscles (bovine, pig, poultry, turkey, fish), bovine milk, hen's eggs		

MRL: maximum residue limit.

poultry muscle sample was positive to oxytetracycline (54.9 µg/kg), one to the fluoroquinolone flumequine (25.4 µg/kg); one pig muscle sample resulted positive to h (74.0 µg/>kg).

During 2014, two poultry muscles were positive to doxycycline (an amount of 49.0 µg/kg and 94.3 µg/kg respectively) and one to tetracycline (amount measured 34.2 µg/kg) (*Table 2*). Moreover, one poultry muscle sample was positive to the fluoroquinolone flumequine (30.0 µg/kg).

In 2015 one pig muscle sample was found positive to doxycycline (12.0 µg/kg), two pig muscle samples resulted positive to sulfamonomethoxine (amount 49.0 µg/kg and 13 µg/kg respectively) while one sample of bovine muscle was positive to sulfamonomethoxine (38.0 µg/kg). One fish muscle sample was positive to flumequine (20.0 µg/kg) as well during 2016.

During 2017 sulfamerazine (11.0 µg/kg) residues were found in one pig muscle sample and enrofloxacin (22.0 µg/kg) residues were found in one poultry muscle sample (*Table 2*).

In all cases, the amount of antibiotic residues found was not considered problematic as the values resulted compliant to UE Regulation 37/2010 in which the admitted maximum residue limits (MRL) are fixed for the different antibiotics. MRL can be defined as the maximum allowed concentration of antibiotic residues in animal derived foodstuff, after a therapeutic treatment, established based on the calculated acceptable daily intake from preclinical data and residue depletion studies in target animal species [21]. These limits are set according to safety assessment, taking into account toxicological risks, environmental contamination, as well as the microbiological and pharmacological effects of residues as reported in the Regulation (EC) 470/2009. The MRL value for the antibiotics found in the muscle samples are: 100 µg/kg for oxytetracycline, doxycycline, tetracycline, sulfamonomethoxine, sulfamerazine, enrofloxacin and 400 µg/kg for flumequine.

The samples resulted positive to antibiotic search (*Table 2*) are compliant to UE Regulation 37/2010 as the concentrations found are below the MRL. However, some important considerations must be done. The first of them is the relative low number of samples analyzed and, even more, the low number of positive samples that makes difficult to obtain statistically significant trends.

Moreover, it should be considered that the samples were analyzed by *ad hoc* methods, optimized for each class of antibiotics considered. The use specific methods have two main limitations: i) each sample should be analyzed for one molecule or group of molecules (one sample for one method), ii) each method is specific for one class of antibiotic molecules thus not useful to detect antibiotics of other classes. Moreover, the sensitivity of the method (limit off detection – LOD) is limited in comparison to other more efficient techniques. For this reason, since 2023 the EU suggested to use multi-residue and more sensitive methods capable of detecting, through the analysis of a single sample, many classes of molecules. LC-MS/MS is one of this technique allowing to detect also levels lower than 70 ppb [22]. Based on these considerations, it could be plausible to hypothesize that antibiotic residues may have been present in samples which resulted negative, due to the limited sensitivity of the analytical methods used.

It is well known the connection between the anti-

Table 2
Resuming table of the food samples analyzed (bovine muscle, pig muscle, poultry muscle, turkey muscle, fish muscle, hen's eggs, bovine milk) in Umbria and Marche regions (Central Italy) in the period 2012-2021. For each year and for each class of antibiotics selected (penicillins, tetracyclines, sulphonamides and fluoroquinolones) are reported: the number of samples analyzed and the number of positive samples. For the positive samples the amount of antibiotic found and the maximum residue limit (MRL) of UE Regulation 37/2010 are reported

Penicillins

Year	2012		2013		2014		2015		2016		2017		2018		2019		2020		2021		
Sample	N tested	N positive	N tested	N positive	N tested	N positive	N tested	N positive	N tested	N positive	N tested	N positive	N tested	N positive	N tested	N positive	N tested	N positive	N tested	N positive	Pos/total samples
Bovine muscle	21	-	58	-	20	-	5	-	1	-	-	-	-	-	1	-	-	-	-	-	0/106
Pig muscle	24	-	11	-	10	-	18	-	11	-	6	-	4	-	6	-	3	-	6	-	0/99
Poultry muscle	12	-	16	-	17	-	1	-	3	-	5	-	1	-	-	-	-	-	1	-	0/56
Turkey muscle	-	-	1	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0/2
Fresh fish muscle	-	-		-	-	-	-	-	2	-	-	-	2	-	1	-	3	-	2	-	0/10
Hen's eggs	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bovine milk	6	-	4	-	2	-	2	-	-	-	-	-	-	-	-	-	-	-	-	-	0/14
	63		**90**		**50**		**26**		**17**		**11**		**7**		**8**		**6**		**9**		**0/287**

N: number.

Tetracyclines

Year	2012		2013		2014		2015		2016		2017		2018		2019		2020		2021		
Sample	N tested	N positive	N tested	N positive	N tested	N positive	N tested	N positive	N tested	N positive	N tested	N positive	N tested	N positive	N tested	N positive	N tested	N positive	N tested	N positive	Pos/total samples
Bovine muscle	21	-	58	-	20	-	5	-	1	-	-	-	-	-	1	-	-	-	-	-	0/106
Pig muscle	39	-	24	-	17	-	27	1[a]	19	-	20	-	15	-	12	-	13	-	19	-	1/205
Poultry muscle	13	-	16	1[b]	17	3[c]	1	-	3	-	5	-	1	-	-	-	-	-	1	-	4/57
Turkey muscle	-	-	1	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0/2
Fresh fish muscle	5	-	2	-	1	-	1	-	4	-	2	-	4	-	4	-	5	-	3	-	0/31
Hen's eggs	4	-	3	-	5	-	5	-	4	-	3	-	3	-	5	-	5	-	2	-	0/39
Bovine milk	6	-	4	-	2	-	2	-	-	-	-	-	-	-	-	-	-	-	-	-	0/14
	88		**108**		**63**		**41**		**31**		**30**		**23**		**22**		**23**		**25**		**5/454**

[a]doxycycline 12.0 µg/kg; [b]oxytetracycline 54.9 µg/kg; [c]doxycycline 49.0 µg/kg, doxycycline 94.3 µg/kg, tetracycline 34.2 µg/kg; the maximum residue limit (MRL) reported in UE Regulation 37/2010 is 100 µg/kg. N: number.

Sulphonamides

Year	2012		2013		2014		2015		2016		2017		2018		2019		2020		2021		
Sample	N tested	N positive	N tested	N positive	N tested	N positive	N tested	N positive	N tested	N positive	N tested	N positive	N tested	N positive	N tested	N positive	N tested	N positive	N tested	N positive	Pos/total samples
Bovine muscle	14		28	-	27	-	28	1a	23	-	21	-	20	-	20	-	19	-	8	-	1/208
Pig muscle	48	-	58	1b	41	-	50	2c	55	-	49	1d	40	-	45	-	44	-	40	-	4/470
Poultry muscle	14	-	25	-	26	-	5	-	26	-	27	-	26	-	24	-	23	-	24	-	0/220
Turkey muscle	-	-	1	-	1	-	1	-	1	-	-	-	-	-	-	-	-	-	-	-	0/4
Fresh fish muscle	1	-	1	-	1	-	1	-	1	-	2	-	3	-	2	-	4	-	2	-	0/18
Hen's eggs	2	-	5	-	5	-	8	-	8	-	3	-	7	-	6	-	9	-	2	-	0/55
Bovine milk	2	-	2	-	2	-	2	-	2	-	1	-	1	-	1	-	1	-	1	-	0/15
	81		**120**		**103**		**95**		**116**		**103**		**97**		**98**		**100**		**77**		**5/990**

[a]sulfamonomethoxine 38 µg/kg; [b]sulfamonomethoxine 74 µg/kg; [c]sulfamonomethoxine 49 µg/kg, sulfamonomethoxine 13 µg/kg; [d]sulfamerazine 11 µg/kg; the maximum residue limit (MRL) reported in UE Regulation 37/2010 is 100 µg/kg. N: number.

Continues

Table 2
Continued

Fluoroquinolones																					
Year	**2012**		**2013**		**2014**		**2015**		**2016**		**2017**		**2018**		**2019**		**2020**		**2021**		
Sample	**N tested**	**N positive**	**N tested**	**N positive**	**N tested**	**N positive**	**N tested**	**N positive**	**N tested**	**N positive**	**N tested**	**N positive**	**N tested**	**N positive**	**N tested**	**N positive**	**N tested**	**N positive**	**N tested**	**N positive**	**Pos/total samples**
Bovine muscle	21	-	58	-	20	-	5	-	1	-	-	-	-	-	1	-	1	-	-	-	0/107
Pig muscle	37	-	23	-	19	-	28	-	20	-	17	-	14	-	11	-	14	-	16	-	0/199
Poultry muscle	32	1[a]	36	1[b]	37	1[c]	6	-	25	-	21	1[d]	20	-	18	-	16	-	18	-	4/229
Turkey muscle	-	-	2	-	2	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	0/5
Fresh fish muscle	5	-	2	-	1	-	1	-	3	1e	2	-	3	-	4	-	5	-	3	-	1/29
Hen's eggs	4	-	3	-	7	-	6	-	4	-	2	-	3	-	4	-	5	-	2	-	0/40
Bovine milk	6	-	4	-	2	-	2	-	-	-	-	-	-	-	-	-	-	-	-	-	0/14
	105		**128**		**88**		**49**		**53**		**42**		**40**		**38**		**41**		**39**		**5/623**

[a]flumequine 47.9 µg/kg; [b]flumequine 25.4 µg/kg; [c]flumequine 30.0 µg/kg; [d]enrofloxacin 22.0 µg/kg; [e]flumequine 20.0 µg/kg; the maximum residue limit (MRL) reported in UE Regulation 37/2010 is 100 µg/kg for enrofloxacin and 400 µg/kg for flumequine. N: number.

biotics consumption and AMR occurrence in bacteria, in both humans and food-producing animals, as confirmed also in the fourth joint report published by EFSA, ECDC and EMA on January 2024 [10].

Data furnished by the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) about the sales or prescription of antimicrobial veterinary medicinal products for food-producing animals shows that during the 2020 (in 31 countries) the main classes of antibiotics used were penicillins (31.1%), tetracyclines (26.7%) and sulfonamides (9.9%). Despite in Italy from 2011 to 2021 the overall use of antibiotics in veterinary field decreased by 53%, unfortunately the consumption in livestock's is still high classifying Italy as third country in Europe for antibiotics use [23].

Data provided by Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA) about the human antibiotic consumption, in both Umbria and Marche regions [24], show that the use of penicillins and their combinations decreased from 2015 (1.6 and 1.4 DDD/1000 ab *die** for Umbria and Marche respectively) to 2021 (0.7 DDD/1000 ab *die** for both Umbria and Marche).

From the data reported in *Table 2* no positive samples were obtained from penicillins analysis. Based on these data, a decrease in AMR should be observed for this class of antibiotics over the same time period.

However, the regional results found in the national report, elaborated by the Istituto Superiore di Sanità (ISS) about the antibiotic-resistance surveillance referred to 2020, show the opposite. An increase of *Streptococcus pneumoniae* strains resistant to penicillin (13.6%) emerged as well as a high resistance of *Enterococcus faecium* toward ampicillin (90.2% of the isolated strains) and methicillin (33.5%). Moreover, *Escherichia coli* resulted particularly resistant towards ampicillin (64.5%) and amoxicillin-clavulanic acid (42.9%) as well as *Klebsiella Pneumoniae* (57.2%) [25].

According to AIFA report 2021, in Italy tetracycline are one of the most prescribed antibiotics in food producing animals [24]. In this study residues of such class of molecules were found in five muscle samples between 2013-2015. Thus, could be hypothesized that the large prescription of this class of antibiotics could contribute to AMR spread observed in veterinary field.

Recently Russo *et al.* [26] observed that multi-drug resistant (MDR) *Salmonella* strains are particularly resistant to tetracycline. This study, performed on samples deriving from the food chain in the Marche region (Central Italy), showed a wide dissemination of tetracycline resistance in *Salmonella* strains (80%). Indeed, the ISS report of 2020 showed that in Italy *Streptococcus pneumoniae* is the main tetracycline-resistant strain (16.8%) [11].

The EU One Health 2020 Zoonoses Report [27] food, animals and feed are provided and interpreted historically. Two events impacted 2020 MS data collection and related statistics: the Coronavirus Disease 2019 (COVID-19, an EFSA/ECDC document, shows that campylobacteriosis is the most common reported zoonosis in Europe, representing more than 60% of all the reported cases in 2020, followed by salmonellosis. A document drafted from EFSA states that *Salmonella* is the second pathogen responsible for foodborne diseases [14]. In the period 2016-2018, statistically significant associations between tetracycline consumption in food-producing animals and tetracycline resistance were identified in both *Salmonella spp.* and *Campylobacter jejuni* from humans. The latter is the consequence of the development of tetracycline resistance in *Campylobacter jejuni* from poultry [28].

Sulfonamides were mostly detected in pig muscle and the highest number of positive compliant samples was registered during the year 2015 (*Table 2*). EFSA report, referring to 2015, shows that in the EU *Salmonella spp.*

* Average number of drug doses consumed daily by 1,000 inhabitants (AIFA 2021).

was isolated from fattening pigs showing a high level of resistance to sulfamethoxazole (~52.6%). The same report describes that *Salmonella* strains, isolated in 2015 from humans, show a fair degree of resistance to sulfonamides/sulfamethoxazole (32.4%) [15, 29]. Data gathered of 2019 and 2020 showed a degree of resistance of 50.6% and 49.2% respectively [30]. It was found that high levels of *Salmonella spp*. detected in Italy are higher than in Europe.

In particular sulfamethoxazole results ineffective in 44.9% of the cases, followed by tetracycline (40.4%) and ampicillin (37.4%) [31]. These data support the verified correlation between antibiotic resistance of *Salmonella* in humans, associated to antimicrobials consumption in the pig farms for food chain [32]. A recent survey of Marche region underlined a high resistance degree of *Salmonella* strains toward sulfisoxazole [26]. These findings are very important as salmonellosis is one of the most frequent foodborne zoonosis, representing one of the major worldwide health concerns [30].

About fluoroquinolones, the positive compliant samples showed residues of the molecule flumequine which is used in human for the treatment of urinary tract infections [33]. This is a second-generation fluoroquinolone, antibiotic used in poultry in the treatment of systemic bacterial infection due to gram-negative bacteria including colibacillosis [34].

During 2019 AIFA [35] and EMA decided to remove this antibiotic (together to cinoxacin, nalidixic acid and pipemidic acid) from the trade of human medicines as responsible for many long-lasting and potentially permanent adverse reactions. Thus, it is still available only for the veterinary purpose. This poses a serious problem about the risks to which humans are exposed through the consumption of food containing residues of this antibiotic [36]. From AIFA report [11] resulted that human consumption of fluoroquinolones in Umbria and Marche regions decreased from 2015 (3.8 and 3.3 DDD/1000 ab *die*** for Umbria and Marche respectively) to 2021 (1.8 and 1.6 DDD/1000 ab *die*** for Umbria and Marche respectively) as assessed by the Italian antibiotics report [24]. However, the problem of resistance toward this class of molecules is still high. Indeed, an Italian report of 2020 showed how antibiotic resistance of *Escherichia coli* was above 30% toward fluoroquinolones, *Pseudomonas aeruginosa* was 29.4% towards levofloxacin and ciprofloxacin was about 18%.

Moreover, few studies are available in literature dealing with the contribution of low levels of flumequine in the induction of mutations and modifications responsible for antibiotic resistance. Such as Wood *et al*. observed some mutations on a virulent wild-type *Aeromonas salmonicida* induced by the exposure to low flumequine concentrations [35, 37].

The contribution to AMR of antibiotic residues in foodstuff is well documented by many scientific studies. It is well established that the presence of antibiotic residues below the MRL value promote the adaptation/selection of resistant strains that become less sensitive to antimicrobial agents that can pass to humans, by food consumption, with consequent AMR problem acceleration and spread. For this reason, despite the EU Regulation 37/2010 reports MRL of antibiotic molecules used in veterinary field, they must be considered the possible problems deriving from the use of UE Regulation 37/2010 compliant foods as that found in the present study (*Table 2*).

For many antibiotics the minimal selective concentration (MSC) has been defined. It represents the lowest antibiotic concentration that can lead in the enrichment of resistant bacteria in a strain population responsible for the selection of high-level resistant bacteria [21]. The antibiotics found in the positive compliant samples of the present study (*Table 2*) are: oxytetracycline, doxycycline, tetracycline, sulfamonomethoxine, sulfamonomethoxine, sulfamerazine, enrofloxacin, flumequine.

In a study performed on *E. coli* and *Salmonella* enterica strains, the growth of resistant bacteria was observed using tetracycline concentrations of 15 ng/ml (corresponding to 1/100 of the minimum inhibitory concentration MIC value) [38]. In a recent work, considering *E. coli* resistant strains, the MSC values were calculated for amoxicillin (0.08 mg/L - 0.8 mg/L), doxycycline (0.4 mg/L - 4 mg/L) and enrofloxacin (0.0125 mg/L - 0.125 mg/L) [39]. MSC identified for oxytetracycline was 0.1 mg/L in *E. coli* strain [40] while in a recent study it was demonstrated that flumequine is able to increase the resistance by inducing mutations in *E. coli* GyrA gene at concentrations of 2 mg/L [41].

Comparing these concentrations with the MRL values of the antibiotics detected in the samples analyzed (*Table 2*), the main concerns could raise for tetracycline, enrofloxacin, oxytetracycline which MSC found in literature are below the MRL values suggesting that the admitted concentrations represent a risk for AMR spreading both in animals and humans.

There is no global consensus on the best strategy to choose in order to alleviate the risks to human, animal and even environmental health [42] but many institutions are very committed to solve this problem. The institutions involved in the changes and management of the system in the veterinary and human sectors in Italy are the Italian Ministry of Health, Zooprophylactic Institutes (Istituti Zooprofilattici Sperimentali, IIZZSS), AIFA and ISS.

The European Commission, EMA, ECDC and EFSA support Member States to achieve the same goal. All draw inspiration from the World Organization for Animal Health (OIE) and the World Health Organization (WHO). During the US-EU summit in 2009, EU and United States (US) established the Transatlantic Task Force on Antimicrobial Resistance (TATFAR) in order to intensify the cooperation in the fight against AMR; EMA is a member of TATFAR.

The objective of the taskforce is to increase levels of communication, coordination and cooperation between the EU and the US on human and veterinary antimicrobials. In October 2015 a plan for the period up to 2020 was launched in New York and then extended

** Average number of drug doses consumed daily by 1,000 inhabitants (AIFA 2020).

to Canada and Norway. It requires global cooperation increasing knowledge and awareness of the AMR problem together to its effects on global health. The vastness of the problem also requires the involvement of different skills.

The One Health approach was adopted as part of a joint plan of action of WHO, Food and Agriculture Organization (FAO), World Organisation for Animal Health (WOAH) and United Nations Environment Programme (UNEP). In the scenario of AMR, it has the objective to "preserve antimicrobial efficacy and ensure sustainable and equitable access to antimicrobials for responsible and prudent use in human, animal and plant health".

The control of specific pathogens and AMR have been extensively funded under European research initiatives such as FP7, Horizon 2020 and Innovative Medicines Initiative (IMI). The surveillance of AMR is the result of the collaboration between EMA, EFSA and ECDC.

Based on the One Health approach, on 30th November 2022, the "Piano Nazionale di Contrasto all'Antibiotico-Resistenza (PNCAR) 2022-2025" was approved in Italy aiming to control AMR through the following points: i) surveillance and monitoring of both antibiotic consumption and AMR; ii) prevention of infectious diseases, zoonoses, healthcare-associated and community-acquired infections; iii) correct use of antibiotics both in human and veterinary field as well as correct disposal of antibiotic-contaminated wastes.

CONCLUSIONS

The data report referring to 2012-2021 presented in this paper, dealing with the search of antibiotic residues in muscles, milk and egg samples, showed that in Umbria and Marche regions no positive non-compliant (irregular) samples were detected.

Despite the obtained results are promising in the perspective of public health preservation however some concerns may arise about the positive samples even though these samples are compliant to the maximum residue limits reported in the UE Regulation 37/2010. The consumption of such food samples can contribute to the expansion of AMR in both humans and animals as the low concentrations of antibiotic residues could be responsible for resistant strains selection. What strategies could be adopted to do this? In the perspective of One Health concept, the European regulation EU 2019/6 about veterinary medicines has the objective to introduce restrictions to limit the use of antibiotics to 50% within 2030 in farmed and aquaculture animals. For example, it could be useful to consider a prolonged wash-out period, after a therapeutic treatment, in order to reach the complete elimination of antibiotics residues in the animal body. Undoubtedly the habitual use of antibiotics must be avoided and it is necessary to find suitable alternatives to conventional antimicrobial treatments, when applicable. Thanks to the advancements of biotechnology and genetic engineering it is possible to exploit new strategies both as prevention (e.g., probiotics) and as therapy (e.g., antimicrobial peptides). Also, natural sources can be a valuable tool in the search of new antimicrobial agents as well.

Acknowledgments

Authors thank Domenico Boccia, Roberta Buratti and Cinzia Fanini from UOS Laboratorio Residui di Farmaci ed Anabolizzanti UOC Chimica, Istituto Zooprofilattico Sperimentale dell'Umbria e delle Marche "Togo Rosati", Perugia, Italy, for technical assistance.

Funding

This research received no external funding.

Conflict of interest statement

The Authors declare no conflict of interest.

Received on 3 July 2024.
Accepted on 20 January 2025.

REFERENCES

1. Mackenzie JS, Jeggo M. The One Health approach-why is it so important? Trop Med Infect Dis. 2019;4(2):88. doi: 10.3390/tropicalmed4020088
2. Bonilla-Aldana DK, Dhama K, Rodriguez-Morales AJ. Revisiting the One Health approach in the context of COVID-19: A look into the ecology of this emerging disease. Adv Anim Vet Sci. 2020;8:234-7. doi: 10.17582/journal.aavs/2020/8.3.234.237
3. Murray CJ, Ikuta KS, Sharara F, Swetschinski L, Robles Aguilar G, Gray A, et al. Global burden of bacterial antimicrobial resistance in 2019: A systematic analysis. Lancet. 2022;399:629-55. doi: 10.1016/S0140-6736(21)02724-0. Erratum in: Lancet. 2022;400(10358):1102. doi: 10.1016/S0140-6736(21)02653-2
4. de Kraker MEA, Stewardson AJ, Harbarth S. Will 10 million people die a year due to antimicrobial resistance by 2050? PLoS Med. 2016;13(11):e1002184. doi: 10.1371/journal.pmed.1002184
5. Xu C, Kong L, Gao H, Cheng X, Wang X. A review of current bacterial resistance to antibiotics in food animals. Front. Microbiol. 2022;13:822689. doi: 10.3389/fmicb.2022.822689
6. Wu-Wu JWF, Guadamuz-Mayorga C, Oviedo-Cerdas D, Zamora WJ. Antibiotic resistance and food safety: Perspectives on new technologies and molecules for microbial control in the food industry. Antibiotics. 2023;12(3):550. doi: 10.3390/antibiotics12030550
7. European Public Health Alliance (EPHA). Ending routine farm antibiotic use in Europe through improving animal health and welfare. Brussels, Belgium: EPHA; 2022. Available from: https://epha.org/ending-routine-farm-antibiotic-use/.
8. Mulchandani R, Wang Y, Gilbert M, Van Boeckel TP. Global trends in antimicrobial use in food-producing animals: 2020 to 2030. PLOS Glob Public Heal. 2023;3(2):e0001305. doi: 10.1371/journal.pgph.0001305
9. Sternberg-Lewerin S, Boqvist S, Nørstebø SF, Grönthal T, Heikinheimo A, Johansson V, et al. Nordic Vets

against AMR – An initiative to share and promote good practices in the Nordic-Baltic Region. Antibiotics. 2022; 11(8):1050. doi: 10.3390/antibiotics11081050
10. European Centre for Disease Prevention and Control (ECDC), European Food Safety Authority (EFSA), European Medicines Agency (EMA). Antimicrobial consumption and resistance in bacteria from humans and food-producing animals: Fourth joint inter-agency report on integrated analysis of antimicrobial agent consumption and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals in the EU/EEA JIACRA IV – 2019-2021. EFSA J. 2024;22:e8589. doi: 10.2903/j.efsa.2024.8589
11. European Medicines Agency (EMA). ESVAC - Sales of veterinary antimicrobial agents in 31 European countries in 2019 and 2020. Trends from 2010 to 2020. Eleventh ESVAC report. Luxembourg: European Union; 2021. Available from: https://www.ema.europa.eu/en/documents/report/sales-veterinary-antimicrobial-agents-31-european-countries-2019-and-2020-trends-2010-2020-eleventh-esvac-report_en.pdf.
12. R-Biopharm AG. Premi® test: Instructions for use. Darmstadt, Germany: R-Biopharm AG. Available from: https://it.scribd.com/document/405914235/Premi-Test-Instruc-for-Use.
13. DSM Food Specialties. Delvotest SP NT instructions. Delft, The Netherlands; 2011. Available from: https://it.scribd.com/document/379584825/Delvotest-Sp-Nt-Instructions.
14. Unisensor. Tetrasensor: Rapid test detecting tetracycline in any animal tissues. Seraing (Ougrée), Belgium: Unisensor; 2020. Available from: https://v3.globalcube.net/clients/beldico/content/medias/tetrasensor-tissue-kit036.pdf.
15. Scortichini G, Annunziata L, Di Girolamo V, Buratti R, Galarini R. Validation of an enzyme-linked immunosorbent assay screening for quinolones in egg, poultry muscle and feed samples. Anal Chim Acta. 2009;637(1-2): 273-8. doi: 10.1016/j.aca.2008.10.007
16. R-Biopharm AG. RIDASCREEN® chinolone/quinolones. Darmstadt, Germany: R-Biopharm AG; 2021. Available from: https://food.r-biopharm.com/wp-content/uploads/2012/06/r3113-chinolone-2021-02-15.pdf.
17. Galarini R, Diana F, Moretti S, Puppini B, Saluti G, Persic L. Development and validation of a new qualitative ELISA screening for multiresidue detection of sulfonamides in food and feed. Food Control. 2014;35(1): 300-10. doi: 10.1016/j.foodcont.2013.07.014.
18. R-Biopharm Nederland BV. Multi-sulfonamides ELISA: A competitive enzyme immunoassay for screening and quantitative analysis of a broad range of sulfonamides in various matrices. Arnhem, The Netherlands: R-Biopharm; 2023. Available from: https://food.r-biopharm.com/wp-content/uploads/Manual-MULTI-SULFONAMIDES-ELISA-5101SULM905.23.pdf.
19. Galarini R, Buratti R, Fioroni L, Contiero L, Lega F. Development, validation and data quality assurance of screening methods: A case study. Anal Chim Acta. 2011;700(1-2):2-10. doi: 10.1016/j.aca.2011.05.008
20. Ministero della Salute. Piano Nazionale Ricerca Residui (PNR): Anno 2021. Roma: Ministero della Salute; 2020. Available from: https://www.izslt.it/wp-content/uploads/2021/02/1PIANO-NAZIONALE-RESIDUI-2021.pdf.
21. Koutsoumanis K, Allende A, Alvarez-Ordóñez A, Bolton D, Bover-Cid S, Chemaly M, et al. Maximum levels of cross-contamination for 24 antimicrobial active substances in non-target feed. Part 1: Methodology, general data gaps and uncertainties. EFSA J. 2021;19(10):6852. doi: 10.2903/j.efsa.2021.6852
22. Chan CL, Wai HKF, Wu P, Lai SW, Chan OSK, Tun HM. A Universal LC-MS/MS method for simultaneous detection of antibiotic residues in animal and environmental samples. Antibiotics. 2022;11(7):845. doi: 10.3390/antibiotics11070845
23. European Medicines Agency (EMA). Sales of veterinary antimicrobial agents in 31 European countries in 2022 – Trends from 2010 to 2022: Thirteenth ESVAC report. Luxembourg: European Union, 2023.
24. Osservatorio Nazionale sull'Impiego dei Medicinali. L'uso degli antibiotici in Italia. Rapporto Nazionale 2021. Roma: Agenzia Italiana del Farmaco (AIFA), 2023. Available from: https://www.aifa.gov.it/documents/20142/1853258/Rapporto_Antibiotici_2021.pdf.
25. Bellino S, Iacchini S, Monaco M, Del Grosso M, Camilli R, Errico G, Giufrè M, Sisi M, D'Ancona F, Pantosti A, Pezzotti P, Patrizia Parodi. AR-ISS: Sorveglianza nazionale dell'antibiotico-resistenza. Dati 2020. Roma: Istituto Superiore di Sanità; 2021. (Rapporti ISS Sorveglianza, RIS-1/2021). Available from: https://www.iss.it/documents/20126/0/RIS-1_2021.pdf/af6da4cc-0f57-3800-68ca-c5f6c05479c0?t=1637230397225.
26. Russo I, Bencardino D, Napoleoni M, Andreoni F, Schiavano GF, Baldelli G, et al. Prevalence, antibiotic-resistance, and replicon-typing of salmonella strains among serovars mainly isolated from food chain in Marche Region, Italy. Antibiotics. 2022;11(6):725. doi: 10.3390/antibiotics11060725
27. European Food Safety Authority, European Centre for Disease Prevention and Control. The European Union One Health 2020 zoonoses report. EFSA J. 2021;19(12):6971. doi: 10.2903/j.efsa.2021.6971.
28. European Centre for Disease Prevention and Control (ECDC), European Food Safety Authority (EFSA), European Medicines Agency (EMA). Third joint inter-agency report on integrated analysis of consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals in the EU/EEA. EFSA J. 2021;19:e06712. doi: 10.2903/j.efsa.2021.6712 10.2903/j.efsa.2021.6712
29. European Food Safety Authority (EFSA), European Centre for Disease Prevention and Control (ECDC). The European Union summary report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2018/2019. EFSA J. 2021;19(4):6490. doi: 10.2903/j.efsa.2021.6490
30. European Food Safety Authority (EFSA), European Centre for Disease Prevention and Control (ECDC). L'antibiotico resistenza in Europa. EFSA; 2020. Available from: https://multimedia.efsa.europa.eu/dataviz-2020/index.htm.
31. Gargano V, Sciortino S, Gambino D, Costa A, Agozzino V, Reale S, et al. Antibiotic susceptibility profile and tetracycline resistance genes detection in salmonella spp. Strains isolated from animals and food. Antibiotics. 2021;10(7):809. doi: 10.3390/antibiotics10070809
32. Campos J, Mourão J, Peixe L, Antunes P. Non-typhoidal salmonella in the pig production chain: A comprehensive analysis of its impact on human health. Pathogens. 2019; 8(1):19. doi: 10.3390/pathogens8010019
33. Schena FP, Gesualdo L, Caracciolo G. Multicentre study of flumequine in the treatment of urinary tract infections. J Antimicrob Chemother. 1988;21:101-6. doi: 10.1093/jac/21.1.101
34. Ferraresi C, Lucatello L, Meucci V, Intorre L, Grilli G, Piccirillo A, et al. Pharmacokinetic/pharmacodynamic

evaluation of the efficacy of flumequine in treating colibacillosis in turkeys. Poult Sci. 2013;92(12):3158-65. doi: 10.3382/ps.2013-03460

35. Agenzia Italiana del Farmaco (AIFA). Nota informativa importante su medicinali contenenti fluorochinoloni. Roma: AIFA; 2019. Available from: https://www.aifa.gov.it/-/nota-informativa-importante-su-medicinali-contenenti-fluorochinolo-1.
36. Koutsoumanis K, Allende A, Alvarez-Ordóñez A, Bolton D, Bover-Cid S, Chemaly M, et al. Maximum levels of cross-contamination for 24 antimicrobial active substances in non-target feed. Part 10: Quinolones: flumequine and oxolinic acid. EFSA J. 2021;19(10):6862. doi: 10.2903/j.efsa.2021.6862
37. Wood SC, McCashion RN, Lynch WH. Mutiple low-level antibiotic resistance in Aeromonas salmonicida. Antimicrob Agents Chemother. 1986;29(6):992-6. doi: 10.1128/AAC.29.6.992
38. Gullberg E, Cao S, Berg OG, Ilbäck C, Sandegren L, Hughes D, et al. Selection of resistant bacteria at very low antibiotic concentrations. PLoS Pathog. 2011;7(7): e1002158. doi: 10.1371/journal.ppat.1002158
39. Swinkels AF, Fischer AJ, Korving L, Kusters NE, Wagenaar JA, Zomer AL. Defining minimal selective concentrations of amoxicillin, doxycycline and enrofloxacin in broiler-derived cecal fermentations by phenotype, microbiome and resistome. bioRxiv. 2023. doi: 10.1101/2023.11.21.568155
40. Tran TT, Cole M, Tomas E, Scott A, Topp E. Potential selection and maintenance of manure originated multidrug resistant plasmids at subclinical antibiotic concentrations. Can J Microbiol. 2023;69(9):339-50. doi: 10.1139/cjm-2022-0240
41. Swinkels AF., Fischer AJ, Korving L, Christodoulou R, Wagenaar JA, Zomer AL. Flumequine, a fluoroquinolone in disguise. NPJ Antimicrob Resist. 2024;2(1)28:1-8. doi: 10.1038/s44259-024-00044-5
42. Sagar P, Aseem A, Banjara SK, Veleri S. The role of food chain in antimicrobial resistance spread and One Health approach to reduce risks. Int J Food Microbiol. 2023;391-3:110148. doi: 10.1016/j.ijfoodmicro.2023.110148

Ann Ist Super Sanità 2025 | Vol. 61, No. 1: 61-67
DOI: 10.4415/ANN_25_01_08

Health promotion at the beach: lessons learned from the "safe beaches" education project

Daniela D'Angelo[1], Serenella Savini[2], Elisabetta Zuchi[3], Carlo Turci[2], Cinzia Sandroni[1], Alessia De Angelis[3], Maurizio Zega[4] and Safe Beaches Working Group*

[1]*Azienda Sanitaria Locale Roma/6, Albano Laziale, Rome, Italy*
[2]*Azienda Sanitaria Locale Roma/4, Civitavecchia, Rome, Italy*
[3]*Azienda Sanitaria Locale Roma/3, Rome, Italy*
[4]*Ordine Professioni Infermieristiche (OPI) di Roma, Rome, Italy*
**The members of the Safe Beaches Working Group are listed before the References*

Abstract

Background. During summer, beach authorities are charged with ensuring the safety of beach visitors, which includes promoting safe behaviour via educational efforts. The purpose of this study was to describe the processes of development and implementation of a promotional project for beach safety.

Methods. A multidisciplinary task force developed the informational material and the content to be provided following the principles of the Health Belief Model (HBM). The health promotion addressed a wide range of topics and was delivered at 65 bathing facilities along the Lazio coast (Central Italy) from June 2, 2023, to September 10, 2023. To evaluate the feedback of the promotion activities, the attendees were asked to answer a post-event self-evaluation survey.

Results. 1,032 people responded to the questionnaire about satisfaction and utility levels. Participants' overall satisfaction scores (98% rated "excellent" or "good") and utility (88%) were high, with higher satisfaction levels for the women, those with higher education, and Italian citizens. Most participants reported that the material was easy to understand; the contents were comprehensive; and the healthcare professionals were prepared, engaging, and available.

Conclusions. This project showed that approaching the summer visitors in the place time is a feasible and well-accepted strategy for summer health-related education.

Key words
- beach safety
- health promotion
- community health
- health education

INTRODUCTION

During the summer, beaches can face various challenges and problems, often related to the increased number of visitors and environmental factors [1]. Some of the most frequent problems at beaches include safety concerns like drownings, beach accidents (contact with jellyfish/weever fish, heat stroke), and water-related incidents [2]. Beach accidents and water-related incidents represent a major public health problem associated with significant personal, societal and economic costs [2, 3].

The beaches on the Lazio coast in Central Italy are tourist-oriented and residential with a population that significantly increases during the summer months. Sunbathing on the Lazio beaches is one of the main attractions for Italian and foreign tourists, mainly because of the beaches' closeness to Rome.

International visitors are often considered to be an "at risk" group at beaches due to their unfamiliarity with the environment and associated hazards, and a lack of attention to safety details as part of being on holiday [3, 4].

Lifeguard services may be strained during peak times, and efforts by local authorities and community organisations are essential to address and mitigate summer beach-related concerns. To prevent and decrease the risks associated with environmental hazards on the beaches and health conditions related to these risks, it is crucial to focus on raising awareness about water safety and to provide helpful information to ensure the well-being of beach visitors. Health promotion programmes are initiatives designed to improve the health and well-being of individuals and communities by enabling people to take control of their health and

Address for correspondence: Serenella Savini, Azienda Sanitaria Locale Roma/4, Via Terme di Traiano 39/A, 00053 Civitavecchia (Rome), Italy. E-mail: serenella.savini@aslroma4.it.

its determinants. They should include a settings-based approach to promote health in specific settings (e.g., schools, workplaces, residential areas, markets) [5] to address priority health problems by taking into account the places where people live and work [6].

The "safe beaches" education project has embraced this vision by creating an action plan based on communities' health problems and needs and offering programmes and education to meet them.

The main aim of the project was to heighten health awareness and changes in attitudes and beliefs on beach safety or beach accident prevention. The theoretical basis of the project was built on the Health Belief Model (HBM) [7], a framework created to explain the lack of participation in public health service programmes. According to the HBM, an individual makes behavioural changes based on their perception of the severity of the potential illness, susceptibility to the illness, benefits of changing their behaviour to prevent or reduce the effect of the illness, and obstacles to the recommended behavioural change [8].

The project was launched as a pilot project by one healthcare organisation in 2022 to test its feasibility [9]; after this, the same project was launched by three healthcare organisations coordinated by the Board of Nurses of Rome (Ordine Professioni Infermieristiche, OPI) with the patronage of the Lazio Region.

The purpose of this study was to describe the processes of development and implementation of the project and to evaluate the achievements of the programme in terms of project's activities and services (process evaluation) and programme results (outcome evaluation).

METHODS

The "safe beaches" promotion programme

Theoretical basis of the project

The rationale for the efficacy of the project relies on the HBM [7] according to which the desired behavioural change is positively influenced by enabling people to understand the potential benefits of reducing some health hazards and by empowering them to implement behavioural changes. The combination of specific outreach (identifying hazards at the beaches), education, and empowerment (simulation) was believed to be essential to the programme's success [10]. For example, regarding tanning, the HBM suggests that individuals will engage in sun protection (e.g., wear sunscreen) if they perceive themselves to be vulnerable (due to family cancer history and skin type) to a severe health threat (skin cancer) and believe that the benefits associated with engaging in the protective behaviour (diminishing risk for skin cancer) outweigh the costs (money spent on sunscreen).

Following the model, the efforts to develop the educational materials and information provided were directed towards influencing individual health behaviours by addressing various psychological factors, as follows:

- perceived susceptibility: informational materials include data, statistics, and scenarios that emphasise the likelihood of individuals being at risk (e.g., for heat exhaustion and heat stroke). The materials help users recognise their personal vulnerability;
- perceived severity: the content and the provided information highlights the serious consequences of not addressing the health issue (e.g., for heat exhaustion: confusion, altered mental status, loss of consciousness) and includes testimonials that make the threat of the condition more tangible;
- perceived benefits: the materials present clear, actionable steps and explain how taking preventive measures or seeking treatment could improve health outcomes (e.g., for heat exhaustion: explaining the benefits of drinking plenty of water and wearing loose fitting, lightweight clothing);
- perceived barriers: the contents address and alleviate common barriers/perceptions (e.g., for heat exhaustion: the amount of sun exposure to obtain a perfect tan) and provide solutions, alternatives, and encouragement to reduce these barriers (e.g., phototypes, UV index).

For further details, the topics addressed in the educational sessions, structured around the factors of the Health Belief Model, are *available online as Supplementary Materials (Appendix A)*. The developed materials can be accessed at the following link: https://opi.roma.it/spiagge-serene-2023/.

Development

The project committee planned and coordinated the health promotion programme, determining the specific health issues that require attention to improve safety at beaches. Since the health promotion programmes should be synergistic and cannot be effectively addressed through interventions focused on a single lifestyle [11], a multidisciplinary task force composed of nurses, midwives, dieticians, physiotherapists, and social workers was instituted. The health promotion programme was based on a wide range of topics, such as healthy dietary habits, beach hazards, water safety, sun safety awareness, breastfeeding and women's personal hygiene at the beach (e.g., menstrual hygiene), and physical activity, while first aid and emergency response were demonstrated through basic life support defibrillation (BLSD) and drowning simulations. These simulations were performed by well-trained personnel who demonstrated the proper management of beach emergencies. The task force developed the informational material (brochures, booklets, posters, etc.) intending to integrate and complement the proposed topics while appealingly presenting them and following the principles of the HBM. The combination of specific outreach (identifying beach hazards in participants' personal experience), education, and empowerment (providing skill through simulations) was believed to be essential to program success.

Implementation

The committee planned programme activities, scheduling places, dates, and timetables. It also determined the modalities of the programme, identified the resources, and invited public and not-for-profit community organisations and voluntary healthcare providers. In order to gather as many beachgoers as possible, the "safe beaches" project was publicised extensively through

various sources: websites, social media, interviews, and posters put up throughout the beaches. The "safe beaches" project was held at 48 bathing facilities along the Lazio coast between 10 am and 6 pm from June 2, 2023, to September 10, 2023. The timetable is available from: https://opi.roma.it/spiagge-serene-2023/.

During the activity days, a multidisciplinary team provided health promotion interventions using the informational material. The team walked along the beaches interacting with beachgoers both through direct one-to-one communication and at the users' beach resorts, talking to groups of a maximum of five people. The content of each educational session consisted of a minimum 15-minute session based on the topic on which the beachgoers declared they were most interested. Indeed, given the multidisciplinary nature of the educational project, which encompasses a wide range of topics, it was impractical to address all subjects within a single session. Consequently, participants were consulted to identify the topics of greatest interest, forming the basis of the educational session.

During the educational session beach goers were asked about their health beliefs on the chosen topic as follows:

- perceived susceptibility (how likely do you think you are to experience [health issue]?);
- perceived severity (how serious do you believe the consequences of [health issue] are?);
- perceived benefits (what do you think are the benefits of taking [health action]?);
- perceived barriers (what factors might prevent you from taking [health action]?).

Then, based on the beachgoers' responses and the arguments outlined in *Appendix A available online as Supplementary Materials*, the healthcare providers enhanced participants' knowledge about beach health and safety and provided guidance on how to modify their behaviours accordingly.

Furthermore, beach visitors were invited to the BLSD stations, where instructors offered cardio-pulmonary resuscitation simulations using a semi-automatic defibrillator and demonstrated what to do in the case of a drowning situation. As part of the drowning simulation program, prepared instructors collaborated with trained rescue dogs to demonstrate water rescue techniques. This initiative was specifically designed to enhance the program's appeal to beachgoers, making it both educational and engaging. Specifically, all the drowning simulations were based on the following actions designed to enhance safety during summer beach outings mainly points:

- teach children and inexperienced swimmers to stay in designated swimming areas marked by safety flags;
- check beach safety warnings, weather conditions, and tide schedules before visiting;
- observe and adhere to posted signs about dangerous areas, such as sudden drop-offs or strong currents;
- avoid swimming during adverse weather conditions or when red or double red safety flags are displayed;
- provide life jackets for children, non-swimmers, and those engaging in water sports;
- use floating devices cautiously, as they can drift into deeper waters or strong currents;
- avoid alcohol consumption while swimming or supervising swimmers;
- never swim alone; use the buddy system to monitor each other's safety;
- act quickly if someone shows signs of distress: signal for help and avoid putting yourself at risk;
- reach or throw lifesaving equipment to the person in need, but do not enter the water unless trained to perform rescues;
- perform cardiopulmonary resuscitation (CPR) immediately if a drowning victim is unresponsive after being pulled from the water.

By combining these proactive measures with a commitment to safety and awareness, beachgoers can significantly reduce the risk of drowning and enjoy a safer summer at the beach.

Evaluation

Study population

To evaluate the feedback of the "safe beaches" promotion activities, the attendees were asked to answer a post-event self-evaluation survey by scanning a QR code printed on the materials distributed. Everyone who had participated in the activities or received health information on the beach could respond. Before answering, they provided written informed consent.

Measures

The research team collected responses between June 2023 and September 2023. The survey consisted of 14 questions and was designed with a focus on two main domains: the satisfaction and the utility perceived.

In the survey, respondents were asked to provide: (i) a Likert scale rating for satisfaction; (ii) a Likert scale rating for utility; and (iii) any additional suggestions or comments in an open text box. The survey also included two questions on respondents' general impressions and included space for suggested improvements.

Statistical analysis

Data were collected and analysed by researchers involved in the project.

To describe and compare the study participants' characteristics, frequencies, means, and standard deviations were calculated. A chi-square test of independence was performed to examine the association between gender (male, female), education level (primary, secondary, high, university), and nationality (Italian, other), with responses to the questions related to the satisfaction and utility of the project. The assumptions of the chi-square test were checked, ensuring that all expected cell frequencies were ≥5. Statistics were analysed using SPSS version 23.

The data were presented alongside qualitative comments and suggestions.

RESULTS

The healthcare professionals provided the health education intervention to increase the participants' knowledge and behaviours related to beach safety. With respect to the coverage of the "safe beaches" project, during the three months of "safe beaches" activities (be-

tween June 2023 and September 2023), 1,032 people responded to the questionnaire about satisfaction and utility levels.

Approximately 10,000 brochures were distributed during the educational sessions. The themes chosen most by beachgoers were on first aid, nutrition and feeding, and the impact of sun exposure on bone health. As for the general characteristics of participants, the mean age of respondents was 42.7 (±SD16) years, the majority (64.3%) of the respondents were female, and around 48% had a university degree. Non-Italian citizens accounted for 6.9% of the sample.

Socio-demographic characteristics of the participants are summarized in *Table 1*.

Programme delivery and result evaluation

Overall, most participants were very satisfied with the educational project. On a 4-point scale, 98% of the participants rated the programme as "excellent" or "good", and almost 100% responded that they would recommend participation in the programme to their friends. Specifically, a majority of participants perceived that things learned during the programme were useful and practical (88%); the material was easy to understand (90%); the contents were clear (89%) and comprehensive (86%); and the healthcare professionals were prepared (90%), engaging (90%), and available (92%) (*Table 2*). Approximately 85% responded that the programme was organised well overall and was run smoothly. However, the least positive experiences were reported with regard to accessibility, dissemination, and the effectiveness of publicity; indeed, 61% of the visitors were at the beach by chance, without having had the opportunity to plan their involvement in advance. The results summarized in *Table 3* indicate that women generally exhibit a higher level of satisfaction than men (X^2=16.1, p=0.013), individuals with higher education tend to be more satisfied with the program (X^2=21.9, p=0.009), and Italians report greater satisfaction compared to foreigners (X^2=10.5, p=0.015). The evaluation score related to utility was higher for younger participants (X^2=20.2, p=0.043) than for older ones (*Table 4*).

Table 1
General characteristics of the of Post-Event Survey Participants (n=1,032)

Variables		Frequency (%)
Gender	Male	353 (34.2)
	Female	664 (64.3)
	Missing	15 (1.4)
Age	Mean (SD)	42.7 (16)
Education	Primary	13 (1.3)
	Secondary	88 (8.5)
	High school	440 (42.6)
	University	491 (47.6)
Citizenship	Italy	831 (80.5)
	Foreign	71 (6.9)
	Missing	130 (12)
How people find out about the programme	Internet, e-mail	31 (3)
	On-site participation	638 (61)
	Institutional announcement	66 (6.4)
	Social media	62 (6)
	Word of mouth	127 (12)
	Others	108 (10)
Frequency of visits to the beaches	Almost never	41 (4)
	<1 month	364 (35)
	1< months <3	366 (35)
	3< months <6	261 (25)

SD: standard deviation.

Participants' free comments

Many respondents suggested desired activities/services in future programmes (n=20), made general suggestions (n=10), and wrote free comments (n=3). Respondents suggested several improvements for future health programmes, including more extensive promotion of the programme, sufficient time for health simulation, extension to other social meeting places, and sustained health programmes regularly over the year rather than as one-time summer events. As for future desired activities/services, various topics were suggested, including what lifeguards do and how they can help people, what to do in case of drowning, and what constitutes inappropriate beach behaviour, with a section on respecting the beach, yourself, and others.

DISCUSSION

The results demonstrated that the "safe beaches" programme effectively provided opportunities for beach visitors to access health information and available health services and resources as well as to improve knowledge, skills, and self-confidence. The educational interventions provided by the healthcare providers allowed participants to learn how to prevent or reduce the risk of an adverse outcome at the beaches, obtain skills on first aid and emergency response, and increase their knowledge on a variety of summer-related issues.

This programme demonstrated the feasibility of delivering health promotion programmes at beaches that represent unique settings for families' health promotion and positive environments that empower and encourage healthy behaviours [12]. Indeed, natural environments are increasingly being considered key settings for health promotion [13, 14]. The efforts to promote beach visitors' health can also positively affect the health of the overall community. As beach visitors are expected to be engaged in the wider world (e.g., with family, the elderly, and vulnerable people), their health promotion will disseminate health messages and resources to the less-connected sectors of society. Furthermore, beach visits are often undertaken by groups of people rather than by individuals, indicating a social dimension to visits during which health promotion can be spread.

Table 2
Participants' level of satisfaction with the "safe beaches" project

Overall, how satisfied were you with the educational project?				
Very satisfied	841 (81)			
Satisfied	181 (17)			
Neither satisfied nor dissatisfied	8 (0.8)			
Dissatisfied	2 (0.2)			
How do you rate the usefulness of the project?				
Excellent	514 (49)			
Good	409 (39)			
Sufficient	103 (10)			
Insufficient	6 (0.6)			
How do you rate the clarity, completeness, and understanding of the informational material?				
	Clarity	**Completeness**	**Understanding**	
Excellent	530 (51)	484 (46)	531 (51)	
Good	394 (28)	420 (40)	400 (39)	
Sufficient	103 (10)	122 (12)	97 (9.4)	
Insufficient	3 (0.3)	6 (0.6)	4 (0.4)	
How do you rate the professionalism, availability, preparation, and involvement of the operators?				
	Professionalism	**Availability**	**Preparation**	**Involvement**
Excellent	588 (57)	600 (58)	594 (57)	587 (56)
Good	360 (34)	353 (34)	356 (34)	355 (34)
Sufficient	80 (7.8)	74 (7.2)	78 (7.6)	83 (8)
Insufficient	4 (0.4)	5 (0.5)	4 (0.4)	7 (0.7)
How do you rate the structure and organization of the educational sessions?				
Excellent	557 (54)			
Good	319 (31)			
Sufficient	150 (15)			
Insufficient	6 (0.6)			
Would you recommend participation in the project to relatives/friends?				
YES	1,029 (99.7)			
NO	3 (0.3)			

Table 3
Demographics of Post-Event Survey Participants and percentage of satisfaction in brackets

		N (%)				X^2 (p value)
		Dissatisfied	**Neither satisfied nor dissatisfied**	**Satisfied**	**Very satisfied**	
Education	Elementary	0	0	2 (15.4)	11 (84.4)	
	Secondary	0	2 (0.4)	21 (23.9)	65 (73.9)	
	High school	1 (0.2)	4 (0.9)	97 (22)	338 (76.8)	
	University	1 (0.2)	2 (0.4)	61 (12.4)	427 (87)	**21.9 (0.009)**
Gender	Female	0	4 (0.6)	108 (16.3)	552 (83.1)	
	Male	1 (0.3)	12 (3.4)	69 (19.5)	271 (76.8)	**16.1 (0.013)**
Citizenship	Italy	2 (0.2)	5 (0.6)	134 (16.1)	690 (83)	
	Foreign	0	0	22 (31)	49 (69)	**10.5 (p=0.015)**
Age	<15	0	1 (4.3)	7 (30.4)	15 (65.2)	
	16-26	1 (0.5)	2 (1.1)	41 (21.9)	143 (76.5)	
	27-37	0	0	33 (16.9)	162 (83.1)	
	38-48	0	2 (1)	20 (10.1)	177 (88.9)	
	49-59	1	2 (0.8)	48 (19)	201 (79.8)	
	60-70	0	0	26 (17.6)	122 (82.4)	
	>70	0	1 (3.6)	6 (21.4)	21 (75)	26.6 (0.08)
Frequency of visits to the beaches	Almost never	0	0	12 (29.3)	29 (70.7)	
	<1 month	0	2 (0.5)	67 (18.4)	295 (81)	
	1< months <3	1 (0.3)	4 (1.1)	70 (19.1)	291 (79.5)	
	>3 months	1 (0.4)	2 (0.8)	32 (12.3)	226 (86.6)	12.06 (0.21)

N: number; X^2: chi-square test; in bold: statistically significant results.

Table 4
Demographics of attendees at 'safe beaches' program and evaluation of usefulness in numbers and percentages

		N (%)				X^2 (p value)
		Insufficent	**Sufficent**	**Good**	**Excellent**	
Education	Elementary	0	3 (23.1)	2 (15.4)	8 (61.5)	
	Secondary	1 (1.1)	7 (8)	33 (37.5)	48 (54.4)	
	High school	2 (0.4)	50 (11.5)	185 (42.6)	199 (45.9)	
	University	3 (0.6)	43 (8.8)	189 (38.5)	259 (52.7)	
Gender	Female	2 (0.3)	66 (10)	273 (41.2)	324 (48.9)	
	Male	3 (0.8)	31 (8.9)	133 (38.1)	185 (53)	10.4 (0.12)
Citizenship	Italy	2 (0.2)	89 (10.7)	334 (40.3)	405 (48.9)	
	Foreign	3 (0.3)	7 (10.1)	28 (40.6)	34 (49.3)	0.24 (0.98)
Age	<15		2 (9.1)	10 (45.5)	10 (45.5)	
	16-26	1 (0.1)	19 (10.2)	82 (44.1)	85 (45.7)	
	27-37	3 (1.5)	8 (4,1)	77(39.7)	109 (56.2)	
	38-48	2 (1)	18 (9)	81 (40.7)	100 (50.3)	
	49-59	0	36 (14.3)	102 (40.6)	113 (45)	
	60-70	0	16 (11)	48 (32.9)	82 (56.2)	
	>70	0	4 (14.3)	9 (32.1)	15 (53.6)	**20.2 (0.043)**
Frequency of visits to the beaches	Almost never	1 (0.3)	7 (18.4)	15 (39.5)	16 (42.1)	
	<1 month	3 (0.8)	38 (10.4)	148 (40.7)	178 (48.9)	
	1< months < 3	2 (0.5)	37 (10.1)	143 (39.2)	185 (50.7)	
	>3 months	0	21 (8.1)	103 (39.8)	135 (52.1)	4.6 (0.54)

N: number; X^2: chi-square test; in bold: statistically significant results.

Participants positively evaluated most of the processes of the programme activities and services, while some improvements will be needed in the areas of accessibility, dissemination, and the effectiveness of the publicity. With respect to satisfaction, from this study it emerged that satisfaction was significantly higher for women, for those with higher education, and for Italian citizens. It is reasonable to think that the topics covered by the programme (e.g., healthy dietary habits, sun safety awareness, breastfeeding and women's personal hygiene at the beach, physical activity) are of greater interest to women. Moreover, it is well recognised that the more educated people are, the more they appreciate the health promotion programme; this is quite challenging, as it is those who are less educated who most need to be involved in such initiatives.

Healthcare providers are called on to take into account the specific needs of the less-educated population [15]; as with mental health issues, specialist skills and specific care pathways for the involvement of the less-educated population and non-Italian citizens should be enhanced by investing in dedicated training and staff. It could be useful to increase the availability of cultural mediators and the use of multilingual materials as key strategic actions to reaching out to foreign beach visitors [16]. The participants highly valued the multi-professional and intersectoral debate of the project, and the high level of utility and satisfaction confirmed the importance of developing interventions and programmes within a common framework [7, 8, 10] to help guide future actions.

The utility of the project was perceived as higher by the younger participants; this is of particular importance as younger people are regular beach users who are knowledgeable and mostly aware of beach-related hazards and risks but often do not make the safest decisions [17]. Moreover, the WHO pointed out that people aged 5-14 years are more exposed to unintentional injury at beaches than those of other ages [18].

We hope that attending the "safe beaches" health promotion programme [10] based on the HBM framework [8, 19] increased the participants' ability to perceive the benefits of positive behaviour and to discourage harmful behaviour as well as driving behavioural change.

Limitations

Various limitations of the project should be noted.

First, the relationship between the programme and behavioural changes was not addressed, as we only reported the level of satisfaction and utility of the project without investigating the impact (e.g., behavioural changes, reduction in incidents at the beaches). In practice, however, no single evaluation is likely to address all dimensions of health promotion programmes; indeed, the effectiveness of such activities remains weak or inconsistent effects have been reported [20].

Second, we used convenience sampling and not a representative sample of all the participants. Obtaining a representative sample in a public health programme is a major challenge because those programmes are usually held as open-ended and unstructured events in a public space with many people coming and going. Since our participants were similar concerning geography (citizens and city of residence), the results may not be generalizable to other communities.

Third, as the survey was conducted during the programme, we cannot be sure the participants' reported perceptions will be sustained in the long term.

CONCLUSIONS

This project has clearly shown that approaching the summer visitors in the place where they spend their free time is a feasible and well-accepted strategy for summer health-related education, including cardio-pulmonary resuscitation simulations to use in cases of drownings. The lessons learned from this project are particularly important as the results demonstrated the utility and satisfaction related to a health promotion project design on the HBM that addressed the key beliefs capable of influencing health-related behaviours in an open-ended setting such as beaches. We believe our results would be useful for sharing information on the planning and implementing of future beach health promotion programmes.

We claim that although health promotion programmes have become very popular in recent years, their successful implementation remains weak, and evaluation suffers from a shortage of evidence. Further efforts are needed to develop a balanced programme of monitoring, process evaluation, and outcome evaluation to understand which health activities are successful and why.

Conflict of interest statement

The Authors declare that there are no conflicts of interest.

Members of the Safe Beaches Working Group

Rita Gentile, Loredana Gigli, Marina Germano, Martina Ciardiello, Angela Cioffi, Gaia Di Laurenzi (Azienda Sanitaria Locale Roma/3, Rome, Italy); Roberta Marchini, Tania Diottasi, Fabio Petracchioli, Giordano Ritti, Nicoletta Fiorentino (Azienda Sanitaria Locale Roma/4, Rome, Italy); Nadia Lolli, Claudio Federici, Letizia Mallia, Simonetta Bartolucci, Daniela Favale, Maria Molinari, Laura Bianchi, Alberto Pisciottana, Cinthia Vercelloni, Paola Capoleva (Azienda Sanitaria Locale Roma/6, Rome, Italy); Francesco Scerbo, Natascia Mazzitelli (Ordine Professioni Infermieristiche, OPI, di Roma, Rome, Italy).

Received on 23 September 2024.
Accepted on 20 January 2025.

REFERENCES

1. Lukoseviciute G, Panagopoulos T. Management priorities from tourists' perspectives and beach quality assessment as tools to support sustainable coastal tourism. Ocean Coast Manag. 2021;208:105646. doi: 10.1016/j.ocecoaman.2021.105646
2. Warton N, Brander R. Improving tourist beach safety awareness: The benefits of watching Bondi Rescue. Tourism Manag. 2017;63:187-200. doi: 10.1016/j.tourman.2017.06.017
3. Clifford KM, Brander RW, Trimble S, Houser C. Beach safety knowledge of visiting international study abroad students to Australia. Tourism Manag. 2018;69:487-97. doi: 10.1016/j.tourman.2018.06.032
4. McKay C, Brander RW, Goff J. Putting tourists in harms way – Coastal tourist parks and hazardous unpatrolled surf beaches in New South Wales, Australia. Tourism Manag. 2014;45:71-84. doi: 10.1016/j.tourman.2014.03.007
5. Kumar S, Preetha G. Health promotion: An effective tool for global health. Indian J Community Med. 2012;37(1):5-12. doi: 10.4103/0970-0218.94009
6. Shaikh BT. Understanding social determinants of health seeking behaviours, providing a rational framework for health policy and systems development. J Pak Med Assoc. 2008;58(1):33-6.
7. Becker MH (Ed). The Health Belief Model and personal health behavior. Thorofare, NJ: Slack; 1974.
8. Rosenstock IM. The Health Belief Model and preventive health behavior. Health Educ Monog. 1974;2(4):354-86. doi: 10.1177/109019817400200405
9. Sandroni C, Boldrini M, Capoleva P, Federici C, Lolli N, Mallia L, Molinari MR, Pisciottana A, Vercelloni C. "Spiagge serene": Un progetto di educazione sanitaria nella Asl Roma 6. Infermiere Oggi. 2022;3:59-60.
10. Forster-Cox SC, Mangadu T, Jacquez B, Fullerton L. The environmental health/home safety education project: a successful and practical U.S.-Mexico border initiative. Health Promot Pract. 2010;11(3):325-31. doi: 10.1177/1524839909341026
11. Kim RW, Nahar VK. A guide for understanding health education and promotion programs. Health Promot Pract. 2018;19(2):167-9. doi: 10.1177/1524839917741487
12. Ashbullby KJ, Pahl S, Webley P, White MP. The beach as a setting for families' health promotion: A qualitative study with parents and children living in coastal regions in Southwest England. Health Place. 2013;23:138-47. doi: 10.1016/j.healthplace.2013.06.005
13. Hansen-Ketchum P, Marck P, Reutter L. Engaging with nature to promote health: New directions for nursing research. J Adv Nurs. 2009;65(7):1527-38. doi: 10.1111/j.1365-2648.2009.04989.x
14. Hansen-Ketchum PA, Halpenny EA. Engaging with nature to promote health: Bridging research silos to examine the evidence. Health Promot Int. 2011;26(1):100-8. doi: 10.1093/heapro/daq053
15. Raghupathi V, Raghupathi W. The influence of education on health: An empirical assessment of OECD countries for the period 1995–2015. Arch Public Health. 2020;78(1):20. doi: 10.1186/s13690-020-00402-5
16. Castro A, Santos M. ROMA municipal mediator project experimental project evaluation results summary report. Lisboa: Alto Comissariado para as Migrações (ACM, IP); 2015.
17. Willcox-Pidgeon S, Kool B, Moran K. Perceptions of the risk of drowning at surf beaches among New Zealand youth. Int J Inj Contr Saf Promot. 2018;25(4):365-71. doi: 10.1080/17457300.2018.1431939
18. Adair T, Mikkelsen L, Hooper J, Badr A, Lopez AD. Assessing the policy utility of routine mortality statistics: A global classification of countries. Bull World Health Organ. 2023;101(12):777-85. doi: 10.2471/blt.22.289036
19. Prochaska JO, Di Clemente CC. Transtheoretical therapy: Toward a more integrative model of change. Psychother Theory Res Pract. 1982;19(3):276-88.
20. Joh HK, Kim HJ, Kim YO, Lee JY, Cho B, Lim CS, et al. Health promotion in young adults at a university in Korea: A cross-sectional study of 625 participants in a university. Medicine. 2017;96(7):e6157. doi: 10.1097/md.0000000000006157

Ann Ist Super Sanità 2025 | Vol. 61, No. 1: 68-81
DOI: 10.4415/ANN_25_01_09

ORIGINAL ARTICLES AND REVIEWS

Relative excess measures of effect and their use in health impact assessment

Orazio Valerio Giannico[1,2]

[1]*Struttura Complessa di Statistica ed Epidemiologia, Azienda Sanitaria Locale (ASL) Taranto, Taranto, Italy*
[2]*Area Epidemiologia e Care Intelligence, Agenzia Regionale Strategica per la Salute ed il Sociale (AReSS) Puglia, Bari, Italy*

Abstract

Introduction. In health impact assessment, relative excess measures of effect are used in combination with exposure and outcome data to estimate the health impacts under an alternative exposure scenario. The aim of this study is to propose: a classification of relative excess measures of effect functional for health impact assessment; a standard and general framework for calculating health impacts; different approaches when using data at different spatial resolutions.

Methods and results. A classification of the relative excess measures of effect was presented, introducing a new measure. A standard framework for calculating attributable and preventable cases based on the nature of the exposure and the imagined change in exposure was described. The marginal and conditional approaches to calculate health impacts using data at different spatial resolutions were illustrated.

Conclusions. The proposed methods and frameworks are designed to be applicable to a range of different situations. As health impact assessment continues to evolve, the insights and tools provided in this paper could help guide effective and equitable assessments, ultimately contributing to better public health decisions and outcomes.

Key words

- health impact assessment
- risk assessment
- effect measure
- epidemiology
- environment

INTRODUCTION

Health impact assessment (HIA) is a method for evaluating how a proposed policy, programme, or initiative might affect the health of a community. Recommendations are made to decision-makers and stakeholders to maximize the beneficial and minimize the harmful health effects of the proposal. The method combines quantitative, qualitative, and participatory approaches, making it applicable to a wide range of economic sectors. To proactively promote health and prevent illness or injury, it helps decision-makers to choose between alternatives and improvements [1-8].

A common approach in health impact assessment is to use exposure-response functions from previous studies. Typically, health impact assessment, also known as epidemiological risk assessment (ERA), uses relative excess measures of effect in combination with exposure and outcome data to estimate the health impacts under an alternative exposure scenario. The exposure-response functions used for the assessment are mainly taken from meta-analyses to ensure the reliability of the estimates [2, 3, 9-24]. Most studies and technical documents focus on assessing the health impacts of harmful exposures (typically air pollution), while less attention has been paid to the health impacts of beneficial exposures (e.g., green spaces) [2-4, 7, 8, 13-24]. Different approaches and equations have been used, depending on the research question, the quality of the available data, and the working group [1-24].

By drawing on the reference literature on epidemiological measures and using mathematical derivations, this paper attempts to fill the knowledge gap on a global framework of standard equations. The first aim of this study is to propose a classification of relative excess measures of effect that is functional for health impact assessment. The second objective is to propose a standard and general framework for estimating health impacts in different situations. The third goal is to propose different approaches to calculating health impacts when using data at different spatial resolutions.

METHODS

Rationale and assumptions

The present work builds on and extends the definitions of effect measures provided by leading epidemiology texts in an attempt to establish a standard and general framework [9-12]. Concepts and equations are based on a counterfactual framework. Namely, one population of size N is considered under two alternative scenarios, baseline – or actual or factual – and counterfactual. The reported definitions are referred to as counterfactual or potential-outcome definitions because at least one of

Address for correspondence: Orazio Valerio Giannico, Struttura Complessa di Statistica ed Epidemiologia, Azienda Sanitaria Locale (ASL) Taranto, Viale Virgilio 31, 74121 Taranto, Italy. E-mail: oraziovaleriogiannico@gmail.com.

the two conditions is contrary to fact. The population may be exposed or non-exposed. If the population is exposed, then the non-exposed condition is counterfactual, and if it is non-exposed, then the exposed condition is counterfactual. Association measures are referred to as effect measures after assuming reasonable absence of bias in the estimation of the exposure-response functions. Strictly speaking, we could never observe a true effect measure. In fact, a true effect measure compares what would happen to one population under two possible but different conditions, only one of which can occur. It is a theoretical – some would say "metaphysical" – concept in that it is logically impossible to observe the population under both conditions, and therefore logically impossible to see the magnitude of the effect directly. In contrast, we necessarily use measures of association from studies that compare what happened in different populations. Identifying these measures with measures of effect in a single population is an approximation that assumes there is no bias in the estimation of the measure. A further assumption is the transportability of the measures from the populations observed in the analytical studies to the population to which the effect measures are applied. The terms "exposure" and "non-exposure" denote the index and reference conditions respectively. Only adverse outcomes are considered in the present study. For simplicity reasons, only risk measures are considered in this study. In the present study, the term "cases" is used to denote the incident cases (new cases) that occur in a given period of time in a population at risk of size *N* at the beginning of the period. Similar effect measures can be calculated using rate or odds measures, and an analogous health impact assessment methodology can be applied by using these measures under the rare disease assumption [1-24].

Classification and calculation of relative excess measures of effect

In a population of size *N*, the attributable risk (*AR*) or risk difference (*RD*) or excess risk (*ER*) represents the quantity which is added to the risk by the exposure (absolute effect measure or excess measure of effect). By using the risks in the exposed (*R*1) and non-exposed (*R*0), or the number of cases in the exposed (*C*1) and non-exposed (*C*0), or the number of attributable cases (*AC*), it is defined according to equation 1.

The relative risk (*RR*) or risk ratio (*RR*) represents the quantity by which the risk is multiplied by the exposure (relative effect measure or ratio measure of effect). It is defined according to equation 2.

Sometimes, it could be useful to consider the negative attributable risk (–*AR*) or preventable risk (*PR*), the negative attributable cases (–*AC*) or preventable cases (*PC*), and the reciprocal relative risk (1/*RR* or *RRR*) according to equations 3 and 4.

Further definitions are provided in *Note 1 available online as Supplementary Materials*. Relative excess measures of effect can be calculated by dividing an absolute effect measure by (relative to) the non-exposed or exposed risk. These definitions have been used in the present work to provide, using mathematical derivations, a simple and systematic classification of the relative excess measures of effect that could be functional for health impact assessment [1-24]. New effect measures (preventable risk, reciprocal relative risk and excess reciprocal relative risk) have been proposed.

Classification and calculation of health impacts

Health impact assessment can be thought as a "reverse" study design. In a classical analytical study, outcome data under two exposure scenarios are compared to estimate an effect measure. In health impact assessment, an estimated effect measure and the outcome data under one exposure scenario (baseline) are combined to estimate the change in outcome data (health impacts) under an alternative exposure scenario (counterfactual) [1-24].

The functional classification of relative excess measures of effects, in conjunction with the literature, has been used in the present work to develop a simple and standard framework for the classification and calculation of attributable and preventable cases in health impact assessment [1-24]. This approach combines the baseline data with one of the four relative excess measures of effects, based on the nature of the exposure and the imagined change in exposure. The nature of the

$$AR = R1 - R0 = \frac{C1}{N} - \frac{C0}{N} = \frac{C1 - C0}{N} = \frac{AC}{N} \quad (1)$$

$$RR = \frac{R1}{R0} = \frac{\frac{C1}{N}}{\frac{C0}{N}} = \frac{C1}{C0} \quad (2)$$

$$-AR = PR = R0 - R1 = \frac{C0}{N} - \frac{C1}{N} = \frac{C0 - C1}{N} = \frac{PC}{N} \quad (3)$$

$$\frac{1}{RR} = RRR = \frac{R0}{R1} = \frac{\frac{C0}{N}}{\frac{C1}{N}} = \frac{C0}{C1} \quad (4)$$

exposure refers to the expected effect of the exposure in relation to the non-exposure: harmful or beneficial to human health. The imagined change in the exposure refers to the counterfactual exposure in relation to the baseline exposure: an increase if the baseline exposure is the non-exposure and the counterfactual exposure is the exposure, or a decrease if the baseline exposure is the exposure and the counterfactual exposure is the non-exposure. The attributable or preventable cases estimated according to the proposed methodology can also be used to calculate other forms of health impacts, such as the attributable or preventable years lived with disability (YLD) or years of life lost (YLL), the calculation of which is beyond the scope of this paper.

Calculation of health impacts using data at different spatial resolutions

Health impact assessments often combine different sources and types of data, so it is common to use data with different spatial levels of measurement. Often, baseline outcome data are available with lower spatial resolution with some degree of statistical aggregation (area level, less detailed) [25], while population and exposure data are available with higher spatial resolution (population level, more detailed) [8, 22, 23, 26]. For example, the total number of deaths (baseline outcome data) could be available for the municipal level (less detailed, lower resolution), while residential greenness (population and exposure data) can be available at the infra-municipal level (more detailed, higher resolution) [8, 25, 26]. Basically, there are different exposure values for the same baseline outcome value. When population and exposure data are more detailed than the baseline outcome data, two main approaches can be used to calculate the measures of effect [8, 9, 11, 13, 19, 20, 22, 23].

One approach is to use the more detailed data to calculate the population-weighted exposure (PWE), which can be used to calculate the effect measure for the less detailed level. Another possible approach is to calculate the effect measures for the more detailed level, and to combine them for the less detailed level. In both approaches, the calculated relative effect measure can ultimately be used to estimate the impacts at a less detailed level, where the baseline outcome data are available [8].

Using an epidemiological terminology and referring to the level of calculation of the relative risk, the present work proposes to define these two approaches as "marginal" and "conditional" with respect to the population (i.e., the more detailed level of measure). Standard analytical solutions with mathematical derivations are elaborated for the two approaches. Two different spatial units are considered, with the area unit representing the less detailed level (e.g., the municipality) and the population unit the more detailed level (e.g., the census tract or the population polygon or point) [8, 20, 25, 26].

RESULTS

Classification and calculation of relative excess measures of effect

Relative excess measures of effect can be calculated for a harmful or beneficial exposure and on the basis of non-exposed or exposed risk. A graphical representation of these measures with numerical examples is shown in *Figure 1*. Attributable risk (*AR*) is used to obtain a positive relative excess measure of effect when the exposure under consideration has a harmful effect ($R1>R0$). Negative attributable risk (*–AR*) or preventable risk (*PR*) is used to obtain a positive relative excess measure of effect when the exposure under consideration has a beneficial effect ($R1<R0$). These measures can be expressed by using relative risk (*RR*) or reciprocal relative risk (1/*RR* or *RRR*).

Excess relative risk

The excess relative risk (*ERR*) is the attributable risk (*AR*) divided by the non-exposed risk (*R*0). It is defined as the amount of risk that is attributable to the exposure relative to the non-exposed risk, according to equations 5 and 6.

Attributable fraction

The attributable fraction (*AF*) or attributable risk fraction (*ARF*) is the attributable risk (*AR*) divided by the exposed risk (*R*1). It is defined as the amount of risk that is attributable to the exposure relative to the exposed risk, according to equations 7 and 8.

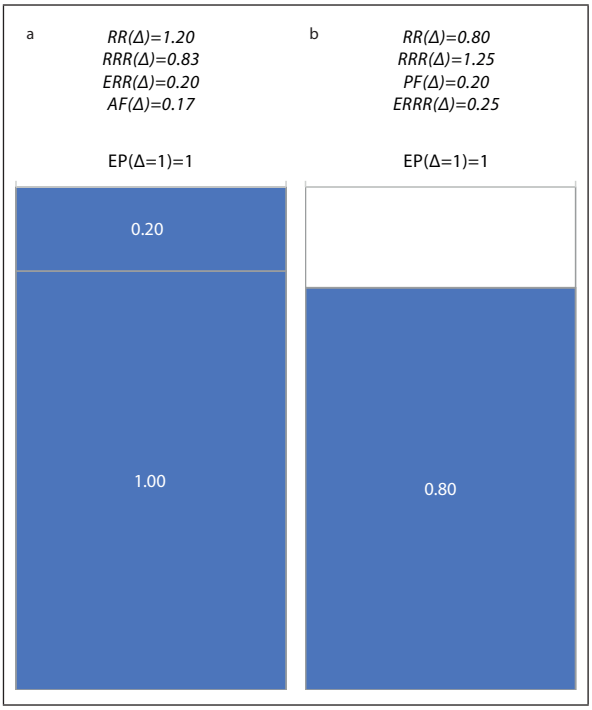


Figure 1

Relative excess measures of effect for a harmful exposure (charts a) and for a beneficial exposure (b). For each chart, the coloured area represents the risk in the exposed and the sum of white numbers is the relative risk. Relative risks are hypothetical.

AF: attributable fraction; *EP*: exposure prevalence; *ERR*: excess relative risk; *ERRR*: excess reciprocal relative risk; *PF*: preventable fraction; *RR*: relative risk; *RRR*: reciprocal relative risk; *X-axis*: population exposed; *Y-axis*: risk of the outcome; *Δ*: difference between exposure and non-exposure.

Preventable fraction

The preventable fraction (*PF*) or preventable risk fraction (*PRF*) is the negative attributable risk (*–AR*) or preventable risk (*PR*) divided by the non-exposed risk (*R0*). It is defined as the amount of risk that is preventable by the exposure relative to the non-exposed risk, according to equations 9 and 10.

Excess reciprocal relative risk

The excess reciprocal relative risk (*ERRR*) is the negative attributable risk (*–AR*) or preventable risk (*PR*) divided by the exposed risk (*R1*). It is defined as the amount of risk that is preventable by the exposure relative to the exposed risk, according to equations 11 and 12.

Classification and calculation of health impacts

Health impacts can be calculated for a harmful or beneficial exposure and on the basis of non-exposed or exposed risk. Attributable cases (*AC*) or attributable incident cases (*AIC*) can be estimated for an increase in a harmful exposure in a non-exposed population or for a decrease in a harmful exposure in an exposed population. Preventable cases (*PC*) or preventable incident cases (*PIC*) can be estimated for an increase in a beneficial exposure in a non-exposed population or for a decrease in a beneficial exposure in an exposed population. The proposed framework for the classification and calculation of health impacts is reported in *Figure 2* and in *Table 1*. Further details on the exposure-response

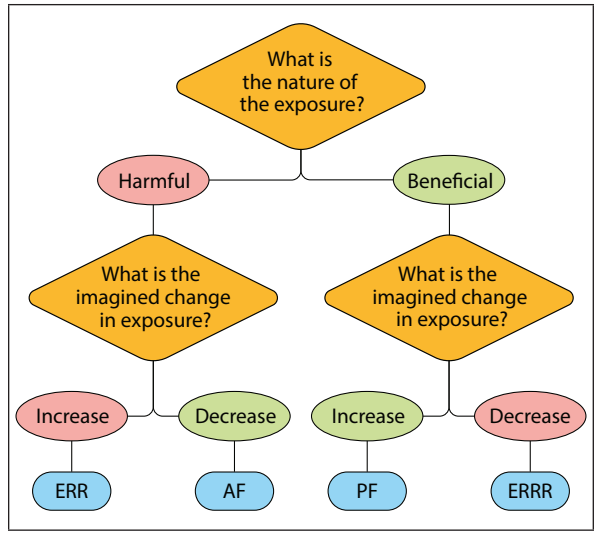


Figure 2
Classification and calculation of health impacts: general framework.
AF: attributable fraction; *ERR*: excess relative risk; *ERRR*: excess reciprocal relative risk; *PF*: preventable fraction.

$$ERR = \frac{AR}{R0} = \frac{R1 - R0}{R0} = \frac{R1}{R0} - 1 = RR - 1 \quad (5)$$

$$ERR = \frac{AR}{R0} = \frac{R1 - R0}{R0} = \frac{\frac{R1 - R0}{R1}}{\frac{R0}{R1}} = \frac{1 - \frac{R0}{R1}}{\frac{R0}{R1}} = \frac{1 - \frac{1}{RR}}{\frac{1}{RR}} = \frac{1 - RRR}{RRR} \quad (6)$$

$$AF = \frac{AR}{R1} = \frac{R1 - R0}{R1} = \frac{\frac{R1 - R0}{R0}}{\frac{R1}{R0}} = \frac{\frac{R1}{R0} - 1}{\frac{R1}{R0}} = \frac{RR - 1}{RR} \quad (7)$$

$$AF = \frac{AR}{R1} = \frac{R1 - R0}{R1} = 1 - \frac{R0}{R1} = 1 - \frac{1}{RR} = 1 - RRR \quad (8)$$

$$PF = \frac{-AR}{R0} = \frac{PR}{R0} = \frac{R0 - R1}{R0} = 1 - \frac{R1}{R0} = 1 - RR \quad (9)$$

$$PF = \frac{-AR}{R0} = \frac{PR}{R0} = \frac{R0 - R1}{R0} = \frac{\frac{R0 - R1}{R1}}{\frac{R0}{R1}} = \frac{\frac{R0}{R1} - 1}{\frac{R0}{R1}} = \frac{\frac{1}{RR} - 1}{\frac{1}{RR}} = \frac{RRR - 1}{RRR} \quad (10)$$

$$ERRR = \frac{-AR}{R1} = \frac{PR}{R1} = \frac{R0 - R1}{R1} = \frac{\frac{R0 - R1}{R0}}{\frac{R1}{R0}} = \frac{1 - \frac{R1}{R0}}{\frac{R1}{R0}} = \frac{1 - RR}{RR} \quad (11)$$

$$ERRR = \frac{-AR}{R1} = \frac{PR}{R1} = \frac{R0 - R1}{R1} = \frac{R0}{R1} - 1 = \frac{1}{RR} - 1 = RRR - 1 \quad (12)$$

Table 1
Classification and calculation of health impacts: detailed framework

Type of health impact assessment	Nature of the exposure	Baseline exposure and outcome (reality)	Counterfactual exposure and outcome (what-if)	Imagined change in exposure	Relative excess measure of effect	Health impacts
1)	Harmful	Non-exposed	Exposed	Increase	Excess relative risk	Attributable cases (they would be attributable and in excess)
2)	Harmful	Exposed	Non-exposed	Decrease	Attributable fraction	Attributable cases (they are attributable and a fraction)
3)	Beneficial	Non-exposed	Exposed	Increase	Preventable fraction	Preventable cases (they are preventable and a fraction)
4)	Beneficial	Exposed	Non-exposed	Decrease	Excess reciprocal relative risk	Preventable cases (they would be preventable and in excess)

functions and example equations using the natural logarithm are reported in *Note 2 available online as Supplementary Materials*. Practical examples of calculation of health impacts using meta-analytic relative risks [27, 28] are reported in *Table 2* and commented in *Note 3 available online as Supplementary Materials*.

The relative risk (*RR*) and the reciprocal relative risk (1/*RR* or *RRR*) to be used in calculating the relative excess measures of effect can be estimated for the difference (*Δ*) between the exposure and the non-exposure by using an exposure-response function (*f*). The exposure difference (*Δ*) is between the counterfactual exposure (*CE*) and the baseline exposure (*BE*) when imagining an increase in exposure, and between the baseline (*BE*) exposure and the counterfactual exposure (*CE*) when imagining a decrease in exposure (equations 13 and 14).

Attributable cases when imagining an increase in exposure (excess)

This type of health impact assessment imagines an increase in a harmful exposure, from non-exposure to exposure. The excess relative risk (*ERR*) could be calculated by using the estimated relative risk or reciprocal relative risk (*RR*–1 or (1–*RRR*)/*RRR*) for the difference (*Δ*) between the counterfactual exposure (the counterfactual level of exposure that is imagined, the exposure corresponding to *R*1) and the baseline exposure (the actual level of exposure that is observed, the non-exposure corresponding to *R*0) in the same population of size *N*. Basically, here the baseline scenario refers to the non-exposure (reality) and the counterfactual scenario refers to the exposure (what-if).

Considering the baseline cases (*BC*, which are the non-exposed cases *C*0), the baseline risk (*BR*, the non-exposed risk *R*0), the counterfactual cases (*CC*, the exposed cases *C*1) and the counterfactual risk (*CR*, the exposed risk *R*1), the excess relative risk can be defined according to equations 15 and 16.

The attributable cases (*AC*) can be calculated by using the excess relative risk and the baseline risk or cases according to equations 17 and 18.

These attributable cases (excess) represent the cases that do not occur under the baseline exposure (non-exposure) and that would be caused by the difference (*Δ*) between the counterfactual exposure (exposure) and the baseline exposure (non-exposure). Under the counterfactual exposure, these cases would be attributable to this difference and in excess of the baseline cases.

Attributable cases when imagining a decrease in exposure (fraction)

This type of health impact assessment imagines a decrease in a harmful exposure, from exposure to non-exposure. The attributable fraction (*AF*) could be calculated by using the estimated relative risk or reciprocal relative risk ((*RR*–1)/*RR* or *1–RRR*) for the difference (*Δ*) between the baseline exposure (the actual level of

Table 2
Classification and calculation of health impacts: practical examples

Type of health impact assessment	Nature of the exposure	Exposure variable	Baseline exposure (reality)	Baseline outcome (reality)	Counterfactual exposure (what if)	Exposure difference (Δ)	Relative risk [27, 28]	Relative excess measure of effect	Health impacts
1)	Harmful	$PM_{2.5}$ (air pollution)	15 μg/m³	1,000 deaths	25 μg/m³	10 μg/m³	1.08	ERR=1.08–1=0.080	AC=80 deaths
2)	Harmful	$PM_{2.5}$ (air pollution)	15 μg/m³	1,000 deaths	5 μg/m³	10 μg/m³	1.08	AF=(1.08–1)/1.08=0.074	AC=74 deaths
3)	Beneficial	NDVI (greenness)	0.3	1,000 deaths	0.4	0.1	0.96	PF=(1–0.96)=0.040	PC=40 deaths
4)	Beneficial	NDVI (greenness)	0.3	1,000 deaths	0.2	0.1	0.96	ERRR=(1–0.96)/0.96=0.042	PC=42 deaths

AC: attributable cases; *AF*: attributable fraction; *ERR*: excess relative risk; *ERRR*: excess reciprocal relative risk; *NDVI*: normalized difference vegetation index; *PC*: preventable cases; *PF*: preventable fraction; *PM*: particulate matter; Time: 1 year; *Δ*: difference between exposure and non-exposure.

exposure that is observed, the exposure corresponding to $R1$) and the counterfactual exposure (the counterfactual level of exposure that is imagined, the non-exposure corresponding to $R0$) in the same population of size N. Basically, here the baseline scenario refers to the exposure (reality) and the counterfactual scenario refers to the non-exposure (what-if).

Considering the baseline cases (BC, which are the exposed cases $C1$), the baseline risk (BR, the exposed risk $R1$), the counterfactual cases (CC, the non-exposed cases $C0$) and the counterfactual risk (CR, the non-exposed risk $R0$), the attributable fraction can be defined according to equations 19 and 20.

The attributable cases (AC) can be calculated by using the attributable fraction and the baseline risk or cases according to equations 21 and 22.

These attributable cases (fraction) represent the cases that would not occur under the counterfactual exposure (non-exposure) and that are caused by the difference (Δ) between the baseline exposure (exposure) and the counterfactual exposure (non-exposure). Under the baseline exposure, these cases are attributable to this difference and a fraction of the baseline cases.

Preventable cases when imagining an increase in exposure (fraction)

This type of health impact assessment imagines an increase in a beneficial exposure, from non-exposure to exposure. The preventable fraction (PF) could be calculated by using the estimated relative risk or reciprocal relative risk (1–RR or (RRR–1)/RRR) for the difference (Δ) between the counterfactual exposure (the counterfactual level of exposure that is imagined, the exposure corresponding to $R1$) and the baseline exposure (the actual level of exposure that is observed, the non-exposure corresponding to $R0$) in the same population of size N. Basically, here the baseline scenario refers to the non-exposure (reality) and the counterfactual scenario refers to the exposure (what-if).

Considering the baseline cases (BC, which are the non-exposed cases $C0$), the baseline risk (BR, the non-exposed risk $R0$), the counterfactual cases (CC, the ex-

$$RR = \frac{R1}{R0} = f(BE, \Delta) \tag{13}$$

$$RRR = \frac{R0}{R1} = \frac{1}{f(BE, \Delta)} \tag{14}$$

$$ERR = \frac{AR}{R0} = \frac{R1 - R0}{R0} = \frac{\frac{C1 - C0}{N}}{\frac{C0}{N}} = \frac{\frac{AC}{N}}{\frac{C0}{N}} = \frac{AC}{C0} \tag{15}$$

$$ERR = \frac{AR}{BR} = \frac{CR - BR}{BR} = \frac{\frac{CC - BC}{N}}{\frac{BC}{N}} = \frac{\frac{AC}{N}}{\frac{BC}{N}} = \frac{AC}{BC} \tag{16}$$

$$AC = \frac{AC}{N} \times N = AR \times N = \frac{AR}{R0} \times R0 \times N = ERR \times R0 \times N = ERR \times BR \times N \tag{17}$$

$$AC = \frac{AC}{C0} \times C0 = ERR \times C0 = ERR \times BC \tag{18}$$

$$AF = \frac{AR}{R1} = \frac{R1 - R0}{R1} = \frac{\frac{C1 - C0}{N}}{\frac{C1}{N}} = \frac{\frac{AC}{N}}{\frac{C1}{N}} = \frac{AC}{C1} \tag{19}$$

$$AF = \frac{AR}{BR} = \frac{BR - CR}{BR} = \frac{\frac{BC - CC}{N}}{\frac{BC}{N}} = \frac{\frac{AC}{N}}{\frac{BC}{N}} = \frac{AC}{BC} \tag{20}$$

$$AC = \frac{AC}{N} \times N = AR \times N = \frac{AR}{R1} \times R1 \times N = AF \times R1 \times N = AF \times BR \times N \tag{21}$$

$$AC = \frac{AC}{C1} \times C1 = AF \times C1 = AF \times BC \tag{22}$$

posed cases *C*1) and the counterfactual risk (*CR*, the exposed risk *R*1), the preventable fraction can be defined according to equations 23 and 24.

The preventable cases (*PC*) can be calculated by using the preventable fraction and the baseline risk or cases according to equations 25 and 26.

These preventable cases (fraction) represent the cases that occur under the baseline exposure (non-exposure) and that would be prevented by the difference (*Δ*) between the counterfactual exposure (exposure) and the baseline exposure (non-exposure). Under the baseline exposure, these cases are preventable by this difference and a fraction of the baseline cases.

Preventable cases when imagining a decrease in exposure (excess)

This type of health impact assessment imagines a decrease in a beneficial exposure, from exposure to non-exposure. The excess reciprocal relative risk (*ERRR*) could be calculated by using the estimated relative risk or reciprocal relative risk ((1-*RR*)/*RR* or *RRR*-1) for the difference (*Δ*) between the baseline exposure (the actual level of exposure that is observed, the exposure corresponding to *R*1) and the counterfactual exposure (the counterfactual level of exposure that is imagined, the non-exposure corresponding to *R*0) in the same population of size *N*. Basically, here the baseline scenario refers to the exposure (reality) and the counterfactual scenario refers to the non-exposure (what-if).

Considering the baseline cases (*BC*, which are the exposed cases *C*1), the baseline risk (*BR*, the exposed risk *R*1), the counterfactual cases (*CC*, the non-exposed cases *C*0) and the counterfactual risk (*CR*, the non-exposed risk *R*0), the excess reciprocal relative risk can be defined according to equations 27 and 28.

The preventable cases (*PC*) can be calculated by using the excess reciprocal relative risk and the baseline risk or cases according to equations 29 and 30.

These preventable cases (excess) represent the cases that would occur under the counterfactual exposure (non-exposure) and that are prevented by the difference (*Δ*) between the baseline exposure (exposure) and the counterfactual exposure (non-exposure). Under the counterfactual exposure, these cases would be preventable by this difference and in excess of the baseline cases.

Calculation of health impacts using data at different spatial resolutions

When the population and exposure data are more detailed (population level) than the baseline outcome data (area level), the effect measures to be used in the above equations (area level) can be estimated by using two different approaches, marginal or conditional. Equations using the natural logarithm are reported in *Note*

$$PF = \frac{-AR}{R0} = \frac{PR}{R0} = \frac{R0 - R1}{R0} = \frac{\frac{C0 - C1}{N}}{\frac{C0}{N}} = \frac{\frac{-AC}{N}}{\frac{C0}{N}} = \frac{\frac{PC}{N}}{\frac{C0}{N}} = \frac{PC}{C0} \quad (23)$$

$$PF = \frac{-AR}{BR} = \frac{PR}{BR} = \frac{BR - CR}{BR} = \frac{\frac{BC - CC}{N}}{\frac{BC}{N}} = \frac{\frac{-AC}{N}}{\frac{BC}{N}} = \frac{\frac{PC}{N}}{\frac{BC}{N}} = \frac{PC}{BC} \quad (24)$$

$$PC = \frac{PC}{N} \times N = PR \times N = \frac{PR}{R0} \times R0 \times N = PF \times R0 \times N = PF \times BR \times N \quad (25)$$

$$PC = \frac{PC}{C0} \times C0 = PF \times C0 = PF \times BC \quad (26)$$

$$ERRR = \frac{-AR}{R1} = \frac{PR}{R1} = \frac{R0 - R1}{R1} = \frac{\frac{C0 - C1}{N}}{\frac{C1}{N}} = \frac{\frac{-AC}{N}}{\frac{C1}{N}} = \frac{\frac{PC}{N}}{\frac{C1}{N}} = \frac{PC}{C1} \quad (27)$$

$$ERRR = \frac{-AR}{BR} = \frac{PR}{BR} = \frac{CR - BR}{BR} = \frac{\frac{CC - BC}{N}}{\frac{BC}{N}} = \frac{\frac{-AC}{N}}{\frac{BC}{N}} = \frac{\frac{PC}{N}}{\frac{BC}{N}} = \frac{PC}{BC} \quad (28)$$

$$PC = \frac{PC}{N} \times N = PR \times N = \frac{PR}{R1} \times R1 \times N = ERRR \times R1 \times N = ERRR \times BR \times N \quad (29)$$

$$PC = \frac{PC}{C1} \times C1 = ERRR \times C1 = ERRR \times BC \quad (30)$$

2 available online as Supplementary Materials. A graphical representation of these measures with numerical examples is shown in *Figure 3* and commented in *Note 4 available online as Supplementary Materials*.

The marginal approach

For the area unit (a), the population-weighted baseline ($PWBE_a$) and counterfactual ($PWCE_a$) exposures can be calculated as a weighted mean of the baseline (BE_{pa}) and counterfactual (CE_{pa}) exposures, respectively, in the n population units included in a (p_a). For the area unit (a), the population-weighted exposure difference ($PW\Delta_a$) can be calculated as a weighted mean of the difference (Δ_{pa}) between the counterfactual (CE_{pa}) and baseline (BE_{pa}) exposures when imagining an increase in exposure, or vice versa when imagining a de-

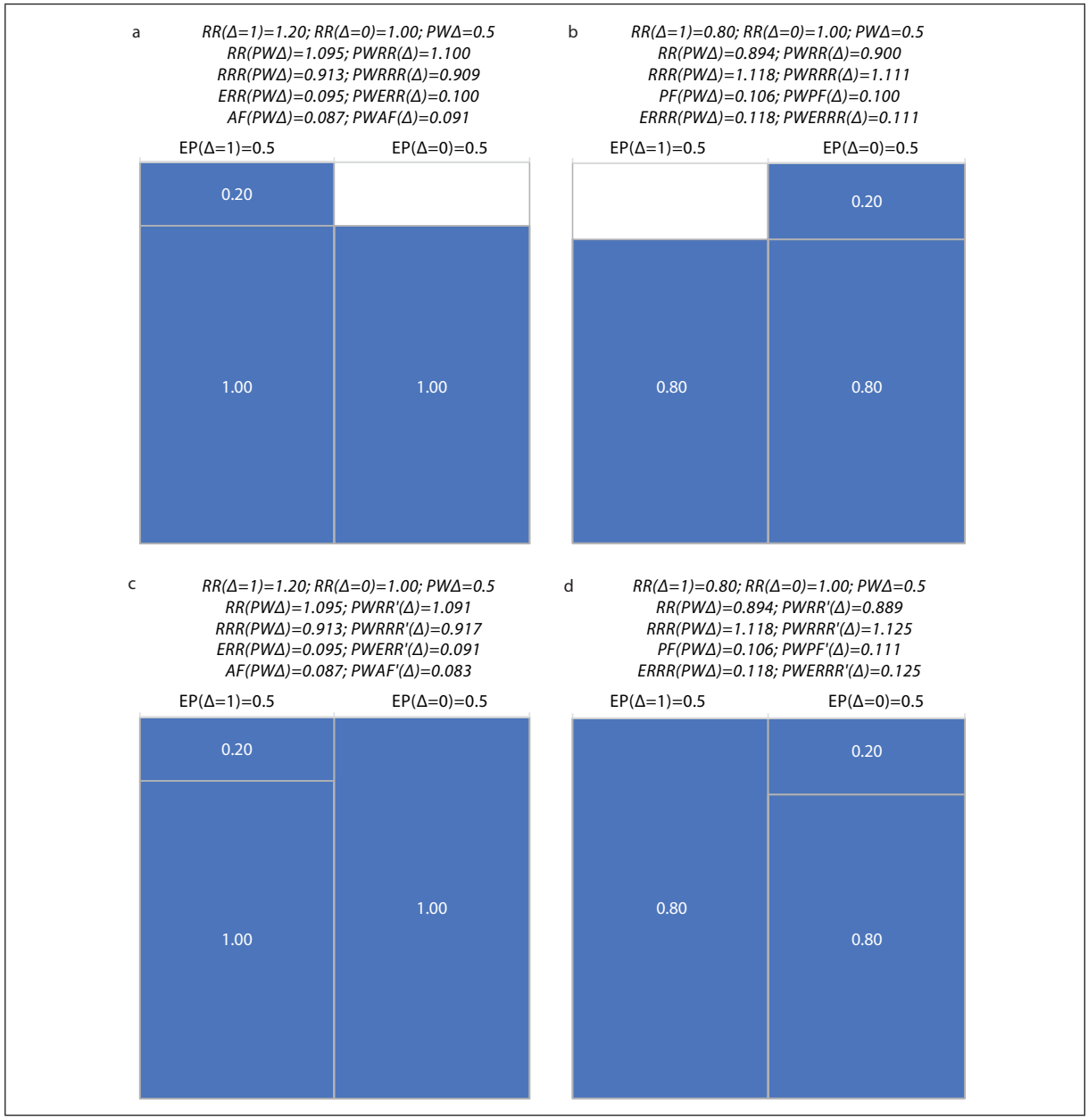


Figure 3

Relative excess measures of effect from marginal approach (PWΔ, RR, RRR, ERR, AF, PF, ERRR), conditional approach with same non-exposed risk (PWRR, PWRRR, PWERR, PWAF, PWPF, PWERRR), and conditional approach with same exposed risk (PWRR', PWRRR', PWERR', PWAF', PWPF', PWERRR'), for a harmful exposure (charts a and c) and for a beneficial exposure (b and d), by assuming in the conditional approach the same non-exposed risk (a and b) or the same exposed risk (c and d). For each chart and column (exposed population unit), the coloured area represents the risk in the exposed and the sum of white numbers is the relative risk. Relative risks are hypothetical and assumed to be natural-log-linearly modelled.

AF: attributable fraction; *EP*: exposure prevalence; *ERR*: excess relative risk; *ERRR*: excess reciprocal relative risk; *PF*: preventable fraction; *PW*: population-weighted; *RR*: relative risk; *RRR*: reciprocal relative risk; *X-axis*: population exposed; *Y-axis*: risk of the outcome; *Δ*: difference between exposure and non-exposure.

crease in exposure, in the n population units included in a (p_a). For each p_a, the weight of the weighted means is the population (POP_{pa}). This formulation is equivalent to using the exposure prevalence (EP_{pa}) corresponding to each p_a, which is the ratio of the population of p_a (POP_{pa}) to the total population of a (POP_a) (equations 31-37).

For the area unit (a), by using the exposure-response function (f_a), the relative risk (RR_a), the reciprocal relative risk ($1/RR_a$ or RRR_a) and the relative excess measures of effect (ERR_a,AF_a,PF_a,$ERRR_a$) can be estimated for the population-weighted exposure difference ($PW\Delta_a$). These effect measures can be interpreted in terms of non-exposed risk ($R0_a$) and exposed risk ($R1_a$) at the area level (a) (equations 38-43).

The conditional approach

For each population unit (p_a) included in the area unit (a), the difference (Δ_{pa}) between the counterfactual (CE_{pa}) and baseline (BE_{pa}) exposures when imagining an increase in exposure, or vice versa when imagining a decrease in exposure, can be calculated.

$$EP_{p_a} = POP_{p_a}/POP_a = POP_{p_a} \Big/ \sum_{p_a=1}^{n} (POP_{p_a}) \tag{31}$$

$$\sum_{p_a=1}^{n} (EP_{p_a}) = 1 \tag{32}$$

$$PWBE_a = \sum_{p_a=1}^{n} (BE_{p_a} \times POP_{p_a}) \Big/ \sum_{p_a=1}^{n} (POP_{p_a}) = \sum_{p_a=1}^{n} (BE_{p_a} \times EP_{p_a}) \tag{33}$$

$$PWCE_a = \sum_{p_a=1}^{n} (CE_{p_a} \times POP_{p_a}) \Big/ \sum_{p_a=1}^{n} (POP_{p_a}) = \sum_{p_a=1}^{n} (CE_{p_a} \times EP_{p_a}) \tag{34}$$

$$PW\Delta_a = \sum_{p_a=1}^{n} (\Delta_{p_a} \times POP_{p_a}) \Big/ \sum_{p_a=1}^{n} (POP_{p_a}) = \sum_{p_a=1}^{n} (\Delta_{p_a} \times EP_{p_a}) \tag{35}$$

$$PW\Delta_a = \sum_{p_a=1}^{n} (\Delta_{p_a} \times EP_{p_a}) = \sum_{p_a=1}^{n} ((CE_{p_a} - BE_{p_a}) \times EP_{p_a}) = \sum_{p_a=1}^{n} (CE_{p_a} \times EP_{p_a}) - \sum_{p_a=1}^{n} (BE_{p_a} \times EP_{p_a}) = PWCE_a - PWBE_a \tag{36}$$

$$PW\Delta_a = \sum_{p_a=1}^{n} (\Delta_{p_a} \times EP_{p_a}) = \sum_{p_a=1}^{n} ((BE_{p_a} - CE_{p_a}) \times EP_{p_a}) = \sum_{p_a=1}^{n} (BE_{p_a} \times EP_{p_a}) - \sum_{p_a=1}^{n} (CE_{p_a} \times EP_{p_a}) = PWBE_a - PWCE_a \tag{37}$$

$$RR_a = \frac{R1_a}{R0_a} = f_a(PWBE_a, PW\Delta_a) \tag{38}$$

$$RRR_a = \frac{R0_a}{R1_a} = \frac{1}{f_a(PWBE_a, PW\Delta_a)} \tag{39}$$

$$ERR_a = RR_a - 1 = \frac{1 - RRR_a}{RRR_a} \tag{40}$$

$$AF_a = \frac{RR_a - 1}{RR_a} = 1 - RRR_a \tag{41}$$

$$PF_a = 1 - RR_a = \frac{RRR_a - 1}{RRR_a} \tag{42}$$

$$ERRR_a = \frac{1 - RR_a}{RR_a} = RRR_a - 1 \tag{43}$$

For each population unit (p_a) included in the area unit (a), by using the exposure-response function (f_{p_a}), the relative risk (RR_{p_a}), the reciprocal relative risk ($1/RR_{p_a}$ or RRR_{p_a}) and the relative excess measures of effect (ERR_{p_a},AF_{p_a},PF_{p_a},$ERRR_{p_a}$) can be estimated for the exposure difference (Δ_{p_a}). These effect measures can be interpreted in terms of non-exposed risk ($R0_{p_a}$) and exposed risk ($R1_{p_a}$) at the population level (p_a) (equations 44-49).

For the area unit (a), when assuming the same non-exposed risk ($R0_a$) in all the p_a, the population-weighted relative risk ($PWRR_a$), reciprocal relative risk ($PWRRR_a$) and relative excess measure of effect ($PWERR_a$,$PWAF_a$,$PWPF_a$,$PWERRR_a$) can be calculated by using the relative risks (RR_{p_a}) and the excess measures of effect relative to the non-exposed risk (ERR_{p_a},PF_{p_a}) in the n population units p_a. These population-weighted effect measures can be interpreted in terms of non-exposed risk ($R0_a$) and population-weighted exposed risk ($PWR1_a$) at the area level (a). For each p_a, the weight of the weighted means is the population (POP_{p_a}). This formulation is equivalent to using the exposure prevalence (EP_{p_a}) corresponding to each p_a, which is the ratio of the population of p_a (POP_{p_a}) to the total population of a (POP_a) (equations 50-55).

For the area unit (a), when assuming the same exposed risk ($R1_a$) in all the p_a, the population-weighted reciprocal relative risk ($PWRRR'_a$), relative risk ($PWRR'_a$), and relative excess measure of effect ($PWERR'_a$, $PWAF'_a$, $PWPF'_a$, $PWERRR'_a$) can be calculated by using the reciprocal relative risks ($1/RR_{p_a}$ or RRR_{p_a}) and the excess measures of effect relative to the exposed risk (AF_{p_a}, $ERRR_{p_a}$) in the n population units p_a. These population-weighted effect measures can be interpreted in terms of exposed risk ($R1_a$) and population-weighted non-exposed risk ($PWR0_a$) at the area level (a). For each p_a, the weight of the weighted means is the population (POP_{p_a}). This formulation is equivalent to using the exposure prevalence (EP_{p_a}) corresponding to each p_a, which is the ratio of the population of p_a (POP_{p_a}) to the total population of a (POP_a) (equations 56-61).

$$RR_{p_a} = \frac{R1_{p_a}}{R0_{p_a}} = f_{p_a}(BE_{p_a}, \Delta_{p_a}) \tag{44}$$

$$RRR_{p_a} = \frac{R0_{p_a}}{R1_{p_a}} = \frac{1}{f_{p_a}(BE_{p_a}, \Delta_{p_a})} \tag{45}$$

$$ERR_{p_a} = RR_{p_a} - 1 = \frac{1 - RRR_{p_a}}{RRR_{p_a}} \tag{46}$$

$$AF_{p_a} = \frac{RR_{p_a} - 1}{RR_{p_a}} = 1 - RRR_{p_a} \tag{47}$$

$$PF_{p_a} = 1 - RR_{p_a} = \frac{RRR_{p_a} - 1}{RRR_{p_a}} \tag{48}$$

$$ERRR_{p_a} = \frac{1 - RR_{p_a}}{RR_{p_a}} = RRR_{p_a} - 1 \tag{49}$$

$$PWRR_a = \sum_{p_a=1}^{n} \left(\frac{R1_{p_a}}{R0_a} \times POP_{p_a}\right) \Big/ \sum_{p_a=1}^{n} (POP_{p_a}) = \sum_{p_a=1}^{n} \left(\frac{R1_{p_a}}{R0_a} \times EP_{p_a}\right) = \frac{PWR1_a}{R0_a} = \sum_{p_a=1}^{n} (RR_{p_a} \times EP_{p_a}) \tag{50}$$

$$PWRRR_a = \frac{R0_a}{PWR1_a} = \frac{1}{PWRR_a} \tag{51}$$

$$PWERR_a = \sum_{p_a=1}^{n} (ERR_{p_a} \times POP_{p_a}) \Big/ \sum_{p_a=1}^{n} (POP_{p_a}) = \sum_{p_a=1}^{n} (ERR_{p_a} \times EP_{p_a}) = \sum_{p_a=1}^{n} \left((RR_{p_a} - 1) \times EP_{p_a}\right) = PWRR_a - 1 = \frac{1 - PWRRR_a}{PWRRR_a} \tag{52}$$

$$PWAF_a = \frac{PWRR_a - 1}{PWRR_a} = 1 - PWRRR_a \tag{53}$$

$$PWPF_a = \sum_{p_a=1}^{n} (PF_{p_a} \times POP_{p_a}) \Big/ \sum_{p_a=1}^{n} (POP_{p_a}) = \sum_{p_a=1}^{n} (PF_{p_a} \times EP_{p_a}) = \sum_{p_a=1}^{n} \left((1 - RR_{p_a}) \times EP_{p_a}\right) = 1 - PWRR_a = \frac{PWRRR_a - 1}{PWRRR_a} \tag{54}$$

$$PWERRR_a = \frac{1 - PWRR_a}{PWRR_a} = PWRRR_a - 1 \tag{55}$$

$$PWRRR'_a = \sum_{p_a=1}^{n} \left(\frac{R0_{p_a}}{R1_a} \times POP_{p_a}\right) \Big/ \sum_{p_a=1}^{n} (POP_{p_a}) = \sum_{p_a=1}^{n} \left(\frac{R0_{p_a}}{R1_a} \times EP_{p_a}\right) = \frac{PWR0_a}{R1_a} = \sum_{p_a=1}^{n} (RRR_{p_a} \times EP_{p_a}) \quad (56)$$

$$PWRR'_a = \frac{R1_a}{PWR0_a} = \frac{1}{PWRRR'_a} \quad (57)$$

$$PWERR'_a = \frac{1 - PWRRR'_a}{PWRRR'_a} = PWRR'_a - 1 \quad (58)$$

$$PWAF'_a = \sum_{p_a=1}^{n} (AF_{p_a} \times POP_{p_a}) \Big/ \sum_{p_a=1}^{n} (POP_{p_a}) = \sum_{p_a=1}^{n} (AF_{p_a} \times EP_{p_a}) = \sum_{p_a=1}^{n} ((1 - RRR_{p_a}) \times EP_{p_a}) = 1 - PWRRR'_a = \frac{PWRR'_a - 1}{PWRR'_a} \quad (59)$$

$$PWPF'_a = \frac{PWRRR'_a - 1}{PWRRR'_a} = 1 - PWRR'_a \quad (60)$$

$$PWERRR'_a = \sum_{p_a=1}^{n} (ERRR_{p_a} \times POP_{p_a}) \Big/ \sum_{p_a=1}^{n} (POP_{p_a}) = \sum_{p_a=1}^{n} (ERRR_{p_a} \times EP_{p_a}) = \sum_{p_a=1}^{n} ((RRR_{p_a} - 1) \times EP_{p_a}) = PWRRR'_a - 1 = \frac{1 - PWRR'_a}{PWRR'_a} \quad (61)$$

DISCUSSION

Health impact assessment can be thought as a "reverse" study design, where an exposure-response function and the outcome data under one exposure scenario are combined to estimate the change in outcome data under an alternative exposure scenario. This paper aims to fill gaps in the HIA literature by proposing a systematic classification of effect measures, reporting a standard conceptual framework, and addressing spatial resolution challenges. The present work proposes a simple approach with four situations based on the nature of the exposure and the imagined change in exposure. In addition, two possible approaches to the problem of different spatial resolutions are proposed. These contributions are expected to improve the robustness and applicability of health impact assessment in different contexts.

Furthermore, the proposed classifications are of epidemiological interest beyond health impact assessment. The functional classification of the four relative excess effect measures and the proposed definitions for preventable risk, reciprocal relative risk and excess reciprocal relative risk could potentially contribute to promoting standard epidemiological terminology. The marginal and conditional approaches were essentially based on and extended the definitions of attributable fractions for the exposed and population, respectively [11]. Our proposal sought to extend the framework to the other relative excess measures of effect. Furthermore, the common definition of the population attributable fraction basically assumed the same non-exposed risk among population units, whereas the present work also explores the assumption of the same exposed risk. In summary, the proposed epidemiological definitions aim to provide a comprehensive and general framework for the relative excess measures of effect.

From a practical point of view for HIA purposes, the difference between *AF* and *ERR*, or between *PF* and *ERRR*, may be negligible with relative risks close to one. Furthermore, it may not always be possible to use baseline outcome data that strictly match to the available non-exposure or exposure scenarios, e.g., non-exposure may be at time 1, baseline outcome data at time 2 and exposure at time 3. A possible solution could be to assume that the available baseline risk is equal to the non-exposed or exposed risk, whichever is assumed to be more similar. In addition, this work explicitly considers a single counterfactual scenario and a single exposure variable for each unit, but an analogous methodology could be applied to multiple counterfactuals and exposures. With regard to the different levels of measurement, the marginal approach may be more general and easier to apply, as it could be mathematically simpler to calculate and doesn't require specific assumptions about the distribution of risks across population units. This last point may be important because risks are, by their nature, highly variable across the population, depending on a whole range of unmeasured variables. The marginal approach can produce effect measures that are somehow an average of the estimates derived from the two possible conditional approaches. A recent work reported both marginal approach (main analysis) and conditional approach (sensitivity analysis) in calculating the mortality impacts of increasing residential greenness for the whole of Italy, with a difference of 1.3% in the estimates [8].

Our results are also consistent with several guidelines and publications [1-24]. While most of the HIA literature focuses on air pollution, the framework and methods developed in the present study can be extended virtually to all other environmental and social determinants of health. Future research could explore health impact assessment in areas such as noise pollution, urban planning, and climate change [29]. The versatility of the proposed framework allows it to be adapted to different types of exposures, thereby increasing its utility across different sectors. The main strength of the present study is that it proposes a simple, standardized

and general approach to health impact assessment that is applicable to virtually all exposures.

In this regard, advances in computational tools and technologies, such as geographic information systems, machine learning, and big data analytics, offer new opportunities to enhance health impact assessment. These tools can improve the accuracy of exposure and outcome assessments, facilitate the analysis of complex datasets, estimate more tailored and accurate exposure-response functions and provide more detailed spatial and temporal analyses. Future studies should explore the integration of these technologies into the HIA framework to improve its effectiveness and accuracy. For example, the Global Human Settlement (GHS) population grid is a European Commission product that shows the distribution of residential population, expressed as the number of people per cell [26]. When the GHS population grid is used for exposure assessment in conjunction with satellite exposure data, there is no need to georeferenced the local population or to address privacy concerns [8]. In fact, this makes it possible to approximate exposure at the municipal level using public population data thar are freely available worldwide at high resolution [8, 26]. The sole outcome information required can be used after aggregation to the municipal level [25]. With the most recent data provided by health and statistical agencies, the HIA can be applied worldwide.

Our proposed standard framework is in line with common HIA approaches reported by different guidelines and documents [1-8, 13-23]. For example, the same framework (use of meta-analytic relative risks to estimate health impacts) has been reported by WHO in the officially provided tools for HIA on air quality (AirQ+) [2]. The WHO HRAPIE (health risks of air pollution in Europe) document on exposure-response functions [3] recommended the same approach and basically provided for air pollutants a list of available metanalytic relative risks for air pollutants to be used in HIA. However, further research is essential and recommended for the future to explore the associations between multiple exposures and health and to provide more reliable exposure-response functions, thus enabling more accurate and complete assessments.

Indeed, there are limitations to the proposed approach, both in terms of the HIA framework and to the quality of the input elements (populations, exposures, outcomes, functions). The accuracy of the HIA is highly dependent on the quality and availability of data and functions. Poor quality of these elements can be a challenge. Future studies should focus on improving data harmonization, estimating exposure-response functions, and developing robust methodologies to fill data gaps. Collaboration between public health agencies, environmental monitoring agencies, and academic institutions is crucial to ensure comprehensive and high quality data for health impact assessment.

One limitation may be the uncertainty of the exposure estimation. The "original sin" of most environmental epidemiology studies may be to use residential exposure as a proxy for total individual exposure, even though people spend only part of their time at home. Another important limitation is the uncertainty in the estimates due to uncertainty in the exposure-response function estimation (confounding, selection and information bias, heterogeneity) and utilization (non-transportability) [9-12]. These limitations are related to the counterfactual definitions of effect measures and to the assumptions described in the *Methods* section. It is therefore crucial to use the more reliable and accurate exposure-response functions from properly conducted analytical studies and meta-analyses when conducting health impact assessment. However, due to the complex nature of the relationship between exposures and health outcomes, some degree of uncertainty remains inherent and unavoidable in health impact assessment. Therefore, future research should also focus on developing methods to quantify and communicate these limits in HIA results. In addition, the marginal and conditional approaches are essentially methods for calculating health impacts when the outcome data are not available at the same spatial detail as the population and exposure data. However, these outcome data could potentially be downscaled to some extent by using other variables not directly included in the health impact assessment. The potential of machine learning models could help in this sense in the future.

With these perspectives in mind, this paper can make an important contribution to the field of health impact assessment by providing a systematic classification of relative excess measures of effect, developing a standardized and evidence-based conceptual framework, and elaborating standard solutions for dealing with different spatial resolutions. Key findings and proposals include a clear and systematic classification that improves the understanding and use of relative excess measures in health impact assessment; a simple conceptual framework that addresses different research questions, making assessments more robust and applicable across different contexts and exposures, and the estimates comparable across different studies; and different analytical solutions for dealing with different levels of spatial detail in HIA that improve the accuracy and reliability of the health impact estimates.

By addressing all these aspects, the study fills existing gaps in the HIA literature and provides a foundation for future research and practice. The proposed methods and frameworks are designed to be applicable to a range of different situations, ensuring their relevance in various settings and applications. As health impact assessment continues to evolve, the insights and tools provided in this paper could help guide more effective and equitable health impact assessments, ultimately contributing to better public health decisions and outcomes.

Conflict of interest statement

The Author declares no competing interests.

Data availability

Not applicable.

Code availability

Not applicable.

Acknowledgments

Special thanks to Lucia Bisceglia, Ida Galise, Sante Minerba, and the Environmental Epidemiology Working Group of Apulia Region (Italy), whose work inspired me. The opinions expressed in this article are my own and do not necessarily reflect the views of the institutions with which the author is affiliated.

Received on 4 November 2024.
Accepted on 20 January 2025.

REFERENCES

1. World Health Organization (WHO). Health impact assessment. Geneva: WHO. Available from: https://www.who.int/health-topics/health-impact-assessment#tab=tab_1.
2. World Health Organization (WHO). AirQ+: Software tool for health risk assessment of air pollution. Geneva: WHO. Available from: https://www.who.int/tools/airq.
3. World Health Organization (WHO). Health risks of air pollution in Europe – HRAPIE project. Recommendations for concentration-response functions for cost–benefit analysis of particulate matter, ozone and nitrogen dioxide. Geneva: WHO; 2013. Available from: https://iris.who.int/handle/10665/153692.
4. World Health Organization (WHO). Health risk assessment of air pollution: general principles. Geneva: WHO; 2016. Available from: https://www.who.int/publications/i/item/9789289051316.
5. Dora C. A perspective on health impact assessment, global health, and the role of the WHO. In Kemm J (Ed). Health impact assessment: Past achievement, current understanding, and future progress. Oxford: Oxford Academic; 2012, online ed. 2013. doi: 10.1093/acprof:oso/9780199656011.003.0031
6. Rigaud M, Buekers J, Bessems J, et al. The methodology of quantitative risk assessment studies. Environ Health. 2024;23(1):13. Published 2024 Jan 27. doi:10.1186/s12940-023-01039-x
7. European Environment Agency (EEA). Harm to human health from air pollution in Europe: Burden of disease 2023. Copenhagen: EEA; 2023. Available from: https://www.eea.europa.eu/publications/harm-to-human-health-from-air-pollution/.
8. Giannico OV, Sardone R, Bisceglia L, Addabbo F, Pirotti F, Minerba S, Mincuzzi A. The mortality impacts of greening Italy. Nat Commun. 2024;15(1):10452. doi: 10.1038/s41467-024-54388-7
9. Rothman KJ, Greenland S, Lash TL. Modern epidemiology. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2008.
10. Rothman KJ. Epidemiology: An introduction. 2nd ed. Oxford: Oxford University Press; 2012.
11. Porta M. A dictionary of epidemiology. 6th ed. Oxford: Oxford University Press; 2014.
12. Hernán MA, Robins JM. Causal Inference: What If. Boca Raton: Chapman & Hall/CRC; 2020. Available from: https://miguelhernan.org/whatifbook.
13. Van den Brenk I. The use of health impact assessment tools in European cities: A guide to support policy towards cleaner air and improvement of citizens' health. Commissioned by: Urban Agenda for the EU, Priority Urban Partnership for Air Quality, Action N°4 – Better focus on the protection and on the improvement of citizens' health. Utrecht: Utrecht University; 2018. Available from: https://ec.europa.eu/futurium/en/system/files/ged/4.the_use_of_health_impact_assessment_tools_in_european_cities.pdf.
14. European Topic Centre on Air Pollution and Climate Change Mitigation (ETC/ACM). Quantifying the health impacts of ambient air pollution: Methodology and input data. Bilthoven, The Netherlands: ETC/ACM; 2017. (ETC/ACM technical paper, 2016/5). Available from: https://www.eionet.europa.eu/etcs/etc-atni/products/etc-atni-reports/etcacm_tp_2016_5_aq_hia_methodology.
15. European Topic Centre on Air Pollution, Transport, Noise and Industrial Pollution (ETC/ATNI). Health risk assessment of air pollution in Europe. Methodology description and 2017 results. Kjeller, Norway: ETC/ATNI; 2020. (Eionet report, ETC/ATNI 2019/13). Available from: https://www.eionet.europa.eu/etcs/etc-atni/products/etc-atni-reports/etc-atni-report-13-2019-health-risk-assessment-of-air-pollution-in-europe-methodology-description-and-2017-results.
16. European Topic Centre on Air Pollution, Transport, Noise and Industrial Pollution (ETC/ATNI). Health risk assessments of air pollution. Estimations of the 2019 HRA, benefit analysis of reaching specific air quality standards and more. Kjeller, Norway: ETC/ATNI; 2021. (Eionet Report, ETC/ATNI 2021/10). Available from: https://www.eionet.europa.eu/etcs/etc-atni/products/etc-atni-reports/etc-atni-report-10-2021-health-risk-assessments-of-air-pollution-estimations-of-the-2019-hra-benefit-analysis-of-reaching-specific-air-quality-standards-and-more.
17. Istituto Superiore per la Protezione e la Ricerca Ambientale (ISPRA). Linee guida per la valutazione integrata di impatto ambientale e sanitario (VIIAS) nelle procedure di autorizzazione ambientale (VAS, VIA, AIA). Roma: ISPRA; 2016. (ISPRA manuali e linee guida, 133/2016).
18. Istituto Superiore di Sanità (ISS). Linee guida per la valutazione di impatto sanitario (DL.vo 104/2017). Roma: ISS; 2019. (Rapporti ISTISAN, 19/9).
19. Bauleo L, Fabri A, De Santis M, Soggiu ME, Ancona C. SENTIERI Project: Air pollution and health impact of population living in industrial areas in Italy. Epidemiol Prev. 2023;47(1-2 Suppl. 1):338-53. Italian. doi: 10.19191/EP23.1-2-S1.007
20. Galise I, Serinelli M, Morabito A, Pastore T, Tanzarella A, Laghezza V, et al. The integrated environmental health impact of emissions from a steel plant in Taranto and from a power plant in Brindisi, (Apulia Region, Southern Italy). Epidemiol Prev. 2019;43(5-6):329-37. doi: 10.19191/EP19.5-6.P329.102
21. European Environmental Agency (EEA). Health impacts of air pollution in Europe, 2022. Copenaghen: EEA; 2022. Available from: https://www.eea.europa.eu/publications/air-quality-in-europe-2022/health-impacts-of-air-pollution.
22. Khomenko S, Cirach M, Pereira-Barboza E, Mueller N, Barrera-Gómez J, Rojas-Rueda D, et al. Premature mortality due to air pollution in European cities: A health impact assessment. Lancet Planet Health. 2021;5(3):e121-e34. doi: 10.1016/S2542-5196(20)30272-2
23. Barboza EP, Cirach M, Khomenko S, et al. Green space and mortality in European cities: A health impact assessment study. Lancet Planet Health. 2021;5(10):e718-e30. doi:10.1016/S2542-5196(21)00229-1
24. Brochu P, Jimenez MP, James P, Kinney PL, Lane K. Benefits of increasing greenness on all-cause mortality in the

largest metropolitan areas of the United States within the past two decades. Front Public Health. 2022;10:841936. doi:10.3389/fpubh.2022.841936

25. Istituto Nazionale di Statistica (ISTAT). Decessi e cause di morte: cosa produce l'Istat. Roma: ISTAT; 2020. Available from: https://www.istat.it/notizia/dati-di-mortalita-cosa-produce-listat/.
26. Global Human Settlement Layer (GHSL). GHS population grid (R2023). Product: GHS-POP, epoch: 2020, resolution: 100m, coordinate system: Mollweide. Bruxelles: European Union. Available from: https://ghsl.jrc.ec.europa.eu/download.php?ds=pop.
27. Chen J, Hoek G. Long-term exposure to PM and all-cause and cause-specific mortality: A systematic review and meta-analysis. Environ Int. 2020;143:105974. doi: 10.1016/j.envint.2020.105974
28. Rojas-Rueda D, Nieuwenhuijsen MJ, Gascon M, Perez-Leon D, Mudu P. Green spaces and mortality: A systematic review and meta-analysis of cohort studies. Lancet Planet Health. 2019;3(11):e469-e77. doi: 10.1016/S2542-5196(19)30215-3. Erratum in: Lancet Planet Health. 2021;5(8):e504.
29. Giannico OV, Baldacci S, Bisceglia L, Minerba S, Conversano M, Mincuzzi A. The mortality cost of carbon dioxide emissions from a steel plant in Southern Italy: a climate change health impact assessment. Epidemiol Prev. 2023;47(4-5):273-80. Italian. doi: 10.19191/EP23.4-5.A616.067

Ann Ist Super Sanità 2025 | Vol. 61, No. 1: 82-86
DOI: 10.4415/ANN_25_01_10

Ten years after Regulation 536/2014: ethical reflection on the role of Ethics Committees in Italy

Chiara Mannelli, Giovanna Floridia, Sabina Gainotti, Luciana Riva and Carlo Petrini

Unità di Bioetica, Istituto Superiore di Sanità, Rome, Italy

Abstract

Since their institution, Ethics Committees (ECs) dedicated to the ethical evaluation of research protocols have been traditionally entrusted with the role of finding a delicate balance between protecting research participants' rights and avoiding the hampering of scientific progress. In Europe, these bodies have evolved significantly over time, shaped by a dynamic regulatory framework culminating in Regulation (EU) 536/2014, which has been fully applied since 2022. Focusing on the Italian scenario, a decade after the adoption of the Regulation (2014-2024), this paper is aimed at shedding light on the extent to which the evolution of the pertinent normative framework has affected ECs' space for reflection within the ethics review process of clinical trials, essential to protect the rights of research participants. Although focused on the Italian scenario, the analysis holds relevance for the broader European context, since the Regulation is unique and developments in a single Member State may impact the others.

Key words

- ethics
- bioethics
- ethics committees
- Regulation (EU) 536/2014
- clinical trials

INTRODUCTION

Throughout history, the scientific discoveries that laid the foundations of modern and contemporary medicine often relied on processes that, by today's ethical and scientific standards, would be deemed unacceptable. One notable example is the efforts to combat smallpox, a devastating disease that once posed a severe threat to public health. In 1717, Sir Hans Sloane studied the technique of "variolation", namely using pus from blisters obtained from patients with smallpox [1]. This technique was also approached by Lady Mary Worley Montagu in 1718 [1]. In the effort to eradicate smallpox, the most notable example involves Edward Jenner's research. He observed that persons (typically dairymaids) who had suffered from the cowpox did not contract smallpox. On these grounds, he started a series of experiments. In 1796, Jenner inoculated, among others, an eight-year-old boy with cowpox and, after his recovery, with smallpox. The boy did not contract smallpox (https://biotech.law.lsu.edu/cphl/history/articles/jenner.htm) [2]. While Jenner's experiments provided a relevant contribution to the history of medicine, at that time no one questioned the involvement of vulnerable people in medical research.

It has been a long time since Jenner's experiments and, following numerous instances of abuse, particularly involving vulnerable individuals, strict ethical requirements have been established to safeguard the rights of those involved in research. As a result, even though Jenner's work significantly contributed to the eradication of a disease that is estimated to have killed more than 300 million people in the 20th century [3], his experiments would not be authorized today [2]. Should we regret, then, the times in which freedom for any method of scientific research was granted? Certainly not: criteria for research ethics and scientific rigor are needed. Research with humans, in fact, can be detrimental to the rights and wellbeing of participants. Yet, while safeguarding rights of persons involved, at the same time ethics should not hamper the scientific progress we all rely on as a society.

Such a delicate, yet essential, role of finding a balance between these two dimensions in the evaluation of research protocols has been conferred to specific bodies with different names depending on the countries in which they are located – some examples are Research Ethics Committees (RECs) or Institutional Review Boards (IRBs). Since this paper focuses on the Italian context, the expression "Ethics Committee (EC)" will be used in compliance with the Italian context. Though ECs in Italy are in charge of different tasks, this analysis will take mainly into consideration the ethical clearance of clinical studies involving humans.

2024 was the tenth anniversary of the adoption of Regulation (EU) 536/2014 (hereafter "the Regulation") of the European Parliament and of the Council of 16 April

Address for correspondence: Chiara Mannelli, Unità di Bioetica, Istituto Superiore di Sanità, Via Giano della Bella 34, 00162 Rome, Italy. E-mail: chiara.mannelli@iss.it.

2014 on clinical trials on medicinal products for human use [4] which revolutionized the whole research field in European countries and is fully applied since 2022. Drawing upon the Italian scenario, this paper aims at exploring whether changes in the normative framework regulating research – with specific focus on the last 10 years – has been affecting the quality and the space for the independent ethical reflection. This aspect is crucial as EC's independent ethical reflection underpins the extremely delicate role of protecting the rights of research participants, traditionally assigned to these bodies.

Although focused on Italy, the analysis is of interest for the entire European context, since the community Regulation is the common regulatory reference and what happens in a single Member State has repercussions for all the others.

ADVENT OF REGULATION (EU) 536/2014: STRENGTHS AND WEAKNESSES

The adoption of the Regulation constituted a breakthrough for ECs in Italy and for the whole medical research field.

The Regulation, aimed at speeding up and harmonizing the extremely fragmented evaluation system across Europe, introduced two main changes to the clinical trials' assessment procedure. First, each Member State involved in a research protocol is required to convey a unique decision uploaded through the EU portal as to whether the clinical trial is authorized, authorized under specific conditions, or whether authorization is denied within strict deadlines. The second innovation concerns the rethinking of the whole procedure of clinical trials' assessment. The Regulation divides clinical trials' assessment reports into two different sections. Part I, described by article 6 of the Regulation, involves verification of: requirements for low-intervention trials where applicable; the anticipated therapeutic and public health benefits; the risks and inconveniences for the subject; compliance with the requirements concerning the manufacturing and import of investigational medicinal products; compliance with labelling requirements; and completeness and adequateness of the investigator's brochure.

Part II, described by article 7, involves compliance requirements: for informed consent; of arrangements for rewarding or compensating subjects and investigators; of arrangements for recruitment of subjects; with Regulation 2016/679 on General Data Protection (GDPR); with Article 49, regarding the suitability of individuals involved in conducting the clinical trial; with Article 50, involving the suitability of clinical trial sites; and with Article 76, regulating Damage compensation.

In this scenario, the Regulation does not provide Member States with guidance and indications aimed at meeting the newly introduced requirements. In relation to the role of RECs, Regulation (EU) 536/2014 requires Member States to organize the involvement of these bodies in the evaluation process at the national level, but does not impose any binding modality for the organization of this process. As a result, each Member State is free to decide how to set the national network in order to reach the required "single decision" and how to distribute the tasks described in assessment report Part I or Part II, provided the strict deadlines imposed by the Regulation are met. This choice grants Member States a certain discretion in choosing and adopting the organizational model each one deems best for their national background. Nevertheless, such a lack of centralization leads to a significant heterogeneity and often Member States do not know what happens "behind the scenes" of the single decision reached by confining countries participating in the same study. The rigor of a Member State's decision, however, does impact the overall evaluation' quality of the European system.

APPLICATION OF REGULATION (EU) 536/2014. THE ITALIAN CASE

The procedural revolution introduced by the Regulation deeply impacted each Member State's research apparatus. Italy, with its extensively articulated network of ECs, was no exception [5]. As in other European countries, it took several years for the rearrangement to be implemented.

Law n.3/2018 [6] intervened to regulate the Italian framework by rethinking the arrangement of ECs. In particular, the network for ethical clearance of medicinal products, considerably reduced, is outlined as follows: 40 Territorial Ethics Committees (TECs), distributed throughout the national territory and chosen among the already existing ECs, in charge to provide a single evaluation for clinical trials with medicinal products, medical devices, and observational studies with medicinal products; and 3 National Ethics Committees (NECs) in charge of the ethical clearance of clinical trials pertaining to specific research areas (pediatrics; advanced therapies; and clinical trials conducted by public research bodies, EPR, and other national public institutions). The already existing ECs that were not incorporated into the structure envisaged by Law n. 3/2018 have been allowed to continue their work subject to regional resolution, for matters not covered by the newly established ECs.

On January 31st, 2022, after 8 years from its publication and entry into force, the Regulation was applied in European Member States.

In Italy, TECs and NECs (henceforth referred to with the expression "ECs") are in charge of completing Part II of the assessment report. They may express observations on Part I as well, yet the Competent Authority (CA), i.e., the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA), is in charge of completing this first part. Abiding by the law, AIFA may hypothetically refuse to endorse observations raised by ethics committees if deemed inadequate, which is controversial given the ethical relevance of Part I.

Also, observations on Part II may have an impact on the evaluation of Part I and vice versa.

The introduction of the Regulation has profoundly influenced how Italian ECs conduct their ethical evaluations. Before its application, in Italy the authorization of AIFA together with that of one or more independent EC(s) was required to start a clinical trial. In this scenario, at least in theory, the opinion of the EC(s) was binding and covered all aspects of the study under review. The situation changed radically within the Regu-

lation: the authorization of both AIFA and EC is still required, but ECs can express their binding evaluation only on some aspects of ethical relevance.

2024 has marked ten years since the adoption of the Regulation in 2014. This anniversary is particularly significant as it calls for a reflection on the evolution of these bodies focused on clinical trials' evaluations.

Has this evolution maintained the quality and scope of ethical analysis – crucial for fulfilling the delicate role of encouraging research advances, while safeguarding participants' rights – that ECs have traditionally been entrusted with?

ITALIAN ETHICS COMMITTEES AND REGULATION: A QUANTITATIVE AND QUALITATIVE ETHICAL FLATTENING?

Ethics has been gaining growing relevance and significance in the global healthcare scenario and, in particular, within the research field (https://www.weforum.org/stories/2024/01/trust-ethics-economics-governance/; https://www.who.int/activities/ensuring-ethical-standards-and-procedures-for-research-with-human-beings). Surprisingly, Italian ECs do not appear to have benefited from this change. The general impression is that, over time, there has been a gradual flattening of the value placed on the ethical reflection that ECs have had the opportunity to contribute to within the Italian medical research field.

Despite such a flattening has been affecting the whole research field in Italy[a], this analysis will focus on changes regarding clinical research. Already in the '90s the huge number of trials to be evaluated by Italian ECs reportedly "poisoned" these bodies and their space for ethical reflection [7].

More recently, this concern has become particularly perceptible in the role the Italian application of the Regulation has attributed to ECs. Such a flattening might be traced back to two main concerns, one regarding *quantity*, and the second one regarding *quality* of the evaluation Italian ECs find themselves in the position to provide within the ethical clearance of clinical trials.

The first concern involves the *quantitative* limitation of the competences currently assigned to Italian ECs in the framework of the Regulation. Such a consideration does not mainly apply to the number of trials assigned to each EC – the number has decreased, but the amount of work and the bureaucratic procedures needed to meet the requirements has increased[b]. Rather, concerns pertain the limitation of aspects of ethical relevance ECs can evaluate within a study. Aspects related to Part I of the assessment report, like the evaluation of anticipated therapeutic and public health benefits associated with the clinical trial or potential risks and inconveniences for the subject enrolled in the study, are matters of concern from an ethical perspective and are deeply intertwined to the aspects ECs are required to evaluate in Part II. To this end, the evaluation of all these elements, particularly relevant from many different points of view, should benefit from an ethical and interdisciplinary perspective, such as the one provided by an EC. Nevertheless, in Italy such aspects are formally reviewed by the CA, whose perspective differs in skills and training from members of an EC. ECs may express their opinion, but in the event of divergent views the CA has the last word. Therefore, this leads to a quantitative limitation of the aspects ECs can express their binding evaluation on. This is a relevant element to consider as, before the adoption of the Regulation, the binding opinion of the EC covered all aspects of the study under review. Such a limitation runs counter to the ethical relevance of these aspects within the clinical trial and affects the chances for ethical contribution ECs may provide within the research scenario.

The second concern regards the *quality* of the evaluation ECs in Italy are in the position to provide. Elements relating to Part II of the assessment report are of marked ethical relevance. However, to promote procedural standardization, the ethical evaluation elaborated by the EC must be expressed within a specific (and tightened) window of time through bulletproof forms, which partly pauperize the significance of the ethical reflection underpinning the evaluation itself. Such an approach has significant benefits: evaluations are now faster and standardized, thus more easily comparable among countries participating to the same protocol. Yet, the ethical pondering, that has characterized the growth and evolution of ECs, must now be squeezed to fit the non-editable grids and be expressed through options to be flagged [8]. The risk of this procedure is to lead to a fragmentation and a debasement of the ethical reflection elaborated by ECs. Moreover, this trend implies a progressive bureaucratization of ECs by monopolizing their activity in order to meet the requirements of the Regulation. In other terms, ECs risk becoming bureaucratic machines whose main occupation is to fill out the forms pertaining Part II[c] without having an overall vision of the ethical implications regarding the protocol under evaluation, precisely because ECs are only responsible for the evaluation of Part II.

ECs' REORGANIZATION AND CHANCES FOR ETHICAL REFLECTION

As described above, ECs in Italy have gone through a profound transformation to meet the requirements of an evolving normative framework. In the last 10 years, since the adoption of the Regulation, their role has sig-

[a]For instance, there is a persistent lack of legislation and of standardized procedures regarding the ethical clearance of research involving humans that does not pertain to medicinal products or medical devices in Italy. Such a normative and procedural blur represents a barrier to the evaluation of these kinds of studies by making it arduous for ECs to express their assessments regarding a huge and heterogeneous research area that offers great opportunities for patients' care.

[b]Moreover, ECs in Italy evaluate many other kinds of study not falling under the Regulation.

[c]Although the Regulation in Italy has had significant direct consequences on the role of ECs in the evaluation of protocols with medicinal products, its application has indirectly influenced the role of ECs in the evaluation of all other types of research as well. The significant focus on the Regulation has had a knock-on effect in the whole field of research. In this framework, the evaluation of studies that do not fall within the umbrella of Regulation 536 could be perceived as of secondary relevance. In any case, these studies float in a persistent regulatory gap with enormous ethical implications.

nificantly changed. Yet, the overall impression is that this evolution has seldom constituted a fertile ground for a flourishing of the ethical depth of ECs' contribution to the research scenario. Such a trend unfolded in contrast to the awareness that ethics is gaining globally in the healthcare field and, in particular, in the research one, and was ultimately ratified, in Italy, by the role assigned to ECs within the application of the Regulation. It is worth highlighting that the present analysis does not intend, in any way, to attribute direct responsibility to the Regulation for such an impoverishment. The European harmonization introduced by the Regulation was necessary to coordinate and to streamline the protocols' evaluation procedures at a communitarian level to make Europe more attractive and competitive in the research field. Rather, the present analysis underlines that, unfortunately, it was the depth of the ethical analysis reserved to ECs, depleted from both a qualitative and quantitative point of view, that paid the price for the Italian strategy.

Reducing the role of ECs to a technical and bureaucratic control is a short-sighted strategy. The delicate role of finding the right balance between subjects' protection and scientific progress ECs have been traditionally entrusted with, requires space and circumstances to be both developed and exercised. Given the relevance of the role of ECs and their value in the delicate mission of safeguarding the rights of trial participants, it is crucial to find solutions for their ethical reflection to be treasured through time, rather than progressively constrained and eroded [9].

Although the role assigned to Italian ECs in the evaluation of clinical trials in the context of the Regulation is only a part of the tasks assigned to these bodies, this shift affects the role ECs play in the evaluation of research not falling under the umbrella of the Regulation, as discussed above. To this end, rethinking the Italian mechanism in order to leave more room for ECs ethical reflection to unravel seems not only desirable, but necessary. Such a call is not only relevant at a national level but, rather, at a European level since a potential flattening of the quality of the ethical reflection produced by a single Member State may affect the overall quality of the system.

To this end, without jeopardizing the effort to harmonize and streamline the evaluation procedures at European level introduced by the Regulation, a possible solution could be to reconsider the role assigned to ECs in Italy, by granting them the chance to express binding considerations also on specific aspects of ethical relevance contained in Part I of the assessment, deeply intertwined to ECs responsibility. The rationale for this proposal has to do with the importance that the assessment of research issues requiring an ethical clearance, such as, indeed, specific aspects of Part I, be effectively validated by the interdisciplinary and professional background typical of an EC. Expertise in ethics allows no improvisation and the uniqueness of the ethics committee is inherent in bringing together professionals of different backgrounds who have, as a common denominator, training in ethics. All these points of view provide a rich perspective to the analysis that cannot be replaced and that must be protected and cherished for the quality of the clearance and the safeguard of research participants. The time has come to reflect on the room we want to leave for ECs, precious institutions that have long been guardians of research participants' rights.

The lack of centralization for some procedural aspects in the application of the Regulation was extremely facilitating in order for each Member State to find autonomously the solution that best suited and valued its own pre-existent national structure. However, now that the Regulation has been finally applied and, after more than 10 years, each Member State has started the gear, a constructive dialogue between Member States concerning the solutions adopted to fulfil the requirements posed by the Regulation should be strongly encouraged. Exposing Member States to the chance to acknowledge different solutions adopted to comply with the Regulation and, possibly, to be inspired by neighbour's ones might improve and enrich the quality, the ethical perspective, and the overall accountability of the European Union research system.

Authors' contributions

CM: concept, drafting article, critical revision of article; GF, SG, LR: critical revision of article; CMP: concept, critical revision of article.

Funding

The Authors report there are no dedicated funds for this paper.

Conflict of interest statement

The Authors report there are no competing interests to declare.

Received on 24 December 2024.
Accepted on 24 January 2025.

REFERENCES

1. Gallin JI, Ognibene FP, Lee Johnson L. Principles and practice of clinical research. 4th ed. London: Academic Press Elsevier; 2018.
2. Davies H. Ethical reflections on Edward Jenner's experimental treatment. J Med Ethics. 2007;33(3):174-6. doi: 10.1136/jme.2005.015339
3. Desmond A, Offit PA. On the shoulders of giants - From Jenner's Cowpox to mRNA Covid vaccines. N Engl J Med. 2021;384:1081-3. doi: 10.1056/NEJMp2034334
4. European Parliament. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials in medicinal products for human use and repealing Directive 2001/20/EC. Official Journal of European Union, 27 May 2014.
5. Petrini C, Brusaferro S. Ethics committees and research in Italy: seeking new regulatory frameworks (with a look

at the past). Ann Ist Super Sanità. 2019;55(4):314-8. doi: 10.4415/ANN_19_04_02

6. Italia. Legge 11 gennaio 2018. n. 3. Delega al Governo in materia di sperimentazione clinica di medicinali nonché disposizioni per il riordino delle professioni sanitarie e per la dirigenza sanitaria del Ministero della salute. Gazzetta Ufficiale – Serie Generale, n. 25, 31 gennaio 2018.
7. Barni M. I comitati etici. In: Comitato Nazionale per la Bioetica. Il Comitato Nazionale per la Bioetica: 1990-2005. Quindici anni di impegno. Atti del Convegno. Roma 30 novembre - 3 dicembre 2005. Presidenza del Consiglio dei Ministri, Dipartimento per l'informazione e l'editoria; 2005.
8. Centro di Coordinamento Nazionale dei Comitati Etici. Guidance on evaluating under art. 7 of Regulation (EU) no 536/2014, by the Territorial Ethics Committees. CCNCE; 2024. Available from: https://www.aifa.gov.it/documents/20142/2198424/guida_valutazione_documenti_parte-2_CCN_22.05.2024_EN.pdf.
9. Lukaseviciene V, Hasford J, Lanzerath D, Gefenas E. Implementation of the EU clinical trial regulation transforms the ethics committee systems and endangers ethical standards. J Med Ethics. 2021;47:e82. doi:10.1136/medethics-2020-106757

Ann Ist Super Sanità 2025 | Vol. 61, No. 1: 87-89
DOI: 10.4415/ANN_25_01_11

Book Reviews, Notes and Comments

Edited by
Federica Napolitani Cheyne

IL VALORE DEI FARMACI
Accesso alle terapie efficaci e sostenibilità della spesa
Giuseppe Traversa
Roma: Il Pensiero Scientifico Editore; 2024
242 p.
ISBN: 9788849007916
€ 25,00

[The value of drugs. Access to effective therapies and sustainable spending]

The book aims to tackle, in a comprehensive and multidimensional way, the complex process of evaluating the value of pharmaceuticals within the Italian regulatory framework – a topic of great importance for the sustainability of the National Health Service (SSN).

Giuseppe Traversa, with expertise and methodological accuracy, analyses the dynamics between innovation and sustainability, highlighting how these two concepts are often perceived as contradictory in the pharmaceutical sector. In fact, the financial balance of the NHS conflicts with the legitimate interests of pharmaceutical companies and the necessity to develop innovative drugs to meet the health needs of the population. While innovation should ideally yield benefits in terms of treatment efficacy and safety, it inevitably brings about an increase in costs.

The challenge, therefore, lies in being able to "pay" for a drug in proportion to the clinical benefit it offers, compared to the alternatives already available. This concept expressed through the definition of "place in therapy," represents the core of the debate. The author emphasizes that, to assign an adequate value to a drug, it must be positioned along a continuum that stretches from therapeutic equivalence to true innovation – a task that he acknowledges is extremely complex.

A chapter examines the price negotiation process, shedding light on the interactions between the regulatory Agencies and pharmaceutical companies. In many instances, the regulatory evaluation does not meet the expectations of the companies, thereby lengthening decision-making times and further complicating the determination of a price based on the drug real therapeutic value. To fairly reward innovative drugs, there must be a shared definition of "innovativeness" and, consequently, a consensus on the principle that a drug offering no advantages over existing alternatives cannot be priced higher. Although this approach is theoretically sound, in practice it clashes with the difficulty of unambiguously defining concepts such as "therapeutic overlap" and "marginal benefit."

Another part of the book is dedicated to managed entry agreements (MEAs), instruments that have played a pioneering role in Italy in managing uncertainty. These agreements represent a pragmatic response to the problem of early access to drugs whose clinical efficacy is still being defined, allowing for risk mitigation for the payer through a shared acceptance of uncertainty. However, Traversa does not spare criticism of these instruments, highlighting their limitations and the decline in their use in recent years considering evidence that questions their actual capacity to ensure a proper evaluation of therapeutic value.

The analysis then extends to the discussion of real-world data (RWD) and real-world evidence (RWE). The author acknowledges the value of these data sources as a complement to randomized clinical trials, while reiterating that, whenever possible, the latter remain the gold standard for establishing the efficacy and safety of new treatments.

Throughout the book, the author follows a multidisciplinary approach, emphasizing that the process of evaluating and negotiating drug prices requires the synergistic contribution of medical, economic, statistical, legal, and pharmacological expertise and underlines that, in an era where an aging population and relentless technological progress further strain healthcare budgets, it is essential to integrate diverse perspectives to ensure equitable and sustainable access to care.

Emphasis is placed on the discussion of spending caps and the increasing demands for financial buffers by companies and Regions. Traversa analyses how, although spending caps serve as a safeguard for public finances, they also highlight a situation in which the expenditure for direct drug purchases consistently exceeds forecasts, thus underlining the urgency for structural interventions and systemic reforms to effectively govern pharmaceutical spending.

In conclusion, the book offers a comprehensive and critical overview of the challenges related to evaluating the value of drugs within a complex and ever-evolving regulatory environment. Its clear exposition and ability to integrate different perspectives make this work an important reference not only for industry professionals, but also, for prescribing physicians, and medical students. The reflections and proposals presented provide stimulating insights for a more balanced and transparent management of the relationship between innovation and sustainability, which is fundamental for ensuring access to quality care in a healthcare system under constant economic pressure.

Thus, Traversa contribution emerges as a valuable resource for both scientific and political debate, offering conceptual and operational tools to address one of the most pressing challenges of our time: reconciling therapeutic progress with the need to contain costs, while simultaneously maintaining a high standard of patient care.

Roberto Da Cas and Francesca Menniti Ippolito
Istituto Superiore di Sanità, Rome, Italy
francesca.menniti@iss.it

NON È MAI MORTO NESSUNO
Dagli impasti crudi al microbiota, viaggio nella microbiologia di tutti i giorni
Alessandro Mustazzolu
Milano: Gribaudo, IF, Idee editoriali Feltrinelli srl; 2024
224 p.
ISBN 978-88-580-4898-6
€ 16,90

[No one ever died from it: from raw dough to microbiota, a journey into everyday microbiology]

"Science isn't finished until it's communicated. The communication to wider audiences is part of the job of being a scientist, and so how you communicate is absolutely vital" [1]. So did Sir Mark Walport capture one of the core duties of scientists. This statement also reflects one of the primary missions of the European Union which, over the past 20 years, acknowledged that citizens are the ultimate beneficiaries of scientific initiatives, and accordingly implemented strategies to involve laypeople in the process of scientific discovery. Over the years, research programmes – from the original Framework Programmes to Horizon 2020 and later Horizon Europe – have progressively increased the dissemination requirements that researchers must meet to secure funding. While earlier initiatives were required to include some form of dissemination to the public, current ones are required to directly engage citizens at nearly every level of the activities, be it in the form of dissemination initiatives, involvement in guideline preparation, or active participation in data acquisition (i.e., citizen science). This effort has a dual aim: to encourage scientists to step out of their "ivory tower" and to raise public awareness of both the benefits of research and the rigorous methods researchers follow to achieve meaningful results. Complementarily, greater transparency will help taxpayers build trust in science and mitigate the scepticism that unclear communication may generate. Ultimately, actively engaging the public in research efforts is expected to help mitigate the growing risks of fake news and conspiracy theories that exploit scientific jargon to mislead.

We believe that the book *Non è mai morto nessuno: dagli impasti crudi al microbiota, viaggio nella microbiologia di tutti i giorni* meets this aim. It exemplifies how scientists can foster meaningful dialogue with the general public to achieve the aforementioned goals. Alessandro Mustazzolu, microbiologist, is truly one of a kind – his strong research expertise (he is a Research Scientist of the Italian National Institute of Health) is matched by a dynamic and impactful presence on social media (over 68000 followers, and counting). He uses his network to educate the public as to the potential outcomes of a reckless consideration of the microbiological risks encountered during our daily lives (e.g., inaccurate handling of poultry, sanitization of surfaces, raw food and so on). Most importantly, Alessandro's activity extends well beyond passive information to incorporate a constant (and to our view often thankless) interaction with his followers. In other words, he constantly answers followers' questions with an unwavering commitment.

This book is a well-structured and highly entertaining reflection of his activities: Alessandro devoted each chapter of his book to answer everyday questions emerged in his interaction with social media followers. For example, Agnese is wondering how to deal with her mother allowing her grandchildren (Agnese's children) to eat the raw shortcut pastry regardless of the potential dangers related to the ingestion of raw eggs. Using this and similar questions as a starting point, Alessandro guides the reader through the fascinating microbiological world that exists within our homes. Grounded in solid experimental evidence, he skillfully balances entertainment with education, raising awareness of the risks we encounter in daily life. And it's not just about raw eggs – sausages and fish are also under scrutiny (sushi lovers may be disappointed, but it's for their own good!). Besides providing "protocols-for-dummies" – like suggestions on how to manipulate and treat foods and beverages, Alessandro takes the opportunity to unfold some of the mysteries of microbiology and their impact on our health: listeria, salmonella, and botulinum will become familiar to the reader. As members of an institute that was originally established to fight malaria, we can do nothing but encourage everyone to read the chapter devoted to this disease. Therein, the reader will also access the fun fact of a Nobel prize that has not been awarded due to jealousy and bitterness.

Alessandro takes a tour of our entire homes, bedrooms included: and in this section, sex becomes the starting point to explain how some diseases may be sexually transmitted but also how our way to generate a progeny is linked to the microbial world. The reader will be surprised to know that our bodies host trillions of bacterial species. And the word microbiome, now pervasive even in TV commercials, will become intelligible.

While the topics covered in the book are numerous, they are all linked by an underlying theme: bias. This term is used to define a set of mental shortcuts that

we typically form (resting on scattered, limited, and inconclusive data) to inform our actions. The title of the book, which can be translated in "No one ever died from it", encapsulates one of the most common biases: the survivorship bias. Since Agnese's mother, and Agnese herself, did not experience any negative outcome following raw egg consumption, this habit has to be safe (we are biased to think that if something hasn't harmed us before, it won't harm us in the future). Alessandro is telling us that this is not the case and is encouraging us to handle our biases in a constructive way. And raw eggs are just one example.

This book has the potential to reach a large audience: not only the public which will learn how to minimise risks in their daily lives, but also scientists who will enjoy the rigour of the information presented in this book (and the selected references too). Just don't read it if your date is waiting for you at the sushi bar!

Simone Macrì and Enrico Alleva
Centre for Behavioural Sciences and Mental Health
Istituto Superiore di Sanità, Rome, Italy

REFERENCE

1. Sophie Yeo. Science is not finished until it's communicated – UK chief scientist. Sir Mark Walport tells Royal Society meeting that climate change experts need to learn how best to translate their findings for a wider audience. Climate Home News. Science. Oct 3, 2013. https://www.climatechangenews.com/2013/10/03/science-is-not-finished-until-its-communicated-uk-chief-scientist/

Ann Ist Super Sanità 2025 | Vol. 61, No. 1: 90-92
DOI: 10.4415/ANN_25_01_12

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 2024. Value-driven transformation of agrifood systems. Rome: Food and Agriculture Organization of the United Nations 2024; 171 p. ISBN 978-92-5-139140-2. The State of Food and Agriculture 2024 builds on the findings of the 2023 edition, delving deeper into the use of true cost accounting assessments of agrifood systems and identifying policy interventions aimed at transformation. Using updated global datasets, the report confirms previous estimates of the quantified hidden costs of agrifood systems and provides a detailed breakdown of the hidden costs associated with unhealthy dietary patterns and non-communicable diseases for 156 countries. These findings are analysed through the lens of six agrifood systems categories to consider various outcomes and hidden costs that require different policy interventions. Case studies offering in-depth assessments of country, local and value chain contexts illustrate the economic, social and environmental impacts of current practices to guide policy interventions.

Global status of salt-affected soils. Main report. Rome: Food and Agriculture Organization of the United Nations 2024; 240 p. ISBN 978-92-5-139307-9. FAO's Global Map of Salt-Affected Soils reveals that over 1381 million hectares, 10.7 percent of global land, are affected, with Australia, Argentina and Kazakhstan among the most impacted countries. Increasing aridity and water demand amplify soil degradation risks, particularly in developing regions. Climate change and water scarcity threaten agricultural productivity, with substantial crop yield losses observed in saline areas. Halophytes and salt-tolerant crops provide a foundation for saline agriculture, yet many salt-affected soils remain unprotected and inadequately regulated. FAO's INSAS (International Network of Salt-Affected Soils) underscores the need for updated data, harmonized salinity measurements, and sustainable management practices, with enhanced training and policy frameworks. Mitigation strategies like improved drainage, soil amendments, and the cultivation of salt-tolerant plants are recommended. Key recommendations include scaling sustainable practices, investing in salt-tolerant crop markets, improving data collection and water quality monitoring, conserving ecosystems, and fostering cross-sector collaboration.

Realizing the right to food in a changing world. The Right to Food Guidelines: 20 years on and beyond. Rome: Food and Agriculture Organization of the United Nations 2024; 82 p. ISBN 978-92-5-139419-9. The fourth report on the status of FAO's Right to Food Guidelines commemorates 20 years of progress since their adoption by the FAO Council in November 2004. It explores how the Guidelines have evolved to address global challenges, strengthened international human rights frameworks, and tackled barriers to food security. By emphasizing a human rights-based approach, the report highlights the roles of states, individuals, civil society, and private entities in advancing this vital agenda. The report concludes with actionable recommendations, and calls for sustainable, inclusive solutions to end hunger and malnutrition.

UNITED NATIONS EDUCATIONAL, SCIENTIFIC AND CULTURAL ORGANIZATION (UNESCO)

Synthetic content and its implications for AI policy: a primer. Paris: UNESCO Publishing 2024; 41 p. ISBN 978-92-3-100727-9. The deployment of advanced Artificial Intelligence (AI) models, particularly generative AI, has sparked discussions regarding the creation and use of synthetic content and its impact on individuals, societies, and economies. This note contributes to shed light on what "synthetic content" may mean and consist of, explores the different ways in which it can be generated and used and proposes a taxonomy that encompasses synthetic media and deepfakes, among others. The taxonomy aims to systematize key characteristics, enhancing understanding and informing policy discussions. Key findings highlight both the potential benefits and concerns associated with synthetic content in fields like data analytics, environmental sustainability, education, creativity, and mis/disinformation and point to the need to frame them ethically, in line with the principles and values of UNESCO Recommendation on the Ethics of Artificial Intelligence. Finally, this note ends with several policy considerations informing the conversation about how to put these powerful technologies at the service of individuals and societies.

JOINT UNITED NATIONS PROGRAMME ON HIV/AIDS (UNAIDS)

The urgency of now: AIDS at a crossroads. Geneva: Joint United Nations Programme on HIV/AIDS 2024; 300 p. The global AIDS response is at a cross-

roads: success or failure will be determined by which path leaders take today. The Urgency of Now: AIDS at a Crossroads shows that the decisions leaders make this year will determine whether countries can achieve the 2030 target of ending AIDS as a public health threat and ensure progress beyond 2030. The report shows that, right now, the world is not on track to succeed, and the inequalities that drive the HIV pandemic are not being addressed sufficiently. It shows that due to the lack of progress on prevention, global numbers of new HIV infections are not declining fast enough, and in three regions of the world numbers of HIV infections are rising. It shows that almost a quarter of people living with HIV are not receiving lifesaving treatment, and consequently, a person dies from AIDS-related causes every minute. This report provides a summary of progress against the 2025 targets that were developed with the Global AIDS Strategy 2021-2026.

Global AIDS monitoring 2025. Geneva: Joint United Nations Programme on HIV/AIDS 2025; 216 p. This document is a detailed compilation of indicators, and a suite of questions on national policies and their implementation. The indicators and policy questions are designed to enable the best use of available data at the national level, to standardize reporting from different HIV epidemics and sociopolitical contexts, and to enable aggregation at the global level. UNAIDS is working with key organizations under the umbrella of the Monitoring Technical Advisory Group (MTAG) to harmonize the indicators to match international standards. Over the past 20 years, the indicators used for global monitoring have evolved as our collective knowledge of effective HIV responses and the barriers to this have improved. This will continue in the coming years. The indicators are reviewed annually and revised by the UNAIDS MTAG.

ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT (OECD)

Health at a glance: Europe 2024. State of health in the EU cycle. Paris: Organization for Economic Co-operation and European Commission 2024; 233 p. ISBN 978-92-64-58300-9 (PDF). The 2024 edition of Health at a Glance: Europe examines the major challenges facing European health systems in the aftermath of the COVID-19 pandemic. The report includes two thematic chapters. The first chapter provides a comprehensive examination of health workforce shortages in Europe, a long-standing problem exacerbated by the immense strain the pandemic placed on health systems. It explores the factors behind these shortages and proposes policy strategies to attract, train and retain the workforce needed to build resilient health systems. The second chapter reviews the most recent trends in the health of Europe's ageing population. With life expectancy continuing to rise and the share of the population over 65 growing steadily, the chapter discusses priorities to promote healthy longevity to reduce demands on health and long-term care systems. The remaining chapters provide a comparative overview of the latest data on health status, risk factors and health system performance across the 27 EU member states, 9 EU candidate countries, 3 European Free Trade Association countries and the United Kingdom.

INTERNATIONAL LABOUR ORGANIZATION (ILO)

Mind the AI divide: shaping a global perspective on the future of work. Geneva: International Labour Organization and United Nations 2024; 24 p. ISBN 9789211066524 (PDF). This report, co-authored by the United Nations and the International Labour Organization, addresses the critical issue of the uneven adoption of Artificial Intelligence (AI) and its implications for global equity, fairness, and social justice. Disparities in access to digital infrastructure, advanced technology, quality education, and training are deepening existing inequalities, particularly as the global economy shifts towards AI-driven production and innovation. Less developed countries risk being left behind, exacerbating economic and social divides. The report stresses the importance of targeted and concerted efforts to bridge this digital divide to ensure AI's potential to foster sustainable development and alleviate poverty. It highlights the role of the workplace in AI adoption, where productivity gains and improved working conditions can be achieved with the right conditions, including digital infrastructure, skills, and a culture of social dialogue. Promoting inclusive growth requires proactive strategies to support AI development in disadvantaged regions, enhance digital infrastructure, build AI skills, and ensure good quality jobs along the AI value chain. International collaboration in AI capacity building is crucial to create a more equitable and resilient AI ecosystem, unlocking opportunities for shared prosperity and human advancement worldwide. This report calls for continued collaborative efforts to shape global AI governance, uphold human dignity and labour standards, and expand economic opportunities for all.

WORLD HEALTH ORGANIZATION (WHO)

World malaria report 2024. Addressing inequity in the global malaria response. Geneva: World Health Organization 2024; 318 p. ISBN 978-92-4-010444-0 (electronic version) ISBN 978-92-4-010445-7 (print version). The world malaria report, published annually by the World Health Organization (WHO), offers an in-depth analysis of trends in malaria control and elimination across the globe. This year's report draws on 2023 data from 83 malaria endemic countries and presents trends in malaria morbidity and mortality globally and by region, as well as progress towards the milestones and targets of the WHO Global technical strategy for malaria 2016-2030 (GTS). It tracks investments in malaria programmes and research, advancements and gaps across all intervention areas (including

prevention, diagnosis, treatment and elimination) and biological threats. This year's report introduces, for the first time, a dedicated chapter emphasizing the need for a more inclusive and effective response, with a focus on reaching the populations most vulnerable to malaria. Groups at high risk of a malaria infection include children under five, women and girls, Indigenous Peoples, migrants, persons with disabilities, and people in remote areas with limited healthcare access.

Global report on infection prevention and control 2024. Geneva: World Health Organization 2024; 210 p. ISBN 978-92-4-010398-6 (electronic version) ISBN 978-92-4-010399-3 (print version). This second global report on infection prevention and control (IPC) provides updated evidence on the harm caused to patients and health workers by health care-associated infections (HAIs) and antimicrobial resistance (AMR) and presents an updated global analysis of the implementation of IPC programmes at the national and health care facility levels across all WHO regions. The report highlights also recent landmark political and implementation documents, which indicate directions, actions, indicators and targets for countries and the international IPC community to help them to progress in the implementation and improvement of IPC. The report is the result of a cross-cutting and multidisciplinary effort involving staff at WHO headquarters and in regional offices, as well as key partners in the field of IPC. It includes information and data from many sources, including the scientific literature, WHO global databases, WHO surveys using standardized tools, as well as WHO publications and reports published by other institutions. It also includes a compilation of data and information providing overviews of IPC at the global and regional levels and by country income level, with examples of IPC implementation at both country and facility level. management services that handle antibiotic waste.

Guidance on global monitoring for diabetes prevention and control: framework, indicators and application. Geneva: World Health Organization 2024; 89 p. ISBN 978-92-4-010224-8 (electronic version) ISBN 978-92-4-010225-5 (print version). The Guidance on global monitoring for diabetes prevention and control provides a comprehensive framework to support countries in tracking and managing diabetes prevention, care, and outcomes. This document outlines indicators across 4 domains: health system determinants, service delivery, risk factors, and outcomes/impacts. The guidance helps countries align their monitoring efforts with WHO's global diabetes targets, Global Diabetes Compact, and relevant global NCD targets. The guideline emphasizes the importance of collecting, analysing, and utilizing data to inform policy and resource allocation. Specific indicators measure aspects like access to essential medications, prevalence of key risk factors, and control of blood glucose and blood pressure. Each indicator includes detailed metadata, which outlines definitions, data sources, and methods of estimation, ensuring standardized data collection and reliable comparisons across countries. Through structured monitoring, the framework aids countries in evaluating their diabetes interventions, identifying gaps, and prioritizing resources. The guidance encourages adaptation to national contexts, emphasizing the integration of innovative data collection methods and digital technologies to improve data quality and accessibility.

Ann Ist Super Sanità 2025 | Vol. 61, No. 1: 93
DOI: 10.4415/ANN_25_01_13

ERRATUM

Erratum for: Efficacy of sodium oxybate plus disulfiram for the maintenance of alcohol abstinence in treatment-resistant patients with alcohol use disorder: a multicentre retrospective study

Fabio Caputo, Caterina Trevisan, Teo Vignoli, Angelo Giovanni Icro Maremmani, Franco Montesano, Gianfranco Carboni, Lisa Lungaro, Anna Costanzini, Giacomo Caio, Gianni Testino, Stefano Volpato and Roberto De Giorgio

Ann Ist Super Sanità 2024 | Vol. 60, No. 4: 252-257 DOI: 10.4415/ANN_24_04_03

In the originally published version of this manuscript, an error occurred in the reporting of the dosage of disulfiram (DF) (Methods section, page 253). The correct sentence should read:

"All patients failed to achieve abstinence either with SO (101 patients) or DF (25 patients) alone, so they were treated with oral doses of SO (50-100 mg/kg of body weight, tid), and DF (**200** mg daily) in combination for 12 weeks"

instead of:

"All patients failed to achieve abstinence either with SO (101 patients) or DF (25 patients) alone, so they were treated with oral doses of SO (50-100 mg/kg of body weight, tid), and DF (**250** mg daily) in combination for 12 weeks."

We apologize for this error and any confusion it may have caused.

Instructions to Authors

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

MANUSCRIPT SUBMISSION

Manuscripts should be submitted online to https://annali.iss.it/.
The submission should include:
- cover letter where the authors declare that the manuscript has not been published or submitted for publication elsewhere;
- manuscript;
- tables and figures;
- authors' contributions statement (individual contribution to the manuscript);
- conflict of interest statement (a conflict of interest exists when authors or their institutions have financial or personal relationship with other people or organizations that could inappropriately bias conduct and findings of the study);
- permission to reproduce figures, if appropriate.

Receipt of author's paper will be acknowledged by an e-mail containing an identification number which should be used in future correspondence.
If Artificial intelligence (AI)-assisted technologies were used in the production of the submitted work, both the cover letter and the submitted work clearly state this and provide detail on their use.

NOTE FOR ISS AUTHORS

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

REVIEW PROCEDURE

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

MANUSCRIPT PRESENTATION

Please ensure that your manuscript follows these guidelines.
Manuscripts should be written in good English, as concisely as possible to allow a clear understanding of the text. The title should be followed by the complete name of the authors, their affiliations – only one per author and in the original language – town and country. The name of the Working Group should appear at the end of the by-line; its composition should be reported before the References, names and affiliations of each member are required. The name and address, telephone and e-mail of the corresponding author should also be indicated. On the same page a running head of no more than 40 characters (including spaces) should be included.
Original articles should normally be organized into different sections (*i.e.*: Introduction, Materials and methods, Results, Discussion, Conclusions). In the Methods section a specific paragraph on the adopted statistical analysis should necessarily be included.
Each article should be accompanied by:
- an abstract of about 150 words; the abstract should be structured when required (such as in original articles);
- key words up to a maximum number of five (MeSH headings, whenever possible. Refer to: www.nlm.nih.gov/mesh/meshhome.html).

Tables and figures should be kept to a minimum and be presented only if necessary.
Authors should deal responsibly and effectively with security issues that might be raised by their papers (see: Statement on Scientific Publication and Security *Science* 2003;299:1149).
This journal has adopted the SAGER reporting Guidelines for Sex and Gender Equity in Research.
These guidelines apply to original research articles and review papers. Authors should use the terms sex and gender carefully in order to avoid confusing both terms. Where subjects can also be differentiated by gender (shaped by social and cultural circumstances), the research should be conducted similarly at this additional level of distinction. Where the subjects of research comprise organisms capable of differentiation by sex, the research should be designed and conducted in a way that can reveal sex-related differences in the results, even if these were not initially expected.
Please consult the guidelines (https://researchintegrityjournal.biomedcentral.com/articles/10.1186/s41073-016-0007-6).

Authors are also encouraged to use fair, accurate and respectful language, but preferences can change and vary across groups and individuals and can also evolve overtime. The following guidelines may help in use of a correct terminology in the area of HIV: https://www.cdc.gov/stophivtogether/library/stop-hiv-stigma/fact-sheets/cdc-lsht-stigma-factsheet-language-guide.pdf
https://www.hptn.org/resources/HIVLanguageGuide
https://unesdoc.unesco.org/ark:/48223/pf0000144725
The name of the bioresource (and identifier, if available) which provided samples/data useful for the conduct of the study should be reported in extense, either in the Material and methods section or in the Acknowledgements.

LENGTH OF THE TEXT

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

FORMATTING GUIDELINES

Text

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

Tables and figures

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

REFERENCES

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

Articles in journal

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

Books and chapters in a book

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

Proceedings

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

Technical reports

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

Legislation

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

ments for making findings about medical equivalence. Final rules. Fed Reg. 2006 Mar 1;71(40):10419-33.
The authors should check that each reference cited in the text appears in the reference list and viceversa. References should not include works submitted for publication but not yet accepted or unpublished results, etc. These can be mentioned in the text in parentheses.

CONVENTIONS

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

LICENSES AND AGREEMENTS

Please, contact the Editorial Office for any other information. Annali Editorial Office - Scientific Communication Service
Istituto Superiore di Sanità
Viale Regina Elena, 299 00161 Rome, Italy
Tel.: +39 06 49902945 Fax: +39 06 49902253
E-mail: annali@iss.it
www.iss.it/annali - https://annali.iss.it/