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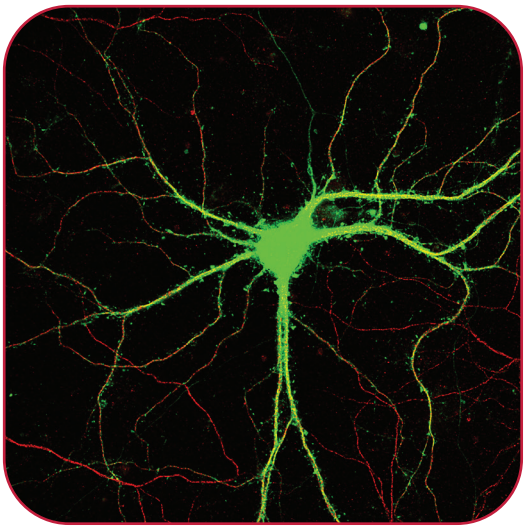
The photograph is a double immunofluorescence of a mouse hippocampal neuron after 21 days in culture infected with a EGFP expressing-recombinant adeno-associated virus (green) and labelled with the neuronal marker MAP2 (red). Image is provided by Cristiana Mollinari, Department of Neuroscience, Istituto Superiore di Sanità, Rome, Italy



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EDITORIAL
Exploitation of immunological approaches for the quality testing of human vaccines to phase out the use of animals

Marilena P. Etna[1], Enrico Alleva[2] and Eliana M. Coccia[1]

[1]*Dipartimento Malattie Infettive, Istituto Superiore di Sanità, Rome, Italy*
[2]*Centro di Riferimento per le Scienze Comportamentali e la Salute Mentale, Istituto Superiore di Sanità, Rome, Italy*

In Europe, the legislation on animals used in biomedical and regulatory research found an important milestone on the Council Directive 86/609/CEE of June 1986 (unfortunately implemented nationally only in 1992) and the more recent text of the Directive 2010/63/EU, which represents a very significant step forward in the protection of animals used in scientific procedures. A nodal issue in those progressive legislative efforts was aimed at reducing the total number of vertebrate nonhuman subjects (and from 2010 of cephalopod molluscs) in experimental studies, while substituting the use animal testing with alternative solutions and procedures.

Indeed, in addition to the use of animal models in fundamental and translational research, it has been estimated that more than 10 million animals per year are used for the development, production and quality assurance of biologicals, namely products that are produced from living organisms or contain components of living organisms, including vaccines, blood components, cells, allergens, tissues, and recombinant proteins [1]. Several concerns have been, thus, raised on a more ethical use of animals employed for scientific purposes leading to different actions worldwide. In this context, National Control Laboratories (NCLs), World Health Organization, European Directorate for the Quality of Medicines and vaccine manufacturers are highly committed in the development of alternative *in vitro* methods complying with the 3Rs Principle, introduced by Russell and Burch in 1959 [2]. Notably, the 3Rs refer to:

a. replacement of the use of animal with *in vitro* technologies or approaches;
b. reduction of animal numbers through appropriate experimental design and statistical evaluation;
c. refinement of husbandry and experimental conditions to minimize animal pain and distress.

In this context, the Istituto Superiore di Sanità (ISS, Italian National Institute of Health) since 1986 has been playing a pivotal role in controlling and monitoring animal experimentation at the national level. Moreover, ISS personnel has been and is constantly involved in educational efforts aiming at fostering the implementation of the 3Rs Principle both within and outside the biomedical community also at international level. Moreover, ISS researchers have been committed in establishing and employing innovative methodological approaches and experimental models alternative to animals, thus becoming a reference institution especially in biomedical research and regulatory activities. As a non-exhaustive example, within the collaborative framework of a European project (VAC2VAC,https://www.imi.europa.eu/projects-results/project-factsheets/vac2vac), ISS was actively involved in the optimization of tests used for the evaluation of pyrogens, fever inducing molecules whose presence or contamination in medicinal products for parenteral use results in unwanted symptoms and noxious side-effects, as fever, myalgia, headache, fatigue, and soreness at the injection site. In particular, the Monocyte Activation Test (MAT, present in the European Pharmacopoeia (Ph. Eur.) as chapter 2.6.30) was applied, as an alternative to the conventional rabbit pyrogen test (RPT, Ph. Eur. 2.6.8), for the pyrogenicity testing of human vaccines against bacterial and viral infections [3, 4]. At variance of RPT, relying on the administration of a product in the rabbit ear vein followed by rectal temperature level measurement to assess any sign of fever, the MAT is carried out with human primary immune cells obtained from blood donation, which

Address for correspondence: Eliana M. Coccia, Dipartimento Malattie Infettive, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy. E-mail: eliana.coccia@iss.it.

are fully equipped to recognize endotoxin and non-endotoxin pyrogens, thus assuring a high-sensitive and species-specific test. For instance, even if the reaction to endotoxins is similar between rabbits and humans, the response to non-endotoxin pyrogens is stronger in humans than rabbits [5].

The successful replacement of the RPT with the MAT for several human vaccines boosted the scientific discussion on the applicability of MAT also for the testing of other biopharmaceuticals [4], thus accomplishing a reduced use of rabbits. This research activity, pioneeringly conducted at ISS, is in line with the vision of the European Pharmacopoeia (Ph. Eur.) Commission to phase out RPT from the Ph. Eur. within 2026 [6] and endorsed ISS as one of the few European NCLs authorized to conduct this not animal test for regulatory purposes. Last but not least, the experience and know-how acquired on this matter allowed the appointment of a delegation of ISS researchers as Italian representatives to the panel of expert for the Ph. Eur. BET (bacterial endotoxin test) working party, involved in the development and modernization of analytical methods for bacterial endotoxin and pyrogen testing as part of the quality control of medicinal products.

Under this umbrella, the BET is currently under discussion at the Ph. Eur. since it is performed with the Limulus Amebocyte Lysate obtained from horseshoe crabs. Indeed, blood sampling required to produce BET reagents causes an estimated dead rate of roughly 150,000 animals per year and exposes the natural *Limulus* population to a high risk of extinction. To accomplish 3Rs principle, a new test for evaluation of endotoxin content is now available and included in the Ph. Eur. (2.6.32), namely the recombinant Factor C test (rFC) and whose reagents are completely synthetic thus, avoiding procedures carried out in *Limulus*.

Moving from the fruitful MAT experience, ISS researchers decided to utilize human primary immune cells to test the immunogenicity of vaccine for human use. Thus, the immunological competences and know-how were exploited for setting a new *in vitro* cell-based model to predict or test vaccine immunogenic potential as alternative non animal method. Indeed, for most of human vaccines, potency test is still conducted through *in vivo* immunization of small laboratory animals followed by lethal challenge with toxin/virus/bacteria or titration of specific antibody in immune sera. Nevertheless, in addition to ethical reasons, animal-based methods are costly, exhibit high inherent variability, poor robustness and limited functional relevance given the physiological inter-species differences in immune responses. Besides causing significant pain, suffering and distress to many sentient animals (i.e., potency testing of viral vaccines requires roughly 80 mice per batch) and showing potency variations of up to 300%, the phylogenetic distance between laboratory animals and humans may limit the predictive value of such *in vivo* potency tests [7]. Considering these differences, the wide portfolio of molecules expressed by pathogens – the so-called pathogen associated molecular patterns (PAMPs), which are included in vaccines as subunit or as component of the inactivated or attenuated version of the pathogen – as well as the exploitation of novel vaccine adjuvants have raised concerns about the reliable applicability of animal-based assays for the testing of the present and forthcoming vaccine formulations.

Interesting data have been recently generated in the context of human peripheral blood mononuclear cells (PBMC) stimulated *in vitro* with the inactivated viral vaccine against the tick-borne encephalitis virus [8] shedding light on the possibility to use the innate immune signature driven by the type I Interferon (IFN) as read-out to monitor vaccine potency or as new correlates of vaccine protection. Being inspired by system vaccinology data revealing the fundamental mechanisms by which the immune system orchestrates protective responses to vaccination, the immunological power of the main immune cells present in blood was analyzed and exploited to facilitate a successful implementation of *in vitro* testing alternatives. By using a selected panel of type I IFN stimulated factors as biomarkers, the high sensitivity of an *in vitro* PBMC model to discriminate between conforming and non-conforming drug substance batches of an anti-TBEV vaccine was demonstrated [8].

Understanding the mechanism through which vaccines interact with the immune system can indeed offer several intriguing cues that could be translated into the quality control testing of vaccines such as the identification of critical microbial components that needs to be retained during the manufacturing process. In addition, the identification of key cellular pathways engaged by the interaction of pathogen structures with the blood immune cells might support the design and/or the selection of potent immunogenic vaccine candidates during the research and development phase.

In conclusion, human PBMC-based assays are promising and malleable experimental setting that can be successfully implemented as *in vitro* testing alternatives given their intrinsic and dynamic biological properties ranging from the capacity to sense all PAMPs, to predict the immunostimulatory potentials as well as possible bias related to inflammatory nature of vaccine formulations.

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COMMENTARY

Tackling the challenge of cardiovascular diseases and diabetes across Europe: a joint action by more than 300 public health professionals

Benedetta Armocida[1], Beatrice Formenti[2], Marco Silano[1], Albert Aszalos[3], Hector Bueno[4], Mounia Elyamani[5], Ane Fullaondo Zabala[6], Matilde Leonardi[7], Jaana Lindstrom[8], Karolina Michalak[9], Bernardino Morillo[10], Michal Nowicki[9], Denis Opresnik[11], Luigi Palmieri[1], Roberta Papa[12], Markku Peltonen[8], Helena Safadi[3], Hanna Shchetynina[13], Natalia Skogberg[8], Hanna Tolonen[8], Edwin Wouters[14], Jelka Zaletel[11] and Graziano Onder[2], on behalf of the JACARDI Consortium

[1]*Dipartimento Malattie Cardiovascolari, Endocrino-Metaboliche e Invecchiamento, Istituto Superiore di Sanità, Rome, Italy*
[2]*Fondazione Policlinico Gemelli, Rome, Italy*
[3]*Gottsegen National Cardiovascular Center, Budapest, Hungary*
[4]*Centro Nacional de Investigaciones Cardiovasculares (CNIC), Hospital Universitario 12 de Octubre, Madrid, Spain*
[5]*Santé Publique France, Paris, France*
[6]*Biosistemak Institute for Health System Research, Barakaldo, Spain*
[7]*Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy*
[8]*Finnish Institute for Health and Welfare, Helsinki, Finland*
[9]*Poznan University of Medical Sciences, PUMS, Poznan, Poland*
[10]*Consejería de Salud y Servicios Sociales of Junta Extremadura (JUNTAEX), Merida, Spain*
[11]*National Institute of Public Health Slovenia and University Medical Center, Ljubljana, Slovenia*
[12]*Agenzia Regionale Sanitaria, Regione Marche, Ancona, Italy*
[13]*Public Health Center of the MOH of Ukraine, Kyiv, Ukraine*
[14]*University of Antwerp, Antwerp, Belgium*

Abstract
Cardiovascular diseases (CVD) and diabetes pose significant health challenges in Europe, affecting millions and burdening healthcare systems. The recent EU4Health Programme places reducing the burden of non-communicable diseases (NCD) at the forefront, through a Joint Action focused on CVD and diabetes (JACARDI, Joint Action on CARdiovascular diseases and DIabetes). This initiative unites 21 European countries, including Ukraine, and over 300 experts. Employing an innovative approach and standardised methodology, JACARDI implements 142 pilot projects covering the entire "patient" journey. Particular focus will be given to improvement of data availability and quality. Additionally, JACARDI will emphasise transversal and intersectional aspects, such as health equity, determinants of health, and social, cultural, and ethnic diversity, while pioneering gender-transformative leadership. Committed to evidence-based interventions, JACARDI aims to harmonise strategies and disseminate knowledge for enhanced CVD and diabetes prevention and management. The goal is to identify effective strategies for wider implementation, fostering cross-national collaboration and fortifying Europe's health resilience.

Key words
- cardiovascular disease
- diabetes
- public health
- EU4health

Address for correspondence: Beatrice Formenti, Università Cattolica del Sacro Cuore, Largo Francesco Vito 1, 00168 Rome, Italy. E-mail: beatrice.formenti@guest.policlinicogemelli.it.

INTRODUCTION

Cardiovascular diseases (CVD) claim millions of lives prematurely on a global scale each year [1]. Within the European Union (EU) almost 63 million people live with CVD, positioning it also as the first cause of death in the region [2]. Simultaneously, diabetes remains a significant public health concern, with the prevalence increased worldwide, and the number of adults with diabetes almost doubled over the last decade in Europe, reaching 32.3 million in 2019 [3, 4]. CVD and diabetes undermine people's health and well-being, and the sustainability of healthcare systems globally and across EU. These chronic conditions have extensive and profound implications, affecting the broader social and economic landscape. CVD and diabetes place a substantial burden on patients, their families, and informal caregivers, affecting people's autonomy in everyday activities and limiting their ability to fully participate in daily work, resulting in productivity losses and undermining economic and societal development [5].

Tackling the substantial global challenge of CVD and diabetes requires a unified and comprehensive response across Europe. This demands an inclusive approach spanning the entire healthcare system and lifespan, aligned with a "health in all policies" framework. European public health requires strong political backing to restructure care pathways, emphasizing integrated services, prevention measures, digitalization, and enhanced patient experiences and outcomes. The recent EU4Health Programme [6] places reducing the burden of non-communicable diseases (NCD) at the forefront, employing a combination of policy initiatives, research, and concrete interventions to bolster health promotion and NCD management.

ADDED VALUES OF JACARDI

In alignment with this overarching goal, a Join Action of European Union Member States (MS) focused on the prevention and management of CVD and diabetes was launched to bridge the gaps and further strengthening the collective efforts on these conditions at a European level. The Joint Action on CVD and diabetes, named JACARDI (Joint Action on CARdiovascular diseases and Diabetes), started in November 2023, with the objective of enhancing the implementation of evidence-based interventions, harmonising strategies, and fostering the dissemination of knowledge and resources, through collaborative endeavours and shared best practices across MS. In doing so, it plays a pivotal role in promoting a more equitable and effective approach to CVD and diabetes prevention and management across the EU.

JACARDI brings together 21 European countries, including Ukraine, and more than 300 public health experts from 76 institutions, to enhance and promote the implementation of (cross-sectional) best practices, and pilot testing of innovative practices in MS. Several key aspects of JACARDI will make it a unique project in the European scenario and internationally.

First, 142 pilot actions are planned in 18 European countries. JACARDI focus is not confined to a single aspect of CVD and diabetes care; rather, it encompasses the whole "patient" journey (*Figure 1*). The latter starts from improving health literacy and increasing awareness of CVD and diabetes to reach general and target populations. It progresses through primary prevention and screening of CVD and diabetes among high-risk populations. It then advances to address patients and their care providers, through improved service pathways and (self-)management, which includes the integration of digital tools. The journey concludes by supporting inclusions maintenance and participation in employment sector of people with these disorders taken as case model for all NCD. Additionally, it transversally covers the improvement of data availability and quality. By implementing these pilot actions, JACARDI is expected to reach and improve the "patient" journey health and well-being of millions of individuals in Europe.

Second, JACARDI targets the uneven distribution of CVD and diabetes, by prioritizing transversal and intersectional aspects such as health equity, determinants of health, and social, cultural, and ethnic diversity in the pilots' actions. The pilots will receive support in understanding and addressing the underlying mechanisms of inequalities by an explanatory framework to identify key social dimensions of inequalities in CVD and diabetes, covering exposure to risk factors, limitations in care access, and social consequences of these conditions.

Third, JACARDI pioneers gender-transformative leadership, driving positive community change with vision, empathy, and strategic thinking. This approach advocates gender equity in public health leadership, addressing systemic barriers hindering women's advancement [7]. It emphasizes deep-rooted change, recognizes leadership across public health, and shatters gender stereotypes to enable women's leadership, without conforming to patriarchal norms [7]. By nurturing female role models and mentors, JACARDI sets a new leadership paradigm, where this collaborative model transcends competition, emphasizing diverse perspectives, collective efforts, and inclusive governance. JACARDI's legacy lies in empowering the next generation, leaving healthier communities through effective public health solutions.

Fourth, the commitment and active involvement of Ukraine's Ministry of Health's Public Health Center in JACARDI are noteworthy. The ongoing conflict that emerged in February 2022 has undeniably posed significant challenges to Ukraine's healthcare system. This is particularly critical in a country where NCD contribute to 91% of total deaths [8]. JACARDI presents an opportunity for Ukraine to implement pilots benefiting between 500 and 2,500 people, focusing on health literacy among patients, and personal/individual level screening and risk assessment.

CONCLUSIONS

The roadmaps resulting from JACARDI pilot implementation will facilitate the scale-up of good practices defined by JACARDI at a regional/national level or their replication in other EU countries. The widespread implementation of 142 pilots across 18 European countries ensures comprehensive action and geographical coverage. Additionally, the employment of a

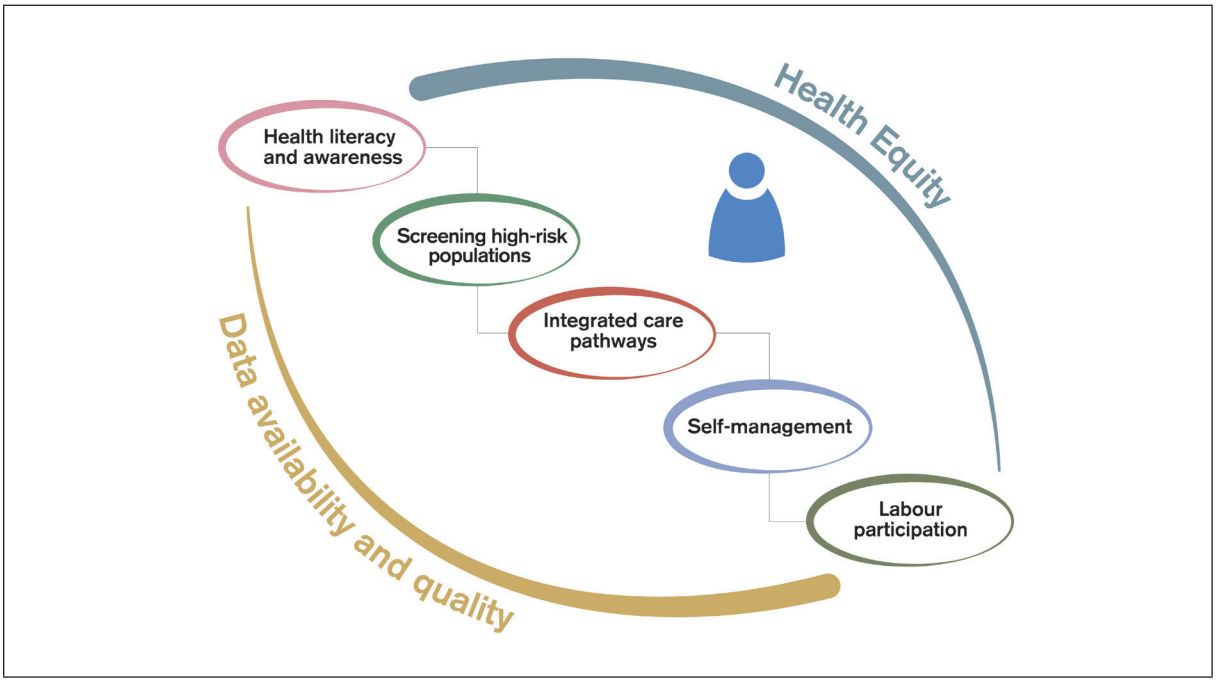

Figure 1
"Patient" journey: addressing healthy individuals and those at risk of developing CVD/DM, progressing to individuals diagnosed with CVD/DM at risk of disease progress and multimorbidity. This encompasses both individual and population levels, within different settings.
CVD: cardiovascular disease; DM: diabetes mellitus.

standardised methodology for the implementation and assessment of pilots supports the adoption and adaptation of pilot experiences and successful strategies in larger settings or contexts throughout the EU.

JACARDI unites over 300 public health experts from all over Europe and beyond, sharing a common vision: to jointly tackle the pervasive burden of CVD and diabetes. They actively advocate for and promote the outlined priorities, all in pursuit of attaining the utmost level of health and well-being for both individuals and society as a whole. Furthermore, they strive to construct a more sustainable, resilient, and equitable public health framework, reflecting their dedication to enhancing the health for all in Europe.

Authors' contributions

BA, BF, and GO conceptualised and drafted the Commentary. All Authors contributed to reviewing and finalising the Commentary. All Authors approved the final version of the manuscript.

Conflict of interest statement

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COMMENTARY
AI will not give us precision medicine

Lorenzo Farina

Dipartimento di Ingegneria Informatica Automatica e Gestionale, Sapienza Università di Roma, Rome, Italy

Abstract
The completion of human DNA sequencing in the early 2000s initially generated widespread excitement and hope that it would revolutionize medicine. Over time, however, it revealed major limitations due to a lack of understanding of the highly complex genotype-phenotype pathway. Precision medicine has emerged as a response to these biotechnological innovations, tailoring treatments based on an array of new molecular and clinical "omics" data. However, the large volume and heterogeneity of data available today requires the use of dedicated and highly efficient computational analyses. Widely used today are artificial intelligence techniques (such as machine learning) based on artificial neural networks, i.e., a mathematical model of how biological neurons work. Here, we show that artificial neural networks have nothing to do with biology, although their popularity is largely due to their alleged ability to simulate the human brain. Furthermore, we argue that the analysis of large molecular datasets cannot be left to the computational side alone, i.e., to be exclusively data-driven, but on the contrary must meet the challenge of integrating data and expertise, of getting clinicians and data analysts to work together to take into account the absolute and ineradicable uniqueness of each patient's characteristics.

Key words
- artificial intelligence
- precision medicine
- neural networks
- machine learning
- phenotype
- genotype

INTRODUCTION

In the early 2000s, immediately following the completion of human DNA sequencing, all of science that matters was swept up in a tumultuous and disjointed wave of enthusiasm and optimism. And we're not talking about a few extravagant and solitary thinkers in white coats, locked up in an ivory tower. We are talking about media in all the languages of the world, we are talking about high personalities of world politics and science. Almost everyone was convinced that: "We are learning the language in which God created life" [1] or that: "The genome project will revolutionize the diagnosis, prevention and treatment of most, if not all, human diseases" [1] and that: "Over the longer term, perhaps in another 15 or 20 years, we will see a complete transformation of therapeutic medicine" [2]. And then the front pages of newspapers and magazines around the world. For example, on June 27, 2000, the *New York Times* ran a full-page headline: "Genetic code of human life is cracked by scientists" and commented: "an achievement that represents a pinnacle of human self-knowledge" [3].

The Human Genome Project has faced many limitations and very serious criticisms. One of the main weaknesses was certainly that it focused mainly on the DNA sequence, initially neglecting the importance of non-coding regions and complex interactions between genes. In addition, genetic variability was underestimated because the sample of individuals used in the project did not have a composition that could adequately represent the vast global genetic diversity. The biggest disappointment of the Human Genome Project was the lack of practical solutions for the treatment of complex diseases, because the relationship between genotype and phenotype was much more complex than expected, and one of the main goals, namely, to identify the molecular causes of diseases specific to each individual, was not achieved. Precision medicine was born to address this critical issue in modern medicine.

THE DREAM OF PRECISION MEDICINE

Precision medicine originated in the field of oncology in the 1990s, when the first targeted therapies emerged that focused on patient-specific genetic mutations associated with specific tumor types. However, the term "precision medicine" has become widely used and recognized in recent years, in parallel with rapid advances in DNA sequencing technologies and molecular biology. Precision medicine has demonstrated success in several fields, including oncology, where the identification of specific mutations allows the development of targeted therapies.

Address for correspondence: Lorenzo Farina, Dipartimento di Ingegneria Informatica Automatica e Gestionale, Sapienza Università di Roma, Via Ariosto 25, 00185 Rome, Italy. E-mail: lorenzo.farina@uniroma1.it.

In recent years, thanks to the explosion of molecular data, it has become clear that most diseases are complex, i.e., multifactorial. For example, tumors, diabetes, autoimmune or cardiovascular diseases are unfortunately common and have many interdependent "causes" related to the patient's history. These diseases develop slowly over years, if not decades, and are often resistant to treatment. They are "long-term" diseases that result from a combination of factors such as inherited genetic predisposition, poor diet, comorbidities, environmental stress, and the aging of our body's organs and immune defenses.

The concept behind "precision medicine" is the molecular and clinical characterization of the complex uniqueness of each disease, such as cancer. President Barack Obama expressed the idea that precision medicine offers the right treatment, at the right time, to the right person, every time [4]. Despite the disappointments and difficulties, the dream of precision medicine is still alive. In fact, in addition to DNA sequence, we now have access to molecular measurements that allow us to see every detail of a diseased cell. This "big data" varies from individual to individual and from cell to cell, and includes data on RNA, proteins, protein-DNA interactions, bacteria, and other factors. This dizzying array of measurements is called "omics" and represents an immense quantitative and qualitative leap toward complexity. Using efficient algorithms and increasingly powerful computing resources, the goal is to extract useful information to precisely define a patient's uniqueness and tailor therapy to the greatest extent possible.

More than twenty years have passed, and despite the availability of large heterogeneous amounts of clinical, physiological, and molecular data, the long-awaited revolution has not yet manifested itself. Complex diseases remain an unsolved challenge, and the peak of knowledge achieved so far seems to be only the top of a modest hill [5]. Curiously, the great merit of the genome project seems to be that it has greatly increased the awareness of our ignorance about the mechanisms of life and disease. However, this should not be seen as a weakness; the importance of this collective enterprise cannot be underestimated, as demonstrated by the new targeted therapies able to attack proteins misfolded by genetic mutations. But we must never forget that there is still a very, very long way to go compared to what was thought in the past.

However, a potentially revolutionary turning point has been reached: we have become aware of the complexity of disease and the large amount and heterogeneity of clinical and molecular data available. Transforming this data into useful information for therapies requires a great deal of computational power from modern computer systems capable of processing data efficiently and adaptively. The key words are therefore: complexity, volume, heterogeneity, and computing power. It is also important to combine the expertise of clinical and data analysis experts to achieve the best results. In this context, artificial intelligence (AI) seems to be the perfect tool to tackle and tame the complexity of diseases. AI has already proven its effectiveness in various fields, such as generating text like ChatGPT or recognizing facial expressions in photos. This computational tool is based on the concept of an "artificial neural network", which is able to "learn" and update itself as new data becomes available, thus proposing customized solutions based on dedicated algorithms and accurate analysis. Just what we need. Really?

THE PROMISES OF ARTIFICIAL INTELLIGENCE

If we take any blog, any newspaper, any more or less specialized magazine, even the scientific ones of the sector, any sector, even medical and biological, we find nothing but articles about articles, projects about projects, talking about the wonders of "artificial intelligence", of new start-ups that are making stellar profits and are desperately looking for experts to hire on the fly. We seem to be in the midst of a gold rush that spares no one. More than any other sector, medicine has been fascinated by so-called "artificial intelligence" in recent years, precisely because of the extreme need to manage the immense amounts of data that are now available even in medium-sized hospitals.

Technological advances in data generation and management – especially in the biomedical field – have been developing at an accelerating pace in recent years, and the trend shows no signs of abating. The term "artificial intelligence" itself has had mixed fortunes over the last 70 years or so, with different characteristics, goals, and results attributed to it, sometimes with very different nuances. Today, it is common to use the term "artificial intelligence" to refer to any computer system that is capable of making automated inferences about the real world based on the data available to it. This is why we speak of "machine learning", i.e., the ability to "learn" to perform tasks from examples provided by humans, such as a self-driving car or translating a language simultaneously. As you know, the applications are endless, and the list grows dramatically every day.

THE NAME OF THE ROSE

In the field of precision medicine, AI can become a very serious obstacle rather than a brilliant solution. How is this possible? To understand the key issue, let's hear what Roger Shank, one of the leading AI theorists, professor of computer science at Yale and Stanford, who recently passed away, has to say. In an interview with CNN (https://youtu.be/PVb0OkRxRfc), we have the opportunity to see Professor Shank suggest an apparent paradox to the interviewer: "What if instead of calling it *artificial intelligence*, we call it a *computer program*?". The interviewer is surprised, disconcerted and confused by this statement, but immediately recovers and continues: "We have been experiencing in recent years an extraordinary process of advancement of technologies and information technology. Don't you think it's time for AI now?". Shank smiles sardonically and adds, "Well, then we'll talk about very fast calculation. But making calculations extremely quickly doesn't tell us anything about intelligence, it tells us that it could be useful to us".

The names we give to things are very important because they define their essence and, above all, they

evoke the context in which they are placed and from which they can refer to other meanings that complete them, specify them, or extend them in new directions. In other words, names create expectations, hidden expectations. It is no coincidence that the name of a pharmaceutical product often suggests its efficacy. That's why using the term "intelligence" for something that is not "intelligence" is certainly a bad idea, but above all a very dangerous idea, especially in precision medicine.

LEARNING NEURONS

New York, 1958. A mild summer, but one of great accomplishment and even greater promise. President Eisenhower signed legislation creating the National Aeronautics and Space Administration (NASA). Jack Kilby and Robert Noyce introduced the world to the first integrated circuit, the basic building block of all electronic devices. In short, an exciting summer for the history of technology, if we forget another nuclear test in the Pacific. But that same summer, another news item, perhaps the most "explosive" of all, appeared in an internal newspaper of the Aeronautical Laboratories of Cornell University, New York. The entire summer issue was devoted to the forbidden dream of mankind: "The Design of an Intelligent Automaton" [6], signed by a senior psychologist in the laboratory who would become director of the Cognitive Systems Research Program the following year, Dr. Frank Rosenblatt, with funding from the US Navy. It is worth reading the subtitle that modestly presents the "Perceptron" to the public, viz: "A machine that senses, recognizes, remembers, and responds like the human mind". Not bad, no doubt. The echo in the general press was surprisingly modest, with the *New York Times* devoting a very brief blurb to the subject with a disenchanted air [7]: "NEW NAVY DEVICE LEARNS BY DOING". Psychologist shows embryo of computer designed to read and grow wiser. The Navy revealed the embryo of an electronic computer today that it expects will be able to walk, talk, see, write, reproduce itself and be conscious of its existence. The embryo – the Weather Bureau's $2,000,000 "704" computer – learned to differentiate between right and left after fifty attempts in the Navy's demonstration for newsmen. The service said it would use this principle to build the first of its Perceptron thinking machines that will be able to read and write. It is expected to be finished in about a year at a cost of $100,000".

What is Rosenblatt's "perceptron"? It is the physical realization (on a large computer) of a mathematical model of a human neuron proposed by Warren S. McCulloch, a neuroscientist, and Walter Pitts, a mathematical logician. The two American scientists published their research in 1943 [8] and the starting point is stated immediately, in the first paragraph of the abstract: "Because of the all-or-none character of nervous activity, neural events and the relations among them can be treated by means of propositional logic".

The authors, based on the knowledge of the physiology of neurons at that time, assume that a neuron has a purely binary activity, and that therefore any event involving neurons and the relations between them can be attributed to propositional logic, that is, to the calculation of binary functions and operators. In this way, the behavior of the neuron is perfectly defined in a formal way by a law that operates on binary numbers, just like a computer. The analogy between neurons and computers is now thrown into the scientific arena.

THE MATHEMATICAL MODEL

The McCulloch and Pitts mathematical model represents the neuron as the basic element for processing data, a kind of computational atom. In fact, artificial neurons are considered as elementary units that receive one or more inputs (representing the excitatory and inhibitory electrical signals on the neuron's dendrites) that are processed to produce an output at the axon terminals (representing the transmitted electrical signal). Each neuron communicates with the others through the axon's ion channels. These channels consist of tiny holes that open or close depending on the voltage and concentration of substances in the regions inside and outside the cell, modulating the electrical signals in transit. The electrical activity of the neuron is typically composed of sequences of very short activations (about a millisecond) called "spikes" or "pulses", and this explains the interpretation in binary terms of all or nothing (0 and 1). It is interesting to note how this neuron model fits perfectly with the "computational" view of the brain, which has elementary functions (inputs to the neuron that are "processed" and then transmitted to others) and the ability to connect to any number of other neurons to perform complex operations between "input" and "output", that is, between the raw signal and the processed one for some purpose, such as "seeing".

The brain, therefore, according to McCulloch and Pitts, would be nothing more than a disproportionately deep neural network, with an immense number of neurons (a hundred of billions) and an astronomical number of connections (about 10,000 per neuron and therefore a total of a quadrillion) and, therefore, the creation of an automaton that speaks, writes, watches "Game of Thrones", waits for winter on the barrier, and is self-conscious is only a matter of the availability of enough time and resources. The processing of a single artificial neuron is very simple: the input signals can be "amplified" or "attenuated" by multiplying them by appropriate values (called weights) and then summing them. This value is then compared with an internal threshold (or a linear function): if it exceeds the threshold, the output is activated (possibly producing a "spike"), otherwise it remains inactive. To fully define an artificial neuron, I must therefore assign a "weight" to each incoming signal and a threshold for each neuron, which defines the activation state of the output, and which is then passed on to the next neuron.

Simply put, McCulloch and Pitts paved the way for the idea that a neuron is a piece of computer that works on binary quantities, namely 0 and 1, and that its functions are defined by how these quantities are manipulated and transmitted to other neurons. On the other hand, the brain thinks, but the brain is made up of interconnected neurons, and neurons are binary functions that can be easily achieved with an integrated circuit or, less easily, with a dedicated computer. *Ergo*,

a computational system of "artificial neurons", the legitimate child of the "perceptron" of which Rosenblatt speaks, can think, dance on Tik Tok, take selfies, write, be conscious. Easy, isn't it?

Not at all. It is not enough to construct a vague approximation and mathematical brutalization of a phenomenon of frightening complexity that has emerged after two billion years of evolution and that has little or nothing to do with the "perceptron", and then to assign to this puppet the properties of the original. It would be like drawing a sketch of a child and then thinking that the drawing can walk because it looks like the child. A tragic error, perhaps tragicomic, if it weren't for the fact that today, more than sixty years after that mild New York summer, the world is again in the grip of the same frenzy, for the same reason and without any substantial novelty, apart from speed and number of connected neurons. But if the difference between artificial and real is so enormous, how did we come to believe that such a simplified and stylized representation could really be useful?

IF THIS IS A NEURON

In fact, McCulloch and Pitts' methodological approach is entirely consistent and typical of modern mathematical modeling. Their success is therefore not surprising. In fact, it must be remembered that scientific activity is characterized by its ability to "neglect" details in order to grasp the essence of the phenomenon [9], which would then be the famous "difalcare gli impedimenti" (remove the obstacles) [10] of Galileo. But the fundamental point remains that among the many simplifications and distortions of reality, it is necessary to find the one that works or is useful for the purposes that interest us.

Unfortunately, there is still a myth in the world that any simplification of reality, as long as it is "mathematical" and seasoned with some vague knowledge of biology, is always enough to do something good. Mathematics in itself would be a guarantee of success. It's not always like that, it's never like that in biology. The idea is always the same: mathematics "captures the essential", even if this "essential" is more like a unicorn in a world where the abstract idea of "tumor" has no place in the Platonic hyperuranium. If in physics and engineering the concept of approximation has had a great and undeniable success, the same cannot be said for biology, where the detail and the essential are not easily separable and where diversity is the heart of life: not the universal, but the particular.

An obvious example is the basic assumption of the McCulloch and Pitts model, which, starting from the empirical observation of an all-or-nothing neural activity, unhesitatingly follows that the processing of the electrical signal takes place as if it were purely logical or binary operations. It is a gigantic *non sequitur*, because electrical signals travel from neuron to neuron through "pulse trains", short sequences of "spikes" or activations, and even today we do not know for sure how the real neuron encodes the information in this pulse train [11]. There are many hypotheses, the most used is that the number of spikes is counted in a certain range, but we still do not even know how the brain uses these impulse trains to manipulate the information that passes through it. But one thing is certain. The idea of the "artificial neuron" as the basic element of the brain, like quarks for elementary particles, is dead and buried, and so are all its legitimate and illegitimate children: real neurons do not speak in binary, and the McCulloch and Pitts mathematical model contains no trace of the "pulse trains" that carry information. No small matter: the encoding process is not present in the neuron model. In reality there is (the binary one), but it is wrong. The incredible thing is that even in the most modern versions of "neural networks" there is no trace of impulses. And then tell me if this is a neuron.

FICTION OR REALITY?

Let's see why an artificial "neuron" has nothing to do with a biological neuron, and therefore has no rational connection with any form of intelligence you may have in mind. In fact, there are many huge differences between the biological neuron and the artificial neuron, even in its most modern form. Let's look at some of them to get an idea of what we're talking about and the sidereal distance between two concepts that share the same name and are said to have similar potential. Here they are:

- the number of neurons and connections in a brain is physically impossible with current technology, and the connections allowed in modern networks are very few compared to the real ones by several orders of magnitude;
- as mentioned above, real neurons encode information in the form of pulse trains;
- the structure of the possible connections of the artificial network does not change over time. That is, new connections are not created or destroyed. The artificial neural network therefore does not have one of the most biologically relevant property of the human brain, the ability to continuously create and destroy new connections during its lifetime;
- increasing the number of layers does not generally improve performance for a given task. This means that, in principle, an artificial neural network of greater complexity behaves worse than a simpler one, in clear contradiction to the observation that real human networks are infinitely more connected than artificial ones and seem to perform much better in many tasks;
- artificial networks have to be programmed for each individual task, they do not program themselves, but require an external operator who organizes the phases leading to the choice of the free parameters of the network, i.e., the weights of the connections and the values characterizing the internal basic function (a threshold in the simplest case);
- one of the most used algorithms for programming a neural network is called "backpropagation". This algorithm has no chance of working in a real brain because there is no biological trace (yet) of it;
- artificial neural networks have no memory, nor elements to store "facts" and "events" of the past, and their behavior is linked only to what is contained in the data used for their programming;

- we should always remember that even if an artificial network behaves in a way that "resembles" human behavior in narrower but significant tasks, such as learning a language, similarity is not a criterion of reality;
- each layer of artificial neurons is programmed separately, rather than having a complete network that works asynchronously, as in the real brain;
- the layers of artificial neural networks are only connected to adjacent layers, while the structure of a brain is not organized in this way but presents neurons that can be connected to a very variable number of other neurons. Experimentally, only a few neurons are extremely well connected, while most have few connections;
- real neural networks are extremely robust and resistant to malfunction and are able to repair themselves even after extensive damage. This is absolutely not the case with artificial neural networks, which must have the state of the system before the malfunction in order to restart once the human programmer has repaired the damage;
- programmed artificial networks can be "copied" and transported to another network, even with a completely different technology, where it will produce exactly the same results. Obviously, we cannot do such experiments on humans, but we know very well that each brain is profoundly different from the other, and for the same inputs, the output can be very different;
- artificial neural networks do not need to sleep, they do not get bored, they can remain without doing anything indefinitely, they can be turned off and on again;
- the white matter of the brain plays an active role in modulating the connections between neurons and is completely absent in an artificial network.

The list goes on, but I think that's enough. The discoverer of DNA, Sir Francis Crick, writes about this [12]: "Most of these neural "models", are not therefore really models at all, because they do not correspond sufficiently closely to the real thing".

THE UNIQUE AND ITS PROPERTIES

In the medicine of "unique cases", also called "personalized medicine", which uses the enormous masses of biomolecular data, the limits of what artificial intelligence can do are exceeded and relying on some form of "learning" from "analogous" cases, which by definition do not exist, would not only be a gamble, but a real mistake, both conceptually and practically, with very serious consequences. What does an interdisciplinary group do? Well, it behaves in exactly the opposite way to an automatic "learning" neural network, because instead of moving on the "descriptive" level of the disease in question, the discussion will focus on the "causes", that is, on the underlying mechanisms that could support the maintenance of the pathological condition. But what if we used a "machine learning neural network" to build a multidisciplinary group *in silico*, i.e., computerized? The problem is that this digital group could never be replaced by a learning machine, not because of "the pride of human intelligence" or "the irreducible intuition of doctors and statisticians", but for a much more down-to-earth reason: there is nothing to learn from the decisions of a multidisciplinary group. I repeat, there is nothing to learn. It seems strange, I know, but if you think about it, it is obvious that to "learn" according to a machine, you need many "similar" cases to "train" artificial neurons. But here the cases are all different! In fact, they ended up in the discussion of the multidisciplinary group for that very reason. So here is the bad news for fans of the latest technological innovation: "Machine learning" is not useful (in fact, it is harmful) in precision medicine, that is, highly personalized medicine that uses large amounts of data, and therefore cannot be of any help to the members of the multidisciplinary group, who will necessarily have to do without it. Instead, they need powerful data integration tools to have a common view of the patient's micro and macro characteristics and, above all, the ability to integrate their skills, that is, to have a common view of the interpretation to be given to the data, which would then be precisely the information that can be extracted from group work.

CONCLUSIONS

The problem considered here is that if we believe that "artificial neural networks" are particularly efficient data analysis tools that can often classify satisfactorily for selected applications, such as recognizing smiling faces or simultaneously translating simple conversations, then we are in the real world, because things will work more or less well if the data we have is "good" (i.e. relevant) and if the algorithm is effective at automatically distinguishing what is relevant from what is not, using the contextual information that the programmer will provide. If, on the other hand, we think that the capabilities of a "neural network" derive precisely from the term "neural", i.e. from its (false) ability to emulate the human neuron and its connections, then we are in the world of fantasy, where anything is possible. Unfortunately, the reason for the great success in the press and in public opinion in general is exclusively due to the fascination that the idea of a machine that thinks and perhaps becomes conscious exerts on us. If this seems exaggerated, just think of the Google employee who said that he was convinced that the artificial intelligence system they had built had developed a consciousness. Think about it: if the term "neural" were not used, could we ever associate the "neural network" with intelligence? I don't think so. What if it were called a "distributed adaptive nonlinear approximation network"? With a name like that, no one would call it smart. Maybe boring, but not smart. Sir Francis Crick writes about this [12]: "How has this curious situation arisen? Apart from a few enthusiasts, most theorists do not believe that, for example, children really learn to speak using a single, simple back-prop network inside their heads. Why, then, are such models considered not only useful, but also exciting?"

Here is his burning observation, but full of healthy realism, on the reasons "hidden" from the general public [12]: "It is not enough to do something that works. How much better if it can be shown to embody some powerful general principle for handling information, expressible in a deep mathematical form, if only to give an

air of intellectual respectability to an otherwise rather low-brow enterprise".

Birds have always inspired humans to fly, but today's airplanes don't look like metal skeletons flapping synthetic-fiber wings and breathing, eating, defecating, and reproducing on their own. They do much less, of course, but what they do (fly) they do very well, and much better than the birds that inspired them. Inspiration is fine, of course, but anthropomorphizing "deep neural networks" will only lead us to misunderstand what artificial intelligence can really do. Do you want to call airplanes "artificial birds"?

The impact on precision medicine of a purely "computational" view of human knowledge can be devastating, and we are already seeing signs of it. Of course, the issue is not whether or not to use these so-called "artificial intelligence" algorithms, but to be fully aware that, as computer scientist Cathy O' Neill says in her Ted Talk entitled "The era of blind trust in algorithms must end" (https://youtu.be/_2u_eHHzRto): "Algorithms are opinions embedded in code. It's really different from what you think most people think of algorithms. They think algorithms are objective and true and scientific. That's a marketing trick. It's also a marketing trick to intimidate you with algorithms, to make you trust and fear algorithms because you trust and fear mathematics. A lot can go wrong when we put blind faith in big data".

One cannot think of using the results of an algorithm without knowing how it was built, on what hypotheses, on what data, and on what vision of the problem that interests us. It is easy to separate the world of data analysis, of more or less intelligent algorithms, from that of the doctor, of the clinician, who must use these algorithms to diagnose, to prognosticate, to treat. The most important thing we have is at stake – our health – and we cannot afford to make mistakes, much less go wrong.

Conflict of interest statement

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Smoking cessation in the management of Chronic Obstructive Pulmonary Disease (COPD): narrative review and recommendations

Rosastella Principe[1], Vincenzo Zagà[2,*], Paola Martucci[3], Loreta Di Michele[4], Carlo Barbetta[5], Antonella Serafini[6], Maria Sofia Cattaruzza[7] and Claudia Giacomozzi[8]

[1]*Ambulatorio Pneumologico e Centro Antifumo, Clinica UPMC Salvator Mundi Internazionale, Rome, Italy*
[2]*Centro Antifumo Presidio di Pneumotisiologia, AUSL Bologna, Bologna, Italy*
[3]*Unità Operativa Complessa di Interventistica Pneumologica, Centro per il Trattamento del Tabagismo, Ospedale Cardarelli, Naples, Italy*
[4]*Unità di Terapia delle Interstiziopatie Polmonari, Ospedale San Camillo Forlanini, Rome, Italy*
[5]*Unità Operativa Semplice di Pneumologia, ULSS4 Veneto Orientale, San Donà di Piave, Venice, Italy*
[6]*Centro Antifumo Struttura Complessa Pneumologia Ospedale Civile di Imperia, Imperia, Italy*
[7]*Dipartimento di Salute Pubblica e Malattie Infettive, Sapienza Università di Roma, Rome, Italy.*
[8]*Dipartimento di Malattie Cardiovascolari, Endocrino-Metaboliche e Invecchiamento, Istituto Superiore di Sanità, Rome, Italy*
**retired*

Abstract

Background. The percentage of smokers who develop COPD (Chronic Obstructive Pulmonary Disease) peaks at 40-50% in most recent publications.

Summary. Tobacco smoke remains the main cause of COPD, though smoking-related limitation of the flow is rather subjective. For patients who keep on smoking, general practitioners (GPs) and pulmonologists should be able to offer smoking cessation programs as an important part of COPD treatment. This narrative article aims to provide the scientific basis to help healthcare professionals develop this therapy; with this aim in mind, the authors have analyzed the most recent literature.

Key messages. Only 3% of smokers who try to quit without availing themselves of any support succeed. Effective smoking cessation methods are counselling and pharmacotherapy, which, combined together, are credited with a 24% success rate. Although there are no therapeutic novelties with strong scientific evidence for smoking cessation, it is however advisable to keep the literature updated to new devices and new digital therapies.

Key words
- COPD
- smoking cessation
- counseling

INTRODUCTION

Tobacco smoking is one of the most serious, frequently avoidable, non-infectious cause of death in the world. According to data released by the World Health Organization (WHO), there are 1.3 billion smokers in the world and more than 8 million deaths from smoking-related diseases every year [1]. About 50% of cigarettes smokers die prematurely; the loss of lifespan due to tobacco-related diseases compared to non-smokers is about ten years. This appears to be caused by a failure to implement effective primary and secondary tobacco prevention programs [2, 3]. Smoking is an addictive condition with a high risk of causing other diseases [4]. This narrative review aims to provide the scientific basis to help healthcare professionals develop effective tobacco quitting therapies. The most recent literature on the subject was analyzed to find possible treatment options available; while this study mainly focuses on smoking cessation therapies in patients with Chronic Obstructive Pulmonary Disease (COPD), its findings remain valid at a much more general level.

THE ROLE OF TOBACCO SMOKING IN THE GENESIS AND EVOLUTION OF COPD

COPD is the fourth cause of death in the world and is likely to become the third by 2030 [5]. Besides being

Address for correspondence: Claudia Giacomozzi, Dipartimento di Malattie Cardiovascolari, Endocrino-Metaboliche e Invecchiamento, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy. E-mail: claudia.giacomozzi@iss.it.

an obstructive bronchial disease characterized by a partial or total irreversibility of bronchial obstruction and a progressive fatal pulmonary deterioration [6], it is also recognized to be a systemic inflammatory disease with pulmonary and extrapulmonary symptoms, including an increased risk of developing lung cancer [7]. COPD has a marked effect on the patients' quality of life and affects up to 50% of smokers [8]. Tobacco smoking remains the leading cause of COPD, although susceptibility to smoking-related flow restriction is rather individual, due to the interaction between environmental factors and the host [9, 10]. In fact, some genetic studies highlight that variants and the upregulation of nicotinic receptors are involved in addiction, COPD and/or lung cancer [11]. Bronchopulmonary damage is caused by oxidative stress, release of inflammatory cytokines, increased protease activity due to the imbalance between proteases/antiproteases and the expression of autoantibodies [12]. All these factors together can lead to chronic bronchitis with alteration of mucociliary clearance and possible progressive evolution towards COPD and pulmonary emphysema; the latter may represent risk factors for lung cancer [13, 14]. A recent meta-analysis [15] confirmed that smokers have a 4.01 times greater risk of developing COPD (RR 4.01; 95% CI, 3.18-5.05). Exposure to passive smoking in adults for an average of 1 hour a day carries a 1.44-fold risk of developing COPD compared to non-exposed people. The percentage of smokers who develop COPD is high: it ranges from 15-20% in the seminal studies of Fletcher and Peto [16] (considered an underestimation [17]) to 40-50% in the most recent publications [18-20]. An early decline in forced expiratory volume (FEV 1) is recorded in adolescent smokers, while the maximum level of respiratory function appears to be partly determined by exposure to smoking in prenatal life and after birth [21]. The risk of COPD is dose-dependent, hat is, related to the duration of tobacco use and the cumulative dose. The lowest FEV 1 value is observed among smokers with exacerbations. A recent study shows that each new exacerbation corresponds to an additional loss of 23 ml/year in addition to the expected 87 ml/year [22]. For this reason, it is advisable to keep the respiratory function under control in smokers for an early detection of alterations that may evolve into COPD [23].

BENEFITS OF SMOKING CESSATION IN COPD PATIENTS

Early smoking cessation brings many benefits: it prevents the onset of the disease, limits its evolution [24], and reduces morbidity and mortality from associated illnesses such as cardiovascular or bronchial diseases and cancer [25]. Smoking cessation should be offered to all patients with chronic bronchitis and COPD regardless of the stage of the disease and the patient's motivations to quit [26]. Indeed, as it happens in France, smokers should be advised to undergo COPD screening in smoking clinics, so that the doctor who diagnoses COPD may be aware from the start that the patient is a chronic smoker [27]. These "challenging" smokers [28] generally have a strong nicotinic dependence, a rather high daily consumption of tobacco and important anxious-depressive traits, the latter also being responsible for flare-ups and difficulties in quitting [29]. Conversely, some studies have showed that smoking cessation is also effective in reducing stress, anxiety and depression in COPD smokers [30]. Complete smoking cessation is necessary, as simply reducing tobacco intake is not enough to limit the decline in respiratory function [31]. Former smokers have fewer lower respiratory tract infections and COPD exacerbations [32], while active smokers show a greater clinical and functional decline [33]. Hospitalizations for COPD can be reduced in those who quit smoking [34], including patients with severe COPD, as demonstrated by a 2008 systematic review [35]. Smoking cessation also has a positive therapeutic impact, since cigarette smoking alters the therapeutic response to medications used to treat respiratory diseases [36] through the induction of liver isoenzymes, pharmacodynamic interactions and reduced sensitivity to corticosteroids. Finally, the cost-effectiveness ratio of smoking cessation is associated with high-intensity cessation interventions [37], also through savings from the reduction of exacerbations and hospitalizations of COPD patients.

TOBACCO AND CANNABIS

Tobacco has long been considered a gateway to cannabis consumption [38] and it is now common in anti-smoking centres to come across smokers who also use cannabis. It is good practice to identify this associated consumption, especially because many young adults believe that smoking cannabis involves little or no health risks, while it is known that as far as consequences on respiratory function are concerned, a single joint equates 2.5-3 tobacco cigarettes [39, 40]. The prevalence of COPD and related risk factors in people on opioid agonist treatment (OAT) is also a fact, because they appear to develop COPD at a lower age than the general population [41]. These kinds of smokers must be told from the start to quit both addictive substances, namely nicotine in tobacco and delta-9-transtetrahydrocannabinol (Δ9-THC, mainly) in cannabis. THC is absorbed by the respiratory tract mucosa, with a bioavailability of approximately 20% and a maximum blood concentration reached in approximately 10 minutes. Furthermore, cannabis is inhaled differently from tobacco: the volume of the puffs is greater with cannabis and the inhalation is quicker and deeper, sometimes followed by a Valsava maneuver to achieve an even greater absorption of THC. To implement a successful de-addiction therapy, it is useful to know that the THC pulmonary retention time is longer than nicotine, whose plasma elimination half-life is about 2 hours: THC in fact, being lipophilic, binds to body fat, in particular in the brain, with a plasma half-life between 25 to 35 hours or even much longer in case of regular consumption [39]. As in the case of tobacco cigarettes, cannabis smoke contains many carcinogenic components, and/or components which alter the respiratory epithelium. Confirmed respiratory effects in chronic cannabis smokers include symptoms of chronic bronchitis with a cumulative effect on COPD due to tobacco, the occurrence of emphysema, with an increased risk of bullous emphysema and pneumothorax, and an increased risk of recurrence after pleu-

ral symphysis. Further, recent prospective studies have shown a negative impact on lung function, with damage to the airways, alteration of carbon monoxide diffusion lung (DLCO) and accelerated decline in forced expiratory volume in the first second (FEV1) [42]. Anti-smoking centers operators should ascertain the dual use of cannabis and tobacco, and advise quitting by offering their help after a careful evaluation of both consumption and its causes. The management of cannabis and tobacco smokers requires psychotherapeutic support; furthermore, if previous medications to help quit cannabis have not been effective, nicotine replacement therapy can limit withdrawal syndrome and cravings, and may improve smokers' adherence to care and monitoring. In a systematic review of the literature it was found that cannabis and tobacco users had greater difficulty quitting cannabis than simple cannabis users, and had more frequent psychosocial disorders, such as anxiety and depression [43]. This greater difficulty is also linked to the fact that, predominantly, these patients intend to stop smoking tobacco while maintaining a reduced use of cannabis, thus underestimating their addiction.

Smokers who also use cannabis can be supported by means of the following strategies:

- inform the patient and evaluate the damage caused by consumption, so that the patient may become aware of the addiction, including that from THC. Inform the patient of the risks associated with use and the advantages of abstinence, offering to help him/her stop [44]. It is necessary to evaluate the level of addiction by using the cannabis abuse screening test (CAST) [45] for cannabis and the Fagerström test (FTND) for nicotine, quantifying the severity of the addiction according to the Diagnostic and Statistical Manual of Mental Disorders 5-Cannabis use Disorders (DSM-5-SUD) items. The psychopathological reasons for consuming cannabis and nicotine and the existence of anxious-depressive disorders must be sought through clinical tests (HAD tests) [46], as well as situations of social precariousness, use of other substances, psychoactive or legal problems. Patients who experience serious difficulties due to cannabis addiction are included in specialist drug addiction consultations. However, anti-smoking centres may also manage occasional cannabis smokers, proposing them to stop both substances at the same time, as they share a common route of administration, neurobiological interactions, and social rituals. The therapy then proceeds in a similar way to tobacco cessation;
- *psychotherapeutic support*: this support, with its various facets (cognitive-behavioral therapies, including psychodynamic and family therapies) allows to create a therapeutic alliance, strengthen motivation to quit, generate adherence to therapeutic monitoring, and facilitate learning about craving and prevention of relapse after cessation [47, 48]. Remote support tools (internet, telephone lines), when available, allow for the provision of further assistance [44];
- *pharmacological support*: this mainly involves nicotine replacement therapy (NRT), in transdermal and oral forms; this approach also allows to limit withdrawal syndrome and cravings when simultaneously trying cessation of nicotine and cannabis. Bupropion is not recommended due to the sleep disturbances it can generate [49] in those patients who, according to the clinical experience of this manuscript's Authors, usually consume cannabis only in the evening for "relaxing" purposes. Varenicline is currently in a test phase for this indication [50]. A recent Cochrane Review, based on 21 studies [51], assessed the benefit of current pharmacological strategies to combat cannabis addiction, and concluded that, given the state of the art, no valid recommendations could be deduced. Some molecules (serotonin reuptake inhibitors, buspirone, atomoxetine, antiepileptics) may, however, find some use. Cannabinoid agonists, although promising, are still in the testing phase, as are gabapentin and N-acetylcysteine. The role of e-cigarettes in helping to stop this dual use is still poorly understood. On the other hand, synthetic cannabinoids mixed with nicotine-containing liquids have been reported to cause severe, sometimes fatal pneumonia [52]. It is necessary to further develop research into pharmacological therapies with integrated preventive measures aimed at reducing the use of these psychoactive substances, ever more widely diffused (as in the case of cannabis) with their undergoing legalization (a legislative process already completed in many countries).

COPD AND SMOKING IN PATIENTS WITH COVID-19

Most studies highlight the importance of anti-smoking therapy in patients with COPD and COVID-19. An interesting meta-analysis based on 15 studies including 2,547 confirmed COVID-19 cases [53] showed that although the prevalence of COPD in COVID-19 cases was low, COVID-19 infection was associated with higher severity and mortality rates in presence of COPD. Compared with former smokers and people who never smoked, smokers were at a higher risk of serious complications and showed a higher mortality rate. Similarly, in the 2020 work by Gallus *et al.* [54], tobacco smoking resulted one of the most important avoidable risk factors. In Italy, an observational, longitudinal, and multicenter study on patients with a diagnosis of COVID-19 confirmed by molecular swab in 24 hospitals and 2 community centers showed that smokers are twice as likely to die from COVID-19 as people who never smoked [55, 56].

SMOKING AND THE WILL TO QUIT

Smoking is not a simple "vice" or "habit": it is fully recognized as an *addictive pathology* by the WHO International Classification of Diseases (ICD-10) and by the American Psychiatric Association (APA) Diagnostic and Statistical Manual of Mental Disorders [57]. Nicotine is a neuro-psychotropic substance that triggers neurochemical alterations, modifies the plasticity of some brain areas and receptor structures, and induces behavioral changes in memory, emotions, and learning, like other psychotropic substances. As clearly demonstrated by Nobel Prize winner Dr Eric Kandel [58], nicotine acts as a "gateway" for other drugs. Unfortunately, the idea of treating smokers is not very wide-

spread because people think that it is enough for them to simply *want* to quit; however, with "do-it-by-yourself" systems only 1-3% of the cases result a "spontaneous cure" [59]. When asked, two thirds of all smokers say they would like to quit, and 20% say they would like to drop tobacco within the following 30 days [60]. Smokers with COPD should be informed of the benefits of smoking cessation therapy, which should be prescribed as an integral part of their treatment following the indications of evidence-based medicine (EBM) and smoking cessation guidelines [61-65].

HOW TO HELP THE SMOKER PATIENT

Smoking cessation: available treatments

The main recommendation in all the guidelines for the treatment of smoking [62-64] is the use of effective pharmacological therapies and counseling on tobacco addiction for all tobacco smokers. Smoking cessation is the most effective strategy to slow down the progression of COPD and to reduce mortality in approximately 50% of smoking COPD patients [66].

As yet, there is no gold standard, intended as a single effective smoking cessation technique; however, there are some common key-points in all the methodologies that are gaining solid scientific validation:

a) individual or group counseling;
b) pharmacological treatments – consisting of nicotine substitutes (nicotine replacement therapy, NRT), bupropion, varenicline and cytisine – are effective and safe therapeutic supports, especially in combination with counseling [59].

Addiction to smoked tobacco is characterized by a *physical* addiction to nicotine and by a *socio-environmentally* conditioned behavior. The best treatment for tobacco addiction must then integrate both counseling and pharmacotherapy in a multidisciplinary approach, as recommended by the United States smoking cessation clinical practice guidelines [67], by the European Network for Smoking Prevention and Cessation (ENSP) [62] and, in Italy, by the recent Italian guidelines published by the Italian National Institute of Health (Istituto Superiore di Sanità, ISS) [63]. The importance of therapeutic education (TE) of smokers with COPD has also recently been evaluated: it aims to strengthen smokers' understanding of their disease and bring out new skills to improve their quality of life hrough sessions based on group dynamics and which exploit the knowledge acquired by the patient on the disease, treatments, respiratory physiotherapy and nutrition. TE, when included in a multidisciplinary management aimed to complement and strengthen smoking cessation follow-up, appears to increase the chances of a successful cessation [68].

Non-pharmacological therapy

Non-pharmacological therapy lays essentially in counseling, in all its forms (individual, group, telephone, short, intensive). The United States Preventive Services Task Force provides a "Grade A" recommendation for physician-provided brief smoking cessation interventions. Counseling by non-medical health professionals, including nurses, oral health professionals, and pharmacists, also increases cessation rates [69]. In clinical counseling, a "consultant" helps patients by providing them with accurate information and psychological support, thus creating a process of empathy. Several studies [67, 69, 70] show that:

a) individual, group and telephone consultations are effective, and their effectiveness increases with treatment intensity;
b) the longer the first interview, the higher the probability of smoking cessation;
c) effectiveness increases when the counseling is intensive and prolonged over time;
d) effectiveness also increases when different kinds of professionals are involved.

Most smokers try to quit smoking without help, by reducing the number of cigarettes or, more drastically, by abstaining from smoking overnight [71].

In addition to counseling, it is worth mentioning further strategies aimed at smoking cessation in the context of non-pharmacological therapies, since they have been proposed with positive results in patients with COPD:

- *monetary incentives*: monetary incentives rewarding the outcome (quit smoking) or the involvement (participation in the treatment) have already shown to be moderately effective [72]. They can be given through different methods, for example through incremental vouchers linked to the reduction of exhaled carbon monoxide and urinary cotinine during the program. Although the results of a randomized pilot study [73] supported the potential effectiveness of such an incentive, further efforts are needed in research activities aimed at increasing the sample size and evaluating long-term abstinence following this intervention;
- *physical activity*: several studies have shown that physical activity can help reduce symptoms of depression in patients with lung problems, and it is known that major depressive disorder (MDD) can have a negative effect on withdrawal during and after cessation treatment smoking [74, 75]. Physical activity was inversely associated with MDD even after controlling for potential confounding variables, such as lung function [76]. Furthermore, secondary analyses showed that physical activity was inversely related to depression in a dose-response manner. Several randomized controlled trials that included physical activity to reduce tobacco craving in smoking cessation have demonstrated the effectiveness of this strategy [77].

Brief advice

This type of help can be provided in the first place by the GP or by a specialist with first-level training, and successively by smoking cessation therapists in anti-smoking centres. The minimal clinical intervention technique (very brief advising and counseling) recommended by the main guidelines of non-European and European National Entities (including the most recent ISS Italian guidelines [63]), is known as the "5As: Ask, Advise, Assess, Assist, Arrange". It is The National Cancer Institute's (NCI) gold standard for short termination advice [78]. In this technique, the first 2 As (Ask and Advice) are part of a rapid approach (Mini-

mal or Brief Advice), that is the minimum advising that all clinicians should deliver during a medical examination of a smoker (Ask: ask all patients if they smoke or have ever smoked, and always report the data in their medical record. Advice: recommend quitting if they are smokers or compliment them if they are former smokers or if they have never smoked. Follow up those who have stopped smoking for at least one year).

The next three As (Assess, Assist, Arrange) are part of a possible therapy. In particular, the third A (Assess) assumes significance only in view of treatment continuation [79-81]. Assess: consists in identifying smokers who are motivated to quit and those who are not, also using questions such as "can I help you quit smoking?" but without ever trying to overcome a determined refusal; in the latter case, the clinician should inform the smoker on the possible advantages in terms of health and relational aspects, and offer the willingness to help in the future. It should be remembered that such patients may respond to brief motivational interventions that are based on principles of motivational interviewing (MI), a directive, patient-centered counseling intervention. There is evidence that MI is effective in increasing future quitting attempts. The four general principles that underlie MI are: (1) express empathy, (2) develop discrepancy, (3) roll with resistance, and (4) support self-efficacy.

Assist: if the smoker accepts to be helped, he/she must be motivated by way of creating a relationship based on empathy and cooperation so that it is up the smoker to bring out the benefits but also the difficulties encountered, and to find his/her own motivations and resources for quitting. Information and recommendations must be provided to overcome any reported problems, and the patient must be continually encouraged to reach the goal. Obviously, in a motivated patient it is best to provide advice on a precise cessation date, and on the use of pharmacological therapy to be shared with other professionals for better compliance.

Arrange: plan a follow-up, i.e., a schedule of visits aimed at checking progress and pharmacological therapy, strengthening motivation and considering possible relapses as events from which to gain experience, and not as failures.

The 5As can be assimilated to an "individual treatment": behavioral support + medication [82]. *Figure 1* is an adaptation from Fiore *et al*. [67] and graphically synthesizes the 5As approach.

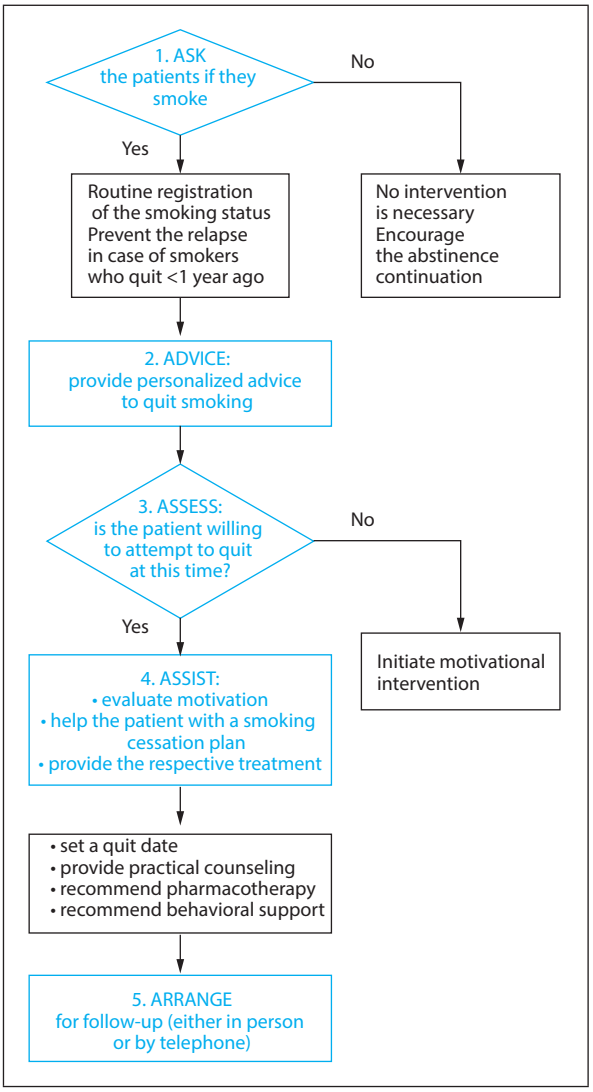

Figure 1
"Patient" journey: addressing healthy individuals and those at risk of developing CVD/DM, progressing to individuals diagnosed with CVD/DM at risk of disease progress and multimorbidity. This encompasses both individual and population levels, within different settings.
CVD: cardiovascular disease; DM: diabetes mellitus.

Intensive smoking cessation counseling, alone or in combination with other therapies

Clinical Practice Guidelines recommend intensive smoking cessation counseling, individually or in groups, in clinical, behavioral, or community settings for smoking cessation treatment [63, 67]. A systematic review of 49 randomized trials with approximately 19,000 participants concluded that intensive counseling alone (without pharmacological support), provided by a cessation counsellor, was more effective than minimal contact (i.e., brief advice and self-help materials) and performed best when combined with smoking cessation medications [70]. It should be noted that, in patients with COPD, combining respiratory rehabilitation with a cognitive-behavioral and pharmacological therapy for smoking cessation proved to be more effective than in smoking patients with COPD who did not have a rehabilitation program [83]. Furthermore, as confirmed by Sundblad *et al.* [84], hospitalization for respiratory rehabilitation is a particularly apt moment for smoking cessation interventions in COPD patients.

Telephone counseling [69] and AI technologies on smartphones (App, Internet, SMS, social networks) [85] have also proved to be a support for smoking cessation although further randomized controlled trials are needed. According to the ISS Italian guidelines [63] it is well worth developing applications for mobile devices to be promoted through media campaigns at national level in the National Health Service. At a European lev-

el, some digital tools to stop smoking are already available, developed within media campaigns that are repeated annually in England [86], the Netherlands [87, 88] and France [89] and which have already involved a large number of patients. As a research priority, the ISS Italian guidelines [63] suggest implementing such media campaigns associated with digital systems, and recommend future studies relying on process indicators such as the number of people accessing the applications for the first time or the frequency of weekly or monthly access, and outcome indicators such as self-reported measures of nicotine consumption and withdrawal. Monitoring could also serve to understand any parts of the application that could be improved.

New digital therapy Apps for smokers with COPD were found to be so popular in an Austrian survey that it was suggested to add "Apps" as the sixth A. Mobile apps combined with psychopharmacological therapy seem to be effective in achieving smoking cessation. In addition, the easy integration of these tools in primary healthcare can improve knowledge about possible treatments and integrate smoking cessation into routine care [90]. An interesting 2019 review of quit-smoking Apps available on the UK market [91] examined the use of *gamification* (the use of game elements in a non-game context) to increase patients' engagement and motivation. The review showed that only a few of the 140 quit-smoking Apps had a high level of gamification, thus welcoming further exploration into its use.

As for telemedicine, the results are still too recent and controversial for a long-term evaluation. However, telemedicine may be a strategic added value in the care of COPD, by reducing the burden of both in-patient and out-patient healthcare [92] as demonstrated by the COVID-19.

Among other possible anti-smoking therapies based on alternative medicine are acupuncture and hypnosis. The few reliable studies report controversial results. For example, Wang *et al.* [93] conducted a randomized controlled trial which concluded that acupuncture is a possible smoking cessation treatment. But in the same issue of the Journal, an editorial by Braillon and Ernst [94] criticized the validity of the same study and the conclusions drawn by its authors for the overly small size of the sample (195 patients), the double blind with nicotine performed with reduced concentrations of transdermal therapeutic system, the high drop-out rate (35%), and the non-independence of the study.

PHARMACOLOGICAL THERAPY

Tobacco smoke determines a state of psychological and pharmacological addiction [57] known as *nicotine disorder*. Chemical dependence can be measured by the nicotinic addiction assessment test (Fagerström test) which scores the degree of addiction as mild, medium, strong, or very strong, thus enabling the grading of the pharmacological therapy [95]. There are three pharmacological mechanisms which can facilitate smoking cessation: (i) reduce nicotine withdrawal symptoms; (ii) reduce nicotine's rewarding effects; and (iii) provide an alternative source of nicotine [69]. As indicated by the guidelines for smoking cessation [63, 64; 67-69], there are three safe and effective "first-line" drugs capable of increasing abstinence rates, including long-term abstinence, from tobacco smoke: nicotine replacement therapy, bupropion SR and varenicline. A new entry, but not yet officially included in the first-line treatment, is cytisine [96].

Nicotine replacement therapy (NRT)

NRT is undoubtedly the most used approach in smoking cessation: it reduces withdrawal symptoms (dysphoric or depressed mood, insomnia, irritability, frustration, anger, anxiety, difficulty in concentrating, hyperactivity, irritability, increased appetite and weight) and decreases the desire to smoke. To avoid overdoses, patients should not smoke while treated with NRT. In fact, although a selection of articles up to April 2018 report that there is "moderate certainty" that use of NRT before quitting can improve quit rates compared with its use after the quit date, the authors of a major 2019 review conclude that more research is needed to ensure the robustness of this claim [92]. The results of the above-mentioned review by Lindson *et al.* [97] are especially valuable: aiming to evaluate the effects of different NRT regimens on smoking cessation, they excluded trials that did not assess smoking cessation as an outcome; they also excluded studies that followed participants for less than six months, in line with the standard methods of the Cochrane Tobacco Addiction Group [98]. For each study included, they used the strictest available criteria to define abstinence: in studies with a biochemical validation of cessation, only participants meeting the criteria for biochemically confirmed abstinence were considered abstinent; sustained cessation was preferred over point prevalence; and the participants lost to follow-up were considered continuing smokers [99]. Different formulations of NRT (nicotine gum, nicotine inhaler, nicotine tablets, nicotine patches and nicotine nasal and oral sprays) can be combined. The combination of a short-term acting NRT (gum, lozenges, sprays or inhalers) with a long-term acting NRT (nicotine patches) produces higher cessation rates than using a single formulation and is recommended as a first-line treatment. NRT products are marketed in different dosages, with higher doses for more dependent smokers [97]. Each route of administration differs in the kinetics, the time to reach nicotine blood peak, and effectiveness. Over the past three decades, several meta-analyses have been published evaluating the safety and effectiveness of NRT (patches, chewing gum, tablets, inhalers, or nasal sprays) [100, 101]. Nicotine patches provide 2 to 3 times greater discontinuation rates than the placebo [102]. The paper by Hartmann-Boyce *et al.* [102] also found that the risk ratio of abstinence for any form of NRT compared to the control was 1.55 (95% CI: 1.49-1.61); the pooled risk ratios for each type were 1.49 (95% CI: 1.40-1.60; 56 trials; 22,581 participants) for nicotine gum; 1.64 (95% CI: 1.53-1.75; 51 trials; 25,754 participants) for nicotine patches; 1.52 (95% CI: 1.32-1.74; 8 trials; 4,439 participants) for oral tablets/lozenges; 1.90 (95% CI: 1.36-2.67; 4 trials; 976 participants) for nicotine inhalators; 2.02 (95% CI: 1.49-2.73; 4 trials; 887 participants) for nicotine nasal sprays.

The Fagerström test on the degree of nicotinic addiction should guide the initial transdermal nicotinic dosage [103], using high-dose patches (from 20 to 30 mg depending on the Fagerström test) for 3 months. High-quality evidence showed that individual counseling was more effective than minimal contact monitoring (brief counseling, usual care, or self-help materials) when pharmacotherapy was not provided (RR 1.57, 95% CI: 1.40-1.77; 27 studies; 11,100 participants) [70].

Gums generally need 30 minutes to reach nicotine plasma peak; one gum is administered every hour up to a maximum of 12 per day. To obtain maximum effectiveness, the gum should be chewed slowly and, after 5-10 chews, should be kept in the mouth without chewing and then chewed again to allow it to release all the nicotine available. Each piece of gum, in 2 and 4 mg dosages, should be chewed for about 20-30 minutes. The use of nicotine gums should be avoided in the presence of dental prostheses and gastropathies. Patches with transdermal nicotine release are more manageable and effective than gums; they contain from 5 to 30 mg of nicotine with release at 16 or 24 hours, thus allowing stable plasma nicotine concentrations throughout use. Nicotine patches are to be avoided in case of dermatopathies and glue allergy.

The 15 and 10 mg nicotine inhalers feature a mouthpiece containing a cartridge fitted with a porous filter soaked in mentholated nicotine. From the cartridges containing 10 mg of nicotine, 4 mg are inhaled, and 2 mg absorbed. It is advisable to explain to patients, especially to asthmatics and COPD patients, to inhale very slowly to avoid coughing, and to use from a minimum of 4 to a maximum of 10 capsules per day in the initial stages of cessation.

Sublingual nicotine tablets have pharmacokinetic characteristics very similar to those of chewing gum. The dosage is 2 mg and they reach peak blood in about 20 minutes. The tablet is dissolved slowly under the tongue without chewing or swallowing. This formulation should also be avoided in patients with gastropathies.

Oral sprays should not be inhaled; a delivery (puff) of 1 mg of nicotine can be repeated once every 30 min but with no more than 2 puffs at a time. The maximum dose is of 64 puffs in a 24-hour day, progressively upscaled over a maximum period of 6 months.

Nasal sprays reach a nicotine blood level faster and more effectively than other forms of NRT [82, 97].

There exists high-certainty evidence that combining NRTs (fast-acting form + patch) results in higher long-term quit rates than a single form (risk ratio 1.25, 95% CI: 1.15-1.36; 14 studies; 11,356 participants; I^2=4%) but no evidence of the effect of duration of nicotine patches (low-certainty evidence) [97]. The reduction in the estimated absolute benefit of NRT between one-year and long-term follow-up is a 30% relapse between the two, with only 2.7% due to the slight reduction in the odds ratio. Tobacco addiction might be better viewed as a chronic, relapsing disorder requiring repeated treatment (more similar to the long-term treatment of other chronic diseases, such as hypertension) rather than to the treatment of acute diseases like infections; nonetheless, this treatment is still likely to be highly cost-effective in terms of life-years gained [104].

Bupropion

Bupropion is an antidepressant which, by acting on the two neurotransmitters dopamine and noradrenaline, can counter nicotine withdrawal symptoms. In one-year controls, used alone for one month, it showed a 33% success rate for smoking cessation, compared to 21% of those using nicotine patches. The combination of bupropion and nicotine patches was more effective (38% *vs* 18% of placebo. Similar results were obtained by Jorenby [105] in a controlled and double-blind study on the effectiveness of slow-release bupropion (244 subjects), transdermal nicotine (244 subjects) and the combination of the two systems (245 subjects) compared to placebo (160 subjects). The 12-month smoking abstinence rate was 15.6% for placebo, 16.4% for transdermal nicotine, 30.3% for bupropion and 35.5% for combination therapy, which showed no statistically significant difference with bupropion alone. The drug is administered with 150 mg/day for 8-10 days, and later with 150 mg twice a day, to achieve complete smoking cessation. Its main contraindications include a history of seizures and eating disorders (bulimia and anorexia). Its possible side effects include seizures, insomnia, dry mouth. Bupropion is marketed as a smoking cessation drug in the form of an extended-release preparation. The usual duration of bupropion treatment is 12 weeks, but prolonged therapy for one year reduces relapses and increases long-term cessation rates [69]. Several studies have documented much higher recurrence rates in COPD patients with higher pack-year history, higher degree of nicotine addiction, higher risk of depressive symptoms, and lower motivation to quit [106, 107].

Though developed as an antidepressant, bupropion affects smoking cessation in ways other than alleviating depressive symptoms [108]. The safety, tolerability, and effectiveness of bupropion for smoking cessation in patients with COPD has also been established thanks to one-year continuous abstinence rates of 16% for bupropion compared to 9% for placebo [109]. Wagena *et al.* [110] also confirmed that the use of bupropion and nortriptyline resulted in higher prolonged abstinence rates compared to placebo. More specifically, they found that bupropion and nortriptyline were effective in patients with COPD, achieving prolonged abstinence while no statistically significant differences were found with placebo in participants at risk for COPD.

It should be noted that patients with COPD struggle for many years to stop using nicotine permanently and may require prolonged treatment and/or sustained nicotine use. After repeated failed attempts under specialist healthcare, the use of alternative methods – electronic cigarettes or heated tobacco – is being proposed, but the topic is controversial due to the use of these same methods by no-smokers, their effectiveness and safety, their short- and long-term health effects, and their adverse effects from passive exposure [66; 111, 112] (for an insight into these topics, see below "electronic cigarettes, EC, and heated tobacco products, HTP").

Varenicline

Varenicline is a partial agonist of the α4β2 nicotinic acetylcholine receptor (nAChR), the main receptor in nicotine addiction. Varenicline activates approximately 50% of the maximum effect of nicotine and blocks nicotine's effects on the α4β2 receptor. The agonist effect serves to reduce withdrawal symptoms, while the antagonistic effects reduce the gratification of nicotine in cigarette smoking. Varenicline treatment before quitting is often associated with a reduction in smoking, presumably because it becomes less satisfactory, which may later facilitate quitting. Safety and effectiveness of varenicline have been investigated in patients with mild to moderate COPD: for treatments ranging between 9 and 52 weeks, the abstinence rate was 18.6%, compared with 5.6% in the case of placebo (OR 4.04; 95% CI: 2.13-7.67; p<0.0001), while safety was found to be comparable with previous studies [113]. In clinical trials, varenicline resulted more effective than bupropion or nicotine patches in promoting smoking cessation, as also the combination of multiple NRT formulations [114]. Varenicline is a molecule approved by the Food and Drug Administration (FDA) in 2006 and authorized in Europe, Middle East and Africa in September 2006 under the trade name of Chantix (USA) – Champix (EU). The drug is used orally, and the recommended regimen dose is 1 mg twice a day. The dosage protocol indicates starting with 0.5 mg and continuing with 0.5 mg once a day for the first 3 days, 0.5 mg twice a day from day 4 to 7, and 1 mg twice a day from day 8. The treatment starts 7 days before the total cessation of tobacco smoking and continues for at least 12 weeks. Varenicline binds to the neuronal nicotinic receptors of acetylcholine α4β2 with a high level of affinity and selectivity. It has a dual action mechanism: 1) a partial agonist effect by stimulating nAChRs to a significantly lower extent than nicotine; 2) an antagonist effect by blocking nicotine's capacity to activate the α4β2 receptors, thus stimulating the dopaminergic mesolimbic system especially in the *nucleus accumbens* (NACc). Varenicline is administered orally and has a high systemic bioavailability, regardless of the alimentary regime or the time of administration. It exhibits linear kinetics, and the maximum plasma concentration (Cmax) is reached within 3-4 hours after oral administration. Varenicline is low in plasma protein binding. Elimination is renal, mainly through glomerular filtration together with active tubular secretion. It has a mean half-life of 24 hours and steady-state concentration (Css) is achieved within 4 days. The drug is contraindicated in subjects with moderate and severe renal insufficiency (creatinine clearance <50 ml/min). Clinical trials and experience have given encouraging results on the effectiveness of this drug: at 6 months, Varenicline was more effective than placebo, NRTs and bupropion SR [61, 115]. According to the American Thoracic Society Clinical Practice Guideline, varenicline performed better than NRT and bupropion in controlling tobacco addiction [116]. Since 2021 the drug has been suspended after an information note agreed with the EMEA on the presence of N-nitroso-varenicline impurity above daily intake levels deemed acceptable by the manufacturing company, which prudently stopped the distribution of the drug pending further checks. Shortly after, the first FDA-approved generic varenicline became available [117]. Both the European Medicines Agency (EMA) and the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA) should also consider this option and this is why the Authors of this review have included varenicline in the section on pharmacological therapy for smoking cessation.

Cytisine

Cytisine is an alkaloid extracted from the seeds of *cytisus laburnum*, commonly known as "golden chain" or "golden shower", a common garden plant in central and southern Europe. Cytisine has been used for smoking cessation in Central and Eastern Europe for over 50 years. Like varenicline, it is a partial agonist of nAChR α4β2. Therefore, it has similar effects to those of nicotine, while at the same time desensitizes and/or blocks the effects of tobacco nicotine on nAChR α4β2. The recommended treatment regimen is a dose reduction over 25 days, a treatment cycle shorter than the 12 weeks recommended for most other smoking cessation drugs, with recorded significant effects compared to placebo (meta-analysis; RR, 1.74; 95% CI, 1.38 to 2.19) [118]. In Italy, to facilitate greater adherence to therapy and based on experiences with other partial nicotine agonists, the Italian Society of Tobaccology (Società Italiana di Tabaccologia, SITAB) has adopted a therapy scheme with: i) 1.5 mg tablets at 40 days with a slow induction of cytisine intake; ii) the following smoking advice: smoking patients are advised to reduce the number of cigarettes in the first four days of treatment, with a recommended stop smoking date of the fifth day. SITAB has been proposing this scheme for about ten years, i.e., since the active ingredient became available in Italy; the scheme, first tested at the Center for the Treatment of Smoking (Centro per il Trattamento del Tabagismo, CTT) in Monza, Italy, consists of induction (2 to 6 tablets/day for the first 7 days), maintenance (6 tablets/day for 7 days) and gradual reduction for 26 days [118, 119]. The cost of cytisine in Europe is several times lower than that of other smoking cessation drugs. The drug is well tolerated, and the most common side effects are nausea, vomiting, dyspepsia, and dry mouth [118, 119]. Cytisine is defined as "a drug with positive effects and without significant adverse events". Since 2024, the drug based on the active ingredient Cytisine (approved by AIFA on April 2023) has also been on the market in Italy.

Combination pharmacotherapy

According to Cochrane Meta-analysis [97], nicotine replacement therapy (NRT) combined with a patch and a more immediate-acting product results in higher smoking cessation rates than NRT alone, with a hazard ratio (RR) of 1.34 and a 95% confidence interval (CI) from 1.18 to 1.48. The combination of varenicline and nicotine patch was evaluated with mixed results [120]. The mechanism through which NRT purportedly enhances the effects of varenicline is unclear, but the combination appears to be safe. This combination may be considered in a smoker who does not quit after using NRT in two forms or varenicline alone. Bupropion in combination

with a nicotine patch or NRT in two forms increases smoking cessation rates compared to the same drugs administered alone. A study with the combination of varenicline and bupropion reported promising results, although neuropsychiatric adverse effects were greater in the first 2 weeks than with varenicline alone [121].

Electronic cigarettes (EC) and heated tobacco products (HTP)

Electronic cigarettes (ECs) are battery-powered devices that work by heating a metal coil which vaporizes a solution (e-liquid): mainly glycerol, propylene glycol (PG), distilled water and flavorings, with or without nicotine. The user inhales the aerosol generated by vaporizing the e-liquid in a process commonly referred to as "vaping". ECs' safety and nicotine delivering efficiency have improved since their introduction on the market in 2006. However, the huge number of devices marketed and the great variety of chemicals used to flavor the e-liquids represent additional sources of complexity when evaluating their toxicity and safety.

Another class of non-burning products aimed at replacing traditional cigarettes are heated tobacco products (HTP). They consist of a support which, instead of burning tobacco, transfers electronically controlled heat at temperatures <350 °C, to tobacco sticks, caps or capsules which then generate aerosols. The user places the tobacco product in a small box and inhales it in the same way as cigarettes or cigars.

Disposable ECs represent the latest product on the market: it is a device that vaporizes a liquid of various flavors, from kiwi to coke, similarly to traditional electronic cigarettes; but unlike the latter, it has a limited duration and is not rechargeable. Once finished, disposable ECs must be disposed of in battery containers. Compared to the traditional ones, this cigarette emits fewer carcinogenic substances but contains nicotine salts, which are 4 times more addictive.

Vaping has been proposed as a potential smoking cessation tool and has been found to increase abstinence [111], but its use among non-smokers has raised great concerns [112]. Moreover, even if carcinogen reduction is observed with ECs [122], vaping is not harmless [123]: it has pro-inflammatory effects, increases airway resistance, friability, and edema, and exposes its users – including passive users – to ultrafine particles and heavy metals [112]. Vaping has been associated with acute lung injury, even before the EVALI outbreak [112]. Furthermore, many smokers are "dual users", smoking both traditional and electronic cigarettes, which makes it more difficult to assess the impact of vaping alone [112].

The use of HTPs is associated with similar problems. While in "dual users" there seems to be a reduction in carcinogenic load, in levels of carbon monoxide in exhaled breath, and in biomarkers, they are still harmful, and their effects on health have started to appear in literature [124, 125]. The latest ISS Italian guidelines [63], which have been developed according to the GRADEpro program (https://gradepro.org/), recommend *not* using the ECs with nicotine (compared to NRT) in traditional tobacco cigarette's smokers who have chosen to follow pharmacological treatment for cessation. This is a conditional recommendation, based on moderate quality of evidence. "Moderate quality" means that further research could change the results on the estimate of the effect; for this reason, among the research priorities listed in the guidelines are future studies aimed at providing further independent evidence that considers as valid outcomes the absence of nicotine consumption, i.e., the cessation of the use of ECs; the evaluation of the effectiveness and safety of ECs; and, above all, the need for long-term longitudinal studies that *specify the dosage, method and frequency of consumption of ECs,* as well as the type of setting and counseling. The Guidelines also recommend addressing the issue of addiction to other components (for example flavourings), and conducting studies to evaluate the quantity of nicotine (which varies with the electronic device used) absorbed by the consumer, since this can influence the comparison of the response with nicotine substitutes or other products. Also, further studies are necessary to understand the degree of dependence on the gestural component linked to the use of these nicotine delivery systems. A recent review published in Cochrane [126] highlighted that, although biomarkers are not indicators of disease rates, the significant reduction in exposures showed by ECs users is a positive indicator for tobacco risk reduction; the review, which is a living systematic review and which has been last updated on November 17th 2022, reported high-certainty evidence (based on 6 RCT studies) that ECs with nicotine increase quit rates compared to NRT, and moderate-certainty evidence (5 studies, limited by imprecision) that ECs with nicotine increase quit rates compared to ECs without nicotine. These results should be considered cautiously for several reasons, such as the still limited number of available high-quality studies and of participants, data variability and imprecision (including dosage, method and frequency of consumption of ECs with nicotine), limited and variable information on adverse and serious adverse short and long-term effects, differences in the quality of nicotine delivery between older and more recent ECs.

As for HTPs, the ISS Italian Guidelines [63] states that they should *not* be used as a treatment for smoking cessation. This recommendation relies mainly on the most relevant outcomes of a 2022 systematic review [127]. The review Authors, who followed standard Cochrane methods for screening and data extraction, searched for measures like abstinence from smoking at the longest follow-up point available, adverse events, serious adverse events, and changes in smoking prevalence or cigarette sales. They included 11 RCTs, all funded by tobacco companies and all judged either at unclear or at high risk of bias, and 2 time-series studies. None of the studies reported on cigarette smoking cessation, and insufficient evidence was found with respect to the risk of adverse or serious adverse events when comparing HTPs smokers, tobacco smokers, and people attempting short-term tobacco abstinence. Thus, the main message from [63] and [127] is that independently funded research is still needed to address the issue of effectiveness and safety of HTPs.

As for the risks associated with the use of ECs and

HTPs, it should be noted that these devices produce numerous harmful substances: metals, organic compounds, and aldehydes, which can also harm those passively exposed to these devices' vapors or smoke, whose longitudinal effects on health are currently unknown [128-130]. The presence of formaldehyde is particularly worrying, the indoor concentration of which is 2.7, 1.2 and 40 µg/m3, respectively for HTP, EC and traditional cigarettes [131]. The evidence of this substance's toxicity, which have already shown to be harmful in numerous epidemiological studies and which has been classified as a group 1 carcinogen [132], highlights the need to make restrictive changes to the legislation governing the use of these devices in public, especially in the presence of minors or pregnant women. The considerable spread of these products among the very young is also worrying, as it may represent their first experience of nicotine addiction [133].

To recap, while the use of ECs by the general population is to be discouraged, in an anti-smoking setting and in selected patients, and after having experienced all the counseling and pharmacological approaches available in the guidelines, the use of ECs can represent an additional tool for smoking cessation centers and in particularly problematic patients such as, for example, psychiatric patients. In Italy this is also the position of experts and scientific societies such as those with which the Authors of this paper are associated. The latest position paper of the Italian Society of Tobaccology (SITAB) on new tobacco products stated that "the use of electronic cigarettes cannot be considered a public health policy applicable to the general population, but an individual intervention, practiced by experts, in selected cases not responding to treatment and in dedicated health settings" [134].

To conclude, specifically for COPD patients, there is the need for independent, well-controlled, clinical trials and large-scale prospective cohort studies with a long-term follow-up, to obtain conclusive, reliable, and independent evidence, for or against the use of ECs.

Pre-cessation pharmacotherapy

Many smokers would like to quit, but are unwilling to set a date when first visiting a healthcare provider. Starting pharmacological therapy while the patient is still smoking, on the basis that it would make later quitting easier, was studied through the use of nicotine patches and varenicline. The pharmacological basis for this approach is that nicotine patches, by desensitizing nicotinic receptors, reduce withdrawal symptoms in the interval between successive cigarettes, while varenicline, by antagonizing the effects of nicotine in cigarettes and providing relief from withdrawal symptoms, reduces smoking satisfaction, thus decreasing the daily number of cigarettes. Evidence of pre-cessation drug therapy with nicotine patches has shown conflicting benefits, although some studies have shown large beneficial effects [135]. Studies on varenicline have shown benefits with a flexible quit date and this approach is FDA approved [136]. Several studies report that a great number of smokers with respiratory diseases make many unsuccessful attempts to quit. The study, based on the administration of a specific online survey by the European Lung Foundation (ELF) [137] found that: 54% of smokers participating in the ELF survey had made 1 to 5 attempts to quit smoking in the previous 12 months; 4% had made more than 20 attempts; 55% wanted a quick stop while 45% preferred to gradually reduce their tobacco addiction. Although most patients wanted to break this addiction, 90% found quitting difficult or very difficult. For these reasons, it is always important to first share the possible smoking cessation options with the smoker. The benefit of pre-release pharmacotherapy is that physicians can propose any smoking patient (and regardless of the patient's willingness to quit at the time of the visit) a drug therapy, explaining that it will help to quit smoking over time, much in the same way any patient with high blood pressure would be advised to take medication so as to prevent future diseases. In this regard, a small study involved heavy smokers with COPD initially unprepared to quit, who were prescribed varenicline for as long as they wanted and with no fixed date to quit; 18 months later, most had quit [138]. Currently, the 2021 NICE guidelines [64] for smoking cessation include a chapter dedicated to smokers who are not ready to quit smoking yet or just want to reduce their habit, recommending the use of medications containing nicotine to prevent relapses or limit smoking for long periods of time.

CONCLUSIONS

Although a gold standard method for smoking cessation does not exist yet, there are some common key-points in the methodologies used in national and international guidelines. Worthy of note are the following:

1) counseling;
2) nicotine replacement therapies;
3) counseling and pharmacotherapy.

In particular, managing a smoker patient with COPD must be done with a global approach. Quitting smoking is the priority goal whatever the stage of the disease, due to several well proven beneficial effects [139, 140].

Tobacco cessation therapists must learn to adapt the integrated supports (counselling + pharmacotherapy) to the specific problems of their patients, in order to adjust cessation programs to each individual context and to each smoker's culture and personal life [141].

Finally, research efforts should include the study of novel EBM strategies such as those currently based on EC/HTP and digital therapies, to further enhance the cost-effectiveness that current smoking cessation therapies have shown [60], also in patients with COPD [37].

Authors' contributions

Conceptualization and methodology: RP, VZ, MSC. Investigation: RP, VZ, MSC. Formal analysis: RP, VZ, MSC. Data interpretation: RP, VZ, PM, LDM, CB, AS, MSC, CG. Writing - original draft: RP, VZ. Writing, review & editing: RP, VZ, PM, LDM, CB, AS, MSC, CG. Project administration: RP.

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Registries or non-pharmacological observational studies? An operational attempt to draw the line and to provide some suggestions for the ethical evaluation of rare disease registries

Sabina Gainotti[1], Paola Torreri[2], Chiara Mannelli[1], Celeste Cagnazzo[3], Bruno Ficara[3] and Carlo Petrini[1]

[1]*Unità di Bioetica, Presidenza, Istituto Superiore di Sanità, Rome, Italy*
[2]*Centro Nazionale Malattie Rare, Istituto Superiore di Sanità, Rome, Italy*
[3]*Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Turin, Italy*

Abstract
Originally established to evaluate the ethical aspects of clinical trials, Ethics Committees (ECs) are now requested to review different types of projects, including, among others, observational studies and disease registries.
In Italy, clinical trials on medicinal products for human use and on medical devices are regulated by EU Regulation 536/2014, EU Regulation 2017/745, and 2017/746 while pharmacological observational studies are regulated by the Italian Medicines Agency guidelines of 2008 and by Ministerial Decree of November 30th, 2021.
The other types of studies are not strictly regulated, causing discrepancies in their definition and assessment by the ECs, and slowdowns in the start of projects.
The present contribution aims to propose definitions and distinctions between non-pharmacological observational studies and disease registries, which constitute different entities but are often assimilated by ECs, and to formulate suggestions for the evaluation of rare disease registries, which are an expanding research area of interest.

Key words
- ethics committees
- ethical review
- observational study
- registries

ETHICS COMMITTEES' EVALUATION ACTIVITIES: INTERVENTIONAL, OBSERVATIONAL STUDIES, AND DISEASE REGISTRIES

According to the Italian law, an Ethics Committee (EC) is "an independent body whose responsibility is to protect the rights, safety and well-being of human subjects involved in a clinical trial and to provide public assurance of that protection (…). Ethics Committees (ECs) may also carry out advisory functions in relation to ethical issues related to scientific and welfare activities, in order to protect and promote the values of the person" [1].

Established to evaluate the ethical aspects related to clinical trials, ECs are now involved in the examination of different types of studies that include, in addition to clinical trials (CTs), observational studies with drugs and/or medical devices, population studies, disease registries and health surveillance activities, surveys, focus groups, studies based on the use and reuse of health data and/or biological samples, to name a few.

Clinical trials with medicinal products and medical devices are fully regulated by EU Regulation 536/2014 [2] and EU Regulation 2017/745 and 2017/746 respectively [3, 4].

Observational studies with drugs are regulated by the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA) "Guidelines for the classification and conduction of observational studies with drugs" [5] and, more recently, the Ministerial Decree of November 30th, 2021 [6], which provides for a standardised procedure for the submission of applications to the ECs and the forms to be attached [7, 8]. The aforementioned decree instructed AIFA to issue a measure aimed at defining the new guidelines for the classification and conduct of observational studies with drugs, within thirty days, which, however, has not yet been adopted.

The "other" types of projects evaluated by ECs are

Address for correspondence: Sabina Gainotti, Unità di Bioetica, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy. E-mail: sabina.gainotti@iss.it.

not specifically regulated. They may differ in the level of risk for participants and also in the methodology and criteria for their evaluation. For these projects there are no clear rules concerning the forms and documentation that should be reviewed by the ECs.

A further grey area arises from the lack of regulatory references to the possibility for these "other" studies to receive an opinion from a single Committee, rather than multiple ECs. Currently, a unique opinion is released only for clinical trials with medicinal products and medical devices and for prospective pharmacological observational studies [2, 5].

Unfortunately, the lack of regulation for studies that do not fall within the umbrella of Regulation 536 and Ministerial Decree of November 30th, 2021, in particular non-pharmacological observational studies and disease registries, is often the cause of confusion and procedural discrepancies in the assessment processes by ECs and delays in starting the projects [9].

Multicentre projects are often reviewed by different ECs, which may request implementations to the documentation submitted by the applicant, with the invitation to fill out centre specific modules, often borrowed from the forms used for clinical trials and observational studies with medicinal products.

These multiple requests have consequences in terms of time and resources for ECs, whose workload is unnecessarily aggravated, and represent a challenge for researchers whose chance to finalize the projects are put at risk.

Indeed, in non-pharmacological observational studies and disease registries, especially those focused on rare diseases (RDs), it is essential to involve as many centres as possible in order to achieve the highest coverage in the population of interest. The timing of involvement of the centres, which also depends on the time of approval by the ECs, is crucial for the possibility for a study or a registry to start in time. The timing of ECs approval directly affects the timing of centres' involvement. Both of them are crucial for studies and registries to start in a timely manner.

In order to streamline the assessment procedures of non-pharmacological observational studies and registries by ECs, it would therefore be necessary to: a) entrust a unique committee with the ethical clearance of these projects, as it already happens for the evaluation of clinical trials on medicinal products and medical devices and for pharmacological observational studies; b) standardise the evaluation procedures for these types of projects, taking into account their lower level of risk as compared to interventional studies, and promoting the adoption of simple and comprehensible standard forms, aimed at protecting and involving participants rather than defending researchers or institutions.

While the first point could be addressed easily through an adequate normative framework, the second one is more complicated since ECs often encounter difficulties in classifying the different types of projects, and thus also in their evaluation. The boundaries between registries and non-pharmacological observational studies may be blurry and may generate a procedural confusion that affects the whole research process.

Given this framework, the aim of this paper is to shed light on the difference between the two types of projects. Starting from the literature, the paper proposes a distinction between non-pharmacological observational studies and registries and presents some aspects that should be considered in the intent to correctly classify them.

Specific proposals for the evaluation of observational studies will not be discussed in this work, which only aims at introducing suggestions for the evaluation of registries and on the documentation to be submitted to the ECs, with specific focus on registries dedicated to RDs.

NON-PHARMACOLOGICAL OBSERVATIONAL STUDIES AND DISEASE REGISTRIES: DEFINITIONS, SIMILARITIES, AND DIFFERENCES

Although non-pharmacological observational studies and disease registries both belong to the category of "non-interventional" projects and have a similar low risk-benefit profile, they constitute two distinct types of initiatives, with different objectives and methodologies to be considered in the assessment criteria and different documentation to be submitted in support for an ethical review.

Observational studies

Regulation 536/2014 defines the observational (or "non-interventional") study as "a clinical study other than a clinical trial" (Article 2, paragraph 2, point 4). Beyond EU Regulation 536/2014, the definition of "observational study", as well as the regulatory framework governing the conduct of such studies and the terminologies used to describe them, vary from country to country and are not harmonised internationally [10].

In the Italian legislation, the category of "observational studies" only includes studies in which a medicinal product is prescribed [5, 6, 11].

However, observational studies are not limited to those focused on prescription of medicines or medical devices. There may be different kinds of observational study, with different designs and methodologies [12]. Unlike what happens in interventional research, these are investigations in which the assignment of the patient to a specific diagnostic/therapeutic/care strategy or exposure to a situation/risk factor are not conditioned by the researcher, but fall within normal behaviour or clinical practice, without applying procedures that may present an experimental character.

According to a recent work an observational study may be defined as "collection and analysis for scientific purposes of epidemiological, administrative, clinical and biometric data related to single human subjects" [13].

Observational studies may include so-called "additional procedures" namely procedures that deviate from standard care. These procedures (like blood sampling, swabs etc.) are aimed at answering the study questions and may involve minimal risk for the subject (for instance swelling, redness, and pain at the site of sampling).

In this regard, the EC responsible for evaluating an observational study that involves "additional procedures" must determine whether they are acceptable or not in terms of invasiveness/dangerousness, and verify whether the information collected through these procedures can in some way influence the subsequent management of the patient: any additional and low-risk procedures (with possible insurance coverage) should not lead to the loss of the observational nature of the study [14]. The EC must also verify that additional procedures are adequately introduced and explained in information sheets for participants.

Registries

Registries are, by definition, instruments of an observational nature. According to the well-known definition of Gliklich *et al*., a patient registry is "an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes" [15].

A slightly different definition comes from Corrao, who defines a registry as "a file for the collection of data, records, administrative, accounting, financial, personal and legal records" [16].

According to the Decree of the President of the Council of Ministers (DPCM) of March 3rd, 2017: "Identification of surveillance systems and registers of mortality, cancer and other diseases" (DPCM March 3rd, 2017), there are different types of registries of health interest, including: disease registries; mortality registries; registries of treatments consisting of cell and tissue transplants; registries of treatments based on advanced therapy medicinal products or tissue engineering products; registries of implantable prostheses.

According to the definition of this law a "disease registry" is "an active system for the systematic collection of personal, health and epidemiological data to record and characterise all cases of risk to health or a particular disease or a relevant health condition in a defined population" [17].

The definitions for "registry" reported here, and there are many others, are not univocal. The paragraph dedicated to RD registries and *Table 1* will highlight that there are many different kinds of registries according to their sponsors, aims and design. This aspect further complicates the effort to find a valid and comprehensive definition. Nevertheless, despite their discrepancies, different definitions share the idea of systematic data collection, aimed at registering most, if not all, cases with a similar condition or exposure in a specific coverage area in a standardised way.

Observational studies and registries: main similarities

Compared to interventional studies, observational studies and registries rarely offer the chance of direct clinical benefit to the participant. However, the risks arising from participation are also low.

Rather than direct for the participant, the benefits of participation in observational studies and disease registries are of a collective nature, and derive from an increase in the scientific knowledge available on certain diseases, exposures, protective factors, or risk factors.

In some cases, collateral benefits of an individual nature are foreseeable, for example if participation in an observational study or a registry provides for the pos-

Table 1
Elements for the definition of a registry (modified from Addis *et al.* 2015 [31] and Kodra *et al.*, 2017 [32])

Field	Elements to be considered
Sponsor	Public, private, patients associations, mixed
Study objective	Single pathology or groups of pathologies
Aim	Natural disease history, genotype-phenotype correlations, epidemiological surveillance, efficacy assessment, cost effectiveness or safety of interventions
Scope and coverage	Hospital, territorial, regional, national, international; coverage of population or non-population
Stakeholders	Regulatory authorities, healthcare companies, pharmaceutical and device companies, patients, scientific societies, clinics, universities
Design	General purpose or comparative efficacy-oriented registries
Outcome	Outcome (e.g., mortality), intermediate, subjective, surrogate, process
Costs	Direct and indirect costs of the registry and the subject matter of these
Data source	Professionals, patients, existing databases, mixed
Data type	Relevant data for the evaluation of the results, periodicity, methods and tools of collection (paper, computer)
Standard	Regulatory Documents, Guidelines
Database	Data management and storage, data security, backup
Quality control	Audit, random checks, clinical monitor
Coding system	Existing coding systems, possible correlations with other databases
Dissemination of data	Open access vs restricted access, publication of reports
Lifecycle of the registry	Expected duration, stopping rules

sibility to come in contact with research groups that could initiate clinical trials for the pathology under investigation.

In addition, if the data and/or the samples collected for an observational study or a registry are periodically re-analysed, new information relevant to the participant may become available (for example, if a participant's genetic sequencing data includes variants initially classified as "variants of unknown significance", VUS, and, in subsequent analysis the variants themselves are attributed significance for certain conditions).

The most common foreseeable risk for those participating in both an observational study or disease registry is related to the processing of personal data, resulting from the accidental disclosure of personal data with possible repercussions for the social, occupational, and emotional sphere of the participant.

These risks must be carefully evaluated by the ECs and by the Data Protection Officer (DPO), also in relation to the level of data sensitivity, the possibility of tracing back the identity of the participant

and the inherent risk of stigmatisation arising from the dissemination of research data and results.

In addition, there may be psychological risks or discomforts, in particular in studies involving the use of questionnaires on particularly sensitive issues that may require psychological support at the time of the interview or immediately after.

The risks described above may require mitigation measures, as well as a specific and detailed description in the participant information documents and informed consent forms.

Observational studies and registries: main differences

Although observational methodology is common, according to Bruzzi, observational studies and disease registries are different entities and should be assessed differently (*Table 2*) [18].

An observational study, like any "study", is intended to address an open question and should be designed with this aim in mind.

Following the definition adopted by the Italian DPCM of March 3rd, 2017, a disease registry is "an active system for the systematic collection of personal, health and epidemiological data to record and characterise all cases of risk to health or a particular disease or a relevant health condition in a defined population" [16], it is not designed to address specific questions and thus it cannot be considered as a "study", even though registries focused on medicinal products or other devices usually aim at evaluating specific outcomes (*Table 1*).

Therefore, the ethical evaluation of observational studies and disease registries should be based on different criteria and require the filling of different study documents.

In this work, we will propose evaluation criteria and documents that ECs should review in the assessment of registries, in particular focused on RDs. Indeed, RD registries are an expanding area of interest for clinicians and researchers and, with increased frequency, researchers are requesting ECs to evaluate these types of proposals.

Rare disease registries

In some areas of research, particularly in RDs, registration activities have grown exponentially in recent years.

In 2021, Orphanet registered a total of 812 RD registries [19], most of them with national (561) coverage, but also European (97), regional (78) and international (76) registries.

The majority of the registries identified by Orphanet is public (84%); however, there are also private non-profit (12%) and private for profit (4%) registries.

In Italy, there are a total of 95 registers recorded by Orphanet, 70 of which with national coverage, 11 with regional coverage, 6 European registries and 8 international registries.

In a work by the EPIRARE (European Platform for Rare Disease Registries) project, which analysed the different regulatory, ethical, technical, and financial issues related to the development of RD registries [20], the latter were classified into three groups:

1) public health registries for epidemiological research, health service planning and disease surveillance. These are population registries and often collect information on more than one disease or condition, such as tumours or congenital anomalies [21, 22];
2) clinical and genetic registries that collect information on phenotypes, genotypes, family history, and clinical data;
3) treatment records aimed at the evaluation and monitoring of orphan drugs in post-marketing surveillance that collect information on the outcomes of the patients taking them.

The three types of registries described above, present very different peculiarities and problems to be analysed, also from an ethical point of view.

Table 2
Main differences between observational studies and registries (modified from Bruzzi, 2015 [18])

Observational study	Registry
Has one or more precise research/evaluation objectives	Can be multipurpose
Has a time limit	Does not have a time limit
Can provide for the *ad hoc* collection of data (e.g., questionnaires) and sometimes additional procedures (e.g., withdrawals)	Usually includes data collected for other purposes (clinical, administrative)
Data collection is aimed at the objectives of the study	Data collection is about information that "might" prove useful
Provides a research protocol with a statistical analysis plan	Should facilitate observational studies or even clinical trials

In fact, public health registries, as well as drug or medical device registries, are usually set up by law, provide almost exhaustive coverage of the phenomenon under consideration, rely on an infrastructure with a capillary network of data collection centres and are provided with long-term financial coverage. Usually, these registries do not require the collection of informed consent for participants, as participation is mandatory. Nevertheless, an information sheet is discussed with participants.

On the contrary, clinical and genetic registries are often initiated spontaneously by individual clinicians or small groups of clinicians in collaboration with patient associations (and in some cases by private sponsors) to collect as many cases as possible with a given disease or condition, in order to survey and compare the cases, their phenotypic and genotypic characteristics, their natural history, to name but a few objectives.

These initiatives are not established by law or decree, they do not include all the cases present in the territory, they do not have an infrastructure and a capillary network of centres for the collection and insertion of data, and they do not have long-term financial coverage. Informed consent of participants is always requested for this type of projects.

However, researchers usually define these initiatives as "registries" as they are aimed at a "systematic and continuous" collection data and share most of the characteristics of the registries listed in *Table 1*.

The rarity of certain diseases or conditions makes these types of activities necessary, and the establishment of such registries is encouraged, among others, by the European Commission already in a 2008 communication, "On Rare Diseases: Europe's challenges" [23], which states "paragraph 5.11, Registries and databases": "Registries and databases constitute key instruments to increase knowledge on rare diseases and develop clinical research. They are the only way to pool data in order to achieve a sufficient sample size for epidemiological research and/or clinical research. Collaborative efforts to establish data collection and maintain them will be considered, provided that these resources are open and accessible. A key issue will also be to ensure the long-term sustainability of such systems, rather than having them funded on the basis of inherently precarious project funding".

The Council of the European Union underlines the importance of rare disease registries in the Council Recommendation of June 8th, 2009, on action in the field of rare diseases [24], referred to in paragraph "II. Adequate definition, codification and inventorying of rare diseases, point 5," is recommended: "Consider supporting at all appropriate levels, including the Community level, on the one hand, specific disease information networks and, on the other hand, for epidemiological purposes, registries and databases, whilst being aware of an independent governance".

Since 2015, the European Medicines Agency (EMA) also recognises the importance of disease registries and, through the "Initiative for patient registries", encourages the regulatory use of existing patient registries and promotes the establishment of new registers where not available or inadequate, in order to collect and analyse high-quality data that can inform regulatory decisions (https:///www.ema.europa.eu/en/human-regulatory/post-authorisation/patient-registries).

More recently, clinical centres across Europe specialised in RDs research and care have built the European Reference Networks (ERNs). The first ERNs were launched in March 2017, involving more than 900 highly-specialised healthcare units in 26 EU countries. 24 ERNs are working on a range of thematic issues including bone disorders, childhood cancer and immunodeficiency (https://health.ec.europa.eu/european-reference-networks/overview_en).

ERNs aim to facilitate discussion on complex or rare diseases and conditions that require both highly specialised treatment, and specific knowledge and resources. The organisation of clinical centres in ERN is likely to foster the setup of new RD registries.

In our contribution, we will not refer to the evaluation of public health epidemiological RD registries, nor to the evaluation of safety, cost and efficacy of orphan drugs, but to RD registries, aimed primarily at describing the natural history of the disease.

CRITERIA FOR THE ETHICAL EVALUATION OF RD DISEASE REGISTRIES

In RD research, the continuous and systematic collection of health data in registries is an ethical imperative. This is particularly important because, compared to more common diseases, the rarity of conditions, the heterogeneity of their manifestations and the geographic dispersion of the cases involved limit the acquisition of useful information to the understanding of the pathological mechanisms and the therapeutic possibilities for the affected persons.

As already highlighted by Bruzzi [18], registries are not "studies" with specific cognitive objectives and structured hypotheses to be tested, but rather they are organized information systems for the census and monitoring of the conditions of interest, potentially useful for the conduct of study projects.

However, in RD research, especially when registration initiatives are undertaken by small groups of clinicians and/or patients' associations, the lack of long-term funding makes registries comparable in some respects to the category of "study projects".

Also, the lack of institutional or regulatory coverage makes these types of activities similar to study projects, for which the acquisition of consent is a necessary element for participation.

Due to the similarities that RD registries share with study projects, ECs may tend to apply to RD registries the same evaluation criteria that they apply in the evaluation of research projects like observational and clinical studies.

However, as already stated, the value of a registry does not lie in its ability to generate inferential knowledge, but in the ability to collect reliable and as complete data as possible, which may prove useful in the design and conduct of "registry based" studies [25]. The type of knowledge generated by a registry is therefore descriptive.

In addition, as compared to other projects and studies, RD registries must meet certain additional criteria and fulfil specific role requirements.

Therefore, in addition to the "traditional" criteria for the ethical evaluation of research with human beings: value, validity, equal selection of subjects, favourable risk-benefit ratio, independent review, informed consent, and respect for participants [26], ECs must consider other aspects [27] summarised in Box 1 available online as *Supplementary Material* [28-30; 33], which also determine the type of documentation to be submitted for evaluation.

EVALUATION OF RD REGISTRIES AND DOCUMENTATION TO SUBMIT TO THE ETHICS COMMITTEE

ECs should not evaluate the elements described above (Box 1 available online as *Supplementary Material*) through the same documents borrowed from clinical trials, but with *ad hoc* documentation, modulated on the purpose and specificities of the registries and possibly through checklists prepared *ad hoc*.

The documents that should be required and those that should not be required for the evaluation by an EC are mentioned below.

Documents required for the evaluation of a RD registry

The documents required for the evaluation of a RD registry are:

- letter of intent to the EC, dated and signed by the registry Sponsor, with the title of the project, the number of centres involved for multicentric studies, the duration of the project, the financial sponsor and the list of attached documents;
- project acceptance letter signed by local principal investigator (PI) and registry promoter for multicentric studies;
- information for participants and informed consent form (Box 2 available online as *Supplementary Material*);
- information and authorization for personal data treatment;
- (if applicable) information and consent form and revocation for: collection of biological samples; storage and conservation in a research biobank;
- Registry Protocol in which are explained (*Table 2*): identification of the promoters, sponsors, and PI of the registry; objectives of the registry; inclusion and exclusion criteria of participants; variables to be collected; data quality management; location of the server and security measures; governance, including the participation of patient organisations; presence of a coordinating committee (governing board) and, where appropriate, other committees (i.e. data access committee); methods of informing participants, including indications for the re-consent of participants under 18 years of age, ethical aspects and protection of privacy; project timeline with intermediate objectives;
- Case Report Form (CRF) with the fields to be completed and the distinction between mandatory and optional fields;
- Data Management Plan with a description of how data is managed during the lifetime of the project and possibly after its completion;
- (model) agreement between sponsor, institution and PI for the study including a detail of costs, availability of human and infrastructural resources;
- list of involved centres and local contacts, with letters of endorsement;
- opinion of the coordinating EC (if applicable);
- curriculum vitae of the PI with a list of relevant publications and declaration of potential conflicts of interest.

Documents not required for the evaluation of RD registries

The following documents are usually required in the evaluation of observational studies, but they are not relevant in the evaluation of RD registries and should not be requested; if deemed necessary, they should be reformulated and adapted to the specificities of the registry:

- statement on the observational nature of the clinical trial (AIFA Determination March 20th, 2008): registries, by definition, are not clinical trials and are not observational studies and the "Statement on the observational nature of the study" does not apply. Instead, it could be useful to add to the study documents a declaration that the parameters required as fields in the registry CRF are normally collected in clinical practice and the request to perform certain examinations for the individual patient is independent of the request to include the patient in the registry;
- declaration on the non-profit nature of the study, if this is the case. This document, often required by the EC amongst the documentation to be attached to the application, may include a request to declare that "the study is not finalized to the industrial and/or commercial development of the medicinal products in study, or however to economic exploitation of the same and/or of the data and results of the same experimentation";
- letter to the general practitioner (GP): generally, data recording activities do not have clinical consequences, so the general practitioner should not be involved. A document dedicated to the involvement of the GP could make sense if the GP was involved in the collection and sharing of patient data;
- statistical analysis plan: unlike clinical studies, which involve the formulation of clear and specific questions to be verified through a study design and a plausible statistical analysis plan, in RD registries the type of analysis envisaged is predominantly descriptive. The request for a statistical analysis plan may not be relevant.

Monitoring of the progress of the registries

Following the approval of a RD registry, the EC should be able to monitor its progress, in order to verify the good performance and compliance with the feasibility and sustainability requirements of the projects.

For this purpose, ECs may request the Promoter or registry PI to submit to the Committee a note docu-

menting the progress of the project on an annual basis. The note could include details on the number of cases entered, possibly indicating the contribution of each participating centre.

The PI may also provide other information documenting the development of the registry, for example, by reporting to the EC any scientific publications generated by the processing of registry data.

If the registry does not achieve the intended objectives in terms of patient inclusion and the completeness of the data collected for each patient, it is conceivable to propose an amendment to the study protocol that goes in the direction of simplification, for example a reduction of the fields in the CRF.

Once the funding period is over, the project should be concluded if it is no longer able to remain operational, if other sources of funding are not available, or if a proper coordination is not feasible.

However, keeping the collected data and making them accessible is crucial for further research projects or for the opportunity to merge the register with other registers dedicated to the same disease or groups of similar diseases.

If the registry is hosted on a platform for RD registries, the platform itself could decide on the operation of the collected data.

In the event of a change of governance of the registries, patients should be informed of the decision with the possibility of continuing or withdrawing participation.

This information should be indicated in the Data Management Plan and shared with participants.

CONCLUSIONS

In RD research there is a huge need of quality data to be collected and made available for researchers to conduct valid research on individual RDs or groups of diseases, potentially leading to scientific discoveries and/or other improvements in the life of patients.

The importance of RD registries is underlined by several recommendations at international and European level and the establishment of new RD registries should not be halted or delayed for unjustified procedural reasons. At the same time, registration activities constitute an expanding area of work and investment on the part of clinicians, institutions, and patient associations. Registries should be conducted following the right criteria and safeguards, otherwise they risk to produce useless data (lacking quality, not accessible or not interoperable), or, lacking a long-term vision and sustainability plan, to be prematurely interrupted with a consequent loss of time, energy, and financial resources.

If RD registries data are intended to support RD registry studies, the registrars responsible for their conduct and management must assure their reliability in term of timeliness and completeness of data. This aspect not only has a practical value, but also ethical implications, particularly regarding the value and validity of the study: ensuring the quality of the data and the study is a duty towards patients.

It is therefore crucial for new registration activities to be guided by tailored criteria. Within this framework, ECs would play a unique role in the evaluation of RD registries, including an assessment of their design, governance and organization. By rationalising the evaluation process and avoiding time-consuming procedures, ECs will be increasing opportunities for RD research.

Conflict of interest statement

The Authors declare that there are no conflicts of interest.

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Consequences of COVID-19 pandemic on weight gain and physical activity: a prospective cohort study from Italy

Chiara Stival[1], Alessandra Lugo[1], Giulia Carreras[2], Anna Odone[3], Piet A van den Brandt[4], Giuseppe Gorini[2], Sabrina Molinaro[5], Sonia Cerrai[5], Roberta Pacifici[6], Silvano Gallus[1] and the "Lost in Toscana" and "Lost in Italy" Investigators*

[1]Dipartimento di Epidemiologia Medica, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy
[2]Istituto per lo Studio, la Prevenzione e la Rete Oncologica, Florence, Italy
[3]Dipartimento di Salute Pubblica, Medicina Sperimentale e Forense, Università di Pavia, Pavia, Italy
[4]Maastricht University Medical Centre, Department of Epidemiology, Maastricht, the Netherlands
[5]Consiglio Nazionale delle Ricerche, Istituto di Fisiologia Clinica, Pisa, Italy
[6]Centro Nazionale Dipendenze e Doping, Istituto Superiore di Sanità, Rome, Italy
**The members of the "Lost in Toscana" and "Lost in Italy" Investigators are listed before the References*

Abstract

Introduction. It is crucial to monitor changes in body weight and physical activity (PA) to understand if short-term effects of COVID-19 pandemic have had implications over time.

Methods. This longitudinal study is based on data from 4,831 Italians aged 18-74 years interviewed during the first phase of COVID-19 pandemic (April-May 2020) and two years later (February-March 2022). Changes in body weight and PA were assessed through multivariable analyses in association with socio-demographic and psychological characteristics.

Results. Over the two years, 17.4% reported a weight gain of at least 5 kg and 32.8% a decreased PA by at least 4 hours per week. Weight gain and decreased PA were more frequent in participants from the less wealthy areas, with lower educational level and those who reported a worsening in mental health.

Conclusions. After two years from the start of the pandemic, in Italy we observed a trend toward a renormalization of body weight and PA. The segments of the population mostly affected by the pandemic are subjects with more disadvantaged socio-economic status and with an impaired mental health.

Key words
- COVID-19
- coronavirus
- lockdown
- obesity
- physical activity
- pandemic

INTRODUCTION

With the rapid spread of the coronavirus disease (COVID-19) in early 2020, due to the absence of any effective drugs or vaccines at that time, governments of more than 100 countries worldwide introduced non-medical countermeasures to limit the spread of the virus. Italy was the first European country to register an important growth in infections in early 2020 [1] and to impose a restrictive national lockdown [2] in March, 2020. The measures included the closure of all non-essential activities, including schools/university, sport activities, shops, and factories [3]. People were forced to stay at home and were only allowed to go out for grocery shopping or for health reasons. All working activities were turned into home-based working or were suspended, apart from few essential activities, including health workers and food supply and sales.

The COVID-19 lockdown caused significant disruption in people's everyday lifestyle. Many studies have already reported a detrimental effect of the confinement period in Italy on mental health [4-6] and addictive behaviours [7-10]. Some studies have already shown that confinement had a relevant impact on people dietary habits and physical activity (PA) [3, 11]. Results from a recent meta-analysis on multiple countries, showed that body weight significantly increased in the general population, with a weight mean difference of +1.57 kg (95% confidence interval, CI 1.01-2.14) after the first COVID-19 lockdown [12]. Another systematic review on PA, based on 23 Italian studies, showed a significant

Address for correspondence: Silvano Gallus, Laboratorio di Ricerca sugli Stili di Vita, Dipartimento di Epidemiologia Medica, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Via Mario Negri 2, 20156 Milan, Italy. E-mail: silvano.gallus@marionegri.it.

reduction in PA during the lockdown compared to before the pandemic [13].

These tendencies are particularly worrying since, although Italy is among the countries with lowest adult obesity prevalence (less than 8%) compared to the rest of Europe (more than 20% in most of the countries) [14], the prevalence of obesity and physical inactivity are increasing steadily worldwide and the COVID-19 pandemic may have boosted these trends. Previously published studies have shown that lifestyle changes, overeating and increasing sedentarism during the COVID-19 lockdown period might have led to an increase in obesity prevalence, and have proposed a new definition of "covibesity" pandemic [15].

Estimates on childhood obesity prevalence are likewise alarming, since Italy ranges among the countries with highest prevalence (around 16%) compared to the rest of Europe (approximately 12%) [16], with large disparities by socio-economic status and geographic area [17].

It is therefore crucial to monitor changes in weight and PA habits and their correlates on a long-time period to understand if short-term effects of COVID-19 pandemic have had implications over time, this to target subgroups of the population that remained mostly hit by the pandemic period. Therefore, the aim of this study is to evaluate the long-term effects of the COVID-19 pandemic on weight gain and PA in a large sample of the Italian adult population.

MATERIALS AND METHODS

This longitudinal study is based on data from the "Lost in Italy" survey [2] and the "Lost in Toscana" survey. The fieldwork was conducted by Doxa, the Italian branch of the Worldwide Independent Network/Gallup International Association, and coordinated by Mario Negri Institute, the Oncologic Network, Prevention and Research Institute (Istituto per lo Studio e la Prevenzione Oncologia, ISPRO), and other Italian universities and research institutes.

The baseline sample, representative of the Italian population aged between 18 and 74 years in terms of age, sex, socio-economic characteristics and geographic area, was extracted from the Doxa online panel, consisting of more than 140,000 adults from all the Italian regions, including about 40,000 active subjects. Overall, 6,003 subjects took part to a first interview (baseline interview) between April 27th and May 3rd, 2020. All participants of the baseline interview accepted to be re-contacted for a follow-up interview, and 4,831 took part to the second interview between February 24 and March 21, 2022.

The study protocol of the "Lost in Italy" study was approved by the ethics committee (EC) of Mario Negri Institute (EC of Istituto Besta, file number: 71-73, April 2020), and that of the "Lost in Toscana" survey was approved by the EC of ISPRO (Comitato Etico Regionale per la Sperimentazione Clinica della Toscana – sezione Area Vasta Centro, file number: CEAVC 19834, April 2021). All participants provided their informed consent to participate to the study. The study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Outcome variables

In the baseline and follow-up interview, individuals were asked to report their height and weight. Body mass index (BMI) was computed as the ratio between self-reported weight (kg) and height (m^2), and was categorized according to the standard classification by the WHO [18] i.e., underweight (BMI <18.5 kg/m^2), normal weight (BMI between 18.5 and 24.9 kg/m^2), overweight (BMI between 25.0 and 29.9 kg/m^2), and obesity (BMI ≥30.0 kg/m^2). Obesity was then categorized in obesity class one (BMI between 30.0 and 34.9 kg/m^2), obesity class two (BMI between 35.0 and 39.9 kg/m^2) and obesity class three (BMI ≥40.0 kg/m^2).

Participants provided also information on the average number of hours per week (h/w) of PA (sports and recreation, bicycle commuting) they practiced.

In the baseline survey, in order to evaluate any change in BMI and PA occurred during COVID-19 lockdown, weight and average number of h/w of PA were reported twice, referring to the moment of the interview (reference time: April-May 2020) and before the start of the pandemic (reference time: early February 2020).

Independent variables

The baseline and follow-up questionnaires collected information on socio-demographic characteristics such as age, sex and level of education, marital status, if they had any children, the crowding of their house and characteristics of the area of residence, including geographic area (i.e., northern, central and southern Italy) and municipality size.

The baseline interview also investigated changes in participants' sexual activity during the lockdown.

A specific section of the questionnaires was focused on selected addictive behaviours. Participants reported their smoking status, if they used cannabis, if they were at risk of alcohol use disorder (according to AUDIT-C scale [19]) and their gambling habits.

Another section was on mental health outcomes, such as quality of life (assessed with the visual analogue scale, VAS [20]), quality and quantity of sleep (using 2 items of the Pittsburgh Sleep Quality Index, PSQI [21]), anxiety (generalized anxiety disorder, GAD-2 scale [22]) and depressive symptoms (patient health questionnaire, PHQ-2 [23]).

In the baseline survey, all the questions on addictive behaviours and mental health outcomes were asked twice referring to two different time periods (before the onset of the pandemic and during the lockdown).

Statistical analysis

Weight and BMI mean, and the distributions of BMI and physical activity levels were assessed in the three different time points (February 2020, April 2020 and March 2022). We used unconditional multiple logistic regression models to estimate odds ratios (OR), and corresponding 95% confidence intervals (CI), of increasing weight by at least 5 kg and of decreasing PA by at least four h/w at follow-up, compared to before the onset of the pandemic (i.e., March 2022 *vs* February 2020). All the models were adjusted for selected socio-demographic variables, i.e., sex, age, level of edu-

cation and geographic area. All statistical analyses were performed using the software SAS, version 9.4 (Cary, North Carolina, USA).

RESULTS

Table 1 and *Supplementary Table 1 (available online)* show the distribution of weight, BMI and PA before the onset of the COVID-19 pandemic, during the COVID-19 lockdown and at follow-up, and their changes in the three different periods, overall and by sex. In general, participants' average weight increased approximately by 1.0 kg during the COVID-19 lockdown (from 72.9 kg to 73.8 kg). After two years, the average weight was 0.5 kg more compared to before the pandemic (from 72.9 kg to 73.4 kg).

The prevalence of overweight participants increased by 3.9% during the COVID-19 lockdown (from 30.9% to 32.1%) and by 6.5% after two years from the start of the pandemic (from 30.9% to 32.9%). Obesity prevalence increased by 17.7% during the lockdown (from 12.4% to 14.6%) and was 8.1% more at follow-up (from 12.4% to 13.4%), compared to before the pandemic. The increase in obesity prevalence during the lockdown and two years later was +20.5% and +8.7%, respectively, among men, and +15.8% and +7.5%, respectively, among women.

Overall, the average h/w of PA approximately halved during the COVID-19 lockdown (from 4.2 h/w to 2.3 h/w) returning to 4.1 h/w after two years. The decrease in the proportion of participants practicing physical activity 4 h/w or more during the lockdown and two years later was -51.1% and -12.1% overall, and respectively, -55.4% and -10.9% among men, and -45.1% and -13.7% among women.

Figure 1 shows the distribution of changes in weight in the three different time periods: the right asymmetry of the first histogram (panel A) reveals that during the COVID-19 lockdown, an increase in weight occurred in the majority of the participants (50.8%). The third histogram (panel C), showing weight change after two years from the start of COVID-19 pandemic compared to before, shows a less asymmetric shape. However, an increase in weight persisted in the majority of the participants (47.3%).

Figure 2 shows the distribution of changes in PA in the three different time periods: the first histogram (panel A), left asymmetric, shows a substantial decrease in the average time spent for PA during the COVID-19 lockdown (in 53.1% of participants). The second histogram (panel B), showing changes that occurred after two years from the start of the pandemic compared to during the lockdown, is mirrored by the first histogram, showing a re-start in PA. The third histogram (panel C), showing changes after two years from the beginning of the COVID-19 pandemic compared to before the pandemic, shows a re-normalization in the time spent in

Table 1
Distribution on 4,831 Italian adults aged 18-74 years, according to their weight, body mass index (BMI) and physical activity, before the COVID-19 lockdown (February 2020), during the COVID-19 lockdown (April-May 2020) and at follow-up (February-March 2022)

	Total (N=4,831)			Men (N=2,487)			Women (N=2,344)		
	Feb 2020	Apr 2020	Mar 2022	Feb 2020	Apr 2020	Mar 2022	Feb 2020	Apr 2020	Mar 2022
Weight (kg), mean (SD)	72.9 (16.2)	73.8 (16.6)	73.4 (15.8)	79.9 (14.1)	81.0 (14.4)	80.5 (13.8)	65.4 (14.9)	66.2 (15.3)	65.9 (14.3)
BMI (kg/m²), mean (SD)	25.0 (4.9)	25.4 (5.0)	25.2 (4.6)	25.8 (4.1)	26.1 (4.2)	26.0 (4.0)	24.2 (5.4)	24.6 (5.6)	24.4 (5.1)
BMI categories (kg/m²)									
Under/normal weight (<25.0)	56.8	53.3	53.8	48.9	44.3	45.5	65.1	62.8	62.5
Overweight (25.0-29.9)	30.9	32.1	32.9	38.4	40.4	40.7	22.9	23.4	24.5
Obese (≥30)	12.4	14.6	13.4	12.7	15.3	13.8	12.0	13.9	12.9
Obese class I (30.0-34.9)	9.4	11.2	10.1	10.0	12.2	11.1	8.7	10.0	9.1
Obese class II (35.0-39.9)	2.0	2.5	2.4	1.9	2.3	2.2	2.1	2.6	2.7
Obese class III (≥40)	1.0	1.0	0.8	0.7	0.8	0.5	1.2	1.2	1.2
Physical activity (hours per week), mean (SD)	4.2 (4.9)	2.3 (4.0)	4.1 (5.9)	4.6 (5.0)	2.3 (3.7)	4.6 (5.9)	3.8 (4.9)	2.2 (4.2)	3.6 (5.8)
Physical activity categories (hours per week)									
0	23.7	45.3	23.2	20.2	43.7	19.7	27.5	46.9	27.0
1-3	29.9	32.0	36.1	28.4	33.4	34.5	31.5	30.6	37.7
4-6	26.0	13.9	23.0	28.2	14.3	25.1	23.6	13.5	20.7
7+	20.4	8.8	17.8	23.2	8.6	20.7	17.4	9.0	14.7

N: number; BMI: body mass index; SD: standard deviation.

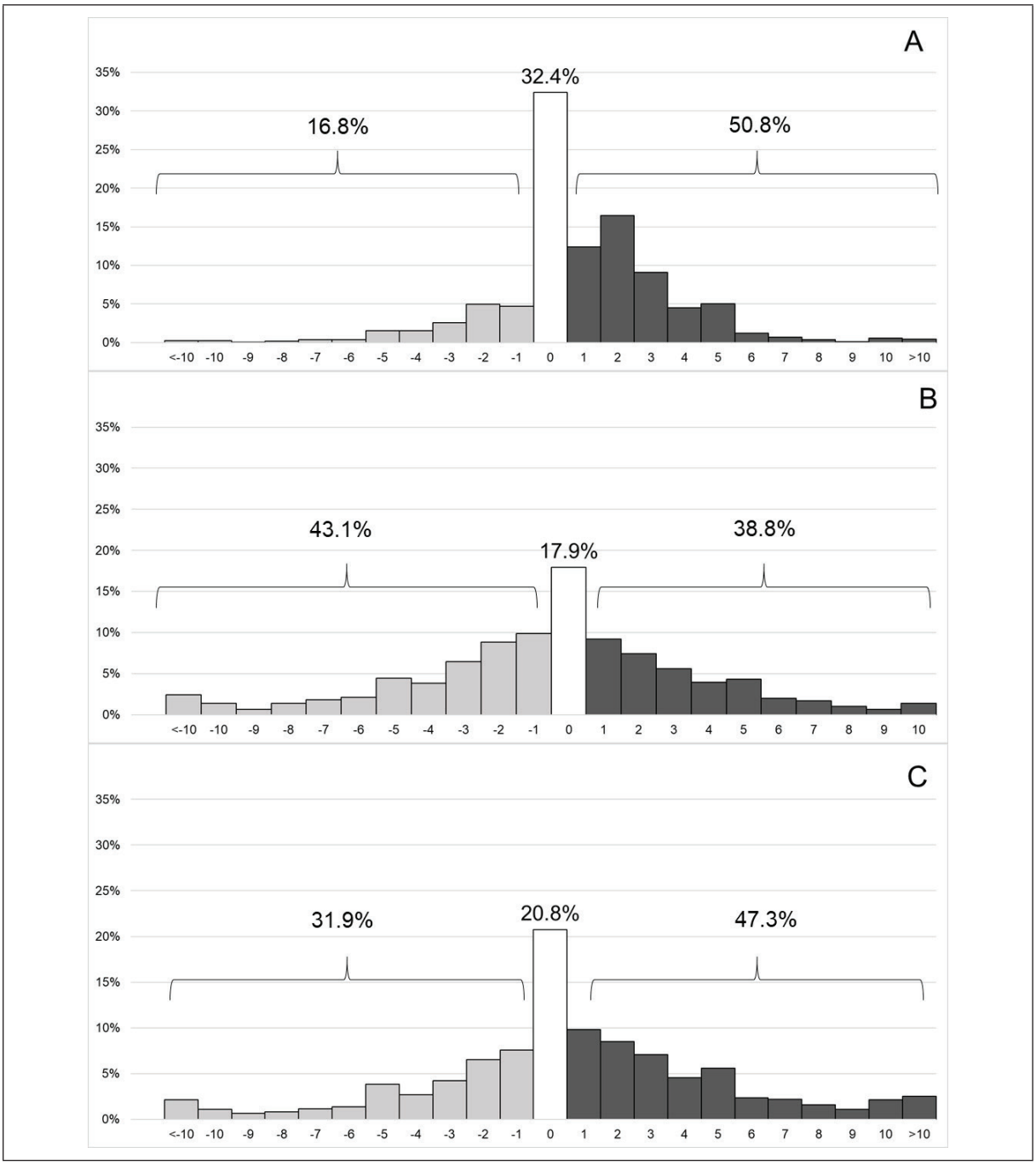

Figure 1
Distribution (%) of 4,831 Italian adults aged 18-74 years, according to a change in weight (kg). Panel A: during the COVID-19 lockdown (April-May 2020) compared to before the COVID-19 lockdown (February 2020); panel B: at follow-up (February-March 2022) compared to during the COVID-19 lockdown; and panel C: at follow-up compared to before the COVID-19 lockdown.

PA, revealing a more balanced distribution of those who increased (32.8%) and decreased (40.4%) the average time spent in PA.

Overall, 47.3% of participants increased their weight by at least 1 kg after two years from the beginning of the pandemic, and 17.4% increased by at least 5 kg (*Table 2*). In the same period, a decrease in PA by at least one h/w occurred in 40.5% of the participants and a decrease by at least 4 h/w was reported in 32.8% of the subjects. Participants increasing their weight by at least 5 kg were more frequently younger people (p for trend <0.001), with a lower level of education (p for trend =0.002) and from southern Italy or Islands (OR=1.35; 95% CI: 1.13-1.60) compared to northern Italy. Participants decreasing their PA by at least 4 h/w were more frequently from southern Italy or Islands, compared to those from northern Italy (OR=1.36; 95% CI: 1.10-1.68). No significant association was observed between sex, age, marital status, municipality size, and household characteristics, and both an increase in weight and a decrease in PA.

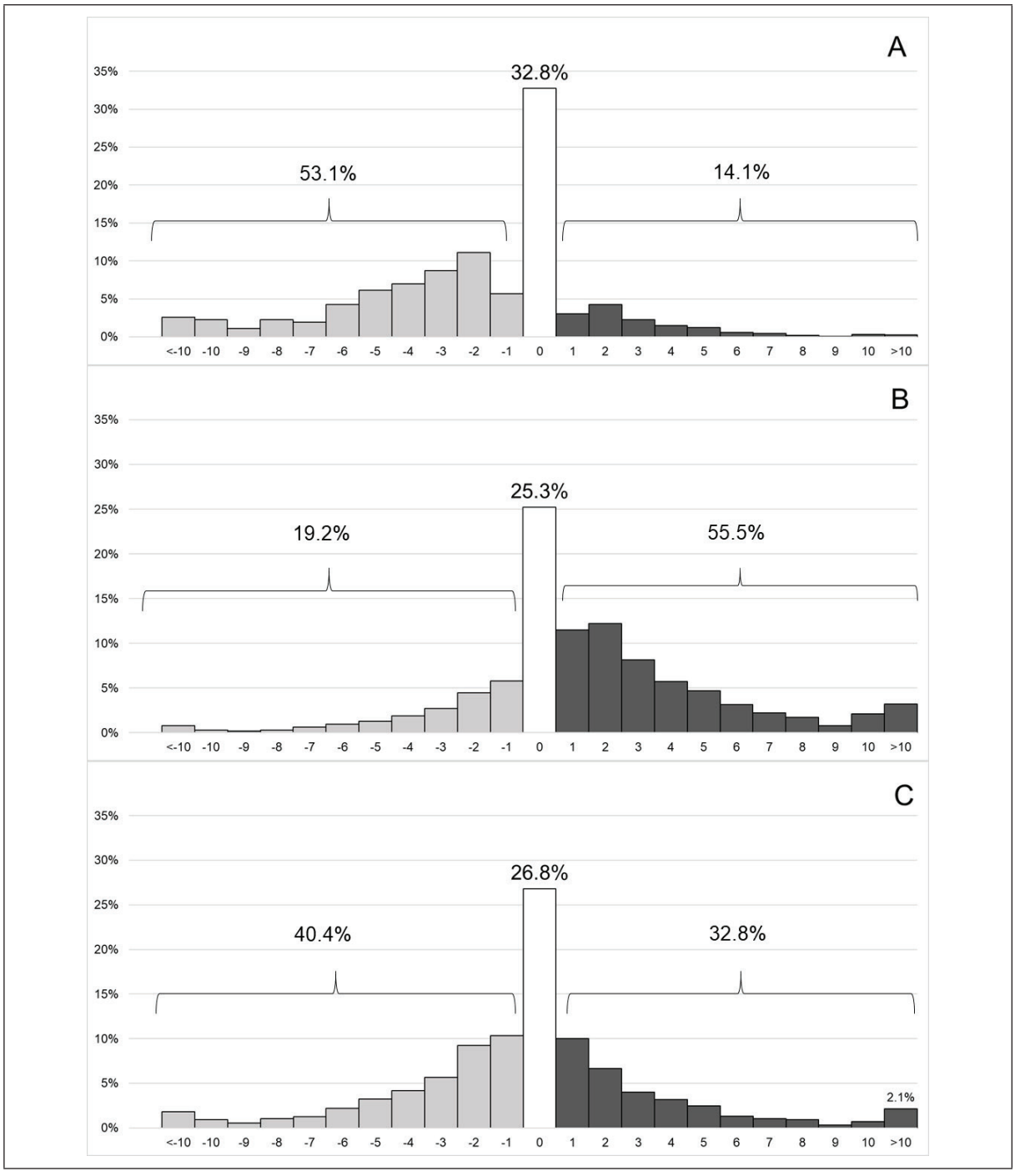

Figure 2
Distribution (%) of 4,831 Italian adults aged 18-74 years, according to a change in hours per week (h/w) of physical activity. Panel A: during the COVID-19 lockdown (April-May 2020) compared to before the COVID-19 lockdown (February 2020); panel B: at follow-up (February-March 2022) compared to during the COVID-19 lockdown; and panel C: at follow-up compared to before the COVID-19 lockdown.

An increase in weight by 5 kg or more was more frequent in participants who reported, during the two years from the start of the pandemic, a decrease in PA (OR=1.37; 95% CI: 1.17-1.59), in quality of life (OR=1.27; 95% CI: 1.09-1.48), in sleep quality (OR=1.20; 95% CI: 1.02-1.41), and an increase in anxiety symptoms (OR=1.20; 95% CI: 1.03-1.40) and depressive symptoms (OR=1.22; 95% CI: 1.04-1.42; *Table 3*). A decrease in PA by 4 h/w or more was more frequently reported in participants who, in the two years from the start of the COVID-19 pandemic, reported an increase in their weight (OR=1.37; 95% CI: 1.14-1.63), a decrease in quality of life (OR=1.20; 95% CI: 1.01-1.43) and an increase in anxiety symptoms (OR=1.23; 95% CI: 1.02-1.48).

Supplementary Table 2 (available online) shows the

Table 2
Distribution of 4,831 Italian adults, according to an increase in weight by 5 kg or more and a decrease in physical activity by 4 hours per week (h/w) or more at follow-up (February-March 2022) compared to before lockdown (February 2020), overall and by selected socio-demographic characteristics. Odds ratios[a] (OR) and 95% confidence intervals (CI). Italy

Characteristics	N	Increase in weight by 5 kg or more at follow-up compared to before COVID-19		N[b]	Decrease in physical activity by 4 h/w or more at follow-up compared to before COVID-19	
		%	OR (95% CI)		%	OR (95% CI)
Total	4,831	17.4		2,241	32.8	
Sex						
Men	2,487	17.3	1.00[c]	1,279	32.1	1.00[c]
Women	2,344	17.5	0.99 (0.85-1.15)	962	33.9	1.10 (0.92-1.32)
Age group						
18-34	1,062	20.8	1.00[c]	497	32.8	1.00[c]
35-54	2,228	17.9	0.86 (0.71-1.03)	998	31.6	0.97 (0.77-1.23)
55-74	1,541	14.4	**0.63 (0.51-0.77)**	746	34.6	1.13 (0.88-1.44)
P for trend			**<0.001**			0.280
Level of education						
Low	662	20.4	1.00[c]	267	37.1	1.00[c]
Intermediate	2,322	17.8	0.82 (0.66-1.02)	1,042	31.3	0.76 (0.57-1.01)
High	1,847	15.9	**0.70 (0.55-0.88)**	932	33.4	0.85 (0.64-1.14)
P for trend			**0.002**			0.738
Geographic area						
North	2,700	16.0	1.00[c]	1,289	30.6	1.00[c]
Center	841	17.2	1.11 (0.90-1.36)	406	34.0	1.16 (0.92-1.47)
South and Islands	1,290	20.5	**1.35 (1.13-1.60)**	546	37.4	**1.36 (1.10-1.68)**
Marital status						
Married	3,315	17.4	1.00[c]	1,564	32.2	1.00[c]
Divorced/separated	316	17.4	1.10 (0.81-1.50)	132	40.2	1.44 (0.99-2.08)
Widowed	69	10.1	0.60 (0.27-1.34)	26	38.5	1.33 (0.60-2.98)
Single	1,131	17.9	0.90 (0.74-1.08)	519	32.6	1.03 (0.82-1.30)
Municipality size (inhabitants)						
<10,000	984	18.8	1.00[c]	439	33.7	1.00[c]
10,000-100,000	2,179	16.9	0.87 (0.71-1.06)	1,009	32.5	0.92 (0.73-1.18)
100,000+	1,668	17.3	0.94 (0.76-1.16)	793	32.8	0.94 (0.73-1.22)
P for trend			0.721			0.723
Number of people at home						
1	519	16.6	1.00[c]	250	35.2	1.00[c]
2-3	2,810	17.3	0.99 (0.77-1.28)	1,297	33.2	0.88 (0.66-1.17)
4+	1,502	17.9	0.97 (0.74-1.27)	694	31.4	0.80 (0.59-1.09)
P for trend			0.783			0.153
Children 0-14						
Yes	1,453	18.2	1.02 (0.86-1.21)	665	31.4	0.93 (0.76-1.15)
No	3,378	17.1	1.00[c]	1,576	33.4	1.00[c]

N: number.
[a]Estimated with unconditional multiple logistic regression models after adjustment for sex, age, level of education and geographic area; estimates in bold type are statistically significant at 0.05.
[b]This analysis is based on subjects who did some physical activity before the lockdown. Thus, 2,590 subjects were excluded because they were inactive (physical activity of 0 h/w) before the beginning of the lockdown.
[c]Reference category.

Table 3
Distribution of 4,831 Italian adults, according to an increase in weight by 5 kg or more and a decrease in physical activity by 4 hours per week (h/w) or more at follow-up (February-March 2022) compared to before lockdown (February 2020), overall and by a change in selected lifestyle habits and mental health characteristics. Odds ratios[a] (OR) and 95% confidence intervals (CI). Italy

Characteristics	N	Increase in weight by 5 kg or more at follow-up compared to before COVID-19		N[b]	Decrease in physical activity by 4 h/w or more at follow-up compared to before COVID-19	
		%	OR (95% CI)		%	OR (95% CI)
Total	4,831	17.4		2,241	32.8	
Increased weight						
Yes				1,119	36.4	**1.37 (1.14-1.63)**
No				1,122	29.3	1.00[c]
Decreased physical activity						
No	2,877	15.7	1.00[c]			
Yes	1,954	20.0	**1.37 (1.17-1.59)**			
Decreased quality of life						
No	2,622	15.9	1.00[c]	1,184	31.0	1.00[c]
Yes	2,209	19.3	**1.27 (1.09-1.48)**	1,057	34.9	**1.20 (1.01-1.43)**
Decreased sleep quantity						
No	2,893	16.7	1.00[c]	1,315	32.2	1.00[c]
Yes	1,938	18.6	1.13 (0.97-1.32)	926	33.8	1.07 (0.89-1.28)
Decreased sleep quality						
No	3,467	16.6	1.00[c]	1,589	32.2	1.00[c]
Yes	1,364	19.4	**1.20 (1.02-1.41**)	652	34.4	1.10 (0.90-1.33)
Increased anxiety symptoms						
No	3,080	16.4	1.00[c]	1,430	31.2	1.00[c]
Yes	1,751	19.2	**1.20 (1.03-1.40**)	811	35.8	**1.23 (1.02-1.48)**
Increased depressive symptoms						
No	3,167	16.4	1.00[c]	1,483	31.8	1.00[c]
Yes	1,664	19.5	**1.22 (1.04-1.42)**	758	34.8	1.13 (0.94-1.37)

N: number.
[a]Estimated with unconditional multiple logistic regression models after adjustment for sex, age, level of education and geographic area; estimates in bold type are statistically significant at 0.05.
[b]This analysis is based on subjects who did some physical activity before the lockdown. Thus, 2,590 subjects were excluded because they were inactive (physical activity of 0 h/w) before the beginning of the lockdown.
[c]Reference category.

ORs of an increase by at least 5 kg in weight and a decrease by 4 h/w in PA, according to selected lifestyle habits and addictive behaviours. An increase in weight and a decrease in PA were more frequently reported with increasing BMI (p for trend=0.020 and p for trend <0.001, respectively). Weight gain occurred more frequently in current smokers (OR=1.22; 95% CI: 1.03-1.45) compared to never smokers. Subjects doing PA 7 or more h/w before the lockdown, more frequently reduced their activity after two years compared to those doing 4-6 h/w (OR=5.11; 95% CI: 4.21-6.21).

DISCUSSION

Using a prospective cohort study, we provide for the first time in Italy the long-term effects of the COVID-19 pandemic on weight gain and PA. During nation-wide COVID-19 lockdown, weight gain occurred in 51% and weight loss in 17% of the participants, whereas after two years from the beginning of the COVID-19 pandemic, weight gain persisted in 47% and weight loss in 32% of the sample. Although PA halved during the COVID-19 lockdown (from 4.2 h/w to 2.3 h/w), it almost re-reached pre-pandemic levels in the following two years. However, the proportion of more active individuals (practicing 4 h/w or more of physical activity) declined two years after the start of the pandemic.

In line with extensive literature from European and non-European studies, [12, 24] during the COVID-19 lockdown we observed an increase in body weight in the Italian adult population. During the lockdown, forced physical inactivity coupling with altered eating habits (e.g., an increased consumption of snacks and comfort food [15]), often associated with stress and emotional turmoil, have led the nutritional energy balance towards weight increase with calorific intake exceeding expenditure [25]. Our data reveal that, two years after the beginning of the COVID-19 pandemic, although weight gain has greatly receded, weight was still higher in approximately 50% of the population. Thus, it is possible that the changes in eating habits occurred during

the lockdown, combined with working from home and increased take-away food purchases, [15, 26, 27] may have persisted over time causing long-term effects.

PA sharply decreased during COVID-19 lockdown. This is in line with two systematic reviews, one based on 23 Italian studies and the second on 18 international studies, showing a significant reduction in PA during the COVID-19 lockdown compared to before the pandemic [13, 24]. Nevertheless, after two years from the beginning of the COVID-19 lockdown we observed an approximate re-normalization in PA habits in the general population.

Overall, our data reveal that the sub-groups of the population who got mostly hit by the pandemic were those from the South of Italy and the Italian islands, the least wealthy areas of the country, and those with a lower level of education. Economic hardship already present prior the pandemic may have further limited the dietary choices. Food insecurity, intensified by job losses and economic uncertainty, may have encouraged purchasing of cheap, poor quality foods with heavily processed, energy-dense nutrient-poor products [28] and discouraged purchasing and consumption of healthy fresh items [25]. A study on Italian older adults [27], evaluating changes towards a Mediterranean lifestyle occurring during the lockdown, revealed a global improvement in the adherence to the Mediterranean diet in the Italian population, partly explained by an increased time spent for home food preparation, typical feature of traditional healthy diets. However, changes were disproportionately distributed across socioeconomic strata, with higher level of education and wealth being independent predictors of improvements in line with a Mediterranean lifestyle during the COVID-19 pandemic. Moreover, low socioeconomic status and educational level have long been linked with fewer opportunities for PA [24] and this aspect may have been exacerbated after the lockdown.

The COVID-19 pandemic has been associated with increased levels of stress, anxiety and depression in the general population [4-6, 29] and these are associated with unhealthy eating patterns and sedentary behaviours [30]. In line with a recent study [31], we identified decreased sleep quality as a risk factor for weight gain. Moreover, people who gained body weight and decreased PA were more likely to report in the same period higher levels of stress and anxiety, and a worsened quality of life [3, 26]. These results suggest that, despite average levels of PA and body weight have tended to reach pre-pandemic periods, the population subgroups on whom the pandemic has left major effects are the most fragile ones, characterized by impaired mental health.

The main strength of this study is that the survey was carried out longitudinally on a sample of the population aged 18-74 years, since most studies on this topic are cross sectional surveys. This enabled us to individually observe the long-term effects of COVID-19 pandemic on weight gain and PA in the Italian population. Future follow-ups of this cohort would allow us to evaluate the implications of the pandemic on a longer time period. Another strength of this study is the large sample size that allowed us to observe small differences. Limitations of our study include the self-reported anthropometric and physical activity data. More importantly, a possible selection bias cannot be ruled out, being this study based on a sample of online panelists, characterized by a higher socio-economic level compared with the general population. Another limitation worth to be mentioned is that we did not have the possibility to consider the differential application of the restriction measures in the different regions during the considered time period, which may have had an influence on changes in body weight and physical activity.

CONCLUSIONS

In conclusion, the study shows that, after two years from the start of the COVID-19 pandemic, although we have observed a trend toward a renormalization of body weight and PA in the Italian population, the segments of the population that remain most affected by the pandemic are the less wealthy and educated ones and the most fragile from a mental health perspective. Therefore, campaigns aimed at promoting healthy lifestyles and correct dietary habits need to target these at-risk subgroups.

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Authors' contributions

All Authors conceptualized and designed the study. AO, RP and GC provided data. CS analysed the data under the supervision of SG and AL. CS, SG and AL wrote the first draft of the manuscript. PAvdB and AO provided important intellectual supports in various steps of the study. All Authors provided important contributions for the interpretation of findings and carefully revised the final version of the manuscript. All Authors have read and approved the last version of the manuscript.

Data availability statement

Data that support the findings of this study and materials are available from the corresponding Author, SG, upon reasonable request.

Conflict of interest statement

The Authors declared no conflict of interest.

The members of the "Lost in Toscana" Investigators

Giulia Carreras, Giuseppe Gorini, Filippo Monti (Oncologic Network, Prevention and Research Institute, Florence, Italy); Sabrina Molinaro, Sonia Cerrai, Silvia Biagioni (National Research Council, Institute of Clinical Physiology, Pisa, Italy); Fabio Voller, Elena Andreoni, Martina Pacifici (Agenzia Regionale di Sanità, ARS Toscana, Florence, Italy); Valentino Patussi, Chiara Cresci, Donatello Cirone (Centro Alcologico Regionale Toscano, CART-Careggi, Florence, Italy).

The members of the "Lost in Italy" Investigators

Silvano Gallus, Alessandra Lugo, Chiara Stival (Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy); Luisa Mastrobattista, Ilaria Palmi, Renata Solimini, Claudia Mortali (Istituto Superiore di Sanità, Rome, Italy); Anna Odone (University of Pavia, Pavia, Italy); Giulia Carreras, Giuseppe Gorini, Filippo Monti (Oncologic Network, Prevention and Research Institute, Florence, Italy); Andrea Amerio (University of Genoa, Genoa, Italy); Tiziana Fanucchi (ASST Fatebenefratelli Sacco, Milan, Italy).

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Post-Acute Sequelae of COVID-19 Checklist (PASC-C): a screening tool for Long COVID physical, psychological, and cognitive symptoms

Daniela Mancini[1], Marina Maffoni[1], Valeria Torlaschi[1], Alessandra Gorini[2], Maria Teresa La Rovere[3], Cira Fundarò[4], Francesco Fanfulla[5], Maurizio Bussotti[6], Sergio Masnaghetti[7] and Antonia Pierobon[1]

[1]*Servizio di Psicologia dell'Istituto di Montescano, Istituti Clinici Scientifici Maugeri IRCCS, Montescano (PV), Italy*
[2]*Servizio di Psicologia dell'Istituto di Milano, Istituti Clinici Scientifici Maugeri IRCCS, Milan, Italy*
[3]*Dipartimento di Cardiologia Riabilitativa dell'Istituto di Montescano, Istituti Clinici Scientifici Maugeri IRCCS, Montescano (PV), Italy*
[4]*Servizio di Neurofisiopatologia dell'Istituto di Montescano, Istituti Clinici Scientifici Maugeri IRCCS, Montescano (PV), Italy*
[5]*Servizio di Medicina del Sonno dell'Istituto di Montescano, Istituti Clinici Scientifici Maugeri IRCCS, Montescano (PV), Italy*
[6]*Servizio di Riabilitazione Cardiorespiratoria dell'Istituto di Milano, Istituti Clinici Scientifici Maugeri IRCCS, Milan, Italy*
[7]*Servizio di Riabilitazione Cardiorespiratoria dell'Istituto di Tradate, Istituti Clinici Scientifici Maugeri IRCCS, Tradate (VA), Italy*

Abstract

Background. The management of Long COVID symptoms is necessary. This study proposes a screening tool for psycho-physical COVID-19 sequelae. Patients' experiences after COVID-19 are also described.

Method. 84 COVID-19 patients (66.2±11.0 years old; 71.4% male) underwent a phone interview 1-2 years after the disease using the *ad-hoc* "Post-Acute Sequelae of COVID-19 Checklist (PASC-C)". It explores 30 physical, psychological, and cognitive symptoms clustered into 10 areas, with possible clinical recommendations in case of high severity scores (>50) of a symptom or the presence of two or more ones within the same area.

Results. Overall, fatigue (69%), dyspnea (52.4%), memory disturbances (44%), joint-muscle pain (41.7%), vision/hearing loss (40.5%), anxiety (40.5%) persist one-two years after COVID-19 disease. Being a survivor was primarily defined in terms of being "lucky".

Conclusions. PASC-C seems promising in monitoring psycho-physical sequelae of Long COVID and providing tailored suggestions to care for the patient over time.

Key words

- Long COVID
- physical symptoms
- psychological disorders
- cognitive impairments
- screening
- rehabilitation

INTRODUCTION

It is evident that COVID-19 [1] may cause enduring effects, as shown by the increasing rate of patients reporting various sequelae of symptoms after infection [2-4], even if the molecular tests no longer show SARS-CoV-2 on swabs. Current evidence suggests that 10-20% of subjects report struggling with a heterogeneous complex of subacute and chronic clinical manifestations [5], which may affect multiple organ systems, precluding a full return to the previous health status [6]. These patients and these multifaceted clinical conditions are known by the terms "Long COVID-haulers" and "Long COVID", respectively [7].

The National Institute for Health and Care Excellence (NICE), the Scottish Intercollegiate Guidelines Network (SIGN), and the Royal College of General Practitioners (RCGP) have identified two different conditions as a result of COVID-19 disease, which are not yet explained by an alternative diagnosis [8]. In detail, after the acute phase of COVID-19, patients

Address for correspondence: Marina Maffoni, Istituti Clinici Scientifici Maugeri IRCCS, Via per Montescano 35, 27040 Montescano (PV), Italy. E-mail: marina.maffoni@icsmaugeri.it.

may cope with both the "persistent symptomatic COVID-19 disease", struggling with signs and symptoms lasting from 4 to 12 weeks, and the "post-COVID-19 syndrome", in case signs and symptoms – developed during or after the acute disease – last for more than 12 weeks [8]. These two terms are included in the "Long COVID" condition, which has been defined as "signs and symptoms that continue or develop after 4 weeks from COVID-19 acute infection" [8, 9].

Overall, the prevalence of Long COVID symptoms varies greatly among different studies, affecting subjects regardless of sex, age, and the severity of the acute infection [8]. Specifically, it has been identified more than one hundred possible symptoms [10], proving the multi-systemic nature of this condition impacting physical, psychological, and cognitive levels. More in detail, it has emerged that the possible and predictable clinical manifestations in COVID-19 survivors may have pulmonary, cardiovascular, renal, hematological, and gastrointestinal nature, as well as they may concern the central nervous system too [11, 12]. At a cognitive level, 36% of Long COVID patients may experiment cognitive impairment [12], leading to a new condition named "brain fog", characterized by mild impairment in memory, language, and executive functions [6, 12, 13]. These cognitive deficits are debilitating, worsening daily functioning and decreasing health-related quality of life (HRQoL) [14], and may evolve into multiple neurocognitive impairments [15]. In fact, mental health consequences may persist after COVID-19 disease even leading to psychopathological outcomes [16], both in hospitalized [17] and non-hospitalized [18] patients. The clinical manifestation includes depression, anxiety, panic disorders, post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), sleep disturbances, chronic pain, and fatigue. Moreover, the variety of symptoms and the focus of professionals on specific symptoms according to their specialization, may leave patients with the impression that they are not fully understood and globally taken in care [19].

To date, in the literature, some clinical tools to assess various COVID-19 sequelae have been proposed. For instance, we can read about an online screening tool comprehensive of 14 questions assessing post-acute COVID-19 syndrome [20]. Specifically, the authors investigated if general PASC symptoms (e.g., fatigue, impairment of sense of smell/taste) were experienced as problematic by the subjects through the use of a 4-point Likert scale. Similarly, a single-center study proposed a questionnaire investigating also comorbidity, characteristics of the acute phase of COVID-19, and the presence of persistent symptoms [21]. Again, a remote COVID-19 rehabilitation assessment tool investigates pain, fatigue, sleep, mood, and functional limitations [22]. Other authors proposed an impact tool that analyses symptoms experienced in the last 30 days, concerning digestion, eyes, skin and hair and others [23]. However, the majority of previous studies focus on specific symptoms [24, 25] and, to the best of our knowledge, a proper clinical and multidisciplinary assessment of this syndrome has not yet been reached, even if it is considered a global health challenge to be addressed [26]. Indeed, current Long COVID tools assess only a small part of the possible sequelae after the acute phase of COVID-19, or only for a limited time, without a focus on the period before, during, and after the acute phase. It is crucial to propose a full-comprehensive clinical screening tool to ameliorate the interface between general practitioners and specialists in order to effectively follow the patients over time [27], as well as to provide the patient with holistic care [19]. To bridge this gap, the main aim of this study is to preliminary present the multidimensional Post-Acute Sequelae of COVID-19 Checklist (PASC-C), a clinical checklist that has been developed to assess possible physical, psychological, and cognitive sequelae over time, focusing on time before and after the disease. Data concerning its feasibility are therefore presented.

A secondary aim is to correlate PASC-C perceived severity symptoms with HRQoL. Specifically, the HRQoL is assessed in relation to functional, pneumological, algic, gastroenteric, cardiological, dermatological, neurocognitive, and psychological symptoms, as well as to sleep disorders and other complaints (i.e. weight loss/gain, hyper-sweating, discontinuous fever).

CHECKLIST PASC-C

PASC-C has been developed by the Units of Psychology, Neurophysiopathology, Respiratory Function and Sleep Medicine and by the Department of Cardiac Rehabilitation of the Montescano Institute of "Istituti Clinici Scientifici Maugeri IRCCS" (*Servizio di Psicologia, Servizio di Neurofisiopatologia, Servizio di Medicina del Sonno e Dipartimento di Cardiologia Riabilitativa dell'Istituto di Montescano*), to assess the presence of possible physical, psychological, and cognitive Long COVID symptoms. This checklist has been constructed through the discussion of the daily clinical experience and the review of existing literature. In particular, Lopez-Leon and colleagues' systematic review was considered a milestone as unveiled more than 50 symptoms related to sequelae of COVID-19 and fostered further studies for procedures and tools useful to take care of these patients [28]. From a practical point of view, after the study of the literature, weekly 1-hour sessions of in-person and online discussions were scheduled among the healthcare professionals from the above-mentioned units in order to select which symptoms deserve consideration and to revise the tool until reaching a full consensus for each item. In this regard, PASC-C included only symptoms that were reported as very frequent according to both Lopez-Leon and colleagues' systematic review and clinical experience [28]. The scope was to address every family symptom that a patient might have after contracting COVID-19, including sleep difficulties, general complaints, dermatological, gastroenteric, cardiological, neurological, and psychological symptoms. Subsequently, the schedule was presented to some colleagues from the same hospitals in order to collect their oral feedback. Thus, PASC-C presented below and used in this pilot study obtained the unanimous agreement of all authors.

This instrument is composed by the two sections described below.

The first one is called "Subjective physical, psychological, and cognitive symptoms" and it is structured into 10 different areas, covering a total of 30 symptoms. The presence of each symptom is investigated at three different times: a) during the COVID-19 disease, with information concerning its duration; b) at the moment of the interview, with a subjective estimation of the perceived severity, rated on a Likert scale from 0 (lowest severity) to 100 (highest severity); c) before the COVID-19 disease. In the case of reported premorbid symptoms, it is investigated whether COVID-19 disease has worsened them. To note, the premorbid condition has been investigated to exclude symptoms not ascribable to COVID-19, thus, unveiling patients who already had symptomatology before the disease and who have not experimented with a worsening health condition.

The presence of high severity score (>50), or in the presence of two or more symptoms for an area would suggest a referral to a healthcare professional with a specific expertise. The areas and symptoms of PASC-C is present in the *Supplementary material* available online in English language. The Italian version of the questionnaire is available upon request to the Authors.

Moreover, PASC-C investigates the occurrence of stressful events or illnesses in the period following COVID-19 disease, if patients have already sought healthcare assistance, and ongoing or past pharmacological or nonpharmacological therapies.

The second PASC-C section, called "subjective experiences of being a COVID-survivor", regards a series of questions to investigate the subjective experiences of patients after COVID-19 disease, in order to get a deep and comprehensive evaluation from a qualitative point of view. Patients have been asked about their subjective experience of surviving COVID-19 disease, for example, based on the attribution of positive or negative personal meaning to this disease experience. Furthermore, it has been investigated if subjective perceptions of their general functionality levels (e.g., physical, cognitive) have worsened, unvaried, or improved due to COVID-19 disease. Possible significant changes made in any area of their lives (e.g., work, family, interpersonal) after the disease have also been explored. Finally, patients have been invited to reveal if they wanted to add anything else: they could say something more, express their emotions, or ask any other questions.

The administration time of PASC-C is around 15 minutes, but the timing might vary depending on the number of symptoms and clinical details reported by patients.

MATERIALS AND METHODS

Participants

The target clinical population was constituted of 104 adult patients (>18 years old) taken in care for SARS-CoV-2 infection in the IRCCS Istituti Clinici Scientifici Maugeri who were entered into a short-term follow-up after the acute event, according to a research protocol aimed to evaluate the possible presence of cardiological COVID-19 sequela. Specifically, the patients of this study were recruited from four different hospitals (Milan, Montescano, Pavia, Tradate) which are affiliated with the same Institution (IRCCS ICS Maugeri). The location of these hospitals is strategic and informative as Lombardy was the Italian region most impacted during the COVID-19 pandemic and healthcare physicians are currently managing the pandemic sequelae over time [29-31].

This study was part of a broader research project and approved by the Institutional Review Board and Central Ethics Committee of the ICS Maugeri SpA SB (Approval Number 2450 CE. Participants signed a written informed consent to take part in this research.

After 1-2 years after the acute infection, these patients were proposed with a phone interview through the PASC-C Checklist (Approval Number 2653 CE).

Participants provided oral consent at the beginning of the phone interview as this research is a prosecution of the above-mentioned study. The interviews were conducted in a silent room by a psychologist through a proper phone line in order to safeguard personal data. No kind of remuneration was provided.

Out of the 104 participants of the former study, 84 completed the full phone interview. Indeed, 20 of them have not carried out the telephone interview for various reasons, such as lack of motivation due to a current good health condition (n=9), unavailability to reach them by phone (n=8), deaths (n=2), and severe clinical conditions (n=1).

Instruments

During the interview, the above-described Post-Acute Sequelae of COVID-19 Checklist (PASC-C) and the EuroQol-Visual Analogue Scale (EQ-VAS) [32] were administered.

EQ-VAS is an instrument developed by the EuroQol Group in 2009 [32] to evaluate patients' subjective actual global health status. It consists of a hybrid Visual Analogue Scale (VAS), which is a vertical line ranging from the worst imaginable health (0) to the best imaginable health (100) [32]. Previous research stated the equivalence of EQ-VAS results between telephone and paper-pencil administration [33].

Data analysis

Descriptive statistics are reported as mean and standard deviation (SD) for continuous variables, and frequency percentages for discrete variables.

Possible differences in the severity of symptoms between gender and age were analysed by t-test and the association between variables was assessed by Pearson correlation coefficient r. Moreover, frequencies have been considered to analyze the patients' subjective perceptions and evaluations of their overall functioning level as a result of the COVID-19 disease.

All statistical analyses were carried out using IBM SPSS Statistics Software (version 27.0).

The qualitative descriptive analysis of patients' narrations of their personal meaning regarding the acute and post-acute disease phase and the experience of being a COVID-19 survivor has been displayed into frequency tables. Patient's personal and significant changes in their lives after COVID-19 disease have been explored

individually, in order to group them into common categories with their frequencies through a bottom-up approach.

RESULTS

Subjective physical, psychological, and cognitive symptoms

The sample was composed of patients with a mean age of 66.2±11.0 years old, mainly male (71.4%), married (64.3%), and in retirement (53.6%), no-smoker people (64.3%).

Moreover, the majority are in pre-obesity status according to BMI (46.4%), and were previously hospitalized due to COVID-19 (89.3%). Overall, 36% stated no comorbidities, while 39% reported at least one comorbidity and the remaining 25% complained of two to four comorbidities.

Moreover, we have analysed possible differences in the severity of symptoms, present at the time of assessment) between gender and age (<65 years old *vs* >66 years old). No similar analysis has been conducted concerning hospitalization as the sample was too unbalanced concerning this variable. Overall, gender was the only factor that varied: women reported higher musculoskeletal pain (56.00±30.89 *vs* 38.26±22.09; t=-2.07; p=.05), higher levels of anxiety (84.00±18.38 *vs* 57.92±29.78; t=-2.56; p=.02) and more traumatic experiences (87.14±11.13 *vs* 58.39±34.24; t=-2.15; p=.04) than men.

Table 1 displays the frequencies of Long COVID symptoms still present and divided in the different areas. In addition, symptoms severity and the percentage of the clinical recommendations are also provided. Briefly, the most frequent symptoms were fatigue (69.0%), dyspnea (52.4%), joint-muscle pain (41.7%), memory problems (44.0%), and anxiety (40.5%). *Table 1* shows also the associations between the global health status (EQ-VAS mean score 68.7±21.2) and symptom severity of each PASC-area.

Overall, self-rated results of the EQ-VAS ranged from the minimum 0 (worst health status) to the maximum 100 (best health status), with 64.3% who have rated themselves under 75.

DISCUSSION

This study presents preliminary data collected through a new tool called "Post-Acute Sequelae of COVID-19 Checklist" (PASC-C) focusing on physical, psychological, and cognitive COVID-19 sequelae over time.

Our patient population with a mean age of around 66 years old is coherent with literature that highlights the relationship between having more than 60 years old and higher severity of COVID-19 symptoms and risk of developing Long COVID syndrome [34-36]. Similarly, the higher prevalence of male gender and the high percentage of comorbidities and overweight are in line with the existing literature suggesting these characteristics as risk factors for highlighting a more complex clinical condition [37, 38]. Concerning gender difference, in our sample, females suffer more from musculoskeletal pain and complain of higher anxiety symptoms and more traumatic experiences. Regarding this, previ-

Table 1. Post-Acute Sequelae of COVID-19 Checklist (PASC-C) results

Areas and symptoms	n (%)	Severity 0-100 M (DS)	Correlation with EQ VAS r (p)
Functional			0.528 (0.0001)
Fatigue	58 (69.0)	49.9 (25.6)	
Hearing/sight loss or tinnitus	34 (40.5)	39.3 (24.7)	
Motor difficulties	27 (32.1)	45.2 (25.6)	
Ageusia	15 (17.9)	45.0 (24.2)	
Anosmia	13 (15.5)	55.0 (25.6)	
Pneumological			0.407 (0.0001)
Dyspnea	44 (52.4)	50.2 (27.6)	
Other respiratory difficulties	33 (39.3)	57.3 (27.0)	
Cough	16 (19.0)	42.4 (28.2)	
Sleep disorders			0.352 (0.001)
Insomnia	33 (39.3)	58.4 (25.4)	
Sleepiness	7 (8.3)	60.0 (25.6)	
Hypersomnia	0	-	
Algic			0.347 (0.001)
Joint/muscle pain	35 (41.7)	45.3 (27.0)	
Headache	10 (11.9)	56.7 (23.1)	
Gastroenteric			0.156 (0.156)
Gastrointestinal complaints	19 (22.6)	54.2 (26.1)	
Nausea/Vomit	7 (8.3)	51.4 (29.7)	
Cardiological			0.145 (0.188)
Palpitation/ increase heart rate	24 (28.6)	43.9 (25.6)	
Chest pain/ discomfort	18 (21.4)	50.0 (24.9)	
Neurocognitive			0.368 (0.001)
Memory problems	37 (44.0)	55.8 (26.0)	
Paraesthesia	31 (36.9)	42.6 (26.6)	
Attention difficulties	25 (29.8)	50.8 (31.1)	
Balance disturbances	18 (21.4)	42.1 (26.6)	
Confusion/ disorientation	11 (13.1)	58.9 (32.5)	
Psychological			0.248 (0.023)
Anxiety	34 (40.5)	65.6 (29.2)	
Mood disorders	26 (31.0)	65.0 (30.7)	
Traumatic experiences	24 (28.6)	66.4 (32.2)	
Dermatological			0.202 (0.065)
Hair loss	23 (27.4)	61.3 (28.5)	
Skin erythema	15 (17.9)	48.7 (26.4)	
Other			0.258 (0.018)
Weight loss/gain	22 (26.2)	42.3 (18.5)	
Hyper-sweating	21 (25.0)	39.1 (22.6)	
Discontinuous fever	1 (1.2)	80.0	

ous literature has shown that COVID-19 affects gender in a different way over time [39]. Specifically, it has been demonstrated that women complain of less severe short-term health problems, but experience worse long-term COVID-19 sequalae, such as depression and poor quality of life, and perform less physical activity [39]. In this sense, our results are aligned with previous data, as depict a female gender more characterized by adverse physical and psychological experiences.

As expected, PASC-C revealed percentages of Long COVID symptoms still persistent one-two years after the disease, consistently with the evidence in literature regarding current and previous coronaviruses (SARS-CoV-1 and MERS-CoV). Symptoms may cover all clinical areas [11]. The most frequent self-reported symptoms in this study were fatigue (69%), dyspnea (52.4%), memory problems (44%), joint/muscle pain (41.7%), vision/hearing loss or tinnitus (40.5%), and anxiety (40.5%). These frequencies confirm the results of the review of López-León, *et al*. [28], who found fatigue (58%) and dyspnea (24%) as the most common Long COVID symptoms in their study. Despite Long COVID symptoms vary enormously across studies and there is still no common agreement, more recent studies tried to categorize persistent symptoms in wider categories or clusters [18, 23, 40]. Moreover, various studies proposed questionnaires and investigations on specific symptoms or aspects or disease phases [20-25], but a general clinical tool to collect the multifaceted plethora of Long COVID symptoms is still lacking. Accordantly, PASC-C was divided into ten symptom areas to cover miscellaneous manifestations and to provide clinical recommendations. In addition, a recent systematic review and meta-regression presented modeled estimates regarding individuals with at least 1 of 3 self-reported Long COVID symptom clusters, such as persistent fatigue with bodily pain or mood swings, cognitive problems, or ongoing respiratory problems, in accordance with psychological (22.1%), pneumological (19.1%), functional (16.6%), neurocognitive (14.8%) areas in our study [40]. As far as we know, this is the first clinical tool trying to both collect all kinds of Long COVID symptoms and to provide tailored further clinical suggestions.

Regarding the general health status of Long COVID patients, in a study of previously hospitalized patients with COVID-19, Taboada, *et al*. [41] found a decrease in their quality of life (EQ-VAS) at six months follow-up (87.58±11.68 *vs* 66.36±18.26, $p<0.001$). Their health status score was equivalent to our EQ-VAS data, which confirmed a poor HRQoL in these patients still struggling with persistent disease. Our study highlighted several significant negative correlations between EQ-VAS total score and PASC-C symptoms' severity in functional, pneumological, sleep disorders, algic, neurocognitive, and psychological areas. These significant associations with a valid instrument as EQ-VAS was already found in another Long COVID study [23]. The added value of PASC-C Checklist is its ability to identify what areas may worsen the quality of life and, in turn, request specific clinical attention. This early detection may allow the optimization of human and economic resources, tailoring the health experience and, in turn, improving the patient's satisfaction and HRQoL.

Overall, considering the wide plethora of symptoms considered, PASC-C operationalizes the recommendations for the detection of all physiological or clinical outcomes provided by the international Delphi consensus study regarding a core outcome set to assess within the clinical population who recovered from COVID-19 condition [42]. Although this tool has been developed and tested with patients suffering from COVID-19 during the initial phases of pandemic in Italy, it is still valid and useful for the detection of symptoms related to COVID-19 condition. Indeed, literature showed as COVID-19 sequalae are significantly persistent over time, with only slight differences between waves [43]. PASC-C is also in line with both the core symptoms deserving attention worldwide [42] and the call for action for the development of a core outcome measurement set (COMS) which has to be updated according to the emerging findings of literature [44].

STRENGTHS AND LIMITS

One of the strengths of the study is the proposal of a new handy tool which may be considered a promising multidimensional clinical tool, leading to multidisciplinary management of Long COVID symptoms, as recommended by NICE [8]. Although other studies are requested, this checklist might be widespread in primary care and support the early detection of COVID-19 sequelae in order to propose tailored interventions, optimize healthcare costs and improve patients' quality of life and satisfaction. Indeed, it can be used by all professionals, despite the specialties and the geographical origin of the patient, in order to quickly take care of the patient through a tailored approach over time.

However, this study has to be considered as a pilot study aimed to present initial attempts for assessing the clinical feasibility of a new clinical tool. Our intent is to catch the attention of the scientific community for developing possible international collaborations to corroborate and improve this checklist. Consequently, this study has some pitfalls which deserve to be declared. Firstly, data could not be generalized, since the sample is small and was enrolled in four different centers affiliated to the same Institute (ICS Maugeri). These centers are all located in Lombardy, a region highly impacted by the pandemic and, as a consequence, able to provide informative data and experiences regarding the short- and long-term care of COVID-19 patients. However, it is necessary to bear in mind that the sample is unbalanced considering the prevalence of males, the geographic region, the high rate of hospitalizations compared to non-hospitalizations during COVID-19 disease, and the high incidence of comorbidities in patients' anamnesis. Secondly, the time spans of the clinical check-ups and consequently of the phone interviews have varied widely within the sample, ranging from 1 to 2 years. Thirdly, PASC-C deserves to be further investigated to assess its feasibility and validity in clinical and research contexts. Fourthly, the patient's adherence to suggested checkups should be also assessed and monitored over time.

FUTURE DEVELOPMENTS

This research project is a pilot study for the validation of PASC-C, as it seems to be feasible and promising for the effective identification and monitoring of Long COVID patients. Further studies should replicate this research and extend it on a large scale to other national and international hospitals and healthcare centers, to consolidate results. With further studies the hope is to provide a tool for promoting tailored treatments, and rehabilitation programs that could be commonly shared among the clinical community. This issue is indeed a global healthcare challenge that needs clinical tool to adequately taking care of the patients over time.

CONCLUSIONS

Although the pandemic seems to be reaching its end, several patients worldwide are still struggling with Long COVID syndrome. This chronic and disabling condition leads to a heterogenous complex of clinical manifestations, and knowledge in literature is in its early stages. To date, there is still consensus on the necessity to assess and monitor core set of Long COVID symptoms to improve the quality and efficacy of care provided. The aim of this study has been to investigate physical, psychological, and cognitive symptoms after 1-2 years from COVID-19 acute infection, contributing to shed light on the existing controversial literature. The symptoms assessed by PASC-C are in line with the core outcome set to monitor in patients recovered from COVID-19 condition, thus this tool can be considered valid and useful in the present healthcare scenario.

The findings showed as it is crucial to identify Long COVID patients, in order to take care of their chronic and disabling conditions, adopting tailored diagnostic and care programs, based on a multidisciplinary approach.

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Conflict of interest statement

The Authors declare no conflict of interest.

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Screening for antenatal maternal depression: comparative performance of the Edinburgh Postnatal Depression Scale and Patient Health Questionnaire-9

Alberto Stefana[1], Loredana Cena[2], Alice Trainini[2], Gabriella Palumbo[3], Antonella Gigantesco[3]* and Fiorino Mirabella[3]*

[1]*Dipartimento di Scienze del Sistema Nervoso e del Comportamento, Università di Pavia, Pavia, Italy*
[2]*Dipartimento di Scienze Cliniche e Sperimentali, Sezione di Neuroscienze, Osservatorio Psicologia Clinica Perinatale, Università di Brescia, Brescia, Italy*
[3]*Centro di Riferimento per le Scienze Comportamentali e la Salute Mentale, Istituto Superiore di Sanità, Rome, Italy*
**These Authors equally contributed to this work and should be considered co-last Authors*

Abstract

Background. Maternal antenatal depression affects 21-28% of expectants globally and negatively impacts both maternal and child health in the short and long term.

Objective. To compare the psychometric properties and clinical utility of the Edinburgh Postnatal Depression Scale (EPDS) and the Patient Health Questionnaire (PHQ-9) in pregnant individuals.

Methods. In this cross-sectional study, 953 third-trimester pregnant Italian individuals completed both the EPDS and the PHQ-9.

Results. Both scales demonstrated good internal consistency (EPDS ω=0.83, PHQ-9 ω=0.80) and a moderate correlation between their scores (r=0.59). Concordance at recommended cut-off points (≥14 for both) was moderate (k=0.55). Factor analyses indicated a bifactor solution for the EPDS (dimensions: "depression" and "anxiety") and for the PHQ-9 (dimensions: "depression", "pregnancy symptoms", "somatic"). Benchmarks for clinical change were also established.

Conclusions. The EPDS and PHQ-9 capture distinct aspects of perinatal depressive symptomatology. Clinically, these findings recommend using both scales in obstetric and gynaecologic settings to minimize false positives and negatives.

Key words
- EPDS
- PHQ-9
- antenatal depression
- anxiety
- screening
- pregnancy

INTRODUCTION

Antenatal depression is a non-psychotic unipolar depressive disorder characterized by specific feelings and thoughts about the parental role [1]. It is one of the leading complications for people during the antepartum period [1] with a worldwide prevalence estimated between 21% and 28% [2-4]. However, despite this high prevalence, antenatal depression is frequently underdiagnosed [5], with about one in five pregnant people not asked about depression during prenatal visits [6].

New-onset or pre-existing depression in pregnant people can be a significant cause of short- and long-term negative consequences on both pregnant health and child development [7, 8], which entails, among other things, an important cost for national health care systems [9]. Studies aimed at developing and evaluating intervention programmes are consistent in highlighting the importance of early screening and prompt intervention to produce more optimal emotional health outcomes [10] and offspring health outcomes [11]. However, in Italy, where the prevalence of antenatal depression has been reported to be around 25% in 2022 [12], such programmes are not adequately integrated into clinical guidelines for appropriate practical care planning routines [13, 14]. This is partly due to the absence of a national Italian policy to screen for perina-

Address for correspondence: Fiorino Mirabella, Centro di Riferimento per le Scienze Comportamentali e la Salute Mentale, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy. E-mail: fiorino.mirabella@iss.it.

tal mental illness. In addition, there is limited training among healthcare providers on how to choose and use the most appropriate screening tool(s) and the cut-off point for a particular period of time.

Routine screening for perinatal depression through valid, reliable, and economical screening tools is probably the most widely accepted option [15-17]. However, no consensus has been reached on what scale can be considered the gold standard. Two of the three most frequently used screening tools are the Edinburgh Postnatal Depression Scale (EPDS) and the Patient Health Questionnaire (PHQ-9) [18, 19].

Aims of the study

The purpose of this study was to compare the psychometric properties and clinical utility of the Italian versions of EPDS and PHQ-9 among pregnant women. This study serves as an initial step toward establishing an effective screening programme for antenatal depression in Italy and possibly other Western countries.

MATERIALS AND METHODS

Study design and sample

The cross-sectional data presented here were collected as part of a larger project on screening and early intervention for maternal perinatal anxiety and depressive disorders [13]. A total of 1,159 consecutive adult pregnant people in their third trimester and of Italian nationality were asked to join the study from March 2017 to June 2018. Pregnant people who agreed to participate underwent an interview led by clinical psychologists to obtain information on current and past maternal experience with psychiatric conditions and use of psychotropic drugs. The exclusion criteria were having problems with drug or substance misuse and/or having ongoing psychotic symptoms. This study was approved by the ethics committee of the Healthcare Centre of Bologna Hospital (Comitato Etico Internazionale Bologna-Imola) (Reg. n. 77808 del 27/6/2017).

Data collection

Pregnant people who said they wanted to participate in the study signed an informed consent form. They were interviewed in a private room inside the health centre by a licensed clinical psychologist trained in evidence-based assessment techniques for perinatal mental health issues to determine their eligibility. Information on the demographic, economic, psychosocial, and reproductive characteristics of eligible participants was collected. The EPDS and PHQ-9 questionnaires were then administered.

Measures

Edinburgh Postnatal Depression Scale. The EPDS [20, 21] is the most chosen self-administered screening scale for perinatal depression [18]. The EPDS can be used to assess depression according to DSM-5 and ICD-10 criteria [22]. It assesses the frequency of each of the following depressive symptoms experienced in the previous seven days: anhedonia (two items); guilt; anxiety; panic attack; overwhelming; sleep disorders; sadness; tearfulness; and suicidal ideas. The EPDS consists of 10 items scored on a 4-point Likert scale ranging from 0 to 3. Its overall score can range from 0 to 30, and scores of 0-9, 10-11, 12-15, and ≥16 are commonly used as thresholds for normal, slightly increased risk of depression, increased risk of depression, and likely depression, respectively [21]. Findings from a systematic review and individual participant data meta-analysis indicate that a cut-off of ≥14 approximated structured clinical interview for diagnostic and statistical manual of mental disorders (SCID)-based prevalence of major depression [23].

Patient Health Questionnaire-9. The PHQ-9 [24, 25] is a self-administered depression screening scale containing nine items corresponding to the DSM-IV criteria for depression. However, it can be used to measure depression severity also according to DSM-5 criteria. The PHQ-9 is the first choice for depressive symptoms in non psychiatric primary care settings [26]. It assesses the frequency of each of the following depressive symptoms experienced in the previous two weeks: anhedonia; depressed mood; insomnia or hypersomnia; fatigue or loss of energy; appetite disturbances; feelings of worthlessness or excessive guilt; diminished ability to think or concentrate; psychomotor agitation or retardation; and suicidal thoughts. The PHQ-9 is comprised of 9 items, each rated on a Likert scale ranging from 0 (not at all) to 3 (nearly every day). Its overall score can range from 0 to 27, and scores of 0-4, 5-9, 10-14, and ≥15 represent the thresholds for normal, mild depressive symptoms, moderate depressive symptoms, and moderately severe to severe depressive symptoms, respectively [24]. Findings from an individual participant data meta-analysis indicate that a cut-off of ≥14 most closely matched SCID major depression prevalence [27].

State Anxiety Scale. The State Anxiety Scale (SAS) of the State-Trait Anxiety Inventory-Form Y (STAI-Y) [28, 29] is a 20-item self-report measure designed to assess situational anxiety, capturing feelings experienced in the present moment. Responses are recorded on a four-point Likert scale, ranging from "not at all" to "very much so", with ten of the items being reverse-scored. The inventory has demonstrated good internal consistency, with Cronbach's alpha values ranging between 0.86 and 0.95 [28, 29]. Notably, recently, a shortened version of the STAI specifically tailored for pregnant women has been developed [30].

Statistical analyses

Descriptive statistics were carried out using means and standard deviations (SD) for continuous variables and using frequencies and percentages for categorical variables. The factor structures of both EPDS and PHQ-9 were explored as follows. Parallel analysis using the R package EFAtools v0.4.3 [31] was conducted on a polychoric correlation matrix using mean eigenvalues and 95th percentile eigenvalues of 5,000 simulated random datasets to evaluate the number of factors that may be supported by our data. The scree plot and the eigenvalues associated with each factor were used to identify the number of meaningful factors. The sample was randomly divided into two mutually independent groups, ensuring

separate and independent samples for the exploratory factor analysis (EFA) and confirmatory factor analysis (CFA), respectively. EFA was conducted on a matrix of inter-item polychoric correlations using the Promax rotation method. This analysis was carried out with the R package EFAtools, version 0.4.3 [31]. CFA using the R packages lavaan v0.6-12 [32] was performed to explore the factor structures of the scale. The overall fit of the models was assessed using the following criteria: a minimum threshold of 0.95 for both the comparative fit index (CFI) and the Tucker-Lewis index (TLI), and maximum thresholds of 0.06 for the root mean square error of approximation (RMSEA), and 0.08 for the standardized root mean square residual (SRMR) [33, 34]. The internal consistency of both EPDS and PHQ-9 was assessed using Cronbach's alpha, McDonald's omega total, and Pearson's product-moment correlation coefficient (r). Omega is a more effective index than alpha for assessing reliability, particularly in the case of short scales or scales with multiple dimensions [35]. Internal consistency values are categorized as follows: values between 0.70 and 0.79 are considered adequate, those between 0.80 and 0.89 are regarded as good, and values of 0.90 or higher are deemed excellent [36]. Additionally, composite reliability (CR) and average variance extracted (AVE) have to be calculated to assess convergent validity. The commonly recommended thresholds for AVE and CR are 0.50 and 0.70, respectively. However, in cases where the AVE value falls below the recommended threshold, yet the CR value is high, this scenario suggests that the convergent validity of the construct may still be considered adequate [37, 38]. The agreement between EPDS and PHQ-9 with cut-off scores ≥14 and ≥14, respectively, was assessed using Cohen's kappa coefficient. The agreement between the two measures at different severity cut-off points (for the EPDS: 0-9, 10-11, 12-15, and ≥16; for PHQ-9: 0-4, 5-9, 10-14, and ≥15) was assessed using the intraclass correlation coefficient (ICC). All tests were two-tailed with the statistical significance level set at p=0.05. All data were coded and analysed using the Statistical Package for Social Science (SPSS) version 24 and R version 4.3.1.

RESULTS

Sample characteristics

Of the 1,159 pregnant people who met the eligibility criteria and were asked to participate in the study, 959 (83%) agreed to join. Of these participants, 953 completed EPDS and PHQ-9. Almost half (47%) of them were aged 30 to 35 years, 31% were aged 36 or older, and 22% were 29 years or younger. Regarding the level of education, 54% of the participants had high (tertiary) education, 36% had middle (secondary) education, and 10% had low (lower than secondary) education. Regarding working status, 75% were permanently employed, 9% were temporarily employed and 16% were unemployed/housewives/students/other. Regarding economic status, 48% of the participants had an average high status, 46% had a few economic problems without specific difficulties, and 6% had economic problems. Sociodemographic and reproductive information is shown in *Table 1*.

Table 1
Socio-demographics and reproductive characteristics of the sample

	n (%)
Age	
18-29	212 (22.1)
30-35	454 (47.4)
>35	292 (30.5)
Marital status	
Married or cohabiting	882 (92.6)
Single, separated, or divorced owidowed	70 (7.4)
Educational level	
University	509 (53.5)
Secondary	343 (36.0)
Primary or illiterate	100 (10.5)
Working status	
Permanent employee	705 (74.5)
Temporary employee	90 (9.5)
Student, homemaker, or unemployed	151 (16.0)
Economic status	
Average high status	454 (47.9)
A few problems without specific difficulties	435 (45.9)
Same or many problems	58 (6.2)

Parallel analysis

The number of factors suggested by the parallel analyses with Hull's method, Principal component analysis (PCA), and EFA was as follows: one, one, and five for the EPDS; and one, two, and three for the PHQ-9. Furthermore, an examination of the scree plot evidenced one or two factors for both scales. Given the number of items, it is not plausible to have more than three factors in the EPDS.

Exploratory factor analysis

Regarding EPDS, EFAs comparing the two models indicated by parallel analyses (i.e., one- and three-factor models) were performed (see *Table 2*). Eigenvalues and percentage of cumulative variance were as follows: 4.49 (44.9%) for the one-factor solution; 3.27 (32.7%) and 1.95 (52.2%) for the two-factor solution. We labeled these two factors as "depression" and "anxiety".

Regarding PHQ-9, EFAs comparing the three models suggested by parallel analyses (i.e., one- two- and three-factor models) were performed (see *Table 3*). Eigenvalues and percentage of cumulative variance were as follows: 3.77 (42.0%) for the one-factor solution; 2.68 (29.8%), 1.43 (45.7%), and 1.34 (60.5%) for the three-factor solution (item 1 loaded on both the first and the second factors). We labeled these three factors as "depression", "pregnancy symptoms" and "somatic". EFA could not be estimated for the two-factor model because no solutions were achieved across which averaging was possible for this model.

Table 2
Loadings and percentage of cumulative variance for the Edinburgh Postnatal Depression Scale (EPDS) and the Patient Health Questionnaire (PHQ-9)

		1-factor model	2-factor models		
	Item content abbreviated	**F1**	**F1**	**F2**	
EPDS	1. Laugh	**0.69**	**0.75**	-0.01	
	2. Enjoyment	**0.68**	**0.81**	-0.09	
	3. Self-blame	**0.61**	0.25	**0.46**	
	4. Anxious	**0.57**	-0.09	**0.83**	
	5. Scared	**0.61**	0.05	**0.71**	
	6. Hard to cope	**0.56**	0.23	**0.42**	
	7. Hard to sleep	**0.70**	**0.59**	0.17	
	8. Sad	**0.83**	**0.78**	0.11	
	9. Crying	**0.78**	**0.69**	0.16	
	10. Self-harm	**0.60**	**0.46**	0.19	
	Cumulative variance/%	44.9	32.7	52.2	
		1-factor model	**3-factor models**		
	Item content abbreviated	**F1**	**F1**	**F2**	**F3**
PHQ-9	1. Anhedonia	**0.75**	**0.44**	**0.36**	0.14
	2. Depressed mood	**0.68**	**0.72**	0.17	-0.10
	3. Sleeping difficulties	**0.33**	-0.22	**0.92**	-0.01
	4. Fatigue.	**0.57**	0.23	**0.56**	0.02
	5. Appetite changes	**0.59**	0.21	0.25	**0.30**
	6. Feeling of worthlessness	**0.74**	**0.80**	-0.06	0.07
	7. Concentrations difficulties	**0.64**	0.20	0.10	**0.49**
	8. Psychomotor agitation	**0.59**	-0.05	-0.04	**0.89**
	9. Suicide ideation	**0.81**	**1.01**	-0.20	0.08
	Cumulative variance/%	42.0	29.8	45.7	60.5

F1: factor 1; F2: factor 2.
Bold fonts show loadings of >0.30.
The table reports average loadings from 72 exploratory factor analyses, conducted using the mean method without any trimming (trim=0). These analyses were performed by the R package EFATools [31] and varied across various factor extraction and rotation methods: initial communalities, criterion type, number of factors for Promax rotation, rotation method type, and type of Varimax rotation.

Table 3
Confirmatory factor analysis indices of the factor models of the Edinburgh Postnatal Depression Scale (EPDS) and the Patient Health Questionnaire (PHQ-9)

Factor solution		**X^2 value**	***df***	**CFI**	**TLI**	**RMSEA**	**SRMR**
EPDS	One-factor model	222.62	35	0.84	0.80	0.11	0.07
	Two-factor model	122.86	34	0.93	0.90	0.08	0.04
	Bi-factor model	66.50	25	0.97	0.94	0.06	0.03
	EPDS-4A	14.61	2	0.98	0.94	0.08	0.03
PHQ-9	One-factor model	167.21	27	0.81	0.74	0.11	0.07
	Three-factor model (item 1 on Factor 1)	89.81	24	0.91	0.87	0.08	0.05
	Bi-factor model (item 1 on Factor 1)	Computation of modification indices for the bifactor model was not feasible					
	Three-factor model (item 1 on Factor 2)	114.93	24	0.88	0.81	0.09	0.06
	Bi-factor model (item 1 on Factor 2)	32.59	18	0.98	0.96	0.04	0.03

The items' scale assignments are those indicated in *Table 2* using bold fonts. CFI: comparative fit index; *df*: degree of freedom; TLI: Tucker-Lewis index, RMSEA: maximum thresholds of 0.06 for the root mean square error of approximation; SRMR: standardized root mean square residual; X^2: chi-squared.

Confirmatory factor analysis

A series of CFAs were conducted to test the solutions indicated by EFAs, including bifactor models. *Table 3* presents the fit indices for each factor model. For both EPDS and PHQ-9, bifactor models demonstrated the best fit.

For the EPDS, the bifactor model comprising a general factor and two specific factors – depression (items 1, 2, 7, 8, 9, and 10) and anxiety (items 3, 4, 5, and 6) – yielded the following fit indices: χ^2(df=25)=66.50, CFI=0.97, TLI=0.94, RMSEA=0.06 (90% CI=0.04, 0.08), and SRMR=0.03. *Supplementary Figure 1a (available online)* provides a graphical representation of this model. Additionally, we tested the EPDS-4A model, which includes the EPDS-3A – consisting of consisting of items 3, 4 and 5 [39, 40] – plus item 6. This addition was suggested by our data and corroborated by the only other study investigating the factorial structure of the Italian version of the EPDS in a perinatal population [41]. The EPDS-4A model demonstrated a good fit: χ^2(df=2)=14.61, CFI=0.98, TLI=0.94, RMSEA=0.08 (90% CI=0.05, 0.12), and SRMR=0.03. *Supplementary Figure 1b (available online)* displays a graphical representation of this model. For the PHQ-9, a bifactor model with a general factor and three specific factors – depression (items 2, 6, and 9), pregnancy symptoms (items 1, 3 and 4), and somatic (items 5, 7 and 8) – showed the following fit indices: χ^2(df=18)=32.59, CFI=0.98, TLI=0.96, RMSEA=0.04 (90% CI=0.02, 0.06), and SRMR=0.03. *Supplementary Figure 1c (available online)* provides a graphical representation of this model.

Reliability

For the EPDS, the Cronbach's alpha value of the EPDS was 0.81, and the McDonald's omega total was 0.83. The CR was 0.81, while the AVE was 0.31. The correlations between the items and the total scores ranged from 0.20 (item 10) to 0.83 (item 8), with an average inter-item correlation of r=0.29. For the PHQ-9, the Cronbach's alpha was 0.76, and the McDonald's omega total was 0.80. The CR was 0.75, and the AVE was 0.31. The correlations between the items and the total scores for the PHQ-9 ranged from 0.33 (item 9) to 0.63 (item 1), with an average inter-item correlation of r=0.24.

Correlation

Pearson's correlation coefficient between EPDS and PHQ-9 was r=0.59 (p <0.001). The correlation coefficients between, on the one hand, the SAS and, on the other hand, the EPDS-4A, the EPDS, and the PHQ-9 were respectively r=0.46 (p <0.001), r=0.55 (p <0.001), and r=0.48 (p <0.001). We also evaluated the correlation between the EPDS-3A and the SAS: and r=0.43 (p <0.001).

Severity ratings

The mean EPDS score was 4.7 (SD=3.9), while the mean PHQ-9 score was 4.3 (SD=3.0). When the scales were divided into four cut-off threshold groups (that is, 0-9, 10-11, 12-15, and ≥16 for the EPDS; 0-4, 5-9, 10-14, and ≥15 for the PHQ-9), the EPDS identified 4% of pregnant people (n=37) as having a possible depressive disorder (score from 12 to 15), while PHQ-9 classified 6% of subjects (n=56) as from moderately to severely depressed (score from 10 to 14). Additionally, 2% of pregnant people (n=19) were identified as likely depressed (score ≥16), while the PHQ-9 scale classified 1% of subjects (n=9) as moderately severely or severely depressed (score ≥15). The ICC was 0.46 (0.32-0.56), indicating poor reliability [42]. *Table 4* shows the distribution of study participants according to their severity of depressive symptoms.

Agreement at different cut-off scores for major depression

When applying EPDS and PHQ-9 cut-off thresholds (which is ≥14 for both scales) to estimate major depression prevalence, 95% (n=902) of pregnant people were concordantly classified. More specifically, 4% (n=35) persons were classified as depressed on both the EPDS and PHQ-9 scales, while 91% (n=867) expectant people were classified as not depressed on both scales (*Table 5*). The % agreement between the two scales was 95%, k=0.55, indicating moderate agreement.

Critical change benchmarks

Table 6 reports the following benchmarks for assessing clinical changes: critical changes at the 90% and 95% confidence intervals, minimally important difference, and minimum change for reliable change [43]. These four benchmarks are essential tools for clinicians, helping to assess whether alterations in a patient's scores are substantial beyond mere measurement error and have clinical relevance. The critical change values at both the 90% and 95% confidence levels signify the least amount of score change necessary to confidently assert that the observed change is not a result of chance or measurement inaccuracies. The minimally important difference denotes the smallest score variation perceived by patients as advantageous, crucial to assessing the impact

Table 4
Depression severity based on the Edinburgh Postnatal Depression Scale (EPDS) and the Patient Health Questionnaire (PHQ-9) (n=1,153)

	Depression severity	n	%
EPDS	0-9: Normal	850	89.2
	10-11 Slightly increased risk of depression	47	4.9
	12-15: Increased risk of depression	37	3.9
	≥16: Likely depression	19	2.0
	Total score (*M* ± *SD*)	953	4.7±3.9
PHQ-9	0-4: Normal	589	61.8
	5-9: Mild depressive symptoms	299	31.4
	10-14: Moderate depressive symptoms	56	5.9
	≥15: Moderately severe to severe depressive symptoms	9	0.9
	Total score (*M* ± *SD*)	953	4.3±3.0

Table 5
Comparison of the Edinburgh Postnatal Depression Scale (EPDS) and the Patient Health Questionnaire (PHQ-9) in identifying probable major depression

	PHQ-9 depression	PHQ-9 no depression	Total
EPDS depression	35 (3.7)	21 (2.2)	56 (5.9)
EPDS no depression	30 (3.1)	867 (91.0)	897 (94.1)
Total	65 (6.8)	888 (93.2)	953 (100%)

Table 6
Critical change benchmarks

	EPDS	PHQ-9
90% CC	2.64	2.21
95% CC	3.15	2.63
MID	1.95	1.5
MCRC	4.46	3.72

CC: critical change; EPDS: Edinburgh Postnatal Depression Scale; MID: minimal important difference; MCRC: minimum change for a reliable change; PHQ-9: Patient Health Questionnaire.

of treatment. Meanwhile, the minimum change for a reliable change indicates the extent of change needed to be deemed statistically robust, confirming that the observed variation is not attributable to random fluctuation. Using these benchmarks, clinicians can effectively track patient progress and judiciously assess the impact of therapeutic interventions, determining when a change in scores is significant enough to warrant modifications to the treatment strategy.

DISCUSSION

Both EPDS and PHQ-9 have been shown to have good internal consistency and homogeneity [44] when administered to a sample of Italian third-trimester pregnant people. The item-total correlations were acceptable for the vast majority of items on both scales and aligned with the results on the internal consistency of the scales. The two scales have a moderate positive correlation [45]. EFA suggested a two-factor model (named "depression" and "anxiety" factors) for EPDS and a three-factor model (named "depression", "somatic", and "pregnancy symptoms" factors) for PHQ-9. CFA showed that for both scales, the bifactor model was the best fit. This model suggests the presence of a general factor assessing antepartum depression, which accounts for the shared variance across all items. Additionally, it identifies group factors (two for the EPDS and three for the PHQ-9) that capture the common variance within specific item clusters, beyond the influence of the general factor [46].

When the scales' recommended cut-off score (i.e., ≥14 for both EPDS and PHQ-9) was used, the EPDS and the PHQ-9 identified comparable proportions of subjects considered as clinically depressed: 6% and 7%, respectively. However, EPDS identified a higher proportion of subjects as normal/not depressed (89% for EPDS *vs* 62% for PHQ-9). Vice versa, PHQ-9 identified a higher proportion of subjects as affected by subdiagnostic symptoms of depression (5% for EPDS *vs* 31% for PHQ-9). Taking into account the different severity cut-off scores, the concordance between the scales was poor [42] in our sample. Overall, these results confirmed that EPDS and PHQ-9 are similar tools, but measure different aspects of antenatal depressive symptoms.

The variation observed between these two scales aligned with results from a previous study with pregnant Peruvians [47] that suggested as a possible explanation the fact that PHQ-9 but not EPDS includes items addressing somatic symptoms. This might be important because some people can emphasize somatic complaints rather than reporting feelings of sadness [48]. However, in our case, this explanation is unlikely since there is evidence suggesting that white women with depression or depressive symptoms report fewer somatic symptoms than Hispanic/Latina women [49]. Furthermore, there exists the possibility of an overlap between (pathological) symptoms of depression and (normal) somatic complaints of pregnancy, which can lead to an overdiagnosis of depressive disorders in such a population [50, 51]. In fact, it has been observed that appetite increase and increase in energy (e.g., agitation) are uninformative with regard to a major depressive disorder diagnosis in pregnant women [52]. Therefore, somatic symptoms, which may be caused by normal physiological changes associated with pregnancy can increase the false-positive rate of depression during the antenatal period; this is the reason for the absence of any somatic symptom items on the EPDS. However, it is possible that the elimination of somatic symptoms (e.g., sleep disturbances, fatigue, psychomotor retardation) from the depression scale might result in the loss of clinically useful information, such as a specific pattern of symptoms or indicators of depression severity.

A further possible explanation for the variation between the scales is that, while EPDS was developed using items drawn from three scales for anxiety and depression (that is, the Irritability, Depression and Anxiety Scale [53], the Hospital Anxiety and Depression Scale [54], and the Anxiety and Depression Scale [55], the PHQ-9 was developed specifically to identify depressive disorders based on DSM-IV [56] criteria. The presence of an EPDS anxiety subscale has been largely demonstrated [57-60] and a positive correlation between the results of the EPDS anxiety subscale and those of scales specifically developed to measure anxiety [61-63].

However, consistent with a previous study [61], we found that the EPDS total score in our sample was more highly correlated with the SAS than both the EPDS-4A and the EPDS-3A. Even the correlation was higher between PHQ-9 and SAS, than between the lat-

ter and the EPDS anxiety subscale score. A possible explanation is that while the ideal tool for assessing anxiety should measure both the negative affect (which is the clinical characteristic shared by anxiety and depression) and the physiological arousal (which is a typical symptom of anxiety), the EPDS-4A does not contain items specifically related to hyperarousal. A further possible explanation rests on the fact that anxiety is a multidimensional construct and can be generalized or focused on specific aspects/situations [64]. Therefore, a four-item anxiety subscale is unlikely to be able to accurately and reliably measure perinatal anxiety. Lastly, given that items 3, 4, and 5 are the only EPDS items that contain a subjective negative judgment about feelings, the measurement of anxiety could be less accurate in people with low self-esteem.

Study limitations

This study has some limitations that are worth mentioning. First, we evaluated depressive symptomatology with self-report instruments without supplementing that assessment with a diagnostic interview to actually make a diagnosis of depression according to the criteria of DSM-5-TR [48]. Thus, validity cannot be established for either scale; a criterion validity comparison between them cannot be tested. Second, the cross-sectional nature of the data prevents the possibility of evaluating whether and how the performance of EPDS and PHQ-9 changes during the perinatal period. Future work should include longitudinal studies with at least two time-point assessments to evaluate the predictive validity of both the instruments, which was not analyzed here.

CONCLUSIONS

The current study offers new evidence on screening tools for antenatal depression. Our results show that EPDS and PHQ-9 have satisfactory internal consistency and identify similar proportions of antenatal depression. However, the observed differences indicate that their ability to screen for depression during pregnancy is not identical because they partially focus on different symptoms of depression. EPDS and PHQ-9 capture partially distinct features of depressive symptomatology: anxiety symptoms and somatic symptoms, respectively. These findings suggest that when using these scales for clinical purposes with people at risk of antenatal depression, they should be used in combination – rather than substituted – to reduce depression both false-positive and false-negative results.

Finally, the current study further highlights the need to continue exploring the psychometric properties of both EPDS and PHQ-9 to assess maternal depression, with the general aim of particularly improving the quality of assessment of antenatal mental health. It remains crucial to establish which symptoms can be considered reliable and valid indicators of antenatal depression. Further validations of both EPDS and PHQ-9 in other countries using larger sample sizes are recommended to support the advancement of research and clinical guidelines for the appropriate screening of maternal mental health.

Authors' contributions

AS and FM developed the outline of this manuscript, performed the statistical analysis, and contributed to the writing; LC, AT, and GP searched the literature, performed quality analysis and contributed to writing; AG contributed to the final version of the manuscript and supervised the entire study. All Authors read and approved the final manuscript.

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Conflict of interest statement

The Authors have no conflicts of interest to declare. All co-Authors have seen and agree with the contents of the manuscript and there is no financial interest to report.

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How to conduct research in palliative care? A perspective from Italy

Camilla Cocchi[1], Maria Beatrice Zazzara[1,2], Rosa Liperoti[1,2], Raffaella Antonione[3], Sabrina Dispenza[2], Gino Gobber[4], Eleonora Meloni[2], Italo Penco[5], Maria Adelaide Ricciotti[2] and Graziano Onder[1,2]

[1]*Università Cattolica del Sacro Cuore, Rome, Italy*
[2]*Fondazione Policlinico Universitario Agostino Gemelli Istituto di Ricovero e Cura a Carattere Scientifico, Rome, Italy*
[3]*Struttura Complessa Rete Cure Palliative e Hospice area Giuliana, Azienda Sanitaria Universitaria Giuliano-Isontina, Trieste, Italy*
[4]*Unità Operativa Cure Palliative, Azienda Provinciale per i Servizi Sanitari, Trento, Italy*
[5]*Fondazione Sanità e Ricerca, Rome, Italy*

Abstract

Background. In western countries, the increasing life expectancy and the growing number of individuals with advanced chronic conditions have resulted in a greater demand for palliative care. Specifically, Italy has witnessed substantial growth in the palliative care field, marked by the establishment of Palliative Care Networks and an academic fellowship program in 2022. To further enhance this field, it is crucial to conduct high-quality scientific research that produces results applicable in clinical practice.

Aim. This article explores challenges and potential solutions in conducting effective palliative care research, considering sample definition, research settings, outcomes, and ethical concerns. While focusing on the Italian context, the presented research framework can be applied to other contexts and regions.

Results. Palliative care research is complex and challenging due to its holistic approach, which encompasses various vital dimensions of patients and their families, including physical, emotional, and social needs. The Italian and worldwide experience provides insights into managing these challenges and enhancing the methodological rigor of studies and the practical application of research findings.

Conclusions. This article emphasizes the importance of developing protocols tailored to palliative care's unique characteristics, and the necessity of dedicated funding for palliative care research, calling for increased support and recognition. The article advocates for improvement of the quality and relevance of palliative care studies, promoting better patient outcomes and enhanced caregiving.

Key words

- methodology
- palliative care
- research
- research methods
- Italy

INTRODUCTION

Advancements in treatment of acute and chronic conditions have significantly contributed to increase life expectancy. However, this epidemiological change is associated with an increment in the number of people living with the consequences of serious chronic diseases towards the end of life, resulting in a greater need for palliative care. According to World Health Organization (WHO) data, every year 56,8 million people worldwide, including 25,7 million in the last year of life, require palliative care [1]. Despite this, only 14% of those in need actually receive a palliative and comprehensive approach [1].

Italy represents one of the countries with the oldest population in the world, with almost one-fourth of the 59 million citizens aged 65 years or older. It has been estimated that more than 500 thousands individuals in the country are in need of palliative care every year, but only 23% of them receives palliative approach [2]. To face this increasing need of palliative care, several organizational and educational measures were taken in the country. The delivery of palliative care is organized based on Palliative Care Networks (PCN), that guarantee access to services and continuity of care to patients with advanced stage chronic diseases, organ failure or cancer [3]. Integrated care pathways are ensured by a close collabora-

Address for correspondence: Camilla Cocchi, Università Cattolica del Sacro Cuore, Largo Francesco Vito 1, 00168 Rome, Italy. E-mail: camilla.cocchi01@icatt.it.

tion of the key nodes of the PCN which include home care, residential care/hospice, hospital and ambulatory care [4]. Furthermore, in order to improve education and training of medical doctors operating in the PNC, starting from 2022 a fellowship program in palliative care was established nationally [5]. The program aims to train a new generation of specialists with specific knowledge related to the clinical, diagnostic, and therapeutic issues that characterize the advanced stages of various chronic diseases. It also aims to develop advanced skills in the communication process, socio-familial, spiritual, and psychological assessment, care and treatment planning, and identifying patients' preferences. Palliative care specialists should be capable of working in team with other specialists or with the general practitioner with the main aim of improving patients' quality of life.

The establishment of PCN and the creation of fellowship programs paved the way to reorganize the care process for patients with palliative care needs and to improve the education and skill of healthcare personnel. To further advance the palliative care sector at a national level, it is crucial to bring in substantial research data that can guide clinical practice in this area. Indeed, palliative care research has been growing both internationally and in Italy. *Figure 1* presents the number of the PubMed records selected based on the search term "Palliative care" (*Panel A*) and the term "Palliative care" and "Italy" (*Panel B*) between 1993 and 2022. Despite the increasing number of PubMed records over the past 30 years, research in palliative care is complex and challenging due to its holistic aim, which addresses multiple vital dimensions of patients and their families, includ-

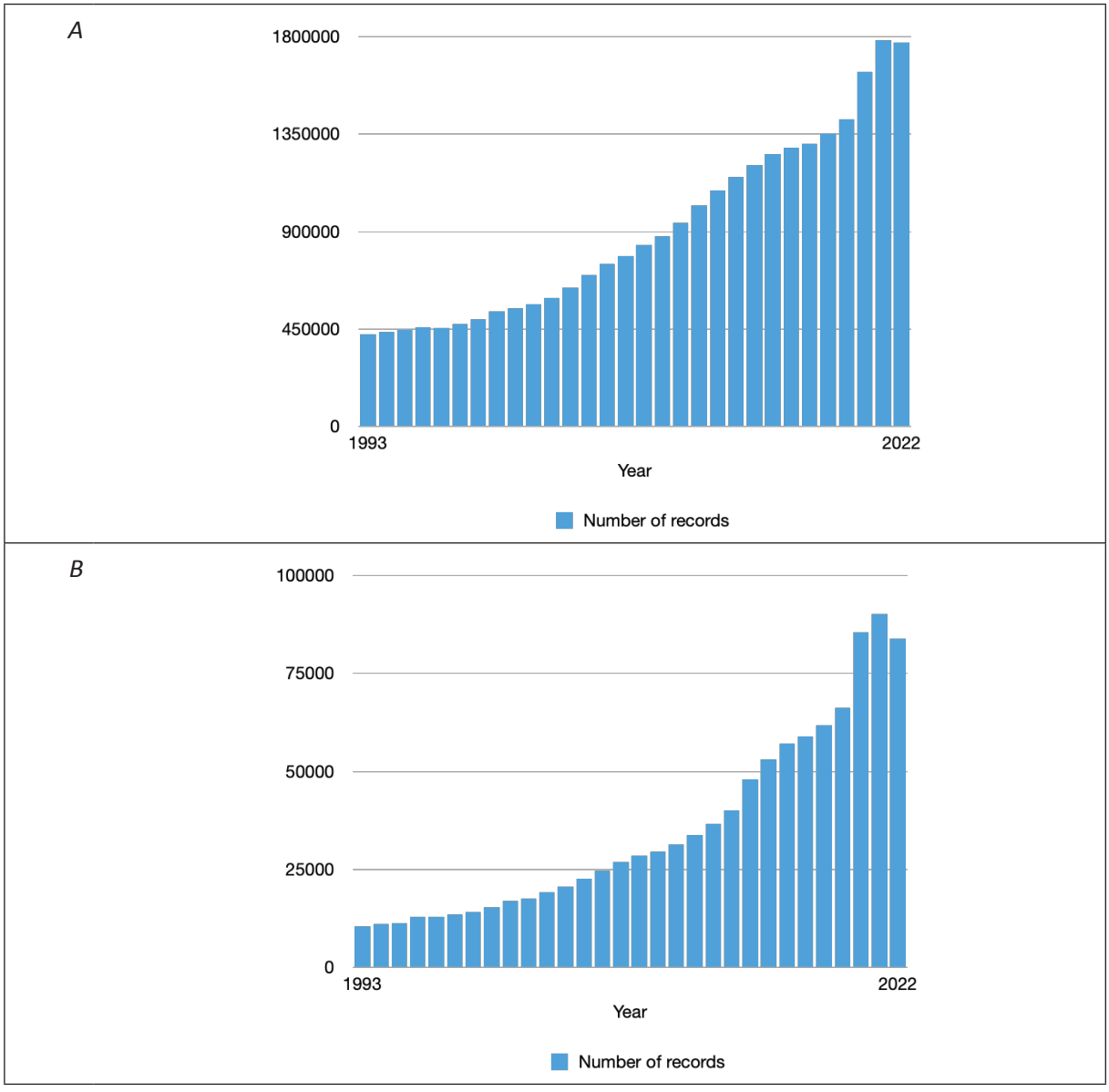

Figure 1
Number of the Pubmed records selected based on the search term "Palliative care" (*Panel A*) and the term "Palliative care" and "Italy" (*Panel B*) between 1993 and 2022.

Table 1
Different aspects of research studies in palliative care: challenges, consequences, potential solutions and barriers to their implementation

Problem	Consequences	Possible solutions	Barriers to implementation of possible solutions
Sample			
Heterogeneity of patients receiving palliative care	Specific needs of particular patients' populations can be not appropriately evaluated Potential benefits of treatments in specific population can be underestimated	Focus on symptoms (i.e., pain, dyspnoea) rather than diseases (oncological and non-oncological) Include heterogeneous samples in sufficient numbers to measure benefits and harms of interventions. Develop and implement risk-stratification models and report harms and benefits according to risk strata	Solutions adoptable in observational studies, but difficult to implement in Randomized Clinical Trials (RCT) due to the need of enrolling a large and heterogeneous sample Need of relevant research funds to enrol large samples
Attrition due to particular characteristics of patients receiving palliative care	High rate of loss to follow Study underpowered and limited validity of study results		
Most studies conducted in a single setting of care and with limited sample	Sample not representative of population suffering from the examined condition Results not generalizable to non-oncological patients Limited applicability and results generalizability of study results in clinical practices		
Most research performed in cancer			
Setting			
Palliative care covers different settings	Research often performed in a single setting Limited generalizability of study results	Enrol samples from or replicate study findings in different PC settings to confirm the consistency of results (hospital, home care, hospice, nursing home)	Organization and resources may limit the possibility of performing research in settings Organization of research protocols may vary depending on setting (i.e., residential *vs.* home care)
Outcomes			
Definition of outcomes that are relevant in palliative care patients	Traditional single disease-oriented outcomes cannot adequately capture multidimensional and patient centered concepts of palliative care Reduced relevance of research findings	Adoption of multidimensional and patient centred outcomes (symptoms control, quality of life, patient reported outcomes) Combine patient centred outcomes with more objective measures (i.e, hospitalizations, ER admissions, procedures performed)	Patient centred outcomes are difficult to assess at the end of life due to lack of collaboration and can be affected by several factors and present with large fluctuations in these measures Patients receiving palliative care are at risk for rapid clinical deterioration and are likely to drop out at follow-up assessment
Ethical issues			
Patients research burden	Need to reduce redundant or unnecessary activities in patients with limited life expectancy Reduced participation to research activities	Simplify study protocols Explain to patients personal and societal benefit of research	
Informed consent	Patients unable to understand research aims and/or accurately interpreting their conditions Impossibility to released informed consent	Consent waivers or alternative consent models Consent released by a proxy	Not always applicable because not sufficiently regulated Models not standardized and codified
IRB evaluation	IRB members not familiar with PC research Inadequate evaluation of IRB protocols	Education of IRB members about palliative care populations and research Creation of a lexicon of key terms in palliative care research Creation of a taxonomy of key potential IRB concerns as related to palliative care	Resistance of deviating from standard rules of traditional research

IRB: institutional review boards.

ing physical, emotional, and social needs. Research in this field substantially differs from traditional clinical research in terms of the population involved, objectives, and methods. In this paper we will define a framework to develop research activities in palliative care in Italy, by assessing problems, consequences and possible solutions related to different aspects of research studies, including sample definition, settings, outcomes and ethical issues (*Table 1*).

DEFINITION OF STUDY SAMPLE

The definition of an appropriate study sample is the first key step in conducting research. The sample must be representative of the examined condition or disease, and the generalizability of study results largely depends on how study participants are selected. Palliative care patients inherently exhibit a high level of heterogeneity [6]. Patients often present with multiple symptoms simultaneously, variable by nature and by response to treatments, regardless of the underlying pathology. Furthermore, the same condition can be observed in patients with different baseline disease and health characteristics. For this reason, samples selected in palliative care research tend to be characterized by a high level of heterogeneity. While this approach improves generalizability of study findings, making its results applicable to a larger population, it may leave specific needs of particular patient populations unmet.

Another concern related to samples selection arises from the fact that the majority of palliative care studies are monocentric, performed in a single setting of care and with a limited sample size, which can have an impact on the power to detect differences between treatment strategies and on the generalizability of results [6]. Additionally, scientific research on palliative care has traditionally focused on oncological diseases. However, pain and other physical, psychosocial, and spiritual problems, which represent the main focus of palliative care, can be observed across a multitude of oncological and non-oncological diseases. Although there has been an increasing number of studies focusing on patients with non-oncological diseases in recent years, the generalizability of findings obtained from an oncological sample to patients suffering from other conditions remains a concern. A final concern related to sample selection in palliative care studies is due to participants drop out and attrition. The rate of survival is difficult to define in this population, especially for non-oncological patients. Short- and mid-term prognosis of these patients is variable, and the risk of loss to follow-up, due to difficulties to attend follow-up visits, is elevated.

All the above-mentioned factors represent important issue to be considered in the identification of an appropriate sample to perform research, since they may influence the generalizability of research results and increase the risk of underpowered studies that lack a sufficiently large sample size to answer the research question. This complexity argues for adapting sample selection by including large, diverse populations, that are representative of the condition cared for in clinical practice. Being the focus of palliative care "(…) the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual", the research sample should be enrolled based on the presence of these conditions rather than specific diseases. Given the heterogeneity due to variability in patients' initial condition and level of risk, responsiveness to specific treatments, and vulnerability, effects can be compared within homogeneous risk strata defined according to their characteristics. Observational research can likely better accommodate the large, heterogeneous populations needed to achieve this goal.

PALLIATIVE CARE SETTINGS

Palliative care spans across various settings, based on different degrees of disease severity and patients' preferences, with the possibility of transition from one setting to another based on specific needs. More specifically, in Italy, the PCN includes the following settings:

- hospital, where an expert medical-nursing team offers palliative care consultations. Hospitals can both activate early palliative care pathways and help carers in the management of terminally ill patients;
- ambulatory services, caring for self-sufficient patients, which are granted multi-dimensional and specialistic medical services aimed at controlling symptoms and assisting their families;
- hospice, providing temporary hospitalization for patients in the last stages of their life;
- home care, providing care to patients in their own homes, aiming not only to enhance their quality of life and functional health status but also to replace hospital care with home-based care for societal reasons [4]. In addition to these settings, despite not being formally included in the PCN, palliative care should cover also nursing homes, that traditionally admit individuals with a high level of complexity, multimorbidity, functional and cognitive impairments, and with a high mortality rate [7].

These settings are interconnected to ensure continuity in the care process, but the development of palliative care shows uneven progress. Currently, 90% of Local Health Authorities (Azienda Sanitaria Locale – ASL) have implemented local PCN; however, only 79% of these have established dedicated care pathways. Despite this, palliative care remains inadequately integrated into hospital settings and dedicated palliative care professionals are absent in over 40% of teams providing home care services [8].

There is also a notable disparity between the northern and southern regions in providing palliative care. Southern regions exhibit a lower number of services, particularly hospice facilities [8]. It is anticipated that efforts will be made to bridge or at least narrow this gap in the coming years. The most recent 2023 Budget Law mandates that by 2028, palliative care should be accessible to 90% of those in need [9].

In terms of research, different settings can vary in terms of care organizations and available resources, and these factors can influence research findings. For this reason, to make research results generalizable to all patients suffering from a certain condition, they should be

found to be consistent across settings. Studies should enroll participants from different settings or replicate their findings across settings, especially those often neglected by clinical research (i.e., nursing homes). This might require the development of setting-specific study protocols that take into account organizational factors and resources.

OUTCOMES

The main goal of palliative care is to improve the quality of life of patients facing life-threatening illness and their caregivers through a multidisciplinary approach. Traditional research tends to focus on disease-specific outcomes, for example, stroke prevention or exacerbation of chronic obstructive pulmonary disease. Such outcomes make little sense in palliative care where the focus should be on "universal" outcomes. Universal health outcomes – outcomes on which all diseases exert an effect – represent the consequences that matter most to patients. Focusing on them would ensure that both harms and benefits of treatments are compared. Examples of universal outcomes include symptom burden (e.g., dyspnea, pain, fatigue), function (physical, cognitive, psychological, social), and health-related quality of life. These factors can be assessed by means of patient-reported outcomes or by standardized professional evaluations. In this context a review showed that efficacy of treatments and symptom control and quality of life are used as primary outcomes in 75% of palliative care research [6]. This finding underlines the patient-oriented nature of palliative care research which is focused on the individual patient's experiences.

In addition to symptoms and quality of life, Patient-Reported Outcomes (PROs) are also considered relevant outcomes in palliative care research. PROs are directly reported by the patient without interpretation by a clinician or anyone else. They pertain to the patient's health status, quality of life, functional status, symptom burden, personal experience of care. The importance of PROs is also emphasized by the Italian Plan for Care of Chronic Diseases (Piano Nazionale Cronicità) released by the Italian Ministry of Health, which underlines the relevance of these measures as research outcomes and for monitoring the quality of care provided. Despite being extremely useful in assessing the impact of specific symptoms and outcome measures that really matters to patients at an individual level, PROs are difficult to standardize and often do not allow direct comparisons among patients [10]. Additionally, outcomes in palliative care research should also focus on caregivers' evaluation. The burden of caring for patients at the end of life may adversely affect caregivers' health, which, in turn, can have negative effects on the quality of life of both patients and caregivers.

The above-mentioned outcomes can adequately capture multidimensional (clinical, psychological, spiritual, functional) and patient centered nuances that differ from those usually assessed in traditional research, which are disease specific and often focused solely on the clinical dimension. However, assessing outcomes in palliative care poses several challenges. First, quality of life, symptoms severity, and PROs are subjective outcomes that require patient collaboration for their evaluation. Patients with cognitive impairment, very severe diseases or in the last days of life may not be adequately assessed by these measures. To address this issue, the use of proxy-reported quality of life assessments has been proposed, but several studies have suggested that evaluations of quality of life by proxies may be inaccurate. [11]. Second, quality of life, symptoms severity and PROs can be affected by internal factors, such as mood, expectations, time, sentiments, and knowledge of prognosis, as well as by external factors, such as treatment context, interactions with the healthcare providers, and patients' socioeconomic situation, leading to fluctuations in these measures. Given this variability, it has been proposed to collect measurements longitudinally and at multiple time points to assess the trajectories of symptoms progression and recovery. Finally, patients receiving palliative care are at risk of rapid clinical deterioration and are likely to drop out at follow-up assessment. For this reason, it seems relevant to select outcomes that may be sufficiently sensitive to change and for which a meaningful change can be easily reached in the short timeframe. Given these issues, it seems reasonable, in performing palliative care research, to combine subjective outcomes (i.e., quality of life, symptoms severity and PRO) with more objective measures (i.e., hospitalizations, ER admissions, procedures performed) in order to have a more comprehensive assessment of patient health trajectories.

ETHICAL ISSUES: PATIENTS' BURDEN AND ETHICS COMMITTEES

Ethical concerns may arise regarding the involvement of complex and sick patients and their families in palliative care research. Some of these concerns can be classified in two main categories: 1) Patient level and 2) Ethics Committees level concerns.

Considering the issue from a patient level, it may be felt within the scientific community that participation of patients receiving palliative care in research can increase their burden, potential distress, and even harm [12]. These concerns are based on the perception that palliative care patients are particularly frail and vulnerable, with very limited life expectancy, therefore warranting extra protection from redundant or unnecessary activities. However, available research data suggests that views expressed by palliative care patients towards research are similar to those of other patient populations. Their participation in research is driven by the potential for personal gain, altruism, and a desire to retain autonomy, despite the wish to avoid complex studies [12].

The acquisition of informed consent relies on the patients' capacity to understand research objectives, their own condition, and the potential risks and benefits associated with study participation. These elements may be lacking in palliative care patients due to the severity of their condition, cognitive impairment, psychiatric illnesses, or pharmacological sedation. Furthermore, obtaining formal written consent can be time-consuming,

cognitively challenging, and burdensome for some participants, especially those with sensory or physical impairments, or other serious illnesses.

As a result, consent waivers or alternative consent models have been proposed in palliative care research, including broadcast notification (general notification, usually by flyers or brochures in clinical areas or via mail), integrated consent (combines clinical and research consent within the same encounter), or consent released by a proxy (or legally authorized representative). These strategies are not addressed in Italian law n. 219/2017, which focuses mainly on clinical consent. An amendment to this law in this direction could lead to a more modern approach to informed consent, facilitating the inclusion of frail patients in clinical studies without compromising their right to self-determination, providing them the chance to get access to trials and treatments from which they would be otherwise excluded [13, 14].

A second level of concern relates to Ethics Committees, which are independent bodies responsible for the ethical clearance of studies. Palliative care is a relatively new discipline and Ethics Committees members may not have sufficient skills in palliative care nor be familiar with the specific research features of palliative care research. As mentioned, palliative care research differs significantly in terms of sample, setting, and outcomes from traditional research, which may lead to inadequate evaluation of research protocols. Possible solutions proposed to solve this issue include better education of Ethics Committees members about palliative care populations and research, the creation of a lexicon of key terms in palliative care research and the development of a taxonomy of key potential Ethics Committees concerns as related to palliative care research [15]. These aspects are particularly relevant to standardize the approach of Ethics Committees, particularly in Italy where a reorganization of Ethics Committees system has been recently realized, with the establishment of 3 National and 40 local Ethics Committees [16].

STUDY DESIGN SELECTION

Quantitative studies have traditionally been considered the gold standard for studying the effects of an intervention and its effectiveness, as they allow for the measurement of a variable and establish clear cause-effect correlation. In clinical trials it is possible to verify hypothesis through a systematic and predefined analysis, whose results can be generalized to the entire population. In the palliative care field, the main study topics are the effects of a non-pharmacological (i.e., acupuncture, music therapy, aromatherapy, relaxation techniques) or pharmacological intervention, or the effectiveness of these measures, intended as their applicability in the real world. The research's main objectives guide the study design choice. Case-control studies can hardly be applicable in this area, unless they investigate the symptom burden in units that routinely document the intensity and prevalence of different symptoms. Prospective studies, either parallel or crossover, are more suitable when a therapeutic intervention is to be studied [17]. Although double-blind randomized clinical trials provide the highest-level evidence data, they are challenging to perform in palliative care due to both organizational and ethical issues, as previously mentioned.

Qualitative studies are also well-suited for investigating end-of-life issues. These studies, having been born in sociological, psychological, and anthropological fields, allow to understand a phenomenon in its complexity rather than just measure it. This approach applies well to research in the palliative field, whose main themes (e.g., symptom burden) present a significant subjective component, also expressed in terms of *perceived* benefit. Qualitative studies employ individual interviews, focus groups and observational groups to gather data. The main objective of those studies is to understand and discover new elements by posing open-ended questions to study participants. This allows the examinators to have a "bottom-up" understanding of the study main topic, which is particularly useful when you want to understand how a treatment intervention is perceived by the patient or family members. The use of open questions allows researchers to obtain a large number of data even from small populations, partially overcoming the problem of small population samples in palliative care research. Qualitative studies are characterized by an iterative process where the data is collected and analyzed simultaneously, providing great flexibility to the whole research process [18]. However, qualitative studies still present uncertainties about the validity of the collected data, mainly linked to the complex assessment of methodological rigor [19]. This can be limited by using descriptive checklists to improve methodological accuracy [19].

A new approach that is gaining ground is mixed-methods research, where qualitative research and randomized clinical trials are combined. Indeed, in the field of palliative care, the effectiveness of interventions and the benefits perceived by patients are both crucial pieces of information [20]. Qualitative research can act as a precursor to quantitative research, bringing to light new study topics based on patient preferences. It can also help clarify why an effective intervention in trials has not been applied to everyday clinical practice, or identify issues related to participant enrollment. Similarly, randomized clinical trials provide methodological rigor to the study. Mixed methods research is a valid approach to study end-of-life issues, since with its holistic vision enriches the quantitative data through the analysis of the context in which those data are collected. However, it should not be forgotten that this approach is relatively new and has limitations. Researchers need ample experience and specialized training, such as in framing questions, honing listening skills, building rapport, and collecting data. Otherwise, there is a risk of diminishing the overall quality of the research. A recent methodological review demonstrated that there is still room for integration in terms of a formal definition of how these two methods are integrated with each other [21]. Finding the right balance between the two methods, in terms of planning and finance management, is also crucial.

FROM RESEARCH TO GUIDELINES

Clinical practice today is guided by evidence-based medicine, a difficult model to apply to the palliative care model. The palliative care field produces fewer studies and of reduced quality compared to those of traditional research [22]. This is probably due to factors described in this article, that make research in palliative care a difficult task: small and heterogeneous samples, difficulties in having an adequate follow-up period, ethical issues, scarce funds allocated to this line of research and a low number of PhD/academic projects focusing on palliative care [22].

Patients features, outcomes, and methods of investigation make this branch of medicine unsuitable for evidence-based methodology. In managing these patients, the priority is the subjective perception of well-being of the individual and the caregiver, and therefore the guidelines which are based on clinical trials that typically assess average effects of a given treatment, might not be applicable to the palliative care population and are not always followed in clinical practice. This deviation from evidence-based methodology can be observed in the example of anticholinergic drugs used to treat excessive respiratory secretion at the end of life. Despite a Cochrane systematic review demonstrating the substantial absence of benefit in this practice [23], a focus group with staff members in inpatient palliative care services showed that they were still used to reduce the psychological stress of staff, patients and family members [24].

A possible solution could be to improve the quality of palliative research by increasing multi-center international studies, with short assessment periods, and adopting a combination of individual and objective outcomes. Similarly, evidence-based medicine must become more flexible, and able to balance quantitative and qualitative elements, to develop a methodologically rigorous clinical practice that does not set aside the subjective well-being of the individual patient. The concept of evidence-based medicine should be reconstructed, not to lose completely the individual-oriented perspective.

CONCLUSIONS

In this article we presented relevant considerations for conducting palliative care research, in order to make results applicable in clinical practice. Aspects related to the Italian palliative care context are presented, but the general research framework described can be adapted to other contexts and regions.

It is crucial to enhance research in palliative care to support all patients (oncologic and non-oncologic), especially given their vulnerability. High-quality research enables more informed clinical practice, bringing benefits to both patients and caregivers. Achieving this goal requires careful selection of study design, including mixed-methods approaches, thoughtful choice of sample and outcomes, and increased collaboration among different centers and internationally.

Artificial intelligence and machine learning techniques have become prominent resources for researchers and can represent valuable instruments to this aim [25-27]. These tools can be employed to predict patient need for palliative care services, support decision-making, streamline data collection and analysis, and guide the selection of the most suitable study design. This holds true for various types of studies, but it can have particularly intriguing implications in the field of palliative care. For instance, the integration of wearable devices (such as smartwatches) with AI could facilitate the acquisition of data (e.g., vital signs), real-time monitoring, and more precise analysis, simultaneously reducing the burden on the patient. On the other hand, given that these technologies are still relatively new and fast-changing, and a comprehensive understanding of their full potential and possible consequences is yet to be achieved, there is a lack of regulations governing their use. This is crucial when considering their utilization as a resource in a sensitive research field like palliative care.

In conclusion, palliative care research is complex and challenging due to its holistic approach, which encompasses various vital dimensions of patients and their families, including physical, emotional, and social needs. The Italian and worldwide experience provides insights into managing these challenges and enhancing the methodological rigor of studies and the practical application of research findings. The definition of appropriate palliative care research protocols requires a clear recognition of the specific characteristics and peculiarities of this field, and calls for specific funds to be allocated to this research area.

Author's contributions

GO, CC and MBZ designed the study. CC and MBZ contributed to the literature search, and the writing of the manuscript. GO, RL, RA, SD, GG, EM, IP, and MAR critically revised the manuscript. All the co-authors reviewed the manuscript and approved the final version.

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BRIEF NOTE

From COVID-19 to a "new normal": could we support a "healthy renaissance" for our cities?

Laura Mancini[1], Ornella Punzo[1] and Silvio Brusaferro[2]

[1]*Dipartimento Ambiente e Salute, Istituto Superiore di Sanità, Rome, Italy*
[2]*Former President, Istituto Superiore di Sanità, Rome, Italy*

Abstract

Background. At the beginning of 2020, worldwide public debate focused on the fight against the climate crisis. Many challenges are ahead of us, from health emergencies, with the pandemics underway, to the exhaustion of natural resources, to major climate change.

Discussion. Many cities face health threats related to urban and land use planning, while infectious diseases thrive in overcrowded cities: living in unhealthy environments killed 12,6 million people in 2012 and air pollution killed 7 million people in 2016. Urbanization is one of the major global trends of the 21st century and has a significant impact on health. Over 55% of the world's population lives in urban areas, a percentage that is expected to increase to 68% by 2050.

Conclusions. Developing new and more sustainable ways of living, moving, utilizing resources, and accessing services including healthcare and education, is crucial to preserve our future and the future of the next generations.

Key words

- urban health
- population health
- preventive medicine
- climate change

INTRODUCTION

At the beginning of 2020, worldwide public debate focused on the fight against climate change. The European Union, through its so-called "Green Deal", ranked the ecological transition as the first goal in its political agenda. Then, the COVID-19 pandemic broke out, putting all other issues on the back burner. COVID-19 is not a priority today as it was at the beginning of the pandemic, as we now feel safer thanks to mostly successful vaccination campaigns all over the world, so much so that we have begun to think about our post-pandemic lives and the future of the planet. However, we know that the consequences of the pandemic will be long-lasting because of its social and economic impact, and we need to update many of our convictions if we want to shape a sustainable world, better prepared for future pandemics.

MATERIALS AND METHODS

In this respect, two questions are crucial:

1) Will the fight against climate change be at the core of the political and social agenda?

Planet Earth faces many challenges, from the health emergency with the recent pandemic, to the exhaustion of natural resources to major climate change. We, therefore, live in syndemic times in which more pandemics are underway. Some words should become everyday words such as prevention, action, mitigation, and adaptation. Health systems have been severely tested by the pandemic and the virus responded to our actions to counter it and prevent its deadly consequences with "adaptation" [1]. The virus adapted to changes with a speed unthinkable for a human being. On the other hand, we must adapt to changes, but we must also lay the foundations for a health renaissance. In this context, where to start setting up a renaissance? On a global geo-political effort?

2) Will cities play a key role in this endeavour?

Cities exert a crucial influence on the fate of the planet (70% of the wealth produced, 75% of the energy consumed, 60% of greenhouse gas emissions, and 54% of the world population) [1], and they must acquire a substantial and formal role in the elaboration of global and local policies: therefore multilateral agencies, periodic conferences and horizontal networks are established, and this theme becomes part of the international debate on sustainable development [2], in particular, thanks to Goal 11 of the 2030 Agenda. In some cases, cities choose to take an independent position as opposed to nation-states, e.g., regarding migration and the fight against climate change [3].

Address for correspondence: Ornella Punzo, Dipartimento Ambiente e Salute, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy.
E-mail: ornella.punzo@iss.it.

RESULTS

Many cities face health threats related to urban and land use planning. Infectious diseases thrive in overcrowded cities or where there is inadequate access to resources; living in unhealthy environments killed 12,6 million people in 2012 and air pollution killed 7 million people in 2016. However, only 1 in 10 cities meets the standards for healthy air, while 9 out of 10 people breathe unsafe air [4]. A recent study conducted by the University of Delft, in the Netherlands [5], focusing on the health-related social costs of air pollution in 432 European cities in 30 countries highlighted that in 2018, on average, everyone living in a European city suffered a welfare loss of over € 1,250 a year owing to direct and indirect health losses associated with poor air quality. This is equivalent to 3.9% of income earned in cities. Most of these costs relate to premature mortality: for the 432 cities investigated, the average contribution of mortality to total social costs is 76.1%. Conversely, the average contribution of morbidity is 23.9%. The researchers also found evidence that transport policies impact the social costs of air pollution, proving further that reducing air pollution in European cities should be among the top priorities in any attempt to improve the welfare of city populations in Europe.

Urbanization is one of the major global trends of the 21st century and has a significant impact on health. Over 55% of the world's population lives in urban areas, which is expected to increase to 68% by 2050 [6]. As most of the future urban growth will occur in developing cities, the world today has a unique opportunity to lead urbanization and other important urban development trends in a way that protects and promotes health. Traditionally, cities have served as vibrant hubs of culture, innovation, and multicultural exchange, making their revitalization and resurgence indispensable to the overall enrichment of the human environment. In 2050 in Italy, it is estimated that about 80% of the population will live in urban areas and United Nations projections [6] estimate urban areas will host just over 80% of the European population at the same date. While there were 4 Italian cities with 1 to 5 million inhabitants in 2018 and they will remain the same in 2050, Italian cities with 500,000-1 million inhabitants will increase from 12 in 2018 to 14 in 2050. In order to guide decision-makers from public health, urban and land use planning sectors, including planners, city administrators, health professionals and others, towards the development of cities designed and built with a focus on human and environmental health, we need to work, plan for and train professionals in risk reduction, which is the only way to do primary prevention, in the attempt to avoid possible consequences for human health [7, 8, 9]. Health is an aggregate of dimensions: which and how many to prioritize to include the largest share of the population? The healthcare system is a whole of political, economic, cultural, technical, and organizational factors, relations, processes and elements, in which individuals, groups and communities interrelate, having the goal of satisfying their health needs [10]. Health and health care can be well understood only in the broadest context of human life. That includes social, economic, and political issues besides understanding biological processes. It also requires a grasp of environmental, historical, and cultural circumstances (*Figure 1*).

In light of the current health and environmental situation, it is necessary to rethink cities and rethink the health systems for a "healthy renaissance" to prepare for a "new normal". This post-COVID-19 era offers some elements of reflection on several aspects of the public health response to major events [11]. First of all, preparation, where speed of action, flexibility, production and logistics are crucial. Prevention is strategic in public health and essential to preserve community health as well as to ensure the growth of the country; coordination among different involved parties is needed; a

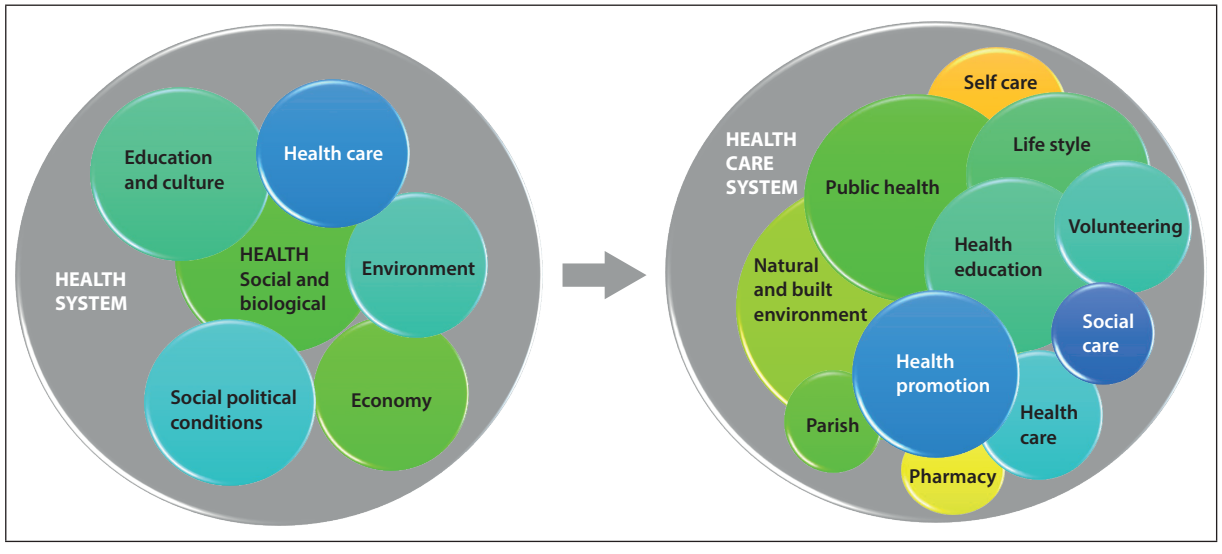

Figure 1
Health system *vs* complexity health care system.

"glocal" approach that considers the national and sub-national or regional dimensions, the regional or local level and the prevention unit based at the local health authorities' level should be encouraged [12, 13]. On the human resources front, there is much need for planning and training for the new challenges posed by climate change and health, especially at the urban level. Medical and social services addressing the elderly and frailty, in particular, should be rethought around new organizational models. In this context, it is crucial to factor in the social determinants of health while reconceptualizing urban services, thereby tackling equity challenges that could potentially exacerbate the risks of morbidity due to communicable and non-communicable diseases. Social services should be integrated into the broader healthcare framework, while proximity should be the beacon of all policies and interventions. Digitalization is also a factor of paramount relevance in this process, including the digitalization of the informative system, the interoperability of platforms, performance rules and pricing, and regional and national coordination. Finally, communication and social media, as we could dramatically appreciate during the COVID-19 pandemic, are crucial for transferring the appropriate information and taking the population on board the intended change. A key role is provided by proximity networks, intermediate structures and telemedicine for territorial healthcare: the interventions of this component intend to improve performance provided on the territory thanks to the strengthening and creation of structures and facilities (such as the Community Houses, Territorial Operational Centers and Community Hospitals), the strengthening of home care, the development of telemedicine and more effective integration with all social and health services. The community of proximity can be defined as the network of quickly accessible contacts around a person, be they real or virtual, that can be activated to satisfy a need for health and support the social relations of an individual (*Figure 1*); Parish, Social care, Volunteering, Pharmacy, Information Technology, Health care, General Practitioners, but also family, friends, acquaintances and services such as bakers, grocers etc.

DISCUSSION

"A healthy renaissance" follows the path of the rebirth of the cities, where the population is more concentrated. Just as the priorities (Ps) have been defined for health, we have thought of 9 "Rs" for the cities (*Figure 2*). From COVID-19 to a "new normal", could we support a "healthy renaissance" for our cities? The city of Vancouver, in Canada, can serve as a role model for other cities facing common challenges such as accessibility, rapid growth, climate resilience and citizen well-being. The city administration worked hard in the last few years for the development of a governance model that increases collaboration around infrastructures, encourages jointly funded projects and stimulates future interactions at all levels. The Vancouver Plan includes a long-term community vision, land use strategy, and core principles of ecological and social sustainability including equitable housing, an inclusive economy, and ecosystem restoration [14]. To promote their health renaissance, it is imperative to perceive cities as intricate ecosystems that harbour a diverse range of both domestic and wild animal and plant species. This in-

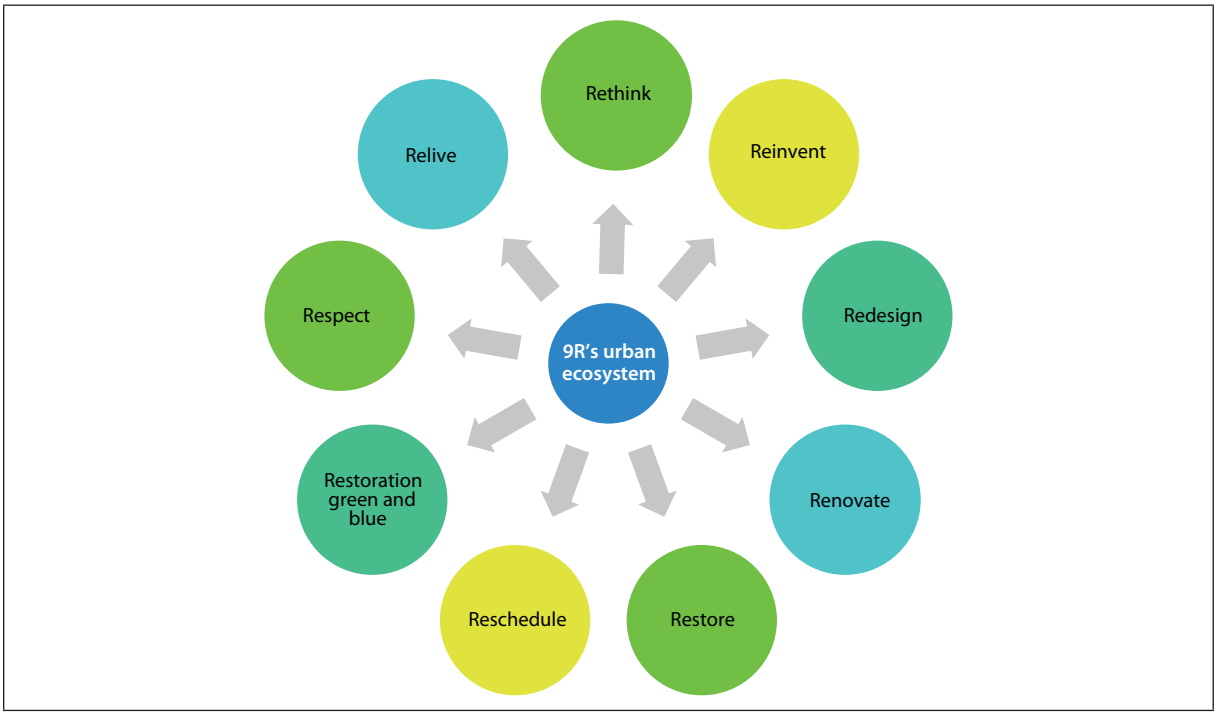

Figure 2
Health system vs complexity health care system.

terconnection is closely linked to their role as primary centres for the consumption of goods, leading to substantial contributions not just to air pollution but also to emissions and waste, housing biological and chemical hazards, including the proliferation of antimicrobial resistance, often referred to as "the silent pandemic". From the scientific evidence to the implementation of change, the resources of the Recovery and Resilience Plan (Piano Nazionale di Ripresa e Resilienza, PNRR) are fundamental. They could still be a great opportunity to strengthen the resilience and capacities of the National Health System [14]. The PNRR rests on six main pillars/missions which include health directly and indirectly, but also include the green revolution and ecological transition. Those related to the healthcare system, envisage the use of new technologies to improve hospitals and home healthcare by enhancing the use of telemedicine while reducing territorial fragmentation (€15,6 billion) [15, 16].

CONCLUSIONS

Our paper does not intend to draw conclusions or give recipes, but we can propose the following key messages as food for thought, development of knowledge, and training to think about a sustainable future which depends on cooperative and interdisciplinary work:

- building smart cities and smart regions;
- building sustainable urban ecosystem services;
- building trust in health systems to eliminate health disparities;
- reducing healthcare's climate footprint;
- implementation science;
- improving proximity networks, and intermediate medicine structures for territorial healthcare;
- improving innovation, research, and digitalization of the national health service;
- improving promotion and prevention, accessibility to services and environmental context can make a difference;
- investing in healthy renaissance;
- investing for the future for a "new normal".

Urban health is the key to interpreting our species and the planet's future. The cities of the future, where health is prioritised, encompass a myriad of factors spanning from the environment to the entire human society. Such cities could and should serve as the ideal ground for developing and implementing One Health strategies, the most suitable approach at our disposal to tackle the complexity we are currently encountering. Developing new and more sustainable ways of living, moving and using public transport, utilizing resources, and accessing services including healthcare and education, is crucial to preserving our future and the future of the next generations.

Authors' contribution statement

LM conceptualised and drafted the manuscript. OP revised the first draft and added important intellectual content. LM, OP and SB commented and contributed to revisions. All Authors have approved the final version of the manuscript for publication.

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Stability/Flexibility: the tightly coupled homeostasis generator is at the same time the driver of change

Alessandro Giuliani[1] and Alessandro Vici[2]

[1]*Dipartimento Ambiente e Salute, Istituto Superiore di Sanità, Rome, Italy*
[2]*Dipartimento Oncologia e Medicina Molecolare, Istituto Superiore di Sanità, Rome, Italy*

Abstract
There is "no Flexibility without Stability and no Stability without Flexibility": this is a crucial feature common to any system interacting with its environment. This tight link between two apparently opposite features is at the basis of the time-honoured concept of homeostasis (the tendency of any adaptive system to go back to its "comfort zone" contrasting the incoming perturbations) and is widely recognized since long time. On the contrary, the fact that the escape from a stable attractor state is a consequence of the same homeostasis mechanisms is often overlooked. In this brief note, we will try to give a proof-of-concept of the relation existing between stability/flexibility based homeostasis and the state changes at all the levels of biological organization. The ubiquity of the same principles across very different systems is a signature of a new attitude to look at scientific enterprise from a network-based viewpoint.

Key words
- biological regulation
- systems biology
- physiology, philosophy of science
- statistical mechanics

INTRODUCTION

In the half of XIX century [1], the French physiologist Claude Bernard stated the first (and probably most important) principle of experimental medicine: organism survival is made possible by the existence of control processes contrasting ever-changing (but relatively small) perturbations and so keeping, on the long run, a substantially invariant internal environment (*milieu interieur*) [2]. The name for this continuous "going back" to a global condition favourable to life is homeostasis (keeping the system in the same state). Since Bernard's times, homeostasis became a fundamental principle of physiology [3], holding at any organization layer from biomolecules to ecological systems [4].

Homeostasis implies the need of a certain degree of flexibility to maintain the global stability of systems embedded into a largely unpredictable ever-changing environment: this is why the two (apparently) opposite flexibility and stability terms constitute, in the case of complex systems, an inseparable couple. In the case of biology, the "agents of stability" often coincide with the "agents of change": the same molecular players assuring the stability-by-flexibility homeostasis can push the system toward a different state.

In the following, we will present this mechanism in action in the cell-fate determination with reference to both similar cases at different levels of biological organization and to the Self-Organized-Criticality (SOC) physical model giving a theoretical explanation to the consilience existing between homeostasis and the (apparently) opposite transition behaviour.

SELF-ORGANIZED CRITICALITY: LIVING ON THE EDGE OF CHAOS

In biological systems, the mechanisms involved in maintaining homeostasis by an increase in flexibility mirroring the ability to cope with external perturbations and those responsible for massive changes are the same [5, 6]. The statistical mechanics model of Self-Organized Complexity (SOC) [6] gives a vivid explanation of such behaviour.

The model of "self-organized complexity" (or "self-organized criticality" when the focus is on the peculiar situation of having an attractor state located in a critical position on the edge of chaos) or SOC (both interpretations give rise to the same acronym) was developed by Per Bak *et al*. [7]. The idea of SOC stems from the so-called sandpile model: think of pouring sand very slowly onto a flat, circular surface, at first, the grains stay close to where they land and soon start to accumulate creating a pile. Adding sand, the grains slide down, causing small avalanches that keep invariant the slope of the pile but, as we add more sand, the slope of the pile steepens, and the average size of avalanches increases. The pile stops growing when the amount of sand added balances the amount of sand falling off. The pile keeps

Address for correspondence: Alessandro Giuliani, Dipartimento Ambiente e Salute, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy. E-mail: alessandro.giuliani@iss.it.

invariant its shape and this state can be considered an "attractor" (stable state) of the dynamics. At odds with classical attractors that are static (e.g., think of a marble rolling down along the walls of a cup, until it reaches the minimum energy state correspondent to the bottom of the cup) or follow a regular orbit (think of a pendulum), the SOC equilibrium state is dynamic. The pile undergoes continuous local destruction/reconstruction events. At equilibrium, the added sand counterbalances avalanches, while the height and shape of the pile remain the same [7].

Occasionally, an added grain initiates a domino effect in which small (homeostatic) avalanches sum-up invading the core of the pile (normally unaffected by perturbations that are confined in the periphery of the system) dramatically altering its height and shape (critical avalanches) [7].

This behaviour is at the basis of an apparent conundrum of many complex systems: the attractor (stable) states of the dynamics are kept stable by a relentless adjustment to relatively small perturbations (added grains) that could foster its state transition (disruption of the sandpile).

Stability, in a continuously varying environment, asks for a relentless oscillation of the system between disruption and rebuilding: the small avalanches make it possible to integrate incoming grains in the sandpile keeping the system in a dynamically stable mode. The variability of periphery elements (involved in homeostatic avalanches) prevents the incoming perturbations to affect the core of the system but at the cost of keeping the system in a critical state prone to disruptive changes. Biological systems live at the "edge-of-chaos" [8].

GENE EXPRESSION: A TRANSIENT STATE CHANGE PROMOTES A LONG-TERM JUMP TO A DIFFERENT ATTRACTOR

In the case of genome expression, the peripheral elements are genes endowed with an elevated spontaneous temporal variability. These genes (partially) escape the strong correlation among different gene expression coming from the need of a tissue-specific mutual balance of different gene expression levels. Formally these constraints correspond to a first principal component (PC1) getting rid of the great part (around 90%) of between genes variability in time, while periphery elements in charge of the continuous adaptation to environmental vagaries are more influences by the second component (PC2) of gene expression variability [5]. The minor axis of variation (PC2, second component, orthogonal to PC1 by construction) depicts the amount of discrepancy of single gene expressions from their average, tissue-specific expression level. The administration of a differentiation stimulus to a breast cancer derived cell culture [5] provokes, after 15-20 minutes, a transient state change increasing by one order of magnitude the variance explained by PC2 and causing a drop of the between expression profiles Pearson r [5]. After approximately five minutes, this perturbation is dissipated, but the changes initiated by this transient modification will provoke a dramatic phenotypic transition of the cells after 3 hours [5].

It is worth noting that the genes with higher values of PC2, despite the different amount of total variability explained by this component, are the same in both transition and "business-as-usual" (homeostasis) conditions. This is both consistent with SOC model and with the identity of the agents (genes) promoting stability and driving state changes [5]. This result suggests the presence of a fluid-like part of the system (peripheral high variability genes) staying side-by-side with a crystal-like core (low variability genes), as we will discuss in the next section.

PROTEINS STRUCTURED AND FLEXIBLE PHASES: NATIVELY UNFOLDED REGIONS AS ENTROPIC RESERVOIRS

Critical equilibrium states are present in many biological systems, and protein science is the most convenient viewpoint for appreciating their structural counterpart [9]. Over the last two decades [10], the discovery that almost all the eukaryotic proteins have intrinsically disordered patches, drastically changed the canonical paradigm of a well-defined quasi-crystalline 3D structure (native structure) as the necessary prerequisite of protein function.

Proteins live in a microenvironment continuously perturbing their native structure, the entity of these perturbations (mainly due to thermal agitation) are of the same order of magnitude of intermolecular forces responsible for protein 3D configuration. This makes necessary to dissipate the "extra energy" coming from thermal noise to keep the structural core invariant (homeostasis). This is the role played by more flexible (disordered, fluid-like phase) protein domains [10]. At the same time, a given protein, in order to carry out its physiological role, is strictly dependent from the generation of a complex network of interaction with other protein molecules implying the mutual recognition of different protein systems. These interactions are crucial for the metabolic and signalling needs of the cell and involve "disordered" (highly flexible) domains that recognize (and mutually arrange with) fluid-like unfolded tracts of protein specific partners. This "fluid-like" phase of proteins ("entropic reservoir" [9]) correspond to highly flexible (natively unfolded) regions of the molecule that both dissipate thermal noise (homeostasis) and drive structural transition necessary to both allosteric behaviour and protein-protein interactions and re-shaping (attractor change). These drastic structural changes happen, thanks to the "invasion" of the protein (rigid) core by a wave of coordinated motion generated by a SOC-like mechanism coming from fluid-like phase. The presence of partially (or total) natively unfolded proteins, allows the cell to display a huge repertoire of biochemical patterns without the need of inflating the number of different protein species.

PSYCHOTHERAPY: THE ALTERNATION OF FLUID AND STRUCTURED PHASES ALONG THERAPY PROCESSES

A recent study by De Felice *et al.* [11] compares "good outcome" and "poor outcome" psychotherapy process-

es; the authors observed that "good outcome" therapies alternate phases of high and low "flexibility" (entity of changes in correlation structure among the items of a psychological multi-item scale). There are significant differences in trajectories of stability and flexibility over time between therapeutic processes leading to a stable restoring of a healthy behaviour from not efficient therapies. The trajectories of good-outcome cases are characterized by cycles of stability (among items invariant correlation) and flexibility (rapidly changing correlation structure), while such cycles are relatively rare in the poor-outcome cases [11]. This behaviour is formally equivalent to order-disorder transitions of protein molecules. In the case of proteins, disordered phases mirror the need of "opening" (so making the system prone to change) a previously structured compact phase to make the molecule to reach a different configuration after the binding to a partner. Thus, it is not by chance that psychotherapy refers to the flexible phases as "openness" and ordered phases as "re-integration" (creation of a new configuration): successful psychotherapy relies on the alternation of these two phases to foster the reach of a new cognitive/motional configuration of patient system of thoughts and feelings.

Psychotherapy is a learning process, in which the attainment of constructive (re-integration) phases needs the disruption of a previous "unhealthy" cognitive "attractor". A good therapist should be able to recognize these phases during the therapeutic processes and consequently trying to canalize the therapy toward the desired goal (or, at least, to monitor the relative progress of the cure) of a global stabilization of the patient toward a "healthy" attractor state. It is worth noting this process can be fruitfully described in terms of a SOC-like mechanism [12].

CONCLUSIONS

At the end of this brief note, we must answer a very important question: "Are the evident phenomenological similarities among the very different fields of investigation rapidly discussed in this review only the consequence of a mainly didactical metaphor or there is something more?".

To answer this question, two important papers appeared in the year 2000 in the same journal issue and having as first author the 1998 Nobel laureate for physics, Robert Laughlin [13, 14]. These two papers deal with the failure of a "Theory of Everything" at the basis of all the aspects of the natural world (an old dream of physics resembling the natural human attitude toward a substantial unity of the world around us) and the consequent need to approach the mesoscopic realm of emergent phenomena by a different attitude.

The authors state [13] "We call this physics of the next century the study of complex adaptive matter. For better or worse we are now witnessing a transition from the science of the past, so intimately linked to reductionism, to the study of complex adaptive matter, firmly based in experiment, with its hope for providing a jumping-off point for new discoveries, new concepts, and new wisdom". They affirm this view is not only confined to a specific scale, but could foster a new definition of what is fundamental, shifting from quantum mechanics to organization principles [14]: "In any event, the applicability of the science of mesoscale organization that we believe can be developed will not be limited to the world between angstroms and centimeters. Organization following similar principles may well be manifested in astrophysics. As we have noted, complex structures already have been proposed for the exotic matter expected in neutron stars, while ideas developed to explain mescoscopic organization on Earth may be useful in explaining the origin of large-scale structure in the Universe".

The authors refer to principles instead of laws, so marking the passage from a top-down approach to emerging (and thus mainly statistical) properties derived from the observation of structure and state changes at different levels of organization. This new attitude is made still more evident (and directly operational) by Donald Mickulecki [15] that demonstrates the existence of two kinds of "laws" named constitutive and relational "(…) constitutive laws for the network elements and the network topology. The use of constitutive laws for the network elements is the way the physical character of each network element is represented abstractly. It is a common feature of the material world. The topology or connected pattern of these elements in a network is an independent reality about the system. The same topology can be realized for an infinite variety of collections of network elements". The author demonstrates how many properties of natural phenomena are only dependent on the wiring structure of the set of correlations among their parts (network topology) with no relation with the intrinsic nature of the nodes of the network.

The search of "unification" of different natural phenomena passes from the recognition that "anything in the world is made by the same fundamental matter" to the acceptance of the fact that "anything in the world can be represented by a set of parts each other interacting".

This network-centric perspective (together with the emphasis on representation that allows putting together very diverse science fields without looking for an impossible to achieve reduction to a shared fundamental organization layer) allows for a direct empirical, largely data-driven, translation of empirical findings into a physically motivated frame. This opens the way to a directly operational common language to describe (and explain) natural phenomena independently of the degree of knowledge of the underlying microscopic laws. This is decidedly much more than a successful metaphor and opens the way to a re-integration of scientific culture after a too long fragmentation period.

Conflict of interest statement

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

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Book Reviews, Notes and Comments

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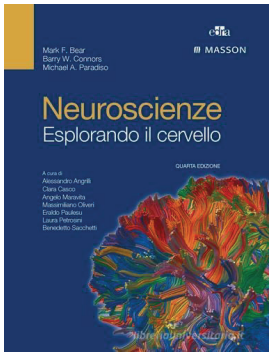

NEUROSCIENZE
Esplorando il cervello
Mark F. Bear, Barry W. Connors, Michael A. Paradiso
Milano: Edra SpA; 2016.
1012 p.
ISBN 9781451109542
€ 79,00

[Neuroscience: Exploring the Brain]

This is definitely a very brilliant volume which is organized as a textbook but can have its own value in the bookshelf of anyone who today operates in similar sectors or in fields not too far from neuroscience. In the scientific and biomedical world, including the area of medical clinic or applied psychology, there is a growing interest, ranging from a spontaneous curiosity toward molecular mechanisms, cellular and tissue processes, central nervous system functioning (the brain, also called "the organ of thought") and the offshoots of the peripheral nervous system. Along with the well-known increases in neurodegenerative pathologies, as from Alzheimer disease to the spectrum of Parkinsonism, there are also increases in peripheral neuropathies, as well as in pain control, especially in the case of long-term cancer survivals.

This wonderful book, composed of 25 chapters (each chapter has many different inserts in depth), is divided into 4 main sections, each of a different topic and color: "Foundations", "Sensory and Motor System", "Brain and Behaviour" and "The Changing Brain". It is the very well accomplished Italian translation of the 2016 version of *Neuroscience: Exploring the Brain* (the 4th edition).

This book is not only a brilliant source of study. It can be used as an encyclopedic reference, almost a sort of dictionary, where you can easily find updated information on various sectors. It is also rich of colored and accurate images and at the end of the first section "Foundations", you can find a guide of over 40 pages illustrating in detail human neuroanatomy. Moreover, at the end of every chapter you find a box with the key words, review questions and suggested reading. A detailed glossary and a relevant index enrich the end of this stimulating text.

As a whole, the book is written fluently, updated from a scientific point of view but in particular it also provides historical perspectives that, especially for what concerns the subsequent stages of methodological improvement, are really a useful complement to a basic narrative.

Stella Falsini and Enrico Alleva
Istituto Superiore di Sanità
Roma
enrico.alleva@iss.it

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Publications from International Organizations on Public Health

Edited by
Annarita Barbaro

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS (FAO)

World Food and Agriculture – Statistical Yearbook 2023. Rome: Food and Agriculture Organization of the United Nations 2023; 384 p. ISBN 978-92-5-138262-2. This publication offers a synthesis of the major factors at play in the global food and agricultural landscape. The Statistical Yearbook is a primary tool and indispensable reference for policymakers, researchers and analysts, as well as laypersons interested in the past, present and future paths of food and agriculture. Drawing on the wealth of information that FAO statisticians produce across the Organization, this publication offers a synthesis of the major factors at play in the global food and agricultural landscape. Statistics are presented in four thematic chapters, covering the economic importance of agricultural activities, inputs, outputs and factors of production, their implications for food security and nutrition and their impacts on the environment. The Yearbook is meant to constitute a primary tool for policymakers, researchers and analysts, as well as the general public interested in the past, present and future path of food and agriculture.

World Food and Agriculture – Statistical Pocketbook 2023. Rome: Food and Agriculture Organization of the United Nations 2023; 138 p. ISBN 978-92-5-138261-5. This Pocketbook complements the Statistical Yearbook by providing quick access to top-level numbers, charts and maps related to many dimensions of food and agriculture – including production, prices, trade, food security and nutrition, and environmental aspects.

The State of Food and Agriculture 2023. Revealing the true cost of food to transform agrifood systems. Rome: Food and Agriculture Organization of the United Nations 2023; 150 p. ISBN 978-92-5-138167-0. The State of Food and Agriculture 2023 looks into the true cost of food for sustainable agrifood systems. This report introduces the concept of hidden environmental, health and social costs and benefits of agrifood systems and proposes an approach – true cost accounting (TCA) – to assess them. To operationalize the TCA approach, the report proposes a two-phase assessment process, first relying on national-level TCA assessments to raise awareness and then moving towards in-depth and targeted evaluations to prioritize solutions and guide transformative actions. The 2023 report highlights the methodological and data challenges that need to be addressed for greater adoption of TCA, especially in low- and lower-middle-income countries. It quantifies, to the extent possible, the hidden costs of national agrifood systems in a consistent and comparable way for 154 countries. These preliminary results cover hidden costs from greenhouse gas emissions, nitrogen emissions, blue water use, land-use transitions, and poverty, as well as losses in productivity caused by unhealthy dietary patterns and undernourishment. Despite the preliminary nature of these estimates, the analysis reveals the urgent need to factor hidden costs into decision-making for the transformation of agrifood systems. Innovations in research and data, alongside investments in data collection and capacity building, are needed to scale the application of TCA, especially in low- and middle-income countries, so that it can become a viable tool to inform decision- and policymaking in a transparent and consistent way.

UNITED NATIONS EDUCATIONAL, SCIENTIFIC AND CULTURAL ORGANIZATION (UNESCO)

The United Nations World Water Development Report 2023: partnerships and cooperation for water. Paris: UNESCO Publishing 2023; 189 p. ISBN 978-92-3-100576-3. The 2023 edition of the United Nations World Water Development Report (WWDR) describes how building partnerships and enhancing cooperation across all dimensions of sustainable development are essential to accelerating progress towards all the targets of SDG 6 and realizing the human rights to water and sanitation. Partnerships and cooperation take place in almost any water-related endeavour and water resources management has a long history of experience with partnerships, both good and bad. This report reviews this experience, highlighting how enhancing positive and meaningful cooperation amongst the water, sanitation and broader "development" communities is required to accelerate progress. This report also addresses how the water and sanitation community can internally collaborate more effectively by maximizing complementarity, as well as reach out to other sectors and realms of decision-making where water plays a critical (but often times misunderstood or ignored) role in meeting their own objectives and amplifying co-benefits.

JOINT UNITED NATIONS PROGRAMME ON HIV/AIDS (UNAIDS)

Global AIDS Monitoring 2024. Indicators and questions for monitoring progress on the 2021 Political Declaration on HIV and AIDS. Geneva: Joint United Nations Programme on HIV/AIDS 2023; 248 p. This document is a detailed compilation of indicators, including on financing, and a suite of questions on national policies and their implementation. These 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. The indicators and questions in this document are designed for use by national AIDS programmes and partners to assess the state of a country's HIV and AIDS response, and to measure progress towards achieving national HIV targets. Countries are encouraged to integrate these indicators and questions into their ongoing monitoring efforts and to report comprehensive national data through the Global AIDS Monitoring (GAM) process. In this way they will contribute to improving understanding of the global response to the HIV epidemic, including progress that has been made towards achieving the commitments and global targets set out in the new United Nations Political Declaration on HIV and AIDS: Ending Inequalities and Getting on Track to End AIDS by 2030, adopted in June 2021, and the linked Sustainable Development Goals.

ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT (OECD)

OECD-FAO Agricultural Outlook 2023-2032. Paris: Organization for Economic Co-operation and Development and Food and Agriculture Organization of the United Nations 2023; 359 p. ISBN 978-92-5-137923-3. The OECD-FAO Agricultural Outlook 2023-2032 provides an assessment of the ten-year prospects for agricultural commodity and fish markets at national, regional, and global levels in a context of continued economic risks, uncertainty, and high energy prices. The report is a collaborative effort between the OECD and FAO, prepared with inputs from Member countries and international commodity organisations. The publication consists of 11 Chapters; Chapter 1 covers agricultural and food markets; Chapter 2 provides regional outlooks and the remaining chapters are dedicated to individual commodities.

INTERNATIONAL LABOUR ORGANIZATION (ILO)

Preventing and addressing violence and harassment in the world of work through occupational safety and health measures. Geneva: International Labour Organization 2024; 151 p. ISBN 9789220386095 (print) ISBN 9789220386101 (web PDF). The report highlights the pervasive issue of violence and harassment (V&H) in workplaces worldwide, affecting more than one in five employed individuals. It underscores the significant impact of V&H on individuals, enterprises, and society, exacerbated by evolving work conditions like digitalization and work-life balance challenges. The report emphasizes the importance of adopting comprehensive strategies, including the ILO Violence and Harassment Convention (No. 190) and occupational safety and health (OSH) measures, to prevent and address V&H, while also examining different national approaches and the effectiveness of collective bargaining agreements and legal frameworks in tackling this issue.

WORLD HEALTH ORGANIZATION (WHO)

Ethics and governance of artificial intelligence for health: Guidance on large multi-modal models. Geneva: World Health Organization 2024; 98 p. ISBN 978-92-4-008475-9 (electronic version) ISBN 978-92-4-008476-6 (print version). This guidance addresses one type of generative AI, large multi-modal models (LMMs), which can accept one or more type of data input and generate diverse outputs that are not limited to the type of data fed into the algorithm. It has been predicted that LMMs will have wide use and application in health care, scientific research, public health and drug development. LMMs are also known as "general-purpose foundation models", although it is not yet proven whether LMMs can accomplish a wide range of tasks and purposes. WHO is issuing this guidance to assist Member States in mapping the benefits and challenges associated with use of LMMs for health and in developing policies and practices for appropriate development, provision and use. The guidance includes recommendations for governance, within companies, by governments and through international collaboration, aligned with the guiding principles. The principles and recommendations, which account for the unique ways in which humans can use generative AI for health, are the basis of this guidance.

WHO global report on trends in prevalence of tobacco use 2000-2030. Geneva: World Health Organization 2024; 135 p. ISBN 978-92-4-008828-3 (electronic version) ISBN 978-92-4-008829-0 (print version). This report presents WHO estimates of tobacco use prevalence for 2022, numbers of users, and trends projected to 2030. Estimates are at global, regional and country-level. This report is a useful companion to the WHO report on the global tobacco epidemic, which tracks the global adoption of tobacco control measures and interventions designed to reduce the use of tobacco. Together these reports allow us to both monitor progress every two years and to identify gaps, challenges and hinderances. In addition to tobacco use prevalence trends and target assessments, other global analyses

presented in this report include global estimates of the prevalence of cigarette smoking and smokeless tobacco use among adults, and the prevalence of tobacco use, cigarette smoking and smokeless tobacco use among adolescents. An estimate the global prevalence of e-cigarette use was attempted, however data are missing in too many countries.

Global competency framework for regulators of medicines. Geneva: World Health Organization 2023; 135 p. ISBN 978-92-4-007875-8 (electronic version) ISBN 978-92-4-007876-5 (print version). The Global competency framework for regulators of medicines ("the Framework") aims to harmonize workforce development efforts for the regulation of medicines by establishing an internationally accepted set of best practice competencies. It will guide the development of regulatory science curricula and maximize the benefit of collaboration and cooperation in medical product regulation globally. The current Global Competency Framework actually covers the regulation of medicines and vaccines, it is expected that the it will eventually expand to cover competencies for the regulation of other health products (such as medical devices) and to consider different regulatory contexts. The Framework will be revised periodically to reflect evolving use and understanding of practical issues related to its implementation.

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Articles in journal

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US Social Security Administration. Evidentiary require-

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