AMP

ACTA MÉDICA PORTUGUESA

A Revista Científica da Ordem dos Médicos

ACTA MED PORT. ISSN 0870-399X e-ISSN 1646-0758

9 | 24

Número 9
Série II
Lisboa

Volume 37
Setembro 2024
Publicação Mensal

AMP ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Propriedade: Ordem dos Médicos (NIPC 500 984 492)
Sede do Editor / Redação: Av. Almirante Gago Coutinho, 151. 1749-084 Lisboa, Portugal. Tel: +351 21 151 71 00 E-mail: secretariado@actamedicaportuguesa.com
ISSN:0870-399X | e-ISSN: 1646-0758

Assinaturas: Nacional: 300 Euros; Internacional: 350 Euros.

AMP37(9) - Setembro de 2024

Registo: Inscrito na Entidade Reguladora para a Comunicação Social com o Nº 106 369
Depósito legal: 20 957/88
Estatuto Editorial: http://www.actamedicaportuguesa.com/normas-de-publicacao

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Climate Change, the Environment, and Health: A Call to Action

Alterações Climáticas, Ambiente e Saúde: Um Apelo à Ação

Luis CAMPOS[1,2]
Acta Med Port 2024 Sep;37(9):579-581 ▪ https://doi.org/10.20344/amp.22100

Keywords: Attitude of Health Personnel; Carbon Footprint; Climate Change; Delivery of Health Care; Environmental Pollution
Palavras-chave: Alterações Climáticas; Atitude dos Profissionais de Saúde; Pegada de Carbono; Poluição Ambiental; Prestação de Cuidados de Saúde

In 2021, the United Nations Food and Agriculture Organization (FAO), the World Organization for Animal Health (WOAH), the United Nations Environment Programme (UNEP), and the World Health Organization (WHO) defined the concept of One Health as an integrated and unifying approach that recognizes the close interconnection and interdependence of human, animal, plant, and environmental health.[1] Following this vision, on July 28, 2022, the United Nations General Assembly recognized a new human right: a clean, healthy, and sustainable environment.[2] However, this right increasingly seems utopian. There is substantial evidence that climate change and ecosystem degradation are progressing according to the most pessimistic scenarios and significantly impacting public health. The influence of environmental determinants on health may be the greatest future challenge for healthcare systems. Conversely, it is known that the healthcare sector — indispensable for addressing the ongoing epidemiological transition and the heightened risk of climate disasters — also contributes to a large carbon footprint, accounting for 4.8% of greenhouse gas (GHG) emissions in Portugal, a percentage higher than the European average.[3] Over 168 million trees would need to be planted to absorb this amount of CO_2 from the atmosphere.

Environmental determinants affecting human health

The primary environmental determinants impacting human health include overpopulation, climate change, ecosystem degradation, biodiversity loss, and the depletion of natural resources.

Regarding overpopulation, it took humanity 200 000 years to reach a population of one billion in 1803 and only 220 years to reach 8 billion people, which happened on November 15, 2023. Since 1970, the Earth system has lost its regenerative capacity to support this population, and currently, we would need 1.75 planets to sustain our needs.[4]

Climate change is due to GHG emissions. We need to cut 43% of these emissions by 2030, compared to 2019, to limit temperature rise to 1.5°C by the end of this century.[5] The year 2023 was the hottest ever recorded, and it may have been the coolest year for the rest of our lives. Some scientists predict that with current policies, we could reach 2°C of global warming by the end of this decade compared to the pre-industrial period. Climate change is already increasing the frequency of floods, droughts, and fires. For instance, in 2023, about 11 000 people died in Libya due to floods, and forest fires in Canada burned an area equivalent to 17 million football fields. Additionally, tipping points such as changes in Atlantic Ocean currents could trigger unpredictable climate shifts. Some of these changes, especially in oceans, ice sheets, and sea levels, are irreversible and may persist for millennia.

Ecosystem degradation has intensified over the past century. Since the Industrial Revolution, human activities have destroyed forests, grasslands, and wetlands, threatening human lives and well-being.[6] An estimated 75% of the ice-free land surface has been significantly altered, and over 85% of wetlands have been lost. Globally, nine out of ten people breathe air with pollutant levels exceeding WHO guidelines.

Biodiversity loss is stark: in the past 50 years, populations of mammals, birds, amphibians, reptiles, and fish have decreased by an average of 70%, and there are a million endangered species.

The depletion of natural resources, particularly water, is alarming, with global drought potentially impacting over 75% of the world population by 2050.

Impact of environmental factors on human health

According to the WHO, environmental factors account for about one in four global deaths. The most affected diseases include cardiovascular and cerebrovascular diseases, chronic respiratory conditions, allergies, cancer, vector-borne diseases, zoonoses, diseases related to water and food quality, and direct effects of extreme weather events like floods, droughts, and fires. Additionally, migrations,

1. CUF Tejo Hospital. Lisbon. Portugal
2. Portuguese Council for Health and the Environment. Lisbon. Portugal.
✉ **Autor correspondente:** Luis Campos. luis.campos@cpsa.pt
Recebido/*Received*: 23/07/2024 - **Aceite/*Accepted*:** 25/07/2024 - **Publicado/*Published*:** 02/09/2024

conflicts, and mental health issues such as eco-anxiety are increasing. A 2021 survey of 10 000 young people in 10 countries revealed that 76% of young people in these countries and 80% in Portugal view the future as 'frightening' These impacts mainly affect vulnerable groups such as children, the elderly, people with multimorbidity, the homeless, and the poor. Heat-related diseases among the elderly have increased by over 50% in the last 20 years

Ecological footprint of the healthcare sector

The healthcare sector's most considerable contribution to GHG emissions is supplying goods and services like medicines and equipment. Still, transport, energy, heating and cooling systems, lighting, anaesthetic gases and inhalers are other sources of emissions. Like other sectors, healthcare must implement mitigation actions to reduce GHG emissions and adaptation actions to climate change and environmental degradation. Reducing the ecological footprint of the healthcare sector must be a political priority, requiring a national strategy and measures such as creating environmental sustainability services in hospitals, updating outdated laws like waste management laws, incorporating environmental sustainability criteria in procurement, developing and implementing guidelines across all sectors, opting for renewable energy, electric transport, and LED lighting, and setting clear decarbonization goals. The UK National Health Service aims to achieve zero emissions by 2040 for directly controlled activities and by 2045 for indirect activities. Many of these measures may require short-term investments but result in substantial medium- and long-term savings.

Efforts to reduce this ecological footprint should extend to clinical sectors as well. Anesthetic gases, which account for about 5% of healthcare sector emissions, can be replaced with alternatives. Using remanufactured catheters instead of single-use ones reduces the impact of global warming by about 50%. Operating room blue wrap can be recycled into clothing or equipment. Food services can be optimized by providing healthier, seasonal and locally sourced food while reducing waste. Organizing healthcare to integrate different levels of care in the same location, promoting proximity care, and implementing telemedicine can drastically reduce patient travel and improve convenience. Enhancing care quality and avoiding overdiagnosis and overtreatment are other ways to reduce the healthcare sector's ecological footprint.

Equipping the healthcare system for uncertainty

Preparing the healthcare system for ongoing changes and increased climate disaster risks is crucial. This requires emergency plans at all levels, flexible and scalable hospitals, optimized communication and coordination across care levels and between public and private sectors, robust information and communication systems, sufficient and prepared human resources, and strengthening generalist specialties like Pediatrics, Internal Medicine, and Family Medicine, whose versatility and multipotentiality are essential for managing uncertainty.

Responsibility of healthcare professionals

Given their awareness of the impact of environmental changes on population health, healthcare professionals have an ethical duty to engage in this global challenge within their organizations and adopt environmentally friendly behaviors. We must not compromise the future of coming generations—our children and grandchildren—and uphold the trust society places in us. We must raise our voices to highlight that this is not just an environmentalist or radical youth issue but affects us all. We have to communicate the severity of the problem without inducing helplessness, as this paralyzes action. The climate emergency must be recognized as a public health emergency.

The WHO, several scientific societies, and professional bodies from various countries have already taken positions on the need for this involvement. The Portuguese Society of Internal Medicine was the first internal medicine society in the world to address and issue public recommendations on this topic.[7] In 2022, the European Federation of Internal Medicine, which includes societies from 41 countries, published a similar appeal.[8] This year, we promoted a consensus in this direction, uniting for the first time all Spanish and Portuguese-speaking internal medicine societies or associations, totaling 29 countries.[9]

The Portuguese Council for Health and the Environment (PCHE)

The PCHE was founded by the author of this article, together with José Victor Malheiros and João Queiroz e Melo, in October 2022 with the objective of bringing together the leading healthcare-related organizations to jointly address climate change, environmental degradation, and their health impacts. The PCHE advocates for reducing the health sector's ecological footprint, promotes public and professional awareness, education, and research, and helps the healthcare system respond to the epidemiological transition and increased risk of unexpected events. The rapid growth of this alliance, now with 85 members, including the Portuguese Medical Association and 21 scientific societies, highlights its timeliness and importance.

Since its inception, we have organized webinars and colloquiums, participated in multiple congresses, co-organized the International Course on Health and the Environment with the National School of Public Health, issued public statements, and we are developing environmental

sustainability recommendations across various sectors. By the end of the year, we will publish the first report of the Portuguese Observatory of Health and Environment and organize the 1st National Congress on Health and the Environment on February 7-8, 2025.

As Robert Swan, the first person to reach both of the earth's poles, said: "The greatest threat to our planet is the belief that someone else will save it."[10]

COMPETING INTERESTS

The author declared that no competing interests exist.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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The Role of Ethical Responsibility in the Management of Environmentally Sustainable Health Care

Responsabilidade Ética na Gestão da Sustentabilidade Ambiental dos Cuidados de Saúde

José CHEN-XU[1,2]
Acta Med Port 2024 Sep;37(9):582-584 ▪ https://doi.org/10.20344/amp.20883

Keywords: Bioethics; Climate Change; Delivery of Health Care; Environment; Environmental Monitoring; Health Facilities; Social Responsibility
Palavras-chave: Ambiente; Alterações Climáticas; Bioética; Estabelecimentos de Saúde; Prestação de Cuidados de Saúde; Responsabilidade Social

INTRODUCTION

In recent years, climate change has gained more prominence, with a focus on the environmental impact on present and future generations, and on the creation of objectives for sustainable cities and communities and climate action. The long-term temperature shifts related to extreme weather events are increasing health threats, by worsening chronic diseases and expanding the geographic distribution of infectious diseases.[1] Therefore, they constitute a major cause of public health concern.

Health institutions play a part in climate change, by aggravating environmental issues with its activities, which account for 4% - 10% of all greenhouse gas (GHG) emissions.[2] Ethical concerns related to the health sector's role have emerged,[3] and have led to environmental footprint assessments.[4] Discussions on the benefits of green measures bring more accountability to institutions, which may strengthen leadership, educate communities, and save money.

Policy-based solutions have been put forward to regulate energy consumption in buildings. This has only been possible with the existence of weighed decisions on the ethical implications of health care activities. The application of sustainable practices and environmental measures within health institutions, as well as green funding and investment in disease prevention, are possible solutions needed to break this vicious circle.

The aim of this article is to provide ethical arguments on the responsibility of the health care sector in adopting environmental sustainability as a central pillar in their practice, which reflects the urgent need of reviewing and adjusting current practices towards a greener health care.

The issue

Health organizations have environmental impacts, which result in negative health consequences. Overall, buildings represent 40% of energy-related CO_2 emissions. The consumption within the health sector outruns that of other tertiary sector buildings, constituting 10.6% of the total energy used for service provision purposes.[5] In England, this may reach up to 21.3 million metric tons of CO_2 in a year, equivalent to 3% of the national GHG emissions.

Common energy waste practices include the use of air conditioning in unoccupied spaces, failure to maintain or repair equipment and neglect to check for air or water leaks, which increases inefficiency and costs. In addition, buildings consume a large amount of water throughout their lifecycle, adding to the increasing amount of energy needed for supply and use, and leading to a greater negative environmental impact.[6]

In the health sector, the main impact is downstream, namely produced waste. Resource use can originate 7000 tons of hospital waste daily across US health care institutions and an annual cost of 10 billion dollars in their management.[7] Additionally, 85% of the waste produced in a general hospital is not hazardous (groups I and II) and is often placed in the biological waste container, which leads to increasing waste management costs and environmental impact through inadequate waste disposal and treatment.

Hospital building management largely contributes to environmental impacts, with 31% - 37% of the overall health sector impact, followed by prescription drug expenditures (33%), medical devices (22%) and hospital care (15%). Power generation and supply chains were the primary processes contributing to acidification of rain, which in turn affects soils and surface waters, whereas surgical and medical instrument manufacturing and pharmaceutical manufacturing contributed to ozone depletion, increasing ultraviolet radiation, exposure and risk of skin cancer.[2] Supply chains have been found to contribute to 62% of the carbon footprint of the National Health Service in England, whereas

1. National School of Public Health. Universidade NOVA de Lisboa. Lisbon. Portugal.
2. Unidade de Saúde Pública. Unidade Local de Saúde do Baixo Mondego. Figueira da Foz. Portugal.
✉ **Autor correspondente:** José Chen-Xu. josechenx@gmail.com
Recebido/*Received*: 01/11/2023 - **Aceite/*Accepted*:** 24/01/2024 - **Publicado *Online*/*Published Online*:** 05/06/2024 - **Publicado/*Published*:** 02/09/2024

healthcare workers' commuting and patient and visitor travel accounted for 10% of GHG emissions.[8] Furthermore, waste management was the main contributor to ecotoxicity and human health toxicity.[2]

It is already acknowledged that extreme weather conditions due to climate change may cause around five million additional deaths every year, with the healthcare sector presenting a relevant contribution to the disease burden, amounting to around 98 000 annual deaths in the United States of America alone.[2]

Organizational ethics in building-up sustainable health institutions

Ethical issues often arise in clinical settings, with medical ethics being a subject lectured in medical schools. However, organizational ethics, a field of applied ethics focusing on environmental health, resource allocation and decision-making processes, is often forgotten.[3] Professionals tend to focus on cost management and saving, efficiency, and quality of care instead.[9]

The sustainability issues regarding buildings are related to their durability – many of the health facilities built in the 1950s and sometimes more recent ones are obsolete, dysfunctional, and costly to maintain. Health facilities must be designed to be pragmatic, ethical, and holistic, considering how they influence the health environment and productivity of healthcare professionals. Organizational vulnerabilities, including management of public funding and risk analysis in health care management, are relevant to assess and prevent ethical risks, including the ones linked to quality of care and allocation of financial resources.[3]

'Social responsibility and health' has been promoted as a bioethics principle. This holistic approach expands bioethics into social issues, determinants of health and health policies, adding aspects of justice and fairness.[10] As a result, health care is an ethical responsibility of governments towards the people they serve. 'Social responsibility and health' is displayed through the criteria used in decision-making in health policy, climate change mitigation, and global health management. Failing to provide mitigation and adaptation actions for climate change would be to disrespect the social responsibility principle. This entails the need to act upstream – to build green, and by implementing green measures before issues appear, through public policies, regulations and procedures in health care management and green funding.[11]

Ethical issues related to the environment are often discussed separately from health issues.[2,6] One way to connect them is through its instrumental value for population health, which comprises climate, food source and green spaces, and by perceiving the environment as an ecosystem service provider. Environmental ethics looks at the potential harmful effects of human health care in the environment, and therefore becomes a driver for change towards more sustainable health care.[10]

Frameworks on environmental health ethics have emerged, as environmental health is an integral part of public health. Even though discussions on climate change and its effects on human health have emerged, as well as political and economic dynamics related to funding climate change research, little mention is made on the role of healthcare institutions. Instead, industries with direct impact on the environment, like the ones related with fossil fuels, are the main focus when discussing environmental health ethics. These frameworks do, however, account for principles such as utility, justice, stewardship, sustainability, and precaution,[10] which will inherently include healthcare institutions in tackling climate change, through the adoption of prevention, mitigation and adaptation measures.

Ethical responsibility of health institutions on environment issues

Ethical issues often arise in decision-making processes, as the environmental impact of healthcare and the need for sustainable healthcare raise questions on environmental stewardship.

The main environmental responsibility in health care is to avoid unnecessary emissions, and this is to be implemented by the management body and guided by ethical values. These values consist of social responsibility, good care, and professionalism, acting together as a driver for improving the organization's environmental practices. Organizational commitment is key, along with training, clear procedures and roles, and a motivational culture, ensuring that health facilities are prepared for implementing green measures.[11]

Environmental sustainability can further be achieved through planning, policies, adaptation of buildings and energy management. This can entail the use of technology to improve efficiency, using solar energy for heating and cooling, water transport pumps, and smart lighting.[5] These measures require investment in energy efficiency, which still represents a small portion of expenditure.

Regarding health institutions, efforts have been made in transforming them into green hospitals. Measures such as the application of energy-saving measures and the reprocessing of single-use materials, can lead to a cost reduction of 15 billion dollars over ten years in US healthcare institutions alone, proving their long-term cost-effectiveness. Another measure is digitalization, with smart controls and connected devices contributing to major energy savings.

Implications for the health care sector

There are many arguments for increasing climate action

across all sectors, including health care. As mentioned, every year, five million deaths are caused by extreme weather events due to climate change,[4] and our sector plays a role in this. In turn, this contributes to overburdening the already burdened healthcare systems, such as the Portuguese National Health Service. Consequently, the health sector itself has an ethical responsibility to break this cycle and improve both management and hospital practices, in order to decrease its contributions to climate change. Six high-priority domains include investments in improving building energy, transportation, and anesthetic gases, as well as pharmaceuticals, medical devices, and sustainable food systems.

Health Care Without Harm, an international organization focused on reducing the carbon footprint of healthcare worldwide, has recently helped to calculate Portugal's carbon footprint and has set clear goals to be achieved by 2030. This includes striving for energy and water efficiency, with an ideal reduction of 40% in primary energy consumption and of 20% in water consumption, as well an increase of 10% in energy self-consumption and a 20% decrease in waste production. The rehabilitation and improvement of buildings is essential to achieve these goals.

The report also identified key areas of high carbon emission intensity, which included the manufacture of chemical products, as well as basic pharmaceutical products and pharmaceutical preparations, consumption of purchased electricity, and direct emissions originating from combustion and from unintentional emissions.

A sustainable healthcare system can only be achieved by changing the priorities on the ground, through an effective sustainability plan and a swift adoption of mitigation and adaptation measures within healthcare facilities, as well as shifting the priority to health promotion and disease prevention, by tackling health determinants, such as air pollution and food safety. As such, strengthening public health plans and interventions will contribute to decreasing vulnerability to climate risks, while also contributing to more sustainable lifestyles.[1]

CONCLUSION

The healthcare sector has an ethical responsibility to evaluate its impact on environmental health through meaningful research and the implementation of sustainable measures, which can result in high economic savings and many lives saved. In recent years, we have witnessed negative changes in waste production, with increasing single-use materials and worsening waste management processes, requiring improvements in waste separation and recycling practices. Moreover, the post-pandemic world must focus on rebuilding and investing in green measures and ensuring resilience of healthcare systems.

This is even more pressing as health care institutions need to operate continuously to provide the needed care to populations. However, ethical concerns and organizational corporate social responsibility are also a duty of other private businesses and public service sectors, making green funding everyone's concern. The investment in environmentally friendly solutions is urgent, with a joint change in all sectors generating a stronger and lasting positive impact in tackling climate change.

COMPETING INTERESTS

JCX received grants from the European Burden of Disease Network; received payment by the Council of Europe for speaking at Study Session "Mobilising Youth Towards Climate & Health Injustice" and by the New Zero World Coalition for the development of the White Paper in Climate Communications; received support from the European Burden of Disease Network for attending the 4th Working Group Meeting; was the Co-Chair of the Trainee Advisory Committee of the Consortium of Universities for Global Health and a member of the National Commission for Residents of Sindicato Independente dos Médicos.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Clinical Trials in Portugal: Past and Future. Position Paper from the Colleges of Clinical Pharmacology and Pharmaceutical Medicine

Ensaios Clínicos em Portugal: Passado e Futuro. Posicionamento dos Colégios de Farmacologia Clínica e de Medicina Farmacêutica

Filipa BORGES-CARNEIRO✉*[1], Miguel TORRE SOUTO*[1], Isabel SILVA[1], Paula LEÃO MOREIRA[1], Paula FERRAZ DE OLIVEIRA[1], Diogo José LOPES[1], Luís FIGUEIRA[1,2,3], Marta REINA-COUTO[1,4,5], Luís CUNHA-MIRANDA[6,7], Diogo PONCES BENTO[7,8], Fernando MAGRO[1,9]

Acta Med Port 2024 Sep;37(9):585-588 ▪ https://doi.org/10.20344/amp.21371

Keywords: Clinical Trials as Topic; Portugal
Palavras-chave: Ensaios Clínicos; Portugal

In recent decades, clinical research, especially clinical trials, has been shown to improve: i) access to new health technologies and frontline scientific knowledge; ii) adoption of better clinical practices; iii) quality of generated data and analysis; iv) education level of the workforce; and v) creation of new jobs and alternative sources of funding for institutions and countries.[1] The massive amounts of data produced by clinical research have become a valuable asset, which is expected to impact economic policies in the coming decades.[2]

Constraints related to clinical research in Portugal were previously acknowledged and remain topical: lack of funding, financial incentives, adequate policies, and a solid strategy for clinical research.[3]

In this article, we aim to evaluate the clinical trials panorama in Portugal regarding structures, procedures, and outcomes (Table 1) and describe possible solutions to the identified problems (Table 2).

Clinical research in Portugal faces intricate challenges rooted in organizational structures, resource limitations, and regulatory complexities. These challenges, spanning the spectrum from clinical trial initiation to patient recruitment, demand a holistic approach for substantial improvement in the Portuguese clinical research landscape.

Structures orchestrating clinical studies encompass pivotal elements such as trial registration, data management infrastructures, and support for engaged researchers. However, the Portuguese clinical investigation scenario reveals constraints in both physical infrastructure and human resources, hampering the development of a robust clinical research ecosystem.

A stark reality emerges from the reduced number of approved clinical trials in Portugal, standing at 152 in 2022,[4] which is indicative of a substantial gap in comparison to European standards. Moreover, the inadequate investment in research and development, with the government allocating only €75.6 per person in 2021 (70% less than the European average),[5] amplifies the challenges. The scarcity of national funding programs for non-commercial clinical research and limited funding for the Portuguese Clinical Research Infrastructure Network (PtCRIN) further hampers progress.[6]

While Portuguese patents and scientific publications show gradual improvement, they remain below the European Union (EU) average.[2] The low level of involvement of primary care physicians in research and challenges in patient recruitment comprise the systemic issues.[3]

Based on the experience of countries like the Netherlands, which are at the forefront of clinical research, we believe that key strategies for enhancing the Portuguese clinical research landscape include educational initiatives, national and international networking, high standards of care, improvement of infrastructure, new recruitment strategies, scientific production, and high quality of data collection and reporting.[7]

Essential to this transformation is the capacitation of qualified human resources dedicated to clinical research,

* Co-first authors.
1. Clinical Pharmacology Unit. Unidade Local de Saúde São João. Porto. Portugal.
2. Center for Drug Discovery and Innovative Medicines (MedInUP). Faculty of Medicine. Universidade do Porto. Porto. Portugal.
3. Department of Ophthalmology. Unidade Local de Saúde São João. Porto. Portugal.
4. Intensive Care Medicine Department. Unidade Local de Saúde São João. Porto. Portugal.
5. College of Clinical Pharmacology. Ordem dos Médicos. Lisbon. Portugal.
6. Portuguese Institute of Rheumatology. Lisbon. Portugal.
7. College of Pharmaceutical Medicine. Ordem dos Médicos. Lisbon. Portugal.
8. Department of Infectious Diseases. Unidade Local de Saúde de São José. Lisbon. Portugal.
9. CINTESIS@RISE. Faculty of Medicine. Universidade do Porto. Porto. Portugal.
✉ **Autor correspondente:** Filipa Borges-Carneiro. filipa.joao.carneiro@chsj.min-saude.pt

Recebido/*Received*: 12/02/2024 - **Aceite/*Accepted*:** 12/06/2024 - **Publicado *Online*/*Published Online*:** 31/07/2024 - **Publicado/*Published*:** 02/09/2024

Table 1 – Definitions and examples of structures, procedures, and outcomes for clinical trials in Portugal

	Definitions and examples
Structures	Encompass the deliberate organization and interplay of the various elements involved in the establishment and execution of a clinical study. This can include critical components such as platforms for the registration of clinical trials, infrastructures necessary for data collection and management, as well as the provision of training and support for researchers engaged in the study.
Procedures	Denote the systematic sequence or methodology employed in conducting a study. This includes various aspects such as legislation and the standardization of documents like informed consent and contracts across different study sites, the systematic collection of data, and the pivotal roles played by governing bodies responsible for the assessment and oversight of the study.
Outcomes	Defined as the conclusive results or effects that constitute a vital component of the study findings, influencing various stakeholders. These effects can include improvements in patient health and well-being, enhancing the quality of care and services offered by healthcare institutions, and providing valuable insights and guidance to healthcare professionals. For instance, outcomes may entail better patient recovery rates, streamlined healthcare processes within institutions, and evidence-based recommendations that aid healthcare professionals in making informed decisions.

a factor hindered by insufficient support from hospitals. The crucial role of physicians in patient enrollment underscores the need for incentives, rigorous feasibility analyses, and enhanced knowledge of ongoing trials.[8] Regulatory amendments, fiscal incentives for private companies supporting university education, business-friendly tax and labor laws, and health and science literacy programs are essential components for a comprehensive solution. Leveraging EU funding through the Recovery and Resilience Plan becomes crucial in counteracting the brain drain phenomenon and boosting work opportunities in knowledge-intensive activities.[2]

Piloting multidisciplinary investigation centers emerges as a tangible solution, incorporating accountability, financial autonomy, protected resources, systematic trial registration, effective leadership, and integration into national and international networks. This approach seeks to test and validate proposed solutions in a controlled environment.[9] Recommendations for performance indicators, such as recruitment metrics and contract timelines, provide a structured approach.

The procedural aspect of clinical research requires a comprehensive evaluation of limitations in Portugal. Achieving better performance requires a convergence of stakeholders' visions, including the Ministry of Health, to shape a governmental agenda and strategic plan.[1,9] Harmonizing documentation and collaboration among regulatory bodies, healthcare providers, pharmaceutical companies, academic institutions, and patient organizations is pivotal. The new clinical trials regulation (CTR) provides a foundation, but additional streamlining and standardization through initiatives like the European Clinical Research Infrastructure Network are vital.[3,9]

Addressing challenges related to sample size, time intervals for trial initiation, and recruitment processes is crucial, as in Portugal the time elapsed between study approval and the recruitment of the first participant is, on average, one year.[3] Urgent steps include reviewing recommendations on advertising clinical trials and standardizing documents like informed consent and contracts across different study sites.

New clinical study models, like collaborative and decentralized trials, are crucial for advancing medical research, improving patient access to trials, and accelerating the development of new treatments. However, they face challenges in compliance, data management, patient engagement, and logistics. Also, increasing capacity to conduct investigator initiated clinical studies could help advance scientific understanding, improve patient care, and spark new treatment research ideas, elevating the country's clinical research environment.

Prominent entities like the Portuguese Pharmaceutical Industry Association (APIFARMA) and the Agency of Clinical Investigation and Biomedical Innovation spearhead training and awareness projects, intending to uplift clinical trial practices in Portugal. Quality improvement in integrity plans gains momentum through initiatives like SOPs4RI, while platforms such as 'The Embassy of Good Science' provide valuable resources and information on responsible and ethical scientific activity.[3]

Horizon Europe is the EU's key funding program for research and innovation, aiming to tackle global challenges, achieve United Nations sustainable development goals, and boost the EU's competitiveness and growth. Participation in Horizon Europe projects can enhance clinical research diversity, broaden research scope, and boost innovation in the Portuguese healthcare sector.

Table 2 – Outcomes and limitations and suggestions regarding the structures and procedures associated with clinical research in Portugal

Structures	
Limitations	**Suggestions**
Lack of platforms for clinical trials dissemination	Systematic registration of trials and recruitable patients
Hospital management not inclined to clinical research	Portuguese National Health Service reform with clinical research as a priority
Lack of funding/incentives	Incentives for healthcare worker involvement in clinical trials (dedicated time, monetary compensation, and education, among others)
Low level of national funding for non-commercial clinical research	Partnerships between government, university hospitals and industry
Scarce professional recognition of investigators	Motivation and support of researchers, promoting their professionalisation
Limited logistical support	Implementation of multidisciplinary research units in hospitals and better collaboration with Contract Research Organisations and pharmaceutical companies
Lack of human resources totally dedicated to clinical trial activities	Multidisciplinary investigation centres with accountability and financial autonomy
Fragmented training and lack of experience in clinical trials	National integration with respect to training requirements
Difficulty in recruiting significant sample sizes	Strategies to improve recruitment and retention of participants (i.e., attractive monetary compensation for healthy volunteers, rigorous feasibility analysis, healthcare worker´s knowledge of ongoing clinical trials)
Limited participation of the private sector in Research & Development	Business-friendly tax and labour laws, Regulatory reforms and fiscal incentives to private companies that fund research
Lack of professional opportunities in business	Collaboration between stakeholders
Need to standardize and strengthen regulatory activities	Long-term national agenda for clinical research
Industry-led investigation is disregarded and is seen as resource consuming	Public education about the contribution of the pharmaceutical industry in improving healthcare
Deficient local infrastructures	Units with management and infrastructures capable of supporting the conduct of clinical trials
Portuguese brain drain	Funding to address Portugal's lack of job opportunities in knowledge-intensive activities
Precarious work conditions for most researchers	Protected and incentivized human resources
Procedures	
Limitations	**Suggestions**
Lack of adequate policies and strategy for clinical research	Convergent vision between the various stakeholders in the definition of a national agenda and a strategic plan for the sector
Inefficient and complex legislative and regulatory framework	Thorough examination of existing laws to ensure consistent documentation and stronger collaboration among key players
Difficulty in effectively collecting data	Implement integrated information systems where patient data can be collected, anonymized, and used to drive innovation
Long time between study submission and first patient recruitment	Develop specific legislation about advertising clinical trials and standardizing documents
Outcomes	
On December 2022, the European Medicines Agency reported an increase of 16% in clinical trial applications under evaluation and a 22% increase in clinical trial applications in the clinical trials information system compared with the previous reporting period.	
In Portugal, the number of clinical trial applications increased from 175 to 230, between 2021 and 2022.	
Data from the second trimester of 2023 seems to suggest that the growing trend persists, with 129 authorized trials until June 2023.	
Regarding therapeutic area, the greatest representation in clinical trials in 2021, 2022 and 2023 (2nd trimester data), were antineoplastics and immunomodulators (with 42%, 40%, and 25% of the total of submitted trials, respectively) followed by central nervous system (with 11%, 15%, and 19% of the total of submitted trials, respectively).	
Portugal has been showing a residual value of trials initiated by the investigator (8% of the total in 2022 and 6.7% of the total as of June 2023).	
Concerning the year of 2022, the medium decision time for clinical trial applications was of 60 days.	

Harnessing the full potential of data demands innovative approaches, including integrated information systems for anonymized patient data. Overcoming time-consuming local feasibility assessments requires defined regulatory limits and pragmatic inspections. Additionally, addressing issues related to reimbursement of medicines and reluctance to prescribe new drugs is crucial for fostering a conducive research environment.

The pivotal outcomes of clinical trials resonate across patient health, healthcare quality, and professional insights. Recognizing this, a 2016 report by APIFARMA and the National School of Public Health outlined a consensus and recommendations, emphasizing the need for government involvement in mapping areas of excellence, defining investment priorities, establishing minimum criteria for research centers, and promoting patient literacy.[9] In this setting, the digital platform 'Portugal Clinical Trials', which was created under the motto "union for cutting-edge health", intends to be the largest aggregator of information regarding clinical research in Portugal.[10]

In the context of recent changes introduced by the new CTR, Portugal is well positioned to undergo a paradigm shift. The implementation of the CTR, with obligations for clinical trial authorization through the clinical trials information system, aims to streamline processes, albeit facing initial challenges for smaller companies.

Empowering patients and involving them in health innovation is a key aspect of the future. The 'Patient Innovation' platform stands as a testament to the innovative capabilities of patients and caregivers, underscoring the need for continued support and dissemination. This digital platform emerges as a beacon, showcasing patient learnings and innovative solutions they have come up with in their daily lives.[2] As part of the future of health innovation, it not only disseminates solutions but also offers mentoring and training programs to empower patients and caregivers.

In conclusion, the multifaceted challenges within the Portuguese clinical research landscape demand a comprehensive and collaborative approach. The proposed strategies, spanning structures, procedures, and outcomes, aim to reshape the narrative by fostering an environment conducive to robust clinical research in Portugal.

AUTHOR CONTRIBUTIONS

FBC, MTS: Study design, literature review, writing and critical review of the manuscript.

IS, PLM, PFO: Study design, literature review, writing of the manuscript.

DJL, LF, MRC, LCM, FM: Study design, critical review of the manuscript.

DPB: Study design, literature review, critical review of the manuscript.

All authors approved the final version to be published.

COMPETING INTERESTS

FM served as a speaker and received honoraria from Merck Sharp & Dohme, Abbvie, Vifor, Falk, Laboratórios Vitória, Ferring, Hospira, and Biogen; is a board member of the Portuguese IBD Study Group and President-Elect of ECCO.

All other authors have declared that no competing interests exist.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Long-term Exposure to Ambient Air Pollution and its Association with Mental Well-Being, Depression and Anxiety: A Nationally Representative Study

Exposição de Longo-prazo a Poluição do Ar Ambiente e sua Associação com Bem-Estar Mental, Depressão e Ansiedade: Um Estudo Representativo a Nível Nacional

Lara PINHEIRO-GUEDES[1,2,3], Mafalda SOUSA-UVA[1,4,5], Ricardo GUSMÃO[3,6,7], Clarisse MARTINHO[2], Carlos MATIAS DIAS[1,4,5], Virgínia DA CONCEIÇÃO[3,6], Carlos GOMES QUELHAS[8], Daniel SALDANHA RESENDES[9], Vânia GAIO[1,4,5]
Acta Med Port 2024 Sep;37(9):589-600 ▪ https://doi.org/10.20344/amp.21245

ABSTRACT

Introduction: Exposure to ambient air pollution may play a role in the onset of common mental disorders like depressive and anxiety disorders. The association of long-term exposure to particles smaller than 10 µm (PM_{10}) with these diseases remains unclear. This study aimed to estimate the association of long-term exposure to PM_{10} with mental well-being and the frequency of probable diagnosis of common mental disorders.

Methods: A nationally representative cross-sectional study was done in mainland Portugal. Long-term exposure was estimated through one-year average concentrations of PM_{10}, calculated with data from the Portuguese Environment Agency, attributed individually considering individuals' postal codes of residence. The mental well-being and the probable diagnosis of common mental disorders were ascertained through the five-item Mental Health Inventory scale. Linear and Robust Poisson regression models were computed to estimate change percentages, prevalence ratios (PR), and their 95% confidence intervals (95% CI).

Results: The median (interquartile range) concentration of PM_{10} was 18.6 (15.3 - 19.3) µg/m³. The mental well-being score was 72 (56 - 84) points, on a scale from 0 to 100. A probable diagnosis of common mental disorders was found in 22.7% (95% CI: 20.0 to 25.6). Long-term exposure to PM_{10} was associated with a non-statistically significant decrease in the mental well-being score [for each 10 µg/m³ increment in one-year average PM_{10} concentrations, there was a 2% (95% CI: -8 to 4) decrease], and with a non-statistically significant increase in the common mental health frequency (PR = 1.012, 95% CI: 0.979 to 1.045).

Conclusion: We did not find statistically significant associations between long-term exposure to PM10 and mental well-being or the frequency of probable diagnosis of common mental disorders. These results may be explained by the reduced variability in the exposure values, given the geographical distribution and functioning of the network of air quality monitoring stations. This study contributes with evidence for low levels of air pollutants, being one of the first to adjust for individual and aggregate-level variables. Moreover, to the best of our knowledge, this was the first nationally representative, population-based study conducted on the Portuguese population using real-life data. Maintaining a robust and nationwide air quality monitoring network is essential for obtaining quality exposure data.

Keywords: Air Pollution/adverse effects; Anxiety Disorders; Depressive Disorders; Environmental Exposure; Mental Health; Particulate Matter/adverse effects; Stress, Psychological

RESUMO

Introdução: A exposição à poluição do ar ambiente poderá associar-se a doenças mentais comuns como as perturbações depressivas e ansiosas. A associação entre a exposição de longo prazo a partículas inferiores a 10 µm (PM_{10}) e estas doenças não está claramente estabelecida. Procurámos estimar a associação da exposição de longo prazo a PM_{10} com o bem-estar mental e a frequência de diagnóstico provável de doenças mentais comuns.

Métodos: Foi realizado um estudo transversal, representativo a nível nacional, em Portugal Continental. A exposição de longo prazo foi estimada através das concentrações médias de PM_{10} anuais, calculadas com dados da Agência Portuguesa do Ambiente e atribuídas individualmente considerando os códigos postais de residência de sete dígitos dos indivíduos. O bem-estar mental e o diagnóstico provável de doenças mentais comuns foram obtidos através da escala de cinco itens *Mental Health Inventory*. Aplicaram-se regressões lineares múltiplas e Poisson robustas para estimar percentuais de mudança, razões de prevalência (RP) e seus intervalos de confiança a 95% (IC 95%).

Resultados: A mediana (intervalo interquartil) da concentração de PM_{10} foi de 18,6 (15,3 - 19,3) µg/m³. A pontuação de bem-estar mental foi de 72 (56 - 84) pontos numa escala de 0 a 100. O diagnóstico provável de doenças mentais comuns foi observado em 22,7% (IC 95%: 20,0 a 25,6). A exposição de longo-prazo a PM^{10} associou-se à diminuição não estatisticamente significativa da pontuação de bem-estar mental [por cada aumento de 10 µg/m³ nas concentrações médias de PM_{10} anuais, ocorreu uma diminuição de 2% (IC 95%: -8 a 4)], e ao aumento não estatisticamente significativo da frequência de doenças mentais comuns (RP = 1,012, IC 95%: 0,979 a 1,045).

Conclusão: Não se verificaram associações estatisticamente significativas entre a exposição de longo prazo a PM_{10} e o bem-estar mental ou a frequência de diagnóstico provável de doenças mentais comuns. Os resultados podem ser explicados pela reduzida variabilidade observada nos valores de exposição, limitada pela disposição geográfica e funcionamento das estações de monitorização da qualidade do ar. Este estudo acrescenta evidência para níveis reduzidos de poluição atmosférica, sendo um dos primeiros a ajustar para variáveis individuais e populacionais. Foi também o primeiro estudo de base populacional, representativo a nível nacional, realizado na população portuguesa com dados de poluição efetivamente medidos.

Palavras-chave: Exposição Ambiental; Partículas em Suspensão/efeitos adversos; Perturbações de Ansiedade; Perturbações Depressivas; Poluição do Ar/efeitos adversos; Saúde Mental; Stress Psicológico

1. Department of Epidemiology. Instituto Nacional de Saúde Doutor Ricardo Jorge. Lisbon. Portugal.
2. Public Health Unit. Unidade Local de Saúde Tâmega e Sousa. Amarante. Portugal.
3. EPIUnit. Instituto de Saúde Pública. Universidade do Porto. Porto. Portugal.
4. Public Health Research Center. Escola Nacional de Saúde Pública. Universidade NOVA de Lisboa. Lisbon. Portugal.
5. Comprehensive Health Research Center. Universidade NOVA de Lisboa. Lisbon. Portugal.
6. Laboratory for Integrative and Translational Research in Population Health (ITR). Universidade do Porto. Porto. Portugal.
7. Department of Public Health and Forensic Sciences, and Medical Education. Faculdade de Medicina. Universidade do Porto. Porto. Portugal.
8. Public Health Unit Amélia Leitão. Agrupamento de Centros de Saúde de Cascais. Cascais. Portugal.
9. Public Health Unit. Unidade Local de Saúde São José. Lisbon. Portugal.

✉ **Autor correspondente:** Lara Pinheiro-Guedes. lpinheiroguedes@gmail.com

Recebido/*Received*: 20/01/2024 - **Aceite/*Accepted*:** 10/05/2024 - **Publicado *Online*/*Published Online*:** 22/07/2024 - **Publicado/*Published*:** 02/09/2024

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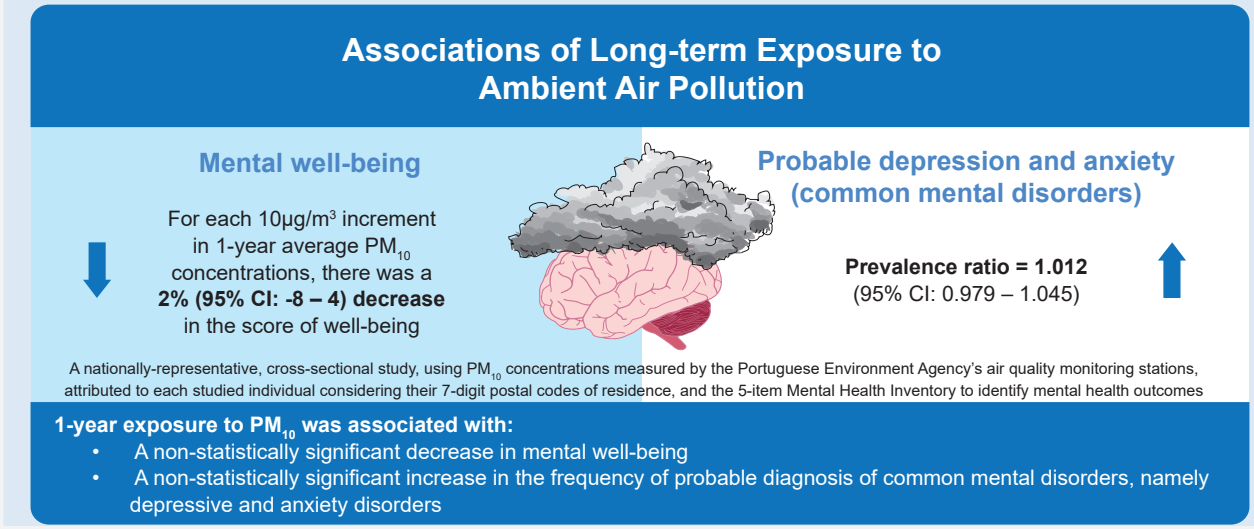
VISUAL ABSTRACT



INTRODUCTION

Ambient air pollution is a global problem and a recognized risk factor for several diseases, including cancer, respiratory, and cardiovascular diseases.[1] Common mental disorders (CMD), namely depressive and anxiety disorders, are the main causes of disease burden worldwide.[3] Furthermore, with the COVID-19 pandemic, their prevalence rate was reported to increase by 28% and 26%, respectively.[3]

The causal path for depressive and anxiety disorders involves genetic, developmental, demographic, socioeconomic, and behavioral factors,[4] but knowledge about the interaction with environmental factors is still limited, especially in terms of exposure to ambient air pollution.[5] Particulate matter (PM) accounts for much of the impact of air pollution on health.[1,6] Some studies have already assessed the association between long-term exposure to particulate matter with a diameter lower than 10 micrometers (PM_{10}) and CMD.[7-12] However, evidence on this association remains inconsistent. In a recently published meta-analysis, for each 10 µg/m³ increment in PM_{10} atmospheric concentration, there was a 9.2% non-statistically significant increase in the incidence of depressive disorders [relative risk (RR) = 1.092, 95% confidence interval (95% CI): 0.988 - 1.206].[7]

Other meta-analyses reported a 8% non-statistically significant increase [odds ratio (OR) = 1.08, 95% CI: 0.98 - 1.19),[8] a 4% non-statistically significant increase (OR = 1.04, 95% CI: 0.85 - 1.26),[9] and even a 11% non-statistically significant decrease (OR = 0.89, 95% CI: 0.50 - 1.58)[10] in the prevalence of depressive disorders. Concerning anxiety disorders, for each 10 µg/m³ increment in PM_{10}, a recent meta-analysis reported a 12% statistically significant decrease in their prevalence (OR = 0.88, 95% CI: 0.78 - 0.98), and a 3% statistically significant increase in the prevalence of psychological stress (OR = 1.03, 95% CI: 1.00 - 1.05).[11] This last meta-analysis considered both short and long-term exposures, with considerable heterogeneity in the estimates [59% (p = 0.01) and 41% (p = 0.17), respectively], which was also noticed in other meta-analyses.[11]

Possible explanatory mechanisms for PM implication on CMD are neuroinflammatory and oxidative stress, dysregulation of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system, with the respective changes on neurotransmitters, neuromodulators, or their metabolites, and epigenetic alterations.[13,14] Some *in vivo* exposure studies in animal models demonstrated that PM may alter brain functions and gene expression in frontolimbic brain regions (associated with emotion processing),[15,16] as well as increase the expression of glucocorticoid-sensitive genes (and the levels of stress hormones).[17] Neuroimaging studies in humans demonstrated that exposure to air pollution was associated with an altered microstructure in the same brain regions.[18] The causal effect of PM_{10} on other chronic diseases may also explain part of the association due to the possible causal path between chronic multimorbidity and

depression.[19]

Therefore, we hypothesized that, through neuroinflammatory mediation, changes in neurotransmitters and neuromodulators (or its metabolites), and through decreased neuroplasticity, ambient air pollution, more specifically long-term exposure to PM_{10}, might be associated with a decreased mental well-being and an increased frequency of CMD.

The present study aimed to estimate the association between long-term exposure to PM_{10} and the mental well-being score, and to estimate the association between long-term exposure to PM_{10} and the frequency of probable diagnosis of common mental disorders, in the population living in mainland Portugal.

METHODS

This study followed the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) reporting guidelines.

Study design and study population

We conducted a population-based, nationally-representative, cross-sectional study, in mainland Portugal. We used data from a restricted sample of the participants in the first Portuguese National Health Examination Survey (INSEF), implemented in Portugal between February 2nd and December 21st, 2015. The INSEF targeted 25- to 74-year-old non-institutionalized individuals, living in Portugal for at least 12 months, who were able to follow an interview in Portuguese. Self-reported data on demographic, socioeconomic, lifestyle and health variables was collected by INSEF. Data collection was performed through computer-assisted interviews made by healthcare professionals, trained according to the European Health Examination Survey guidelines. The design and implementation of this survey were detailed elsewhere.[20]

The study individuals were the INSEF participants from mainland Portugal who consented on data linkage, had their seven-digit postal codes of residence available in the database, and who were living within a 30-km radius from a background air quality monitoring station (with available data on PM_{10} atmospheric concentration), like previously detailed.[21-23] Additionally, we excluded individuals with missing data on any of the five items of the Mental Health Inventory (MHI-5) scale, the instrument used to operationalize the two outcomes in study.

Data availability statement

The datasets analyzed during the current study are not publicly available due to ethical restrictions. Data is available from the authors upon reasonable request.

Ethical considerations

In this study, no ethical or legal issues of confidentiality were raised, since all the data came from anonymized databases.

The INSEF had its scientific protocol approved by the Ethics Committee for Health of the National Health Institute Doutor Ricardo Jorge (INSA) (Internal Note No. 7/2011), by the National Data Protection Commission (Authorization No. 199/2001), and by the Ethics Commissions of the Northern Region Health Administration (Authorization No. 91/2014), the Regional Health Administration of Centro (Authorization No. 44/2014), the Regional Health Administration of Lisbon and Tagus Valley (Authorization No. 17/2014), the Algarve Regional Health Administration (Authorization No. 2742 of 04/03/2015), and the Health Service of the Autonomous Region of Madeira (Authorization No. 32/2014). All the participants were asked to sign a declaration of informed consent to participate in the INSEF, which consisted of accepting to respond to a general health interview, perform the physical examination, and donate a blood sample for clinical analysis.

The protocol of this study was also approved by the INSA Ethics Committee and by the Board of Review of the INSEF (INSA-IM60_05/February 2023).

Ambient air pollution assessment

Previous studies considered long-term exposure to PM_{10} as a period equal or higher than six months, with one year being the most common timeframe.[6-8,10,12] In this study, long-term exposure to PM_{10} was defined as the one-year average PM_{10} concentration (μg/m³), attributed to each individual according to their seven-digit postal code of residence, as the INSEF participants reported living in the same place for at least one year before their assessment day.

We computed individually allocated annual averages using the daily average PM_{10} concentrations available for the 365 days before each individual's assessment day. These daily averages were computed using the 24-hour PM_{10} concentrations available from each station. Hourly PM_{10} concentrations were obtained between February 2nd, 2014 (365 days before the first INSEF fieldwork day) and December 21st, 2015 (the last INSEF fieldwork day), through the air quality monitoring stations database (QualAR), available online at the Portuguese Environment Agency website (https://qualar.apambiente.pt/).

Only background stations located within 30 km from the individuals' residence, with daily and annually data collection efficiencies of at least 75%, were considered. For each individual, there was a unique allocated one-year average of exposure to PM_{10}. When two or more stations coexisted in the defined 30-km radius, we weighted annual average concentrations by the inverse of the squared distance

between the individual's residence and each air quality monitoring station, as previously reported.[21-23]

Mental health outcomes definition and identification

We ascertained mental well-being and the frequency of probable diagnosis of CMD (proxy of prevalent CMD) through the scores obtained on MHI-5, in its numerical form (0 to 100 points) and categorical form (≤ 52 points or > 52 points), respectively. In its numerical form, a score of 0 represents the minimum on the continuum of mental well-being, while a score of 100 represents the maximum. In its categorical form, a score ≤ 52 represents a situation that requires proper clinical evaluation by a doctor (a 'Probable diagnosis of CMD'), while a score > 52 represents a situation that does not require proper clinical evaluation.

MHI-5 is a five-item self-reported questionnaire that measures negative and positive dimensions of mental health, in the four weeks prior to the day of assessment [Appendix 1 - Supplementary Fig. 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/21245/15477)].[24] It was nationally[25,26] and internationally[27,28] validated for the screening of major depressive disorder, affective disorders, (unipolar and bipolar depressive disorders) and anxiety disorders.

Covariates

Based on our literature review, we elaborated a directed acyclic graph, in DAGitty version 3.0 (https://dagitty.net/), to select the minimal sufficient set of variables needed to account for confounding during data analysis [Appendix 1 - Supplementary Fig. 2 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/21245/15477)].[19,23,29-31]

Age was categorized into four categories: 25 - 34 years, 35 - 49 years, 50 - 64 years, and 65 - 74 years, according to the cut-offs used in The World Mental Health Survey.[32] Sex and degree of urbanization were studied as available in the INSEF database: female/male and rural/urban, respectively.[20] Education level was categorized into three categories, considering the highest level of education completed and according to the 2011 International Standard Classification of Education (ISCED)[33]: low education (levels 0 - 2 of ISCED, 2011), medium education (levels 3 - 4 of ISCED, 2011), and high education (levels 5 - 8 of ISCED, 2011). Employment status was categorized into three categories, as in previous studies[34]: employed, unemployed, and other without a professional activity (student, retired, disabled, housewife, or other). Professional occupation was categorized into two categories, according to the International Standard Classification of Occupations (ISCO-08)[35]: white-collar (managers; professionals; technicians, and associate professionals; clerical support workers; and services, and sales workers) and blue-collar (skilled agricultural workers; craft, and related trades workers; plant, machine operators, and assemblers; and elementary occupations). Area-level socioeconomic deprivation is the Portuguese version of the European Deprivation Index, a variable available online for all the Portuguese boroughs, here used in terciles of increasing deprivation.[31,36] Individually allocated one-year average temperatures were obtained through a similar methodology to the one applied to estimate exposure to PM_{10}, making use of one-year average temperatures collected from the National Oceanic and Atmospheric Administration database.[21-23,37] Area-level walkability was obtained through the weighted sum of residential density, street connectivity, and a land use mix index, for all the boroughs of mainland Portugal, and is available upon reasonable request, in terciles of increasing walkability.

Four health status variables were used in the sensitivity analyses: two yes/no self-reported medical diagnoses of depression and chronic anxiety relative to the six months prior to the assessment time (or predicted to last for at least six months from that time), and two yes/no self-reported use of prescribed medication for these disorders (relative to the two weeks prior to the assessment time).[38]

Statistical analysis

Participants' characteristics were presented, for continuous variables, as mean ± standard deviation (SD) or as median [interquartile range (IQR)], according to the normality or not of their distributions, respectively, and, for categorical variables, as relative frequencies, specifically as percentages.

Pearson's chi-squared tests were used to assess the association between two categorical variables. Robust confidence intervals for generalized Hodges-Lehmann median differences were used to assess differences in numerical variables with non-normal distributions between two groups.[39]

The characteristics of the included and excluded individuals were compared, through descriptive and bivariate analysis, to assess selection bias.

We performed single-level multivariable analyses, even though we used individual and aggregated variables (at borough level) in our models, as the assumptions for carrying out a multilevel analysis were not met, namely because some boroughs had just one individual.

Regarding the numerical outcome, since no transformation was able to normalize the distribution of its residuals, we compared various generalized linear regression models (linear, gamma, Poisson, and negative binomial) using Akaike Information Criteria (AIC). We chose the model with the lowest AIC to ensure the best fit of the model. As the linear regression model was the best fit, but its assumptions

were not met, we used the link function 'log' to help handle heteroscedasticity and transform the distribution of the response variable in a more symmetrical one. We estimated regression coefficients and calculated the percentage of change (% change) and its 95% CI, for each 10 μg/m³ increment in PM_{10}, through the formula 100 x (e^{β} – 1) x 10.[22]

Regarding the categorical outcome, since its frequency was higher than 10%,[40] we used the robust Poisson regression to estimate the prevalence ratio (PR) of probable diagnosis of CMD, and its 95% CI. The AIC confirmed the best fit of this model against log-binomial and negative binomial models.

As we confirmed that female individuals scored significantly higher in MHI-5 than males,[34] we performed stratified analyses by sex, for both outcomes.

Several sensitivity analyses were conducted to verify the robustness of the results and assess possible biases. First, to minimize the influence of reverse causality, we excluded individuals self-reported depression, chronic anxiety, or the use of prescribed medication for one or both. Second, we performed the analysis only in these individuals (those self-reporting at least one of the following: medical diagnosis of depression, medical diagnosis of anxiety, use of prescribed medication for depression, use of prescribed medication for anxiety). Third, to assess the validity of our analyses for the 30-km exposure radius, we fitted all the models considering only participants living within a 20-km radius of a background air quality monitoring station with sufficient PM_{10} data. No further radius reduction was tested, as it implied a near 50% sample reduction, which compromised the estimates' precision.

The statistical analysis was performed in Stata®, version 15. All estimates were weighted to account for different selection probabilities resulting from the complex sampling design, and to match the population distribution in terms of geographic region, age group and sex, unless specifically stated. The significance level was set at 5%.

RESULTS

A total of 2 398 individuals, distributed around 24 air quality monitoring stations, were included in the primary analysis [Appendix 1 - Supplementary Fig. 3 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/21245/15477)]. Included and excluded individuals were similar regarding most of the analyzed characteristics. Differences between the two groups were only found regarding the individual allocated one-year average temperature, and the area-level walkability terciles [Appendix 1 - Supplementary Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/21245/15477)].

The study population had higher percentages of female participants (52.6%, 95% IC: 50.2 - 55.1) and individuals belonging to the age groups 35 - 49 years (34.1%, 95% IC: 32.0 - 36.4) and 50 - 64 years (31.5%, 95% IC: 29.4 - 33.7) (Table 1). The median (IQR) individual allocated one-year average PM_{10} concentration was 18.6 (15.3 - 19.3) μg/m³ (Table 2, Fig. 1). The median (IQR) score of mental well-being was 72 (56 - 84) points, in a scale from 0 to 100. A probable diagnosis of CMD was found in 22.7% (95% CI: 20.0 - 25.6) (Table 1).

No statistically significant association was found between PM_{10} and mental well-being, after adjustment for all the defined potential confounders. Despite that, a nonsignificant decrease in the score of well-being was observed. For each 10 μg/m³ increment in PM_{10}, there was a 2% (95% CI: - 8,4) decrease in the score, or two points in 100. A subgroup analysis showed that the decrease tended to be higher in male (% change = -3; 95% CI: -13,7) than in female individuals (% change = -1; 95% CI: -9,6), but this association was not statistically significant (Table 3).

No statistically significant association was found between PM_{10} and the frequency of probable diagnosis of CMD, after adjustment. Nonetheless, a nonsignificant increase was observed (PR = 1.012, 95% CI: 0.979 - 1.045). Subgroup analyses showed that the association between PM_{10} and the prevalence of CMD tended to be higher in males (PR = 1.021, 95% CI: 0.945 - 1.102) than in females (PR = 1.011; 95% CI: 0.988 - 1.035), but this association was also not statistically significant (Table 4, Fig. 2).

Results were robust in all the sensitivity analyses, with a slight change in the estimates of the analyses restricting for individuals without self-report of CMD, nor use of prescription medication, which showed a nonsignificant decrease in the probable diagnosis of CMD, after adjustment [Appendix 1 - Supplementary Tables 2 to 10 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/21245/15477)].

DISCUSSION

This study contributes to fill in the gap in evidence about the association between long-term air pollution and CMD. Our findings showed that individually allocated long-term exposure to PM_{10} was associated with a non-statistically significant decrease in mental well-being, and with a non-statistically significant increase in the frequency of probable diagnosis of common mental disorders. Our findings are consistent with recent meta-analyses estimates.[7-9]

A recent national cohort reported a statistically significant positive association of long-term exposure to PM_{10} and depressive disorders assessed by psychiatrists (gold-standard method).[41] However, another population-based cohort study found a non-statistically significant association with an increased risk of CMD.[42]

Table 1 – Estimates for the characteristics in study of the included individuals

	n	Sample estimates (%/median)[$]	Weighted estimates (95% CI) (%/median)[$]	
Exposure				
Individual allocated 1-year average PM_{10} (µg/m³)	2398	19.0	18.6	(18.4, 18.7)
Covariates				
Sex				
Female	1294	54.0	52.6	(50.2, 55.1)
Male	1104	46.0	47.4	(44.9, 49.9)
Age group				
25 - 34 years	353	14.7	18.9	(17.2, 20.7)
35 - 49 years	826	34.4	34.1	(32.0, 36.4)
50 - 64 years	827	34.5	31.5	(29.4, 33.7)
65 - 74 years	392	16.4	15.5	(13.9, 17.2)
Education level*				
Low[a]	679	28.3	26.5	(24.4, 28.7)
Medium[b]	1279	53.4	53.5	(50.2, 56.8)
High[c]	439	18.3	20.0	(16.7, 23.7)
Employment status*				
Employed	1448	60.4	62.3	(59.4, 65.0)
Unemployed	272	11.4	11.4	(9.7, 13.4)
Other[d]	677	28.2	26.3	(24.1, 28.7)
Professional occupation*				
White-collar[e]	1376	62.3	62.9	(58.5, 67.1)
Blue-collar[f]	834	37.7	37.1	(32.9, 41.5)
Area-level socioeconomic deprivation terciles				
Low deprivation (T1)	475	19.8	16.0	(10.5, 24.5)
Moderate deprivation (T2)	609	25.4	31.6	(19.3, 47.2)
High deprivation (T3)	1314	54.8	52.4	(37.8, 66.6)
Individual allocated 1-year average temperature (ºC)	2398	15.2	15.0	(14.8, 15.3)
Area-level walkability terciles				
Low walkability (T1)	84	3.5	1.3	(0.6, 2.9)
Moderate walkability (T2)	574	23.9	18.4	(13.5, 24.6)
High walkability (T3)	1740	72.6	80.3	(73.2, 85.9)
Degree of urbanization				
Rural	702	29.3	28.2	(22.7, 34.5)
Urban	1696	70.7	71.8	(65.5, 77.3)
Outcomes				
Mental well-being[§]	2398	72.0	72.0	(70.7, 73.3)
Probable diagnosis of common mental health disorders				
Yes	555	23.1	22.7	(20.0, 25.6)
No	1843	76.9	77.3	(74.4, 80.0)

95% CI: 95% confidence intervals; PM10: particulate matter with an aerodynamic diameter less than or equal to 10 µm T1: first tercile; T2: second tercile; T3: third tercile.
*: 1 missing in education level, 1 missing in employment status, 188 missing in professional occupation.
$: percentages or medians were presented according to the type of variable being described (categorical or continuous, respectively).
§: Assessed through the score on 5-item Mental Health Inventory, being 0 the absence of mental well-being and 100 the complete mental well-being.
a: Low education: levels 0 - 2 of ISCED, 2011 (no education, primary education).
b: Medium education: levels 3 - 4 of ISCED, 2011 (basic, secondary, post-secondary education).
c: High education: levels 5 - 8 of ISCED, 2011 (higher education).
d: Other without professional activity: students, retired people, housewives, other.
e: White-collar: managers, professionals, technicians and associate professional, clerical support workers, and services and sales workers.
f: Blue-collar: skilled agricultural workers, craft and related trades workers, plant and machine operators, and elementary occupations.

Table 2 – Characteristics of the included individuals (n = 2398) and comparison between groups of probable diagnosis of common mental health disorders

	Total (n = 2398)		Probable diagnosis of CMD (n = 555)		Without probable diagnosis of CMD (n = 1843)		*p*-value/95% CI[§]
Individual allocated 1-year average PM_{10} ($\mu g/m^3$) – median (IQR)	18.6	(15.3, 19.3)	18.3	(15.2,19.2)	18.6	(15.3,19.3)	(0.012, 0.423)
Sex - %							< 0.001
Female		52.6		70.4		47.4	
Male		47.4		29.6		52.6	
Age group - %							0.072
25 - 34 years		18.9		14.3		20.2	
35 - 49 years		34.1		31.1		35.0	
50 - 64 years		31.5		37.3		29.9	
65 - 74 years		15.5		17.3		14.9	
Education level* - %							< 0.001
Low[a]		26.5		33.2		24.5	
Medium[b]		53.5		53.2		53.6	
High[c]		20.0		13.6		21.9	
Employment status* - %							< 0.001
Employed		62.3		51.5		65.4	
Unemployed		11.4		14.3		10.6	
Other[d]		26.3		34.2		24.0	
Professional occupation* - %							0.071
White-collar[e]		62.9		58.1		64.2	
Blue-collar[f]		37.1		41.9		35.8	
Area-level socioeconomic deprivation terciles - %							0.087
Low deprivation (T1)		16.0		16.4		15.9	
Moderate deprivation (T2)		31.6		36.0		30.3	
High deprivation (T3)		52.4		47.6		53.8	
Individual allocated 1-year average temperature (ºC) – median (IQR)	15.0	(14.8, 16.7)	14.9	(14.6, 16.7)	15.2	(14.8, 16.7)	(0.015, 0.141)
Area-level walkability terciles - %							0.489
Low walkability (T1)		1.3		1.5		1.3	
Moderate walkability (T2)		18.4		20.6		17.7	
High walkability (T3)		80.3		77.9		81.0	
Degree of urbanization - %							0.051
Rural		28.2		33.0		26.9	
Urban		71.8		67.0		73.1	

CMD: common mental health disorders; 95% CI: 95% confidence intervals; PM_{10}: particulate matter with an aerodynamic diameter less than or equal to 10 µm T1: first tercile; T2: second tercile; T3: third tercile.
*: 1 missing in education level, 1 missing in employment status, 188 missing in professional occupation.
$: percentages or medians were presented according to the type of variable being described (categorical or continuous, respectively).
§: Assessed through the score on 5-item Mental Health Inventory, being 0 the absence of mental well-being and 100 the complete mental well-being.
a: Low education: levels 0 - 2 of ISCED, 2011 (no education, primary education).
b: Medium education: levels 3 - 4 of ISCED, 2011 (basic, secondary, post-secondary education).
c: High education: levels 5 - 8 of ISCED, 2011 (higher education).
d: Other without professional activity: students, retired people, housewives, other.
e: White-collar: managers, professionals, technicians and associate professional, clerical support workers, and services and sales workers.
f: Blue-collar: skilled agricultural workers, craft and related trades workers, plant and machine operators, and elementary occupations.
All the estimates were weighted to account for different selection probabilities and population distribution.

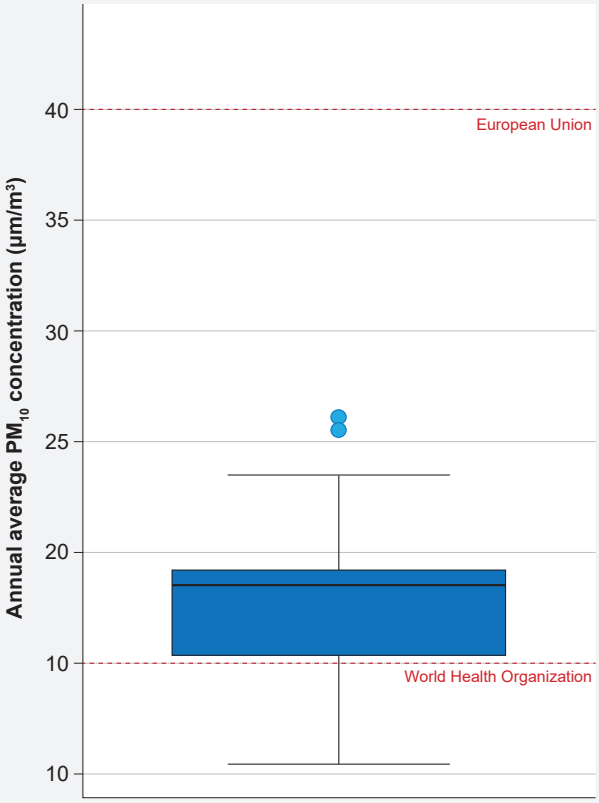


Figure 1 – Boxplot of the individually allocated one-year average PM_{10} concentrations, as measured in the mainland Portugal, compared to the recommended values of the World Health Organization Global Air Quality Guidelines and of the European Union Air Quality Directives

PM_{10}: particulate matter with an aerodynamic diameter less than or equal to 10 micrometers.

Table 3 – Percent change in mental well-being, measured in a scale from 0 to 100, for each 10 µg/m³ increment in annual average PM_{10} concentrations, among all individuals, and by sex

	n	% change*	(95% CI)
All included individuals			
Crude model	2 398	5	(- 4, 14)
Adjusted model 1[a]	2 398	5	(- 4, 14)
Adjusted model 2[b]	2 210	4	(- 5, 12)
Adjusted model 3[c]	2 210	3	(- 6, 11)
Adjusted model 4[d]	2 210	-2	(- 8, 4)
Male individuals			
Crude model	1 104	4	(- 7, 15)
Adjusted model 1[a]	1 104	3	(- 8, 15)
Adjusted model 2[b]	1 061	3	(- 9, 15)
Adjusted model 3[c]	1 061	2	(- 10, 14)
Adjusted model 4[d]	1 061	-3	(- 13, 7)
Female individuals			
Crude model	1 294	7	(-1, 15)
Adjusted model 1[a]	1 294	7	(-1, 15)
Adjusted model 2[b]	1 149	4	(-4, 12)
Adjusted model 3[c]	1 149	3	(-5, 11)
Adjusted model 4[d]	1 149	-1	(-9, 6)

PM_{10}: particulate matter with an aerodynamic diameter less than or equal to 10 µm 95% CI: 95% confidence interval.

*: Percent change was computed through the formula 100×(exp(regression coefficient)−1)×10, per 10 µg/m³ increment in annual average PM_{10} concentrations, having the coefficients been computed through linear regression models with the link function 'log'.

a: Adjusted for sex (only when all individuals included), and age group.

b: Adjusted for sex (only when all individuals included), age group, education level, employment status, and professional occupation.

c: Adjusted for sex (only when all individuals included), age group, education level, employment status, and professional occupation, and area-level socioeconomic deprivation terciles.

d: Adjusted for sex (only when all individuals included), age group, education level, employment status, professional occupation, area-level socioeconomic deprivation terciles, individual allocated 1-year average temperature, area-level walkability terciles, degree of urbanization.

All the estimates were weighted to account for different selection probabilities and population distribution.

To our knowledge, this was one of the first studies to adjust not only for individual, but also for aggregate-level variables (namely area-level socioeconomic deprivation, degree of urbanization, and area-level walkability), which are being reported to account for bigger portions of the environmental effects on physical and mental health.[43-45] Moreover, this was the first nationally-representative, population-based study on these associations conducted in the Portuguese population

Furthermore, this study contributes to fill in the gap in evidence about the association between measured concentrations of air pollutants and CMD for low levels of air pollution. In fact, we assessed exposure to PM_{10} in Portugal, a country with a median of one-year average PM_{10} concentration (18.6 µg/m³) above the 15 µg/m³ recommended by the World Health Organization Global Air Quality Guidelines,[6] but well below the 40 µg/m³ annual value recommended by the European Union (EU Air Quality Directives 2008/50/EC and 2004/107/EC). In Asia, and even in several European countries (such as Belgium, Germany, the Netherlands, and Spain), higher median concentrations were observed, with equally larger variation intervals.[7,8] China, for instance, had medians of annual average PM_{10} concentrations ranging from 72.6 and 76.0 µg/m³, in the period from 2014 to 2015, to 155.6 µg/m³ between the maximum and minimum values observed, and India presented even more extreme levels.[46]

Although a minimum threshold for the effect of exposure to PM_{10} on mental health was not yet established,[7] the low variability of the observed exposure levels may explain the lack of statistical significance in our findings. It should

Table 4 – Prevalence ratios computed through modified Poisson regression models for the association between individually allocated long-term PM_{10} concentrations and the probable diagnosis of common mental disorders, among all individuals, and by sex

	n	PR (95%CI)	
All included individuals			
Crude model	2 398	0.972	(0.927, 1.018)
Adjusted model 1[a]	2 210	0.973	(0.931, 1.016)
Adjusted model 2[b]	2 210	0.982	(0.939, 1.028)
Adjusted model 3[c]	2 210	0.990	(0.951, 1.031)
Adjusted model 4[d]	2 210	1.012	(0.979, 1.045)
Male individuals			
Crude model	1 104	0.976	(0.886, 1.076)
Adjusted model 1[a]	1 104	0.978	(0.888, 1.077)
Adjusted model 2[b]	1 061	0.979	(0.881, 1.088)
Adjusted model 3[c]	1 061	0.987	(0.911, 1.069)
Adjusted model 4[d]	1 061	1.021	(0.945, 1.102)
Female individuals			
Crude model	1 294	0.970	(0.937, 1.003)
Adjusted model 1[a]	1 294	0.970	(0.939, 1.002)
Adjusted model 2[b]	1 149	0.983	(0.951, 1.015)
Adjusted model 3[c]	1 149	0.989	(0.958, 1.022)
Adjusted model 4[d]	1 149	1.011	(0.988, 1.035)

PM_{10}: particulate matter with an aerodynamic diameter less than or equal to 10 μm; 95% CI: 95% confidence interval.

*: Percent change was computed through the formula 100×(exp(regression coefficient)−1)×10, per 10 μg/m³ increment in annual average PM_{10} concentrations, having the coefficients been computed through linear regression models with the link function 'log'.

a: Adjusted for sex (only when all individuals included), and age group.

b: Adjusted for sex (only when all individuals included), age group, education level, employment status, and professional occupation.

c: Adjusted for sex (only when all individuals included), age group, education level, employment status, and professional occupation, and area-level socioeconomic deprivation terciles.

d: Adjusted for sex (only when all individuals included), age group, education level, employment status, professional occupation, area-level socioeconomic deprivation terciles, individual allocated 1-year average temperature, area-level walkability terciles, degree of urbanization.

All the estimates were weighted to account for different selection probabilities and population distribution.

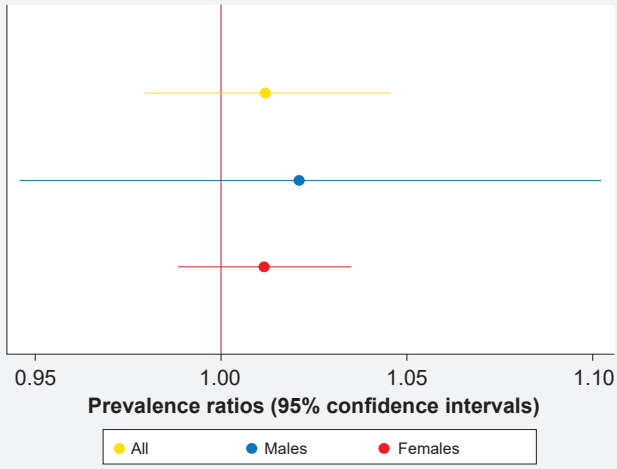


Figure 2 – Prevalence ratios plot for the association between individually allocated one-year average PM_{10} concentrations and the probable diagnosis of common mental disorders

PM_{10}: particulate matter with an aerodynamic diameter less than or equal to 10 micrometers.

The dots are estimates of the prevalence ratios, the lines intersecting the dots are the intervals of confidence for these estimates.

be noted that the INSEF considered the distribution of the population in its sampling process, so its participants resided mostly in urban areas rather than rural areas, since the former had a higher number of individuals than the latter.[38] Moreover, in Portugal, most air quality monitoring stations are located on the coast, in urban areas, making it difficult to assess observed pollutant concentrations in rural areas.[23] Therefore, we recognize that exposure levels may have been somehow biased, which could also explain the lack of associations since it is expected that in INSEF there were higher median levels of PM_{10} concentrations than in Portugal generally, with a lower proportion of lower levels (typical of rural areas) for comparison, which limited not only the variability of our exposure values but also the power of this study.[47]

It is important to acknowledge that our findings reflect the influence of a single air pollutant, and not a joint exposure to multiple air pollutants, as in real-life. It is also important to note that studies reporting statistically significant results are more likely to be published, preventing authors from establishing methodological comparisons that allow the leveraging of new and more robust studies.[48] Recent meta-analyses that studied the association between air pollution and CMD reported publication bias on this topic.[11,48]

Considering the estimates of our subgroup analyses, sex might play a modulating role between exposure to PM_{10} and mental well-being, or CMD. Recent findings from a longitudinal, joint exposure study support this hypothesis.[42] Nonetheless, as our findings were not statistically significant, this interpretation must be done with caution, and more studies are needed to understand the role of this variable in the studied associations.

Strengths and limitations

Our study has several strengths. First, it contributes to a better understanding of the associations between long-term exposure to air pollution and mental health outcomes at low concentration levels. Second, we assessed individually allocated long-term exposures, obtained from ground air quality monitoring stations measurements (real data

and not modeled data), following a robust and previously reviewed methodology.[21-23] Third, we used an analytical methodology to confirm the absence of selection bias and the national representativeness of this study. Fourth, all the estimates were weighted to account for different selection probabilities and to match the population distribution in terms of geographic region, age group and sex, allowing us to infer the results for the Portuguese population aged 25 to 75 years old. Fifth, the INSEF database, the main source of the data for this study, has been developed following standard quality procedures, providing reliable information about the covariates in study, which contributed to minimize confounding and classification bias.[38] Sixth, we controlled for confounding for a minimally defined set based on the best available evidence, including individual and aggregate-level variables. Finally, we compared different statistical models for our estimates, choosing the best fitting ones according to standard statistical procedures, which increased not only their validity, but also contributed to overcome the unreliable estimation provided by odds ratios, in the case of cross-sectional studies addressing outcomes which are not rare.[40]

Some limitations of our study should also be noted. First, we focused on PM_{10} as sufficient data from other air pollutants (for instance, $PM_{2.5}$, nitrogen dioxide, or ozone) was not available in the air quality monitoring stations database of the Portuguese Environment Agency. We could have chosen to assess exposure through modeled values, but we chose to stick to objectively measured values to increase exposure validity. Second, this study was a cross-sectional study, and thus reverse causality and survival biases might exist, even if it is not likely due to the nature of the exposure. A recent meta-analysis reported the existence of a statistically significant and positive association between exposure to PM_{10} and suicide, which increases the possibility of survival bias in this study.[49] Another recent meta-analysis found that, despite the association between long-term exposure to PM_{10} and depression was not statistically significant when the subgroup of cross-sectional studies was considered, it was statistically significant when only cohort studies were considered.[8] To lessen the impact of a possible reverse causality bias, as well as to reduce the misclassification bias of the outcomes, we sought to ensure that the exposure occurred before the beginning of the outcomes, using the annual average computed for the 365 days prior to the day of the assessment of each of the INSEF participants. The observed results were robust in the sensitivity analyses, indicating these biases are unlikely. Third, we assessed exposure to air pollution from a static point of view, considering the seven-digit postal code of residence of each of the studied individuals as the fixed reference (and not their everyday movements), which might not reflect the real exposure levels of a dynamic life. To minimize exposure misclassification bias, we performed inverse distance weighting to attribute individual exposures in individuals with more than two stations nearby, not only for a 30-km radius but also for a 20-km radius, in our sensitivity analyses, with robust results. No further reduction of the exposure radius was possible due to the loss of a considerable part of our sample and power. Fourth, CMD not only have long latency periods, but they are also frequently underdiagnosed, with their caseness being complex to establish and the validity of self-reported diagnoses being questionable.[50,51] Moreover, the latency of the exposure effects, which is also unknown,[52] must be long. To minimize outcome misclassification, we used the MHI-5 scale to operationalize our outcomes, and not data on self-reported diagnoses. Furthermore, as mentioned, our sensitivity analyses results were robust. Lastly, some residual confounding is inevitable, even if a comprehensive set of covariates was used for adjustment.

CONCLUSION

This nationally-representative, population-based cross-sectional study found that long-term exposure to PM_{10}, at the observed levels, was associated with a non-statistically significant decreased score in mental well-being, and with a non-statistically significant increased frequency of probable diagnosis of common mental disorders. These results may be explained by the reduced variability in the exposure values, limited also by the geographical distribution and data availability of the network of air quality monitoring stations.

Considering that the European Union air quality standards are more permissive than the World Health Organization Global guidelines, that no threshold is known for the dose-response curve of air pollution and its health effects, and that virtually everyone is exposed to air pollutants at different levels, more studies on this topic are needed. These studies could confirm the reported findings and provide, along with this study, solid evidence that can serve as the basis for the formulation of more restrictive air quality control policies in the European Union, and for the design of public health interventions tailored to the most vulnerable populations. Maintaining a robust and nationwide air quality monitoring network is essential for obtaining accurate exposure data, which plays a pivotal role in supporting research endeavors.

Future studies should assess joint exposures to multiple pollutants, evaluated dynamically through a longitudinal study design with a follow-up period of several years, providing estimates of its association with incident mental health disorders.

KEY MESSAGES

- This study underscored the potential link between long-term exposure to ambient air pollution, specifically PM10, and mental health outcomes. Despite finding non-statistically significant associations, the observed trends suggest that even low levels of air pollution might adversely affect mental well-being. These findings highlight the need for continued research in this area, particularly studies that can confirm these trends and provide more robust evidence. Future studies should explore joint exposures to multiple pollutants and employ longitudinal designs to assess the long-term effects of air pollution on mental health.
- The study emphasized the importance of maintaining a robust and nationwide air quality monitoring network. Accurate and comprehensive exposure data is essential for conducting high-quality research and supporting evidence-based policy decisions.

PREVIOUS AWARDS AND PRESENTATIONS

A poster of this work was presented in *the IV Congresso Nacional dos Médicos de Saúde Pública*.

AUTHOR CONTRIBUTIONS

LPG: Conceptualization, methodology, formal analysis and investigation, writing - original draft preparation.

MSU: Software, validation, formal analysis, investigation, writing - review & editing.

RG: Investigation, writing - review & editing, supervision.

CM: Investigation, writing - review & editing.

CMD: Resources, investigation, writing - review & editing, supervision.

VC: Investigation, writing - review & editing.

CGQ, DSR: Software, data curation, Investigation, Writing - review & editing.

VG: Software, investigation, writing - review & editing, project administration.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

FUNDING SOURCES

The Portuguese National Health Examination Survey was developed as part of a project financed under the Public Health Initiatives Programme ("Improvement of epidemiological health information to support public health decision and management in Portugal. Towards reduced inequalities, improved health and bilateral cooperation") with a €1 500 000 grant from Iceland, Liechtenstein and Norway, the EEA Grants and the Portuguese Government.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Quality of Informed Consent in Phase III Clinical Trials in Portugal: The Participants' Perspective

Qualidade do Consentimento Informado em Ensaios Clínicos de Fase III em Portugal: A Perspetiva dos Participantes

Pedro L. FERREIRA✉[1], Ana BARRADAS[1], Inês RIBEIRO[1]
Acta Med Port 2024 Sep;37(9):601-608 ▪ https://doi.org/10.20344/amp.20570

ABSTRACT

Introduction: Some studies show that participants do not always fully understand the informed consent form (ICF), which is one of the reasons for drop-outs. This study aimed to adapt the Quality of Informed Consent (QuIC) questionnaire into a valid instrument to be applied to the Portuguese population and to measure its reliability and validity in the Portuguese population, by applying it to a sample of participants in controlled trials.

Methods: The QuIC questionnaire was developed to assess the quality of informed consent in clinical trials and consists of two parts, addressing both the objective (part A) and the subjective (part B) understanding. After being translated and validated into Portuguese, it was implemented in 100 cardiac participants of phase III clinical trials in a University Hospital Center.

Results: The QuIC-PT questionnaire showed excellent stability over time and good validity. All patients evaluated their participation and their health positively and recognized the main purpose of the clinical trial. Almost all participants understood their role in helping future patients and the purpose of the trial and realized that, by signing the ICF, they were participating in a clinical trial. However, none of them knew that their experimental treatment was not proven to be the best alternative for their condition.

Conclusion: The QuIC-PT questionnaire seems to be a valid and useful instrument to evaluate the participants' understanding of the ICF. In this study, we found that some concepts, like 'study protocol' or 'randomization', were not well understood by participants when signing the ICF, especially by participants with lower education levels. They also believed that the experimental intervention would solve their health condition. Greater awareness about the importance of the informed consent process and ICF is necessary so that participants can fully understand the protocol, especially the risks involved, and their rights as participants.

Keywords: Informed Consent; Clinical Trials, Phase III as Topic; Comprehension; Patient Reported Outcome Measures

RESUMO

Introdução: Alguns estudos revelam que os participantes nem sempre compreendem completamente o formulário do consentimento informado (FCI), sendo uma das razões que levam à desistência. Este estudo teve como objetivo adaptar o questionário *Quality of Informed Consent* (QuIC) num instrumento válido para ser aplicado à população portuguesa e medir a sua fiabilidade e validade, aplicando-o a uma amostra de participantes em ensaios clínicos.

Métodos: O questionário QuIC foi desenvolvido para avaliar a qualidade do consentimento informado em ensaios clínicos e é constituído por duas partes, avaliando a compreensão objetiva (parte A) e a subjetiva (parte B). Depois de traduzido e validado para português, foi aplicado em 100 participantes cardíacos de ensaios clínicos de fase III num Centro Hospitalar Universitário.

Resultados: O questionário QuIC-PT mostrou uma excelente estabilidade ao longo do tempo e boa validade. Todos os doentes avaliaram positivamente a sua participação e a sua saúde, e reconheceram o principal objetivo do ensaio clínico. Quase todos os participantes compreenderam o seu papel em ajudar futuros doentes, perceberam que ao assinar o consentimento informado estariam a participar num ensaio clínico, e compreenderam o seu principal objetivo. Contudo, nenhum deles sabia que o tratamento experimental não estava comprovado como a melhor alternativa para a sua doença.

Conclusão: O questionário QuIC-PT provou ser um instrumento válido e útil para avaliar a compreensão dos participantes do FCI. Neste estudo, verificou-se que alguns conceitos, como 'protocolo do estudo' ou 'aleatorização' não foram bem compreendidos pelos participantes quando assinaram o FCI, especialmente pelos de baixa escolaridade. Os participantes também consideraram que a intervenção experimental resolveria sua condição de saúde. É necessária uma maior consciencialização sobre a importância da leitura do FCI, para que os participantes possam compreender plenamente o protocolo, especialmente os riscos envolvidos, e seus direitos como participantes.

Palavras-chave: Compreensão; Consentimento Informado; Ensaios Clínicos, Fase III; Resultados Relatados pelo Doente

INTRODUCTION

In Portugal, the National Ethics Committee for Clinical Research received, in 2022, 181 clinical trial (CT) submissions, 98.8% with a favorable decision. The main therapeutic area of the CT submissions was oncology (26), followed by bioequivalence and bioavailability studies (21), infectious diseases (10), neurobiology (6), and hematology (6).[1] On that date, a centralized submission was initiated.

After the Second World War, concerns about the procedures and norms of human research grew substantially. The Nuremberg Code was then developed in 1947, defining ethical principles to be followed by healthcare professionals in clinical research. This document alluded to the concept of free and informed consent, to be given by the participant before the beginning of the research.[2,3] Other documents with similar aims were also developed, including the Declaration of Helsinki (1964), the Belmont Report (1979), and the Guideline for Good Clinical Practice (1996).

In 1994, a law was introduced in Portugal, establishing

1. Centre for Health Studies and Research. Universidade de Coimbra. Coimbra. Portugal.
✉ **Autor correspondente:** Pedro L. Ferreira. pedrof@fe.uc.pt
Recebido/*Received*: 18/08/2023 - **Aceite/*Accepted*:** 08/05/2024 - **Publicado *Online*/*Published Online*:** 19/07/2024 - **Publicado/*Published*:** 02/09/2024

rules for the conduct of CT, namely the respect for the physical and moral integrity of the participants. Later, in 2014, a Clinical Research Law was created to regulate all CT conducted on humans in Portugal, requiring high ethical standards, dignity, and safety of participants, as well as highlighting the importance of IC (informed consent) (Decree-law no. 73/2015, July 27th).[4] Following this legislation, and beyond any scientific interest, all CT must respect and preserve the dignity and rights of the participants.

Within this context, IC is defined as "a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate".[5] Before any data collection or protocol-defined procedure, all information regarding the CT should be given and explained to the participant, such as the procedures involved and potential benefits and risks. The investigator, or a person appointed by him/her, plays an important role in the IC process, and should be available to answer the participant's questions and clarify his/her doubts. In addition, the investigator should ensure that participants may freely decide to participate. The written signature of the informed consent form (ICF) by the participant indicates his/her commitment, understanding, and voluntary decision to engage in the clinical research.[6]

Some studies indicate that the ICF in CT are perceived as complex. There is evidence that participants, particularly those with a lower level of education, may not understand the randomization process[7,8] or frequently used research terms like 'blinding' and 'placebo'.[9,10] The fact that the information may not be fully understood may influence the participants' decisions or their behavior during the research.[11]

A systematic review done by Montalvo *et al* states that the participants' health literacy, reading, and comprehension skills should be assessed before the assignment of the IC, using validated tools.[10] However, there is no standardized method to measure the participant's level of understanding of the ICF before s/he decides to accept or reject to participate in the research.[12] Nevertheless, some questionnaires have been created such as the Hoyos' questionnaire,[13] the Process and Quality of IC,[14] and the Quality of IC (QuIC).[15] The QuIC, developed by Joffe *et al* in 2001, is a pioneering assessment tool of subjects' objective and subjective understanding of CT.[13-16] It is a self-administered questionnaire to be implemented between three to 14 days after the patient signs the ICF for the CT.

This study aimed to adapt the QuIC questionnaire into a valid instrument to be applied to the Portuguese population, and to measure its reliability and validity by applying it to a sample of participants enrolled in CT at a Portuguese hospital center.

METHODS

Cultural and linguistic adaptation

The QuIC cultural and linguistic adaptation was based on the sequential approach, following the International Society for Pharmacoeconomics and Outcomes Research criteria.[17] The adaptation of the QuIC for the Portuguese population was authorized by the original author, Steven Joffe from the Boston Children's Hospital, in the United States of America. The translation of the QuIC from English to European Portuguese was performed by two professional Portuguese bilingual translators. The two versions were compared, and a reconciled version was obtained and sent to an English bilingual translator for backtranslation, allowing its comparison with the original version of the questionnaire. After this process, two CT specialists made a clinical review of the Portuguese version of the questionnaire. We also conducted a cognitive debriefing session with ten CT participants to evaluate the level of understanding and acceptability of the Portuguese version of the QuIC (QuIC-PT).

Study design and participants

We implemented the QuIC-PT in participants of CT conducted at a University Hospital Centre in Portugal. This observational study started after the favorable decision of the Ethics Committee of the University Hospital Centre (095-CES-2019) and the Ethics Committee of the Faculty of Medicine (025-CE-2019).

Eligible participants in our validation study were (i) participating in a phase III CT for drug development, (ii) aged 18 years or older, (iii) without cognitive impairment that would not allow them to complete the questionnaire, (iv) able to understand and speak Portuguese, and (v) who provided their IC to our study. Participants were selected at enrolment for one of nine CT in cardiology taking place at the hospital.

Data collection

Participants were asked to complete the QuIC-PT form in a separate room without any external help, except for the participants who could not read. For these, the questions and response options were read out loud so as to not interfere with the participant's choices. We collected sociodemographic characteristics of the participants like sex, age, employment and marital status, and educational level. Each participant was asked to give, from 0 to 10, his/her opinion about (i) his/her participation in the CT and (ii) the perception of his/her health status. We also collected data about the CT where they were enrolled, such as study type and phase, the administration type (intravenous, oral, subcutaneous), and the place of recruitment (in a medical appointment, during hospitalization or after hospitalization). All data

was collected without the identification of the participants.

The quality of IC measurement instrument

The QuIC questionnaire comprises a total of 35 items to assess the objective understanding (part A, 21 items), and subjective understanding (part B, 14 items) of the ICF. According to its author, it requires about seven minutes to be completed.[15] The possible answers in part A are "disagree", "unsure" and "agree". A wrong answer is always scored with 0 points, a correct one receives the maximum scores of 33, 50 or 100, depending on the importance of the item in comparison to others, and an "unsure" answer receives a score equal to half of the maximum value. The total score of this part A is achieved by adding all points of each item and dividing them by the number of answered items. On the other hand, the possible answers in part B range from 1 ("I didn't understand this at all") to 5 ("I understood this very well") and are scored by calculating the average of the 14 items and scaling it to a 0 to 100 interval.[15] Items with a mean score of 75% or above mean that the participants understood the sentence and its meaning.

In the original study, the content validity was verified by an expert panel and the test-retest reliability was considered good, with an intraclass correlation coefficient (ICC) of 0.66 for part A and 0.77 for part B.[15]

In this study, we dropped three questions from the original part A (A6, A7 and A8) because they were oriented towards phase I and II CT. As our sample only included participants in phase III CT, the QuIC-PT has a total of 32 items. We calculated the mean score for each item of QuIC and computed the number of correct answers in part A.

Reliability

To test the reliability of the QuIC-PT, we assessed its stability over time. We randomly asked 30 participants to fill out the QuIC-PT twice, depending on their availability to go to the hospital, and we used the ICC to test. An ICC score lower than 0.50 means a weak correlation, between 0.50 and 0.75 a moderate correlation, between 0.75 and 0.90 a good correlation, and a score higher than 0.90 an excellent correlation.[18]

Validity

To test the validity of the QuIC-PT, we assessed the content, construct and criterion validity.[19] Content validity was assessed through the clinical review performed by two CT experts and through a cognitive debriefing session with ten participants in CT to guarantee the relevance of the QuIC-PT items.

Construct validity was assessed by hypothesis testing the number of correct answers in known groups or subsamples.[19] Therefore, we analyzed the number of correct answers and sociodemographic characteristics. Student's *t*-test and ANOVA were used for each variable and multiple linear regression for more than one independent variable.

Criterion validity was tested by comparing the number of correct answers with the self-assessment of the patient's participation in the CT.

At last, we also compared the number of correct answers with the characteristics of CT.

RESULTS

Cultural and linguistic adaptation

In the original study of the QuIC, the authors applied this instrument to patients participating in cancer CT. Similar to other studies which used QuIC in other conditions or diseases than cancer CT,[20,21] the cultural and linguistic adaptation required the change of the expression "cancer patients" (in A2 and A14) to "patients", "cancer clinical trial" (introduction of part A and A2) to "clinical trial" and "my type of cancer" (A4, A5, A8, A9 and A12) to "my disease". These changes turned the Portuguese version of the QuIC more generalizable and applicable to other diseases. Tables 1 and 2 in Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/20570/15475) describe the original version of QuIC and the Portuguese version.

After the clinical review and the cognitive debriefing with patients, no ambiguity or difficulties in the questionnaire acceptance were observed, demonstrating the content validity of this measurement instrument.

Sample characteristics

By following COSMIN guidelines,[19] we obtained a sample of 100 participants enrolled in cardiology CT. Its sociodemographic characteristics are presented in Table 1.

Eighty-five percent of the participants were male, and the mean age was 67.3 years. Most were retired (70%) and married or cohabiting (74%). About half of the participants had completed four years of education or less. When assessing their health status in a 0 - 10 scale, 79% of the participants chose the levels between 7 and 10, and none of them selected levels 1 and 2.

Regarding the CT characteristics (Table 2), 55% of the participants were from open-label CT, against 45% participating in randomized controlled trials. In most CT, investigational treatment required subcutaneous administration, and 76% of the participants were recruited during a medical appointment. Most participants (91%) classified their satisfaction with CT participation as "good" or "very good".

Participants' objective understanding (part A)

Most of the part A items showed high mean score (Table 3). Item A2 had 100% of correct answers, the questions

Table 1 – Sociodemographic and health perception characteristics of the sample (n = 100)

Variable	Value	n
Sex	Male	85
	Female	15
Age (years)	< 65	33
	≥ 65	67
	Min - max	40 - 84
	Mean ± standard deviation	67.3 ± 9.2
Marital status	Single	5
	Married / cohabiting	74
	Widowed	10
	Separated / divorced	11
Employment status	Employed	19
	Unemployed	5
	Retired	70
	Disabled	3
	Does housework	1
	Inactive	2
Years of education	None	1
	≤ 4	49
	5 - 6	22
	7 - 9	9
	10 - 12	12
	> 12	7
Self-assessment health	Poor / very poor (0-3)	1
	Average (4-6)	20
	Good / very good (7-10)	79
	Min - max	3 - 10
	Mean ± standard deviation	7.5 ± 1.6

Table 2 – Characteristics of CT

Variable	Value	n
Type of study	Open-label	55
	Randomized controlled trial	45
Administration path	Intravenous	10
	Oral	35
	Subcutaneous	55
Place of recruitment	During consultation	76
	On inpatient admission	12
	After inpatient admission	12
Assessment of the participation in the CT	Very good (1)	30
	Good (2)	61
	Reasonable (3)	9
	Bad (4)	0
	Very bad (5)	0
	Min - max	1 - 3
	Mean ± standard deviation	1.8 ± 0.6

CT: clinical trial

A1, A11 and A17 had, at least, 90% of correct answers, and A3, A5, A9, A12, A13, A14, A16 and A18 presented a percentage between 50% and 79%. Also, 42% of participants answered item A8 correctly, and four items (A4, A7, A10 and A15) obtained between 20% and 22% of correct answers. Lastly, all the participants did not answer item A6 correctly.

Participants' subjective understanding (part B)

Table 4 presents the mean score of part B of the QuIC-PT, in which the respondents assess their knowledge about their CT, from 1 to 5. The final score ranged from 0 to 100.

Items with a mean score of 75% or above mean that the participants understood the sentence and its meaning. We detected that eight out of the 14 items were understood or very well understood by the participants (B1, B4, B5, B7, B8, B10, B12 and B13). Item B11 was the least understood item, with more than half of the participants answering that they "did not understand" it, or "did not understand at all".

Reliability and validity

All ICC scores were equal to 1.000, except for items B2 (0.997), B4 and B14 (0.998) and B10 (0.994), all of them higher than 0.90. Therefore, the QuIC-PT questionnaire showed good stability over time.

Regarding construct validity (Table 5), among the socio-demographic variables, only age, employment status and education determined the number of correct answers. Younger patients (less than 65 years old) and those employed or with more than elementary education tend to provide higher numbers of correct answers. However, following multiple linear regression, only education level was significantly associated with the number of correct answers (β = 0.417; $p < 0.001$). On the other hand, we did not find any association between CT characteristics and the number of correct answers.

Finally, for the criterion validity, the number of correct answers was not associated with patient assessment of CT participation.

DISCUSSION

We found that the QuIC-PT questionnaire is a feasible tool to measure the knowledge and quality of the IC in the Portuguese population and that, even though the QuIC questionnaire was originally developed for CT in oncology, it was possible to adapt this questionnaire to other diseases.[20,21]

The QuIC questionnaire was one of the first measuring instruments aiming to measure participants' objective and subjective understanding of CT. This means that this questionnaire measures not only if the participants are well-informed, but also if they feel well-informed.[14] The QuIC-PT questionnaire can also provide insight about which CT information should be clarified in the written ICF and further by the investigator when collecting the IC.

The results from items concerning the recognition of participating in a CT (items A1 and B1), helping future participants (A11 and B8), knowing who to contact to clarify

Table 3 – Mean score and percentage of correct answers of the Part A of the QuIC-PT

Questions	Disagree	Unsure	Agree	Mean
A1. When I signed the consent form for my current therapy, I knew that I was agreeing to participate in a CT.	1%	1%	**98%**	98.5[1]
A2. The main reason CTs are done is to improve the treatment of future patients.	0%	0%	**100%**	50.0[2]
A3. I have been informed how long my participation in this CT is likely to last.	18	6%	**76%**	79.0[1]
A4. All the treatments and procedures in my CT are standard for my disease.	24%	54%	**22%**	49.0[1]
A5. In my CT, one of researchers' major purposes is to compare the effect (good and bad) of two or more different ways of treating patients with my disease, in order to see which is better.	9%	15%	**76%**	41.8[2]
A6. The treatment being researched in my CT has been proven to be the best treatment for my disease.	**0%**	35%	65%	8.8[2]
A7. In my CT, each group of patients receive a higher dose of the treatment than the group before, until some patients have serious side effects.	**20%**	72%	8%	18.8[3]
A8. After I agreed to participate in my clinical, my treatment was chosen randomly (by chance) from two or more possibilities.	25%	33%	**42%**	19.5[3]
A9. Compared with standard treatments for my disease, my CT does not carry any additional risks or discomforts.	**59%**	18%	23%	68.0[1]
A10. There may not be direct medical benefit to me from my participation in this CT.	72%	14%	**14%**	10.5[2]
A11. By participating in this CT, I am helping the researchers learn information that may benefit future patients.	0%	3%	**97%**	98.5[1]
A12. While you are in this CT, its rules determine how my doctor can change my treatment.	12%	35%	**53%**	23.4[3]
A13. Because I am participating in a CT, it is possible that the study sponsor, various government agencies, or others who are not directly involved in my care could review my medical records.	14%	17%	**69%**	77.5[1]
A14. My doctors did not offer me any alternatives besides treatment in this CT.	**63%**	9%	28%	67.5[1]
A15. The consent form I signed describes who will pay for treatment if I am injured or become ill as a result of participation in this CT.	23%	55%	**22%**	49.5[1]
A16. The consent form I signed lists the name of the person (or persons) whom I should contact if I have any questions or concerns about the CT.	8%	13%	**79%**	85.5[1]
A17. If I had not wanted to participate in this CT, I could have declined to sign the consent form.	4%	6%	**90%**	46.5[2]
A18. I will have to remain in the CT even if I decide someday that I want to withdraw.	**54%**	14%	32%	30.5[2]

CT: Clinical trial.
[1]: Score between 0 and 100.
[2]: Score between 0 and 50
[3]: Score between 0 and 33.
Numbers in **bold** mean correct answers

doubts about the research (A16 and B12), the acceptance or refusal to sign the IC is voluntary (A17 and B13) and the rights of sharing clinical and personal data (A13 and B10), demonstrate that these are the most understood domains, in which the knowledge and understanding are in concordance. Similarly to other studies,[20,21] almost all participants (90% or more) of our sample were aware that signing the ICF represented their agreement to take part in the CT (items A1 and A17) and recognized that the CT may add information and improve treatment of future patients (A2, A11). Most participants (65%) reported having understood the CT "well" or "very well" when signing the ICF, but several ICF aspects were not fully understood.

According to a systematic review by Montalvo and Larson (2014), the participants showed a lack of basic understanding of research terms such as 'randomization', 'placebo', 'risks', and 'therapeutic misconception'.[10] In our study, less than a third of participants answered questions related to treatment correctly, including that CT evaluate treatments that are not standard of care (A4) nor proved to be the best

Table 4 – Mean score of the Part B of the QuIC-PT

Questions	I did not understand this at all				I understood this very well	Mean score
B1. That fact that your treatment involves research.	2%	2%	2%	9%	85%	93.3
B2. What the researchers are trying to find out in the CT.	13%	7%	19%	25%	36%	66.0
B3. How long you will be in the CT.	19%	4%	6%	8%	63%	73.0
B4. The treatments and procedures you will undergo.	9%	1%	10%	22%	58%	79.8
B5. Which of these treatments and procedures are experimental?	6%	2%	5%	9%	78%	87.8
B6. The possible risks and discomforts of participating in the CT.	26%	4%	12%	20%	38%	60.0
B7. The possible benefits to you of participating in the CT.	4%	1%	7%	20%	68%	86.8
B8. How your participation in this CT may benefit future patients.	1%	1%	2%	9%	87%	95.0
B9. The alternatives to participation in the CT.	29%	11%	10%	10%	40%	55.3
B10. The effect of the CT on the confidentiality of your medical records.	7%	1%	5%	18%	69%	85.3
B11. Who will pay for treatment if you are injured or become ill because of participation in this CT.	57%	6%	11%	10%	16%	30.5
B12. Whom you should contact if you have questions or concerns about the CT.	5%	1%	2%	4%	88%	92.3
B13. The fact that participation in the CT is voluntary.	0%	0%	1%	1%	98%	99.3
B14. Overall, how well did you understand your clinical when you signed the consent form?	3%	9%	23%	32%	33%	70.8

CT: Clinical trial

treatment options (A6), despite mentioning that they understood the treatment very well (B4 and B5). These results are quite concerning since the participants believed that the treatment provided was already approved, which was the purpose of that CT. Additionally, more than half of the participants did not understand the concept of randomization and that they might not receive the experimental treatment (A8). This may translate into false expectations of the participants, which is consistent with the vast majority of patients expecting a "direct medical benefit" due to CT participation (A10 and B7).

Despite almost all participants having recognized the voluntary nature of participating in the CT, not all seemed to be aware of its implications or their rights as participants. Certain aspects, such as the study's length (A3), its lack of assessment of safe treatment doses (A7) and its lack of information on cost-bearers in case of injury (A15 and B11), were also not fully clear. In addition, item B6 showed that respondents were not familiar with possible risks of participating in the CT, despite having agreed to participate. Moreover, some participants mentioned that participating in the study was their only treatment option (A14, B9), and almost 50% believed that they were not able to withdraw (A18). Atal and Dune found similar results, which highlights a poor understanding of the experimental nature of the treatment, the possible risks and compensation proceedings.[20]

The individuals' lack of understanding of relevant topics, such as their rights as participants and the option to withdraw during the CT, is concerning. In general, we observed lower mean scores in part A of the questionnaire than in part B, indicating that the participants were not as well informed as they felt. It is not the signed document that indicates the participant's correct understanding of all the information, and although the researcher has a duty to guarantee this, our results do not fully confirm it.

These results highlight the need for some adaptations, not only to the ICF, but also when answering participants' questions. The ICF should contain simple language and focus on relevant information, while the person responsible for clarifying the participant should repeat the information in a few simple words, give the participant the opportunity to ask questions and clarify doubts and, above all, ensure that the participant knows the main points of the IC.[3,22] Some studies in the literature showed that interactive computer presentations, videos, vignettes and visual aids, as well as simplified paper documents with shorter and concise phrasing are some examples of interventions that may result in a significant improvement of participants' understanding of the IC.[23,24] Therefore, as the CT evolves, it is possible to have new data related to the experimental treatment/intervention (such as new adverse effects, safety, changes in methodologies, procedures and outcomes), and it should be provided to the participants. Therefore, the participants 're-consent' must be obtained, and the research team must

Table 5 – Determinants of the correct answers

Variable	Value	n	Mean	Standard deviation	|t|	Sig
Sex	Male Female	85 15	10.5 9.6	1.9 1.7	1.638	0.105
Age (years)	< 65 ≥ 65	34 66	11.2 9.9	1.7 1.9	3.550	< 0.001
Marital status	Married Not married	74 26	10.2 10.8	1.9 1.8	1.335	0.185
Employment status	Employed / housework Not employed / retired	20 76	11.4 10.0	1.8 1.9	2.941	0.004
Education	Basic (≤ 4 years) > Basic	50 50	9.4 11.3	1.7 1.6	5.781	< 0.001
Self-assessment health	Good / very good (7 - 10) Lower (≤ 6)	79 21	10.3 10.6	0.2 0.4	0.622	0.536
Type of study	Open-label Randomized controlled trial	55 45	10.4 10.2	1.8 2.0	0.660	0.511
Administration path	Intravenous / oral Subcutaneous	45 55	10.0 10.6	1.9 1.9	1.654	0.101
Place of recruitment	During consultation Other	76 24	10.5 9.8	1.8 2.1	1.624	0.108
Assessment of the participation in CT	Very good Good / reasonable	30 70	10.8 10.1	2.0 1.9	1.704	0.092

CT: Clinical trial

make sure that s/he has understood the new information.[22]

This study suggests that the participants' understanding of the IC should be assessed. Subsequently, this additional information brings about the responsibility to act.[25] The research team is responsible for identifying, clarifying, and discussing any confusing topics with the participant, making sure that s/he feels and actually is well-informed. The distinction between those who fully understand the ICF and those who do not should be part of the study and a checkpoint for joining the CT.

One of the strengths of this study was showing that it was possible to adapt the original QuIC to other diseases than cancer. The participants were attending cardiology CT (in the areas of dyslipidemia, acute coronary syndrome, heart failure and angina pectoris). In addition, most of the participants were men (85%), and 67% of them were aged 65 or older. As such, we also found that the sample used is representative of the Portuguese reality, since this type of diseases are more prevalent in older men.[26] Since the adapted QuIC has the potential to be used for other diseases, it allows for the comparison of consent processes within healthcare institutions.

However, the Portuguese version may have some limitations, the first being that it was designed for phase III clinical trials, and we are not sure whether that could be appropriate to other designs. We are also aware that this questionnaire does not address all the relevant issues of an ICF, such as the complexity of procedures/treatments, the awareness that they have to transmit all relevant aspects to the investigators (the medication they take, symptoms they have, emergency room visits), or the importance of compliance, and that ICF differ between CT and sponsor companies. Despite this, our results suggest several aspects to be improved in the IC process. The participants' education level, reading, and comprehension skills should be considered during the IC process, as well as the presence of the three essential elements (voluntarism, informed consent, and decision-making capacity),[22] to ensure that the participant's written consent is truly informed and free. In fact, we observed that educational level was independently associated with lower scores, reflecting the need to adjust information for these groups. Interestingly, we found no association with patient satisfaction regarding their CT participation, perhaps because 91% of patients rated it as 'very good' or 'good'.

Further studies with a larger sample, with other diseases, and with participants from different CT phases are needed to compare results and improve the questionnaire so that it can become a widely usable instrument to measure the quality of the ICF of a CT. The development of strategies and/or interventions to improve participants' understanding of ICF in CT, as well as the evaluation of their effectiveness, can be extremely valuable for the people involved.

CONCLUSION

The QuIC-PT seems to be a valid and useful instrument to evaluate the participants' understanding of the ICF,

allowing the improvement of the ICF and the best explanation possible adjusted to the individual's needs. Relevant concepts, like study procedures, randomization, and safety risks, were not well understood by participants when they signed the ICF. Furthermore, the participants' belief that the experimental intervention would solve their health condition is the main reason why they agreed to participate in the research, which may be misleading.

AUTHOR CONTRIBUTIONS

PLF: Conceptualization, methodology, formal analysis, data curation, writing - original draft, writing - review & editing, project administration, supervision.

AB: Conceptualization, formal analysis, investigation, writing - original draft, writing - review & editing.

IR: Validation, writing - review & editing.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

DATA AVAILABILITY

Data will be made available on request.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

FUNDING SOURCES

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. CEISUC/CIBB is funded by national funds through FCT Foundation for Science and Technology, I.P., under the Multiannual Financing of R&D Units 2020–2023.

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ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Usability of APIMedOlder: A Web Application to Manage Potentially Inappropriate Medication in Older Adults

Usabilidade da APIMedOlder: Uma Aplicação Web para a Gestão de Medicamentos Potencialmente Inapropriados em Idosos

Daniela A. RODRIGUES[1,2,3], Ana I. PLÁCIDO[1], Ramona MATEOS-CAMPOS[4], Adolfo FIGUEIRAS[5,6,7], Maria Teresa HERDEIRO[8], Fátima ROQUE✉[1,2,]
Acta Med Port 2024 Sep;37(9):609-616 ▪ https://doi.org/10.20344/amp.21537

ABSTRACT

Introduction: Considering the increase in the proportion of the older population worldwide, the demand for health system resources also arises. These tools optimize clinical decision-making, thus avoiding iatrogenesis and thus contributing to a better quality of life for the older population. In response, we created an online web application, the APIMedOlder, that provides access to healthcare professionals to allow healthcare professionals to access potentially inappropriate medication identification criteria through a useful tool with a simplified profile, allowing its applicability in clinical practice. This study aims to assess the usability of the APIMedOlder online web application by healthcare professionals.

Methods: A questionnaire, based on the System Usability Scale, was distributed among 15 healthcare professionals (five pharmacists, four physicians, three pharmacy technicians, and three nurses), to fully explore the website.

Results: Overall, healthcare professionals' evaluation of the usability of the APIMedOlder online web application was rated as "Best imaginable" (mean score of 87.17 points), with individual scores ranging from 75 to 100 points. Internal consistency of α = 0.881 (CI 95%: 0.766 - 0.953) was achieved. Specific questionnaire items contributing to this high score included ease of use, learning efficiency, and integration of functions.

Conclusion: The overall evaluation of the developed tool was positive, with this online application being recognized as being easy to use and having well-integrated functions.

Keywords: Aged; Decision Support Systems, Clinical; Inappropriate Prescribing/prevention & control; Internet; Medication Errors/prevention & control; Potentially Inappropriate Medication List

RESUMO

Introdução: Tendo em conta o aumento da proporção da população idosa em todo o mundo, surge também a demanda por recursos dos sistemas de saúde. Estas ferramentas otimizam a decisão clínica, evitando iatrogenia, contribuindo assim para uma melhor qualidade de vida dos idosos. Em resposta, criámos uma aplicação *web online*, APIMedOlder, para proporcionar acesso por parte dos profissionais de saúde aos critérios de identificação de medicamentos potencialmente inapropriados através de uma ferramenta útil com um perfil simplificado, permitindo a sua aplicabilidade na prática clínica. Este estudo tem como objetivo a avaliação da usabilidade da aplicação *web online* APIMedOlder por parte dos profissionais de saúde.

Métodos: Foi distribuído um questionário, baseado na Escala de Usabilidade do Sistema, a 15 profissionais de saúde (cinco farmacêuticos, quatro médicos, três técnicos de farmácia e três enfermeiros), de forma a explorar completamente a aplicação *web*.

Resultados: No geral, a avaliação dos profissionais de saúde sobre a usabilidade da aplicação *web online* APIMedOlder foi classificada como "*Best imaginable*" (pontuação média de 87,17 pontos), com pontuações individuais a variar entre 75 e 100 pontos. Foi alcançada uma consistência interna de α = 0,881 (IC 95%: 0,766 - 0,953). Os itens específicos do questionário que contribuíram para esta pontuação incluíram facilidade de uso, eficiência de aprendizagem e integração de funções.

Conclusão: A avaliação geral da ferramenta desenvolvida foi positiva, tendo sido reconhecida como fácil de utilizar e com funções bem integradas.

Palavras-chave: Erros de Medicação/prevenção e controlo; Idoso; Internet; Lista de Medicamentos Potencialmente Inapropriados; Prescrição Inapropriada/prevenção e controlo; Sistemas de Apoio à Decisão Clínica

Key-messages

- APIMedOlder online web application is a useful tool that provides access to health professionals to Potentially Inappropriate Medication identification criteria.
- Overall evaluation of the APIMedOlder tool by healthcare professionals was positive.
- Usability testing results can lead to a more user-friendly, efficient, and enjoyable tool.
- The relatively small sample size may limit the generalizability of findings.

1. Biotechnology Research, Innovation and Design for Health Products (BRIDGES) - Research Laboratory on Epidemiology and Population Health. Instituto Politécnico da Guarda. Guarda. Portugal.
2. Health Sciences Research Centre (CICS). Universidade da Beira Interior. Covilhã. Portugal.
3. Universidad de Salamanca. Salamanca. Spain.
4. Area of Preventive Medicine and Public Health. Department of Biomedical and Diagnostic Sciences. Universidad de Salamanca. Salamanca. Spain.
5. Department of Preventive Medicine and Public Health. Universidade de Santiago de Compostela. Santiago de Compostela. Spain.
6. Health Research Institute of Santiago de Compostela (IDIS). Santiago de Compostela. Spain.
7. Consortium for Biomedical Research in Epidemiology and Public Health (CIBER Epidemiology and Public Health-CIBERESP). Madrid. Spain.
8. Department of Medical Sciences. Institute of Biomedicine (iBiMED). Universidade de Aveiro. Aveiro. Portugal.

✉ **Autor correspondente:** Fátima Roque. froque@ipg.pt

Recebido/*Received*: 18/03/2024 - **Aceite/*Accepted*:** 05/04/2024 - **Publicado/*Published*:** 02/09/2024

INTRODUCTION

The global population is living longer and aging fast,[1] which increases the risk of suffering from chronic diseases and exposes older adults to the occurrence of polypharmacy.[2] Besides, age-related pharmacokinetic and pharmacodynamic changes potentiate the use of potentially inappropriate medication (PIM) in older people.[3,4] Potentially inappropriate medication are drugs that should be avoided in older adults since the risk of potential adverse events may outweigh the clinical benefit, particularly when safer or more effective alternatives are recommended for use in this population.[5-7]

As the proportion of the older population increases, the demand for health system resources also rises.[8-10] Technology-based solutions have the potential to take healthcare systems into the 21st century, and therefore to disseminate information and knowledge all around the world.[11] Digital health technologies are important tools for healthcare professionals since they offer ready access to information and resources designed to help save time.[12] E-health tools can improve care by allowing access to health resources and healthcare by electronic means.[13] Therefore, e-health technology can be used to help healthcare professionals optimize clinical decision-making and prevent iatrogenesis,[14,15] thereby contributing to improving older patients' quality of life. Moreover, digital information can be easily updated in line with the new evidence.[16]

Recently, some studies have been carried out in Portugal that showed a high percentage of use of PIM.[17-21] In older individuals living in residential facilities from different geographical regions of the country the average number of PIM according to the Beers 2015 criteria was 4.8 ± 2.0.[21] In a sample of older inpatients of an internal medicine ward, 79.7%, 92.0%, and 76.5%, used at least one PIM according to the EU(7)-PIM list, Beers, and STOPP criteria, respectively.[17] The use of PIM was also observed in 86.4% (mean ± SD per patient = 2.30 ± 0.10) of a sample of nursing homes' older adult residents, in 2020 and according to the EU(7)-PIM list.[18] The prescriptions of PIM for all older adults in mainland Portugal were analyzed between 2019 and 2021, and the results showed that the defined daily dose (DDD) of PIM represented 9.20% of the total DDD-prescribed medicines in the same period.[19] Moreover, the use of PIM was found in 12.8% of the adverse drug reactions reported to the Portuguese pharmacovigilance system in 2019 in older patients ≥ 65 years old, and 10.6% of the suspected medicines identified were classified as PIM.[20]

According to a recent systematic review that assessed the impact of interventions designed to reduce the prescription of PIM, no studies have been published in Portugal reinforcing the need to develop interventions in this field.[22] Moreover, the implementation of clinical decision support system interventions showed a positive impact on the reduction of PIM.[22] In response, we have developed a web application, the APIMedOlder,[23] addressed to healthcare professionals, that intends to be applicable in clinical practice and is a useful tool with a simplified profile.

The usability level is a fundamental characteristic to evaluate the success of a website,[24] which is defined as the extent to which a product can be used by specified users to achieve specified goals with effectiveness, efficiency, and satisfaction in a specified context of use.[25] Therefore, the aim of this study was to assess the usability of the APIMedOlder online web application.

METHODS

Study design

A usability study was conducted through several steps as represented in the flowchart (Fig. 1). After ethics committee approval, the participants were invited to take part in the study and signed an informed consent form. After being provided within the URL of the APIMedOlder application, the participants had complete autonomy to thoroughly explore it. After familiarizing themselves with the tool, healthcare professionals answered the System Usability Scale questionnaire.

Description of the web application

The APIMedOlder website was developed as part of a research project funded by the Fundação para a Ciência e a Tecnologia (FCT) (PTDC/MED-FAR/31598/2017), aiming to prevent the use of PIM in older adults through the development of a clinical decision support system. The APIMedOlder web application is embedded into the project's website, which includes details about the research

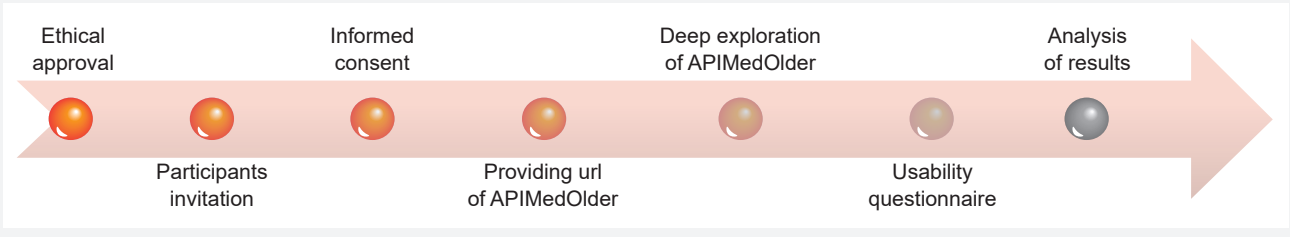

Figure 1 – APIMedOlder usability study flowchart

project, the research team, scientific publications, and a contacts section. This web application allows the healthcare professional to identify a particular drug as a PIM or not according to the Portuguese version of the EU(7)-PIM list.[26] The search can be performed using the International Nonproprietary Name (INN) or the Anatomical Therapeutic Chemical (ATC) code of a specific drug. If a drug is reported as a PIM, the main reason, dose adjustment/special considerations of use and alternative drugs and/or therapies are presented to the user. It is also optimized for mobile phones and tablet devices. APIMedOlder aims to be a useful tool with a simplified profile, allowing its applicability in clinical practice.

Participants

A non-probabilistic method of convenience sampling was used to ensure easier access to the participants. So, fifteen healthcare professionals, a sample size normally recommended in this type of studies,[27,28] without any involvement in the design or development of the web application, were recruited via e-mail between June and October 2022, to explore the web application on their mobile phones, personal computers, or tablets with an internet connection (Fig. 2). They were instructed to integrate this tool into their daily practice during a defined period (one week) and use it with their patients (test in real real-life setting). According to the General Data Protection Regulation-Directive 95/46/EC (GDPR), the security, anonymity, and confidentiality of all data provided by the participants were guaranteed. Participation in the study was voluntary, and informed consent was obtained from all participants to allow for the use of their e-mail addresses to inform them about the study aims and to provide access to the website's URL and the usability questionnaire. Additionally, in order to gain a better insight into the participants' perspectives, they were invited to make additional and optional comments or suggestions at the end of the questionnaire.

Usability test

The SUS was developed in 1986 by John Brooke.[29] It is an inexpensive tool and has become a standard questionnaire for the assessment of perceived usability since it allows the evaluation of a wide variety of products and services, such as hardware, software, mobile devices, websites, and applications.[30] It is composed of 10 statements, each having a 5-point Likert scale that ranges from 1 "Strongly Disagree" to 5 "Strongly Agree".[29] Its translation for European Portuguese was validated in 2015.[31] Considering that the statements alternate between positive (items 1,3,5,7, and 9) and negative (items 2,4,6,8, and 10), care must be taken to calculate the SUS score.[32] For positive items, the score contribution is the scale position minus 1, and for negative items, the contribution is 5 minus the scale position. Then, the sum of the scores of all items is multiplied by 2.5 to obtain the overall score.[29] The final score ranges from 0 to 100 and higher scores indicate better usability. Better products score in the high 70s to upper 80s, with superior products scoring better than 90, while products with SUS scores below 70 should be considered for improvement and with less than 50 should be cause for significant concern.[32] Based

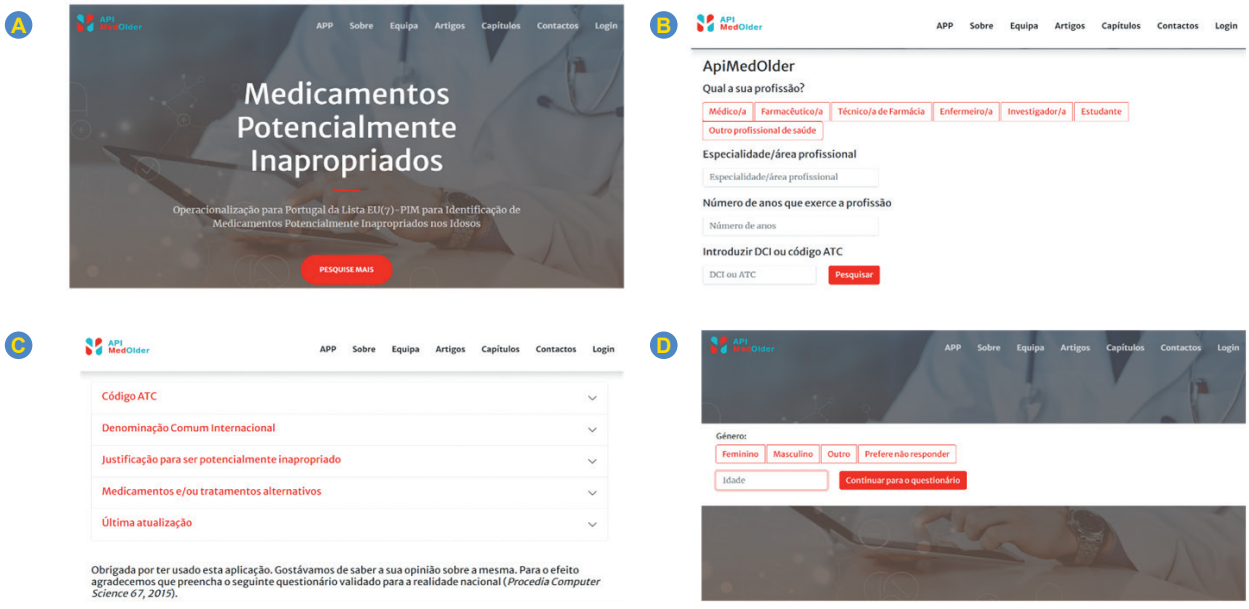

Figure 2 – APIMedOlder screenshots: (A) website main menu; (B) web application main menu; (C) PIM information page; (D) SUS questionnaire access page

on the total usability scores, a qualitative scale was applied to assign adjectives to the overall experience in using the platform, through a classification adjective anchored with numerical equivalents of 1 through 7, from "Worst Imaginable" corresponding to usability scores from 0 - 25, to "Best Imaginable" with scores from 86 - 100, respectively.[32]

Statistical analysis

Descriptive statistical analyses were conducted to determine if the online application was overall well-designed and highly usable through the SUS. To measure the internal consistency of the applied survey, Cronbach's alpha (CI 95%) was calculated using the Statistical Package for Social Sciences (SPSS 20, IBM Corp., New York, NY, USA). This value can range from 0 to 1 and evaluate how well the 10 statements correlate with the hypothetical statements regarding the concept of usability.

RESULTS

Fifteen healthcare professionals (five pharmacists, four physicians, three pharmacy technicians and three nurses) were recruited via e-mail. They were aged between 23 and 45 years old (86.67% were women) and from different regions of Portugal.

The final scores ranged from 75 to 100 points, and the mean value was 87.17 with a standard deviation of 9.70. The overall perception of healthcare professionals on the online web application APIMedOlder is presented in Table 1.

The reliability analysis was performed and the absolute ratings (i.e., transformed responses for statements 2, 4, 6, 8, and 10 so all scales have 1 as "Strongly Disagree" and 5 as the "Strongly Agree") for the 10 statements were used to compute Cronbach's alpha, achieving an internal consistency of α = 0.881 (CI 95%: 0.766 - 0.953).

All the positive items (1, 3, 5, 7 and 9) revealed scores above 4.30 with standard deviation values ranging from 0.49 to 0.60. Regarding negative items (2, 4, 6, 8 and 10), scores below 1.73 with standard deviation values between 0.40 and 0.85 were obtained.

Overall, the mean evaluation of this study corresponded to the "Best Imaginable". The individual results for adjective ratings are presented in Table 2.

DISCUSSION

This study evaluated the recently created web application APIMedOlder and collected feedback from healthcare professionals to optimize this tool according to the obtained results.

Overall, the SUS results showed that the APIMedOlder web application provided users with good usability with a mean value of 87.17, and most of the questions expressed highly positive results. This is in line with other e-health tools' medication-related usability studies.[33-38] The positive items presented an average score above 4.30 points, reflecting the desire to use the APIMedOlder web application frequently, its easy usage and quick learning of how to use it, the well-integrated functions, and the confidence in using it. The negative items also presented good results with scores below 1.73, showing that the web application was not perceived as complex or inconsistent. Since the

Table 1 – Overall perception of healthcare professionals on the online web application APIMedOlder (results by item)

Item EN (PT)	Mean score (1 - 5)	Standard deviation
1. I think that I would like to use this system frequently. (Acho que gostaria de utilizar este produto com frequência.)	4.33	0.60
2. I found the system unnecessarily complex. (Considerei o produto mais complexo do que necessário.)	1.73	0.85
3. I thought the system was easy to use. (Achei o produto fácil de utilizar.)	4.53	0.50
4. I think that I would need the support of a technical person to be able to use this system. (Acho que necessitaria de ajuda de um técnico para conseguir utilizar este produto.)	1.27	0.44
5. I found the various functions in this system were well integrated. (Considerei que as várias funcionalidades deste produto estavam bem integradas.)	4.40	0.49
6. I thought there was too much inconsistency in this system. (Achei que este produto tinha muitas inconsistências.)	1.67	0.60
7. I would imagine that most people would learn to use this system very quickly. (Suponho que a maioria das pessoas aprenderia a utilizar rapidamente este produto.)	4.47	0.50
8. I found the system very cumbersome to use. (Considerei o produto muito complicado de utilizar.)	1.33	0.47
9. I felt very confident using the system. (Senti-me muito confiante a utilizar este produto.)	4.33	0.60
10. I needed to learn a lot of things before I could get going with this system. (Tive que aprender muito antes de conseguir lidar com este produto.)	1.20	0.40

Table 2 – Descriptive statistics of the System Usability Scale (SUS) scores for adjective ratings

Adjective	Count	Mean SUS score	Standard deviation
Worst imaginable	0	-	-
Awful	0	-	-
Poor	0	-	-
Ok	0	-	-
Good	0	-	-
Excellent	7	78.93	3.98
Best imaginable	8	94.38	7.15

Correspondence between adjective scale and total SUS score: Best Imaginable [85.59 – 100.00]; Excellent [72.76 – 85.58]; Good [52.02 – 72.75]; OK [39.18 – 52.01]; Poor [25.01 – 39.17]; Awful [Not Applicable]; Worst Imaginable [0.00 – 25.00].[32]

SUS is composed only of closed questions, the participants were allowed to make additional comments to complement this study. However, no major suggestions arose during the questionnaire filling. Nonetheless, the two respondents who wrote a comment emphasized their satisfaction with APIMedOlder.

For this usability analysis, the SUS tool was chosen since it is a free, easy-to-setup and administer to participants, reliable tool that has been available for approximately 30 years and can be easily retrieved and scored quickly.[29,39] Besides, SUS can measure the usability of a wide variety of systems, and its psychometric properties, such as reliability, validity, and sensitivity, are well established.[32,40-42] This tool has also proven to be flexible and not affected by minor wording changes.[32] Moreover, SUS has been strongly recommended for researchers and practitioners over other similar tools, such as the Usability Metric for User Experience (UMUX), UMUX-Lite, or the Standardized User Experience Percentile Rank Questionnaire (SUPR-Q), since it presents several advantages.[32,39,43,44]

To make the measure more meaningful, a single-item adjective scale was added and serves as a good supplement to the SUS since Likert scale scores correlate extremely well,[45] with this study reaching the maximum classification of “Best Imaginable”.

The Cronbach’s alpha test was performed to measure the reliability of the survey applied, and in this study, an internal consistency of α = 0.881 was obtained. This value shows that the items are highly correlated with each other since a maximum Cronbach’s alpha value of 0.90 has been recommended.[46,47]

Besides the good level of usability perceived, the positive feedback obtained through this study could be related to several factors. When questions from everyday practice arise, healthcare professionals frequently use the internet to obtain information.[48,49] However, the huge amount of online medical information available may be overwhelming.[50] Therefore, APIMedOlder can be a reliable source of information that can be easily obtained. The APIMedOlder online website is also optimized for several devices, such as computers, mobile phones, and tablets, promoting quick and easy access to the information, allowing healthcare professionals to closely follow the therapeutic regimen of older people and a faster detection of PIM. So, this type of technology can enable quick and efficient management of medical conditions.[51] In the primary healthcare context, such technology can also contribute to reducing consultation time and improving patient health outcomes in the long term.[52] Besides, health information technology has been shown to decrease medication errors[53] and APIMedOlder presents a varied list of therapeutic alternatives and recommendations for the use of specific drugs, also providing the opportunity to ensure personalized medical care and guarantee older people’s healthcare demands.[51] Therefore, incorporating APIMedOlder in primary health care will allow family physicians to better manage treatment for older patients. However, the application of the criteria provided does not replace the clinical judgment and individual assessment of healthcare professionals regarding prescribing appropriateness.

According to datareportal.com,[54] there were 8.63 million internet users in Portugal in January 2022 (85.00% of the total population in the same period) with an increase of 245 thousand (+ 2.90%) since 2021. Therefore, mobile technologies represent an excellent opportunity to quickly access information and to improve the range and quality of services provided by healthcare professionals.[55]

Regarding limitations, the small sample of participants in this study (n = 15) could restrain the extrapolation of the results. However, according to the literature, a sample size of three to 20 participants is typically valid,[27] with five to 10 participants being considered as a sensible baseline range. With 10 users, the lowest percentage of problems detected was 80%, and with 20 users was 95%.[28] While there is not a specific number of participants required to uncover all usability problems, the rule of 16 ± 4 can often yield significant insights in user testing.[56] In addition, it is important to note that, while the SUS provided valuable insights into the usability of APIMedOlder, it may not have captured all dimensions, such as concerns, trust, comfort, and agreement with

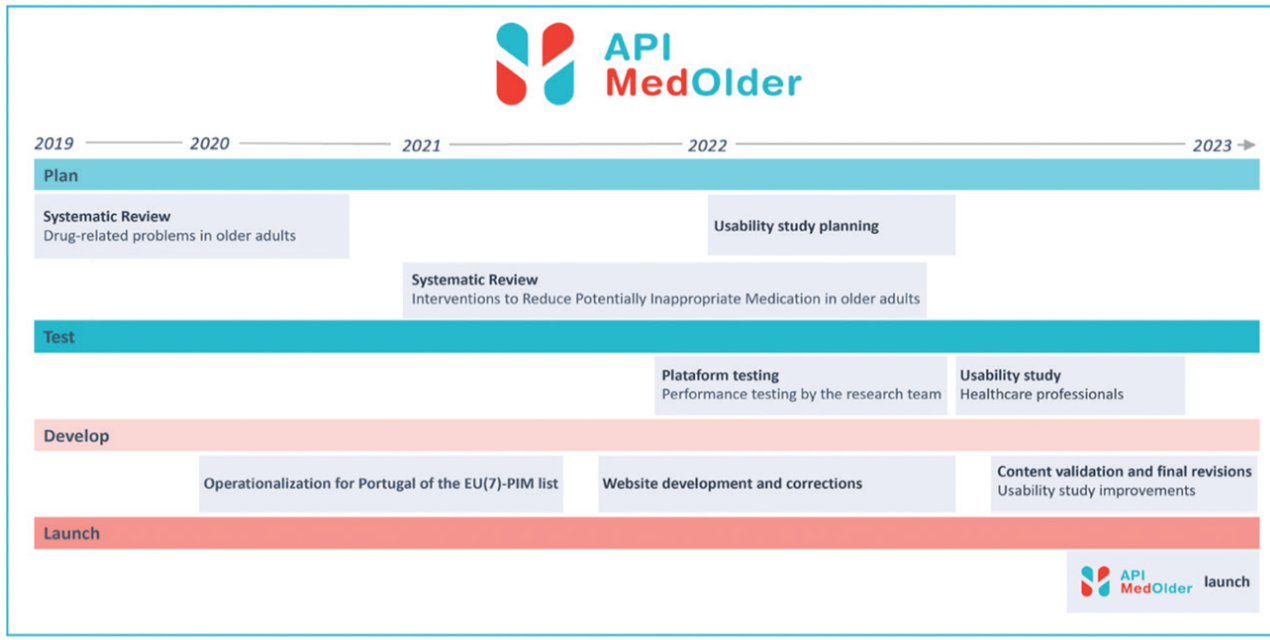

Figure 3 – APIMedOlder development roadmap

recommendations.[57] Therefore, future studies should consider incorporating these additional dimensions in order to provide a more comprehensive evaluation of APIMedOlder.

The development of the APIMedOlder website followed a well-established plan (Fig. 3) and following this usability study, a randomized-cluster control trial will be conducted at the local health unit in the Centre of Portugal. Educational interventions will be organized in sessions with family physicians, through outreach visits and will include (i) information about PIM and its impact on health outcomes in older patients; (ii) PIM prescription data in Portugal (iii) factors previously identified as underlying PIM prescribing; (iv) barriers/facilitators previously identified as influencing the use of digital health tools; and (v) presentation of the APIMedOlder application with a deep exploration of its functionalities. The interventions will be structured to engage family physicians in using the APIMedOlder application in their clinical practice, ensuring safe medication prescribing practices for older patients.

Future research directions may involve updating the EU(7)-PIM list and the APIMedOlder application and performing longitudinal studies to assess the impact of using APIMedOlder in clinical practice and explore the possibility of integrating this tool into existing electronic health record systems both in primary and secondary care settings. This could facilitate healthcare professionals' access to information about PIM during medication prescribing and review. Furthermore, future studies could explore the effectiveness of educational interventions targeting pharmacists and nurses in improving patient follow-up and medication management.

CONCLUSION

The APIMedOlder web application was designed to help healthcare professionals with prescribing PIM and medication review, improving older patient safety through the development of a clinical decision support system tool that is easy to use and applicable in clinical practice.

The overall evaluation of the developed tool was positive, and this study validated the research for the next phase.

ACKNOWLEDGMENTS

The authors would like to acknowledge all healthcare professionals who participated in this study.

AUTHOR CONTRIBUTIONS

DAR: Study design, data collection and analysis, writing of the manuscript.

AIP, RMC, AF, MTH, FR: Study design, critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

FUNDING SOURCES

This work was supported by the project APIMedOlder (PTDC/MED-FAR/31598/2017), funded by FEDER, through COMPETE2020—Programa Operacional Competitividade e Internacionalização (POCI-01-0145-FEDER-031598) and by national funds (OE), through FCT/MCTES. Daniela Almeida Rodrigues is funded by an individual grant from the Foundation for Science and Technology (FCT) (ref 2022.10605.BD). The participation of Ana Isabel Plácido in this work was funded by grant CENTRO-04-3559-FSE-000162, financed by the Operational Program from the budget of the Central Region of Portugal, within the European Social Fund (ESF) component.

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ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Limits of Viability: Perspectives of Portuguese Neonatologists and Obstetricians

Limiar da Viabilidade: A Perspetiva dos Neonatologistas e Obstetras Portugueses

Inês PAIS-CUNHA✉[1,2], Sara PEIXOTO[1,3], Henrique SOARES[1,2], Sandra COSTA[1,2]
Acta Med Port 2024 Sep;37(9):617-625 ▪ https://doi.org/10.20344/amp.21473

ABSTRACT

Introduction: Advances in neonatal care have improved the prognosis in extremely preterm infants. The gestational age considered for active treatment has decreased globally. Despite implemented guidelines, several studies show variability in practice. The aim of this study was to understand the perspectives of Portuguese neonatologists and obstetricians regarding the management of extremely preterm infants.

Methods: An online survey was sent through the Portuguese Neonatology Society and the Portuguese Society of Obstetrics and Maternal-Fetal Medicine from August to September 2023.

Results: We obtained 117 responses: 53% neonatologists, 18% pediatricians, and 29% obstetricians, with 62% having more than 10 years of experience. The majority (80%) were familiar with the Portuguese Neonatology Society consensus on the limits of viability and 46% used it in practice; 62% were unaware of Portuguese morbidity-mortality statistics associated with extremely preterm infants. Most (91%) informed parents about morbidity-mortality concerning the gestational age more frequently upon admission (64%) and considered their opinion in the limit of viability situations (95%). At 22 weeks gestational age, 71% proposed only comfort care, while at 25 and 26 weeks, the majority suggested active care (80% and 96%, respectively). Less consensus was observed at 23 and 24 weeks. At 24 weeks, most obstetricians offered active care with the option of comfort care by parental choice (59%), while the neonatology group provided active care (65%), $p < 0.001$. Regarding the lower limit of gestational age for *in utero* transfer, corticosteroid administration, cesarean section for fetal indication, neonatologist presence during delivery, and endotracheal intubation; neonatologists considered a lower gestational age than obstetricians (23 *vs* 24 weeks; $p = 0.036$; $p < 0.001$; $p < 0.001$; $p = 0.021$; $p < 0.001$, respectively).

Conclusion: Differences in perspectives between obstetricians and neonatologists in limits of viability situations were identified. Neonatologists considered a lower gestational age in various scenarios and proposed active care earlier. Standardized counseling for extremely preterm infants is crucial to avoid ambiguity, parental confusion, and conflicts in perinatal care.

Keywords: Decision Making; Gestational Age; Infant, Premature; Neonatology; Obstetrics; Physicians; Portugal; Surveys and Questionnaires

RESUMO

Introdução: Os avanços em cuidados neonatais têm melhorado o prognóstico na prematuridade extrema. A idade gestacional considerada para tratamento ativo tem diminuído mundialmente. Apesar das normas de orientação clínica implementadas, vários estudos mostram variabilidade de atuação. Pretendemos investigar a perspetiva dos neonatologistas e dos obstetras portugueses sobre a atuação na prematuridade extrema.

Métodos: Questionário *online* divulgado através das Sociedades de Neonatologia e de Obstetrícia e Medicina Materno-Fetal, entre agosto e setembro 2023.

Resultados: Obtivemos 117 respostas: 53% neonatologistas, 18% pediatras e 29% obstetras; 62% com mais de 10 anos de experiência. A maioria (80%) conhecia o consenso do limite da viabilidade da Sociedade Portuguesa de Neonatologia e 46% utilizava-o na prática, 62% referia desconhecer as estatísticas portuguesas de morbimortalidade na prematuridade extrema. A maioria (91%) informava os pais acerca da morbimortalidade para a idade gestacional, mais frequentemente à admissão (64%) e 111 (95%) considerava a sua opinião no limite de viabilidade. Às 22 semanas de idade gestacional, 71% propunham apenas cuidados de conforto e às 25 e 26 semanas, a maioria propunha cuidados intensivos (80% e 96%, respetivamente). Observou-se menos consenso às 23 e 24 semanas. Às 24 semanas, a maioria dos obstetras oferecia cuidados intensivos com possibilidade de cuidados de conforto por opção parental (59%), enquanto os neonatologias ofereciam cuidados intensivos (65%), $p < 0,001$. Relativamente ao limite inferior de idade gestacional para transferência *in utero*, administração de corticoides, cesariana por indicação fetal, neonatologista na sala de partos e intubação endotraqueal, os neonatologistas tinham em consideração uma idade gestacional inferior à considerada pelos obstetras (23 *vs* 24 semanas; $p = 0,036$; $p < 0,001$; $p < 0,001$; $p = 0,021$; $p < 0,001$, respetivamente).

Conclusão: Verificámos diferenças na perspetiva de obstetras e neonatologistas em situações de limite de viabilidade. Os neonatologistas consideram uma idade gestacional inferior em vários cenários e propõem cuidados intensivos mais cedo. O aconselhamento na prematuridade extrema deve ser uniformizado para evitar ambiguidade, confusão parental e conflito nos cuidados perinatais.

Palavras-chave: Idade Gestacional; Inquéritos e Questionários; Médicos; Neonatologia; Obstetrícia; Portugal; Recém-Nascido Prematuro; Tomada de Decisão

INTRODUCTION

Infants born before 28 completed weeks of gestation, as defined by the World Health Organization (WHO), are referred to as extremely preterm infants (EPI).[1] Less than 1% of pregnancies end before 28 weeks of gestation.[2] Despite its low prevalence, extreme prematurity is an important cause of infant mortality and morbidity, being related to future learning, motor, visual and hearing disabilities.[3,4]

Advancements in neonatal care have demonstrated improvements in the prognosis of EPI. In fact, the gestational age (GA) considered for active treatment has been decreasing globally.[5,6] Nevertheless, a 'grey zone', where the limits of viability are questionable, still remains.[7] The literature

1. Serviço de Neonatologia. Unidade Autónoma de Gestão da Mulher e Criança. Unidade Local de Saúde São João. Porto. Portugal.
2. Faculdade de Medicina. Universidade do Porto. Porto. Portugal.
3. Serviço de Neonatologia. Hospital Pedro Hispano. Unidade Local de Saúde de Matosinhos. Matosinhos. Portugal.
✉ **Autor correspondente:** Inês Pais-Cunha. inespaiscunha@gmail.com
Recebido/*Received*: 10/03/2024 - **Aceite/*Accepted*:** 18/06/2024 - **Publicado *Online*/*Published Online*:** 26/07/2024 - **Publicado/*Published*:** 02/09/2024

suggests that the likelihood of survival without sequelae for newborn with a GA below 23 weeks and birthweight below 500 g is highly unlikely.[8,9] On the other hand, preterm infants born after 25 weeks with a birthweight exceeding 600 g have a survival rate over 60%, with at least half avoiding severe long-term deficits.[4,9] The group of newborn born between 23+0 and 24+6 weeks with a birthweight between 500 g and 600 g constitutes the 'grey zone' of viability.[7] In these cases, meticulous consideration of additional risk factors, as well as parental opinion, should be considered. Moreover, when treatment is started, ongoing assessment of its impact both in the delivery room as well as in the Neonatal Intensive Care Unit (NICU) is essential.[7]

The difficulty in predicting the short and long-term prognosis of these newborns raises ethical questions about the best course of action.[8] In addition, the need for rapid decision-making in these scenarios poses an additional challenge for healthcare professionals.[10]

Despite the implementation of local guidelines, various international studies have shown significant variability in the approach to EPI among healthcare professionals, both at an individual and professional group level.[11-13] This discordance causes ambiguity and parental confusion and can, in extreme cases, lead to conflicts in perinatal care.[14]

Our study aims to investigate medical perspectives regarding treatment options in cases of extreme prematurity and to explore potential differences between Portuguese neonatologists and obstetricians.

METHODS

Study design and ethical approval

We conducted a cross-sectional multicenter study, using an online anonymous questionnaire. The study was approved by the ethics committee of Centro Hospitalar de São João.

Setting and study population

We developed an online questionnaire which was disseminated via email through Google Forms. The e-mails were sent through the Portuguese Neonatology Society (SPN) and the Portuguese Society of Obstetrics and Maternal-Fetal Medicine (SPOMMF) to their society members (n = 354 and n = 200, respectively), from August to September 2023.

The study population included specialists or residents in the fields of obstetrics or pediatrics, and neonatologists.

Participation was voluntary and each participant could only complete the survey once. Two e-mail reminders were sent to SPN members while SPOMMF members received a single reminder.

Survey design

Our survey comprised multiple-choice questions, developed based on the international literature concerning prenatal counseling, previous study surveys, and the 2014 Portuguese consensus on the limits of viability. The conceptual questionnaire was assessed by perinatal experts and subsequently pilot-tested by three neonatologists and one obstetrician for clarity and content.

The initial questions gathered participants' demographic information, including their field of expertise (obstetrics, neonatology, or pediatrics), age, sex, current practice status (yes/no), years of professional experience, geographical area of practice, and NICU level. Additionally, we assessed participants' knowledge of the current national consensus,[7] as well as their familiarity with their own hospitals' guidelines. We also evaluated their insight on national and local statistics of extreme prematurity, based on the up-to-date national very low birthweight registry (accessed in May 2023), and assessed factors considered to influence the prognosis of these infants (birthweight; sex; congenital anomalies, *in utero* growth restriction, multiple pregnancy, intra-uterine infection, signs of fetal distress, prenatal corticosteroids). Furthermore, our questionnaire included a section on parental involvement and counseling.

As we were particularly interested in understanding physicians' perspectives on treatment decisions, we evaluated which type of treatment (comfort treatment; active treatment; comfort with the possibility of active treatment by parents' choice; active treatment with the possibility of comfort treatment by parents' choice) participants would offer at a given GA. In addition, we presented different scenarios of perinatal management and treatment (*in utero* transfer in the absence of maternal indication; corticosteroid treatment for fetal maturation; c-section for fetal indication; presence of a neonatologist/pediatrician in the delivery room; endotracheal intubation; thoracic compressions and adrenaline administration for resuscitation) where participants would have to select the lowest GA for each of them.

Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/21473/15480) includes the final version of the implemented survey translated to English.

Data analysis

Statistical analysis was carried out using IBM SPSS, version 29.0 (IBM Corp., Armonk, New York, USA). Categorical variables were expressed in frequencies and percentages and compared using the χ^2 and Fisher's test. Continuous variables were expressed as median and range and compared using the Mann-Whitney test. In case of survey

questions 31 to 37, we converted the discrete variables in the multiple-choice question to a continuous variable to facilitate the statistical analysis (e.g., 22+0 - 22+6 weeks of GA was converted to 22 weeks of GA). A *p* value < 0.05 was considered statistically significant.

RESULTS

We collected a total of 117 responses (neonatologists n = 62; pediatricians n = 21 and obstetricians n = 34), resulting in a global response rate of 22% (23% SPN and 17% SPOMMF). Participant characteristics are detailed in Table 1. Of the respondents, 15% were male. The overall median age was 43 years (28 - 72), with a higher median age observed in the neonatologists/pediatricians (NN/P) group compared to obstetricians [46 (28 - 72) *vs* 39 (28 - 63), *p* = 0.003]. In total, 97% were currently practicing and 62% had more than 10 years of experience. Regarding the geographical area of practice, 55% of participants worked in the north of Portugal. Furthermore, 80% of participants were affiliated with a level III ICU - 41 at level IIIa and 53 at level IIIb. Additionally, 63% of participants reported involvement in situations of limits of viability one to 10 times a year.

Limits of viability consensus, statistics and prognostic factors

Ninety-three participants (80%) responded that they were familiar with the 2014 SPN consensus on the limits of viability, with a significantly higher percentage in the NN/P group compared to obstetricians (98% *vs* 35%, *p* < 0.001, respectively). Of these, 46% reported always using it in clinical practice – 50% of NN/P and 17% of obstetricians, with a statistically significant difference between both groups (*p* = 0.041). When asked about the definition of limits of viability, 68% responded that it was defined by "Gestational age, well determined by early ultrasound, from which ≥ 50% of newborn have a chance of survival, and at least 50% of survivors are without severe long-term sequelae"; 26% answered "Gestational age or birthweight from which ≥ 50% of newborn have a chance of survival, and at least 50% of survivors are without severe long-term sequelae" and 7% responded that they did not know, with no differences between groups (*p* = 0.713). Furthermore, 34% participants

Table 1 – Participants' characteristics

	Total (n = 117)	Neonatologists/pediatricians (n = 83)	Obstetricians (n = 34)	*p*-value
Male participants, n (%)	17 (15%)	12 (15%)	5 (15%)	0.589
Median age, (min. - max.)	43 (28 - 72)	46 (28 - 72)	39 (28 - 63)	0.003
Currently practicing, n (%)	114 (97%)	80 (96%)	34 (100%)	-
Years of professional experience				
< 5	22 (19%)	17 (20.5%)	5 (15%)	0.468
5 - 10	23 (20%)	17 (20.5%)	6 (51%)	0.726
> 10	72 (62%)	49 (59.0%)	23 (68%)	0.385
Geographical area				
North	64 (55%)	46 (55%)	18 (53%)	0.807
Center	19 (16%)	12 (14%)	7 (21%)	0.414
South	27 (23%)	21 (25%)	6 (18%)	0.372
Madeira	3 (3%)	2 (2%)	1 (3%)	1.000
Azores	4 (3%)	2 (2%)	2 (6%)	0.579
NICU level				
I	8 (7%)	8 (10%)	0	0.103
II	15 (13%)	8 (10%)	7 (21%)	0.131
IIIa	53 (45%)	41 (49%)	12 (35%)	0.164
IIIb	41 (35%)	26 (31%)	15 (44%)	0.188
How frequently are you involved in situations of limits of viability?				
< 1 x/year	19 (16%)	17 (20%)	2 (6%)	0.205
1 - 10 x/year	74 (63%)	49 (59%)	25 (74%)	0.058
> 10 x/year	19 (16%)	13 (16%)	6 (18%)	0.792
Never	5 (4%)	4 (5%)	1 (3%)	1.000

NICU: neonatal intensive care unit.

had their own hospital protocol on the limits of viability.

Regarding the knowledge on national and local statistics: 38% responded that they were aware of national statistics regarding survival at 22 - 26 GA (41% NN/P *vs* 32% obstetricians, $p = 0.256$) and 60% were aware of their local hospital's statistics with a higher percentage in the NN/P group (70% NN/P *vs* 35% obstetricians, $p < 0.001$). In Appendix 2 (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/21473/15481) we show the participants' answers regarding each GA's national survival statistics. Globally, 33% of answers were in accordance with the national very low birthweight registry. The higher percentage of correct answers were at < 23 weeks of GA (56% - 57% NN/P and 53% obstetricians) and 25 weeks of GA (42% - 43% NN/P and 38% obstetricians). There were no statistically significant differences between groups ($p = 0.336$ for statistics regarding < 23 weeks of GA; $p = 0.279$ for 23 weeks of GA; $p = 0.233$ for 24 weeks of GA and $p = 0.510$ for 25 weeks of GA).

Regarding factors influencing prognosis at the limits of viability (Fig. 1), the most answered were congenital anomalies (n = 111, 95%) and the least answered was gender (n = 79, 68%). There were no statistically significant differences between groups.

Parental involvement

Ninety-seven percent of participants responded they usually inform parents about the morbimortality for GA, with no statistically significant differences between groups (96% NN/P *vs* 97% obstetricians, $p = 0.669$). Of these, the majority provided information at admission (64%), 30% at the time of complications, 5% at the time of imminent delivery and 1% when asked for, with no differences between groups ($p = 0.151$). A minority (8%) provided parents with written information (8% NN/P *vs* 6% obstetricians, $p = 0.480$). 91% agreed that information should be provided by both neonatologists and obstetricians, 6% considered it should be provided by neonatologists and 3% by obstetricians, with no differences between groups ($p = 0.988$). The majority (95%) agreed that parents' opinions should be considered when deciding the approach in situations at the limits of viability, with no statistically significant differences between groups (93% NN/P *vs* 100% obstetricians, $p = 0.121$).

Different gestational age scenarios

Fig. 2 represents what participants recommended for newborn care in case of an imminent delivery. At 22+0 - 22+6 weeks of GA the majority (71%) of participants agreed

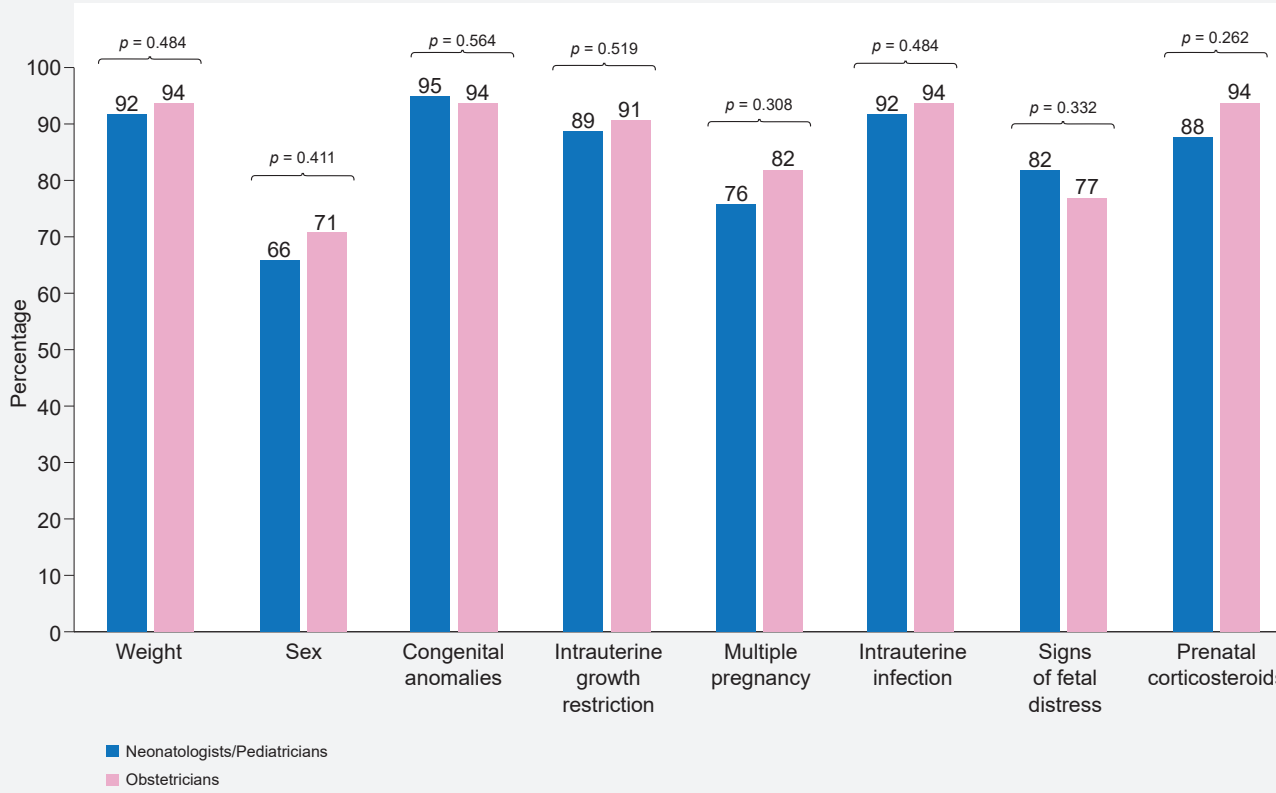

Figure 1 – Prognostic factors for newborn at the limits of viability, n = 117 (% for each group, neonatologists/pediatricians n = 83; obstetricians n = 34)

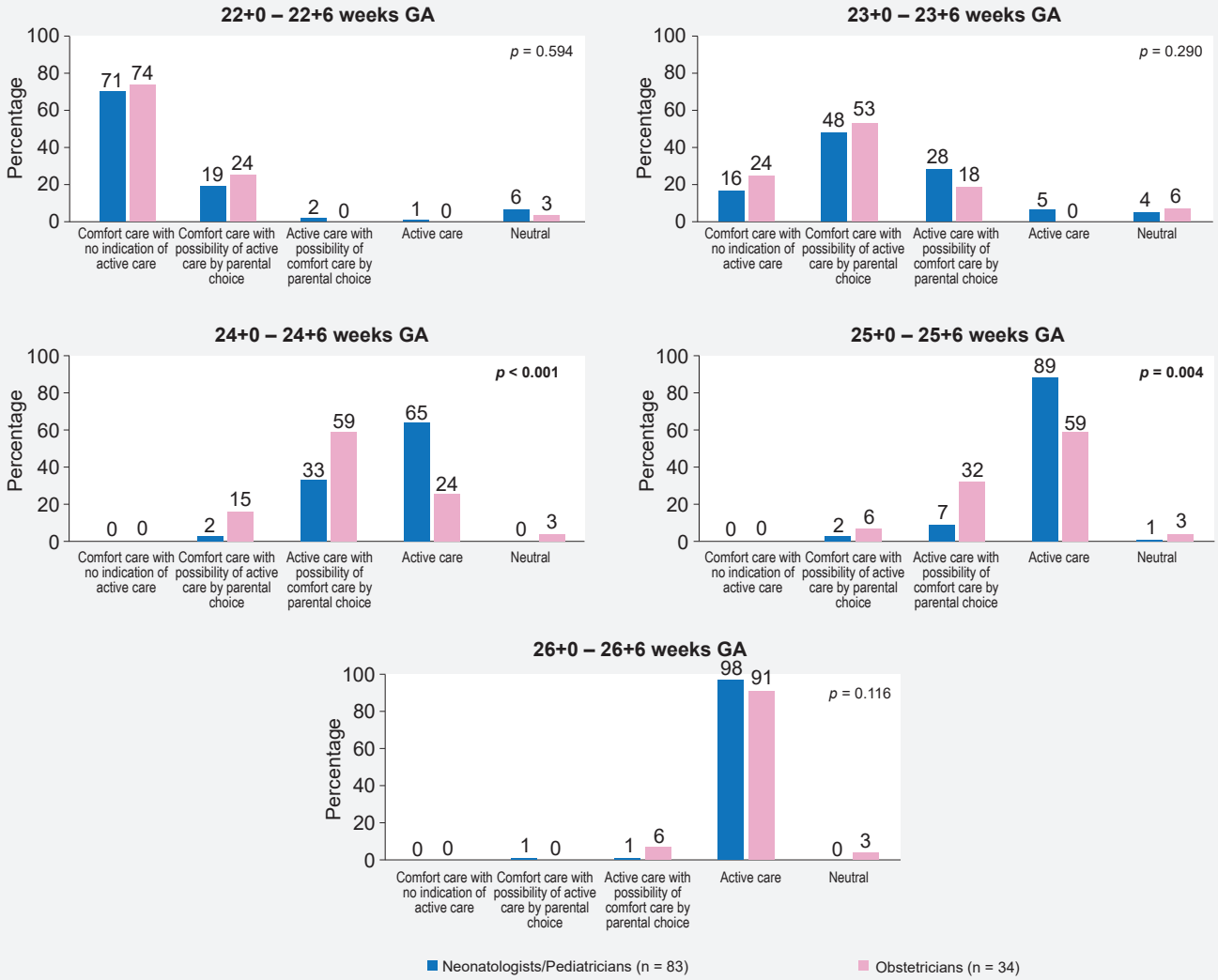

Figure 2 – Recommendations in case of imminent delivery at a given gestational age (GA), n = 117 (% for each group, neonatologists/pediatricians n = 83; obstetricians n = 34)

on offering comfort care with no indication for active care and at 26+0 - 26+6 weeks of GA, the majority (96%) agreed on offering active care, with no statistically significant differences between groups (p = 0.594 and p = 0.166, respectively). At 23+0 - 23+6 weeks of GA, there were no differences between groups (p = 0.290), the option of comfort care with the possibility of intensive care by parental choice was the most chosen by both NN/P and obstetricians (48% and 53%, respectively); 24% of obstetricians believed that only comfort care should be offered and 28% of NN/P answered that they would offer active care with the possibility of comfort care by parental choice. At 24+0 - 24+6 weeks of GA, there was a difference between both groups – the majority of NN/P would offer active care while most obstetricians would offer active care with possibility of comfort care by parental choice (65% *vs* 59%, p < 0.001, respectively). At 25+0 - 25+6 weeks of GA, 89% of NN/P would offer active care while in the obstetricians' group, 59% would offer active care and 32% would offer active care with possibility of comfort care by parental choice (p = 0.004).

Regarding the median lower GA considered appropriate for each clinical scenario (in case of an *in utero* transfer to a specialized perinatal support hospital in the absence of maternal indication; administration of corticosteroids for fetal maturation; presence of a neonatologist/pediatrician in the delivery room; endotracheal intubation in the context of neonatal resuscitation at birth) NN/P considered the lower limit to be 23 weeks, while obstetricians considered it to be 24 weeks of GA (p = 0.036, p < 0.001, p = 0.021, and p < 0.001, respectively). In case of cesarean section due to fetal

indication, NN/P considered the lower limit to be 24 weeks while obstetricians considered it to be 25 weeks of GA ($p < 0.001$). Both groups agreed that the lowest GA for starting chest compressions and administrating adrenaline in the context of neonatal resuscitation at birth was 24 weeks ($p = 0.483$ and $p = 0.070$).

Limits of viability threshold revision

The majority (59%) of participants considered that, given recent technological developments, it is necessary to review the GA currently considered in Portugal as the viability threshold, with no differences between groups (60% NN/P *vs* 56% obstetricians, $p = 0.408$).

DISCUSSION

Our article and the obtained results reflect the complexity of decision-making in cases of birth at the limits of viability and how this is conveyed in different attitudes and points of view between neonatologists/pediatricians and obstetricians. We highlight three key points from our results: 1) neonatologists and pediatricians seemed to be more aware of the 2014 Portuguese consensus on the limits of viability; 2) the majority of participants agreed that parental information on the limits of viability should be provided jointly by obstetricians and neonatologists; and 3) there seems to be a discrepancy in attitudes between the two groups, with neonatologists and pediatricians advocating for earlier and more intensive care for newborns.

Firstly, our results showed that neonatologists and pediatricians appeared to have a greater awareness of the national consensus regarding the limits of viability and were more inclined to consistently apply it in their everyday practice. Furthermore, only a minority of participants were familiar with Portuguese statistics concerning the survival of newborns at the limits of viability. Although the percentage was higher when asked about their local hospital statistics, it still fell short of optimal (60%), and once again, the percentage was higher among neonatologists and pediatricians. The heterogeneity in consensus awareness and its application among different healthcare specialists raises concerns. In addition, decision-making should be based not only on broad international consensus and guidelines, but also on national contexts. This includes taking into account updated national and local survival statistics, which are crucial in defining the limits of viability.[7] Interestingly, we found that a third of participants reported having local hospital guidelines on this topic, which may be a way of standardizing local practice and adapting it to local circumstances. Studies have shown that healthcare professionals' decisions on interventions for extremely premature newborn and perception of prognosis heavily depend on their knowledge and beliefs.[15,16] Therefore, it is crucial to improve awareness of guidelines and of national, regional, and local survival statistics in order to standardize knowledge and avoid bias. Addressing the lack of recent national publications on morbimortality among EPI presents an opportunity to tackle this issue. Furthermore, simplifying the access to the very low birth registry could facilitate the awareness of national statistics. At a local level, it is essential to conduct internal audits of medical departments to objectively assess their performance and identify key factors related to long-term neonatal outcomes, in order to develop tailored recommendations and ensure standardized interventions.

Secondly, the majority of participants from both groups informed parents about morbimortality for GA, and most of them agreed that parents' opinions should be considered when deciding the approach in situations at the limits of viability. This reflects a trend towards increasing parental involvement in end-of-life decisions which has also been reported in other countries.[14,17-19] Different studies and guidelines have proposed that health care professionals and parents share decision-making, aiming for a collaborative decision.[20-22] In fact, the decision-making process for neonates in the scenario of extreme prematurity transcends the realm of medical expertise alone, as we are considering a vulnerable infant who will possibly face life with potential heavy handicaps or death in the end of palliative/comfort care.[23] In order to make an ethical decision, parental values must also be taken into account, giving meaning to the prognosis.[24] Fortunately, our results show that Portuguese health care professionals are sensitive to this issue. Furthermore, the majority of participants agreed that information should be provided jointly by neonatologists/pediatricians and obstetricians, emphasizing the importance of teamwork in this context. On the other hand, we found that only a minority of participants provided written information to parents. Several guidelines advocate the use of written material, allowing parents to revisit the provided information as they may forget or be unable to understand what they were told at the time.[21,25,26] Additional efforts to bridge this gap should be made to promote transparency and guarantee informed decisions in the challenging context of neonatal care.

Thirdly, and in contrast with the identified need to provide joint information to parents, we identified variations in treatment choices for different gestational ages at the limits of viability between neonatologists and pediatricians *versus* obstetricians. Our findings are in line with the growing body of literature that describes different interventions and attitudes in this complex scenario of extreme prematurity between obstetric and neonatal healthcare professionals.[11-13,27,28] When considering different GA scenarios, the most important difference was found at 24 weeks. Given that this GA is considered to be in the grey zone, a difference in attitudes could be expected. Nevertheless, we also

found differences at 25 weeks, which are not in the grey zone.[4,9] As in previous studies,[13,28] our results showed a tendency towards a more conservative approach in the group of obstetricians. At 25 weeks of GA, they still tended to offer the possibility of comfort care and also tended to delay treatment, such as the administration of corticosteroids for fetal maturation, for higher GA, possibly because the consequences of these interventions are less visible to obstetricians than to neonatologists, as the latter are the ones who manage the newborn in intensive care and are more aware of their short and, especially, long term prognosis. In contrast, neonatologists and pediatricians seemed to intervene earlier and provide more intensive care, possibly reflecting the integration of successful technological medical advances into the intensive care of extremely preterm infants.[11,29]

It should also be noted that at 22 weeks of GA, although the majority agreed that comfort care should be offered, there was still a non-negligible percentage of participants in both groups who would offer active treatment by parental choice, which may be a reflection of the healthcare professionals' perception that technology is evolving in neonatal care units and that other centers around the world, for example in Japan, have recently reported a better prognosis in this low GA age.[30]

As stated before, obstetricians and neonatologists should work as a team in informing parents and providing neonatal care. This variety and disagreement can lead to unwanted inconsistent practices causing potential conflicts in perinatal care and parental confusion. Consequently, these communication issues and lack of clear information may affect the shared decision-making process, ultimately impacting the newborn's prognosis. The presence of national and international guidelines appears to be a means of standardizing practices.[12] Considering that the majority of our participants expressed a need to reassess the current viability threshold consensus, this could be seen as an opportunity to engage both groups of healthcare professionals in updating national guidelines and standardizing practices. It is essential to encourage more regular and formal collaborations between neonatologists and obstetricians in discussing clinical cases and developing recommendations together. The involvement of both groups has the potential to ensure that the recommended guidelines are accepted by all those involved in the fetal survival scenario.

This study has its limitations: although we contacted all members of the SPN and SPOMMF, we still did not reach half of the target population and the results may be constrained by our sample size. Future strategies to improve response rates could include the use of shorter questionnaires focused on specific questions, a more personalized approach to the target population, and additional methods of dissemination such as publicizing the survey through department meetings. On the other hand, our results may have been influenced by the difference in the median age of each group. Future studies targeting specific age groups could provide a more detailed understanding and complement our findings. Given our study design, there is the possibility of response bias, as participants may have adjusted their answers due to the awareness of being part of a study. Furthermore, the fact that our questionnaire relied on multiple-choice answers may limit the depth of the participants' responses. A qualitative study with focus groups could be of value to supplement our findings. Nevertheless, we were able to conduct a national-level survey with responses from all of Portugal's areas of practice which enhanced our understanding of the Portuguese reality. The inclusion of questions directly related to our national consensus and statistics enhances its relevance for daily practice.

CONCLUSION

Differences in perspectives between obstetricians and neonatologists in limited viability situations were identified. Neonatologists considered a lower gestational age in various scenarios and proposed active care earlier.

Standardizing counseling in perinatal ethics is essential to prevent ambiguity, parental confusion, and conflicts in perinatal care. A collaborative and multidisciplinary approach is crucial to ensuring that guidelines and practices align with evidence and meet the diverse needs of extremely preterm infants.

KEY MESSAGES

- Neonatologists and pediatricians seemed to be more aware of the consensus on the limits of viability when compared to obstetricians.
- The majority included and informed parents about morbidity and mortality associated with extreme prematurity.
- The majority agreed that information on the limits of viability should be provided jointly by obstetricians and neonatologists.
- There seems to be a discrepancy in attitudes with neonatologists and pediatricians advocating for earlier and more active care for newborns.
- The majority agreed that the national consensus should be reassessed, which comes as an opportunity to create multidisciplinary teams to update national guidelines and standardize practice.

ACKNOWLEDGEMENTS

We would like to express our gratitude to the Sociedade Portuguesa de Neonatologia for their invaluable support in disseminating the questionnaires and providing access to national statistical data. Additionally, our sincere appreciation goes to the Sociedade Portuguesa de Obstetrícia e Medicina Materno-Fetal for their assistance in promoting the distribution of the questionnaires. Their collaboration and contributions have greatly enriched the research process and strengthened the foundation of this study.

PREVIOUS AWARDS AND PRESENTATIONS

This paper was presented as an oral communication at the 51st National Neonatology Congress held in Tomar, in November 2023.

AUTHOR CONTRIBUTIONS

IPC: Study design, literature search, writing and critical review of the manuscript.

SP, HS: Critical review of the manuscript

SC: Study design and supervision, literature search, critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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ACTA MÉDICA PORTUGUESA
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The Impacts of Climate Change on the Emergence and Reemergence of Mosquito-Borne Diseases in Temperate Zones: An Umbrella Review Protocol

As Alterações Climáticas e a (Re)Emergência de Doenças Transmitidas por Mosquitos nas Regiões Temperadas: Protocolo de uma Umbrella Review

Raquel ROSADO E SILVA[1,2], Christopher MILLETT[3,4], Sabine DITTRICH[2,5], Helena DONATO[6]
Acta Med Port 2024 Sep;37(9):626-633 ▪ https://doi.org/10.20344/amp.21355

ABSTRACT

Introduction: Mosquito-borne diseases represent a global public health concern and are responsible for over 700 000 deaths globally every year. Additionally, many mosquito species have undergone a dramatic global expansion due to various factors, including climate change, and forecasts indicate that mosquito populations will persist in dispersing beyond their present geographic range, namely in temperate climates. The research literature on this topic has grown in recent years, including some systematic evidence synthesis. However, to provide a comprehensive overview of this growing literature needed for policy action, a summary of this evidence, including existing systematic reviews, is required. This study aims to undertake an umbrella review that explores the impacts of climate change on the emergence and reemergence of diseases transmitted by mosquitoes in temperate zones and the publication of the protocol is a fundamental step to ensure the credibility, transparency and reproducibility of this research.

Methods and Analysis: Studies published in scientific journals indexed by PubMed, EMBASE, Cochrane Library, Epistemonikos, and Web of Science Core Collection to be included in this umbrella review will meet the following criteria: the topic of study (climate change and mosquito-borne diseases), regions (temperate zones), study designs (systematic reviews and meta-analysis), language (any) and date (since inception until December 31st, 2023). Titles and abstracts from selected articles will be evaluated by two authors independently and any discrepancy will be resolved through consensus or, if not possible, through a third author. The data will be extracted, and the risk of bias will be evaluated. The quality of the methodology of the included reviews will be assessed using AMSTAR 2. A narrative synthesis will examine the included systematic reviews. The quality of evidence for all outcomes will be judged using the Grading of Recommendations Assessment, Development and Evaluation working group methodology.

Keywords: Climate Change; Meta-Analyses; Systematic Review; Vector Borne Diseases

RESUMO

Introdução: As doenças transmitidas por mosquitos representam um problema de saúde pública global, sendo responsáveis por mais de 700 000 mortes anualmente. Reconhece-se também que muitas espécies de mosquitos sofreram uma expansão global dramática por vários fatores, incluindo as alterações climáticas, e as previsões indicam que as populações de mosquitos persistirão na dispersão para além da sua atual distribuição geográfica, nomeadamente para regiões com climas temperados. A literatura científica sobre o tema tem crescido nos últimos anos, incluindo algumas revisões sistemáticas. No entanto, para fornecer uma visão abrangente desta literatura crescente necessária para a ação política, é necessário um resumo dessa evidência, incluindo das revisões sistemáticas existentes. O objetivo deste estudo é realizar uma revisão abrangente que explore os impactos das alterações climáticas na emergência e reemergência de doenças transmitidas por mosquitos nas regiões temperadas, e a publicação do seu protocolo constitui um passo fundamental para garantir a sua credibilidade, transparência e reprodutibilidade.

Métodos e Análise: Serão incluídos estudos publicados em revistas científicas indexadas pela PubMed, EMBASE, Cochrane Library, Epistemonikos e Web of Science Core Collection, que atendam aos seguintes critérios: tema de estudo (alterações climáticas e doenças transmitidas por mosquitos), regiões (regiões com clima temperado), desenhos de estudo (revisões sistemáticas e metanálises), idioma (qualquer um) e data (todos até 31 de dezembro de 2023). As revisões obtidas pela pesquisa serão analisadas de forma independente por dois autores e quaisquer discrepâncias serão resolvidas por consenso ou recorrendo a um terceiro autor. Os revisores extrairão os dados e avaliarão o risco de viés nos estudos selecionados. A AMSTAR 2 será utilizada como ferramenta de avaliação crítica da metodologia dos diferentes estudos. Uma síntese narrativa examinará as revisões sistemáticas incluídas. Posteriormente, a qualidade dos resultados será julgada usando a metodologia do grupo de trabalho de Avaliação, Desenvolvimento e Avaliação de Classificação de Recomendações.

Palavras-chave: Alterações Climáticas; Doenças Transmitidas por Vectores; Meta-Análises; Revisão Sistemática

INTRODUCTION

Vector-borne diseases (VBD) are infections that affect both humans and animals. They occur when a vector (such as mosquitoes, aquatic snails, blackflies, fleas, lice, sandflies, ticks, triatome bugs and tsetse flies) transmits an infectious agent (like parasites, viruses and bacteria) to a human or animal.[1]

More than 80% of the global population is at risk of vector-borne disease, with mosquito-borne diseases (MBD) being the largest contributor to human vector-borne disease burden, transmitting diseases such as malaria, dengue, Zika, West Nile virus infection, and Chikungunya.[2-4] Together they cause over 700 000 human deaths globally every year, which

1. Direção-Geral da Saúde. Lisbon. Portugal.
2. Deggendorf Institute of Technology. Deggendorf. Germany.
3. Imperial College of London. London. United Kingdom.
4. NOVA National School of Public Health. Public Health Research Centre. Comprehensive Health Research Center (CHRC). Universidade NOVA de Lisboa. Lisbon. Portugal.
5. University of Oxford. Oxford. United Kingdom.
6. Documentation and Scientific Information Service. Hospitais da Universidade de Coimbra, Unidade Local de Saúde de Coimbra. Coimbra. Portugal.

✉ **Autor correspondente:** Raquel Rosado e Silva. raquelrosadoesilva@dgs.min-saude.pt

Recebido/*Received*: 08/02/2024 - **Aceite/*Accepted*:** 21/05/2024 - **Publicado *Online*/*Published Online*:** 07/08/2024 - **Publicado/*Published*:** 02/09/2024

represents more than 17% of deaths from infectious diseases.[5,6]

Therefore, it is well recognized that MBD represents a global public health concern, spanning the whole continuum from low-income to high-income countries.[7] Nevertheless, socioeconomic factors are known to play a significant role, with a negative association between disease and the national gross domestic product per person.[4]

These diseases not only have major health impacts and an increased risk of mortality but cause substantial morbidity, disability and productivity losses. However, many diseases spread by mosquitoes can be avoided through preventive measures and community mobilization (Table 1).[5,8,9]

The Earth's climate is changing with increasing global temperatures projected. The magnitude will depend on the amount of heat-trapping greenhouse gases emitted, which directly influences the average global temperature.[10,11]

Climate change affects more than simply the environment; it poses a serious threat to human health. Growing global concerns about climate change highlight the need of developing mitigation and adaptation strategies.[12] In the field of infectious diseases, a key adaptation strategy is to improve surveillance of VBD. However, there is also a need for better surveillance, monitoring, and research to determine whether and how different vector-borne diseases are affected by meteorological patterns and climate change.[12]

The literature describes that many mosquito species have undergone a dramatic global expansion due to factors such as anthropogenic environmental changes, ecological plasticity, competitive aptitude, increased international trade and travel, rapid and unplanned urbanization, lack of surveillance and lack of control.[4,5] Specifically, the rise in global temperatures and precipitation patterns seems to be affecting the physiology of mosquitos, poikilotherm species (the environmental temperature influences their body temperature), by altering their ability to survive, reproduce, and transmit disease.[12,15-18] Furthermore, extreme climate events, such as floods and droughts, are expected to be more frequent and both contribute to areas of still water, which is a key factor for mosquito reproduction and can cause migration and displacement that increases human density.[19,20-22]

The latest forecasts indicate that mosquito populations that used to be seen exclusively in tropical and some subtropical climates will further disperse beyond their present geographic range, namely in temperate climates.[6,12-14,23,24]

While human life expectancy continues to increase and life years lost to infectious diseases decline, future threats of infectious diseases will probably emerge from diseases that have newly appeared in a population (emerging infections) or that have existed previously but are rapidly increasing in incidence or geographic range (reemerging infections).[25] Over the last two decades, nearly a third of all events linked to emerging infectious diseases were vector-borne, in particular, infections spread by mosquitoes.[12]

An integrated, unifying approach that aims to sustainably balance and optimize the health of people, animals, and ecosystems, recognizing the interdependence between each other's health as defined in the World Health Organization's 'One Health' concept, is required to address challenges such as the (re)emergence of infectious diseases and to find strategies to tackle them at all levels with holistic solutions.[26]

The research literature on this topic has grown in recent years, including some systematic synthesis of evidence. Nonetheless, to provide the comprehensive overview

Table 1 – Prevention and control from mosquitoes

Level	Action to reduce the risk	
Individual	Mosquito-avoidance	Avoid outdoor activities when mosquitoes are most active and high virus activity levels have been detected.
	Use of personal repellents	Use adequate insect repellents all day. Wear long-sleeved clothing. Sleep under an impregnated mosquito net.
	Removal of residential mosquito sources (breeding sites)	Empty, cover or throw out items that hold water weekly. Close windows and doors or use screens. Indoor residual spraying.
	Every traveler returning from a MBD endemic country to a country where vectors of MBD exist, should be extra careful during the first three weeks.	
Community	Community education and awareness	About prevention, symptoms, promote online resources, create partnerships with media and the community.
	Research and innovation	To discover new control methods and improve the existing ones.
	Vector control programs	Implement integrated vector management strategies.
	Environmental management	Reduce mosquito breeding habitats.
	Health systems strengthening	Improve access, surveillance, diagnosis, and treatment.

needed for policy action, a summary of this evidence, including existing systematic reviews, is required.[12]

This umbrella review will have a main objective: to define the impact of climate change on the emergence and reemergence of MBD in countries with a temperate climate. Our secondary interrelated objectives will be: (1) to characterize the extent, range, and nature of evidence synthesis on climate change and MBD in the temperate region; (2) to analyze the connections between climate change in the temperate regions and MBD; (3) to explore, if any, the strategies to mitigate the (re)emergence of MBD; (4) to evaluate the health burden; and (5) to characterize the economic impact.[27]

The publication of this study protocol aims to promote collaboration within the research community and is a fundamental step in ensuring the credibility, transparency, and reproducibility of this research.

METHODS AND ANALYSIS

This umbrella review (systematic review of systematic reviews) will follow the methodological guidelines published in a measurement tool to assess systematic reviews, AMSTAR 2. The AMSTAR 2 is a 16-item checklist designed to assist in the identification of high-quality systematic reviews of studies of healthcare interventions through a rating process that classifies the overall confidence of the results (high, moderate, low and critically low).[28]

This project was registered in the International Prospective Register of Systematic Reviews (PROSPERO, registration number CRD42023482368).

Eligibility criteria

We will identify systematic reviews and meta-analyses that correlate climate change with MBD in the countries of the temperate region.

Studies to be included in this umbrella review will meet the following criteria: topic of study (climate change and mosquito-borne diseases), regions (temperate regions), study designs (systematic reviews and meta-analysis), language (any) and date (since inception until December 31st, 2023). Articles that were not systematic reviews or meta-analyses and duplicated articles will be excluded. The eligibility criteria are shown in Table 2.

The Köppen-Geiger climate classification system will be used to define the regions with a temperate climate.[29] For countries with more than one classification, we will select the climate present in the regions with the highest proportion of the population. Countries will be organized according to their continent, income, healthcare system, and literacy rate.

Information sources

All articles published in scientific journals indexed by PubMed, EMBASE, Cochrane Library, Epistemonikos, and Web of Science Core Collection until December 31st, 2023, in any language, will be considered.

Search strategy

Comprehensive search strategies will be carried out in the aforementioned databases, under the guidance of a medical librarian skilled in conducting systematic review searches. A literature search strategy will contain controlled vocabulary [e.g., Medical Subject Headings-(MeSH)] and text word searches adapted to each one of the databases regarding its own special requirements. The search strategy to be used in PubMed is illustrated in Table 3. Furthermore, the reference list of included publications will be scrutinized to identify any additional pertinent studies.

Data management

Once the literature search is complete, the results from different electronic databases will be exported to EndNote to exclude duplication.

Selection process

Firstly, selected article titles and abstracts will be evaluated by two authors independently and will be screened considering the inclusion and exclusion criteria. At this stage, records meeting all inclusion criteria with the answer “yes” or “unclear” will proceed. Any discrepancy will be resolved through consensus or, if not possible, through a third author.

Then, a list of publications to be read in full-text will be created and evaluated, once again, by two independent authors, and will be screened using the inclusion and exclusion criteria again (at this point, “unclear” will not be an option). The justifications for exclusion will be documented.

The PRISMA flow diagram (Fig. 1) will be used to

Table 2 – Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Only systematic reviews or meta-analysis	Not a systematic reviews or meta-analysis
Studies that target diseases in humans	Duplicated articles
Studies that include countries from the temperate region	Non-human studies
Studies that explicitly connects climate factors and mosquito borne diseases	Primary research
Since inception until December 31st, 2023	Studies published in 2024
Any language	

Table 3 – Search strategy

PubMed/MEDLINE	
MeSH	"Vector Borne Diseases"[Mesh] AND ("Climate Change"[Mesh] OR "Environment"[Mesh] OR "Climate"[Mesh] OR "Weather"[Mesh] OR "Humidity"[Mesh] OR "Altitude"[Mesh]) Filters applied: Meta-Analysis, Review, Systematic Review OR
MBD and Vectors (All fields)	((('encephalitis' AND 'mosquito*') OR ('dengue' OR 'chikungunya' OR 'zika' OR 'west nile' OR 'west' AND 'nile' OR 'malaria' OR 'yellow fever' OR 'rift valley fever' OR 'leishmaniasis' OR 'arboviruses' OR 'mosquito-borne' OR 'mosquito' OR 'Aedes' OR 'albopictus' OR 'aegypti' OR 'atropalpus' OR 'japonicus' OR 'koreicus' OR 'Anopheles' OR 'Coquillettidia' OR 'Culex' OR 'Culiseta' OR Mansonia' OR 'Ochlerotatus' OR 'Phlebotomus' OR 'Stegomyia') OR 'mosquito-borne' OR 'mosquito')) AND
Temperate countries (All fields)	('temperate' OR 'temperate countries' OR 'temperate region' OR 'temperate zone' OR 'Albania' OR 'Argentina' OR 'Australia' OR 'Austria' OR 'Bangladesh' OR 'Belgium' OR 'Bhutan' OR 'Bosnia' OR 'Herzegovina' OR 'Bosnia and Herzegovina' OR 'Brazil' OR 'Bulgaria' OR 'Chile' OR 'China' OR 'Croatia' OR 'Denmark' OR 'Faroe Islands' OR 'France' OR 'Georgia' OR 'Germany' OR 'Greece' OR 'Hungary' OR 'Ireland' OR 'Israel' OR 'Italy' OR 'Japan' OR 'Kosovo' OR 'Laos' OR 'Lebanon' OR 'Lesotho' OR 'Liechtenstein' OR 'Luxembourg' OR 'Malawi' OR 'Malta' OR 'Monaco' OR 'Montenegro' OR 'Myanmar' OR 'Nepal' OR 'Netherlands' OR 'New Zealand' OR 'North Macedonia' OR 'Paraguay' OR 'Portugal' OR 'Romania' OR 'San Marino' OR 'Serbia' OR 'Slovakia' OR 'Slovenia' OR 'South Africa' OR 'South Korea' OR 'Spain' OR 'Switzerland' OR 'Taiwan' OR 'Turkey' OR 'United Kingdom' OR United States of America' OR 'Uruguay' OR 'Vatican City' OR 'Vietnam' OR 'Zambia') AND
Climate change (All fields)	('climate change' OR climate OR environment OR temperature OR warm OR droughts OR floods OR heatwaves OR rainfall OR precipitation OR 'land use' OR humidity OR rainfall OR altitude OR 'geographic information system') AND
Study design (All fields)	('systematic reviews' OR 'meta-analyses' OR 'reviews')

summarize the study selection processes.

Data collection process and items

One author will extract the data through the proposed form (Table 4) and perform a narrative analysis, and a second reviewer will check the extracted data.[27] Once again, disagreements will be resolved by discussion or by a third author. The overall process will be checked by a third and fourth author. References will be managed through EndNote.

This study will include mosquito-related infections with dengue virus, chikungunya virus, zika virus, west Nile virus, yellow fever virus, Rift Valley fever virus, arboviruses, encephalitis, leishmaniasis, and malaria. Therefore, these mosquitoes will include *Aedes* species, *Anopheles* species, *Coquillettidia* species, *Culex* species, *Culiseta* species, *Mansonia* species, *Ochletotatus* species, *Phlebotomus* genus and *Stegomyia* species.

Outcomes and prioritization

The primary outcome of this review is to identify the mosquito borne diseases that are emerging and reemerging due to climate changes in temperate zones. The secondary outcomes are: (1) to characterize the extent, range, and nature of evidence synthesis on climate change and MBD in the temperate zone; (2) to analyze the connections between climate change in the temperate regions and MBD; (3) to explore, if any, the strategies to mitigate the (re) emergence of MBD; (4) to evaluate the health burden; and (5) to characterize the economic impact.[27]

Risk of bias in individual studies

Two reviewers will independently assess the methodological quality of the included reviews using 'A MeaSurement Tool to Assess Systematic Reviews 2' (AMSTAR 2), a critical appraisal tool for systematic reviews.[28] In cases of disagreement, consensus will be reached through discussion and, if not possible, through a third reviewer.

Data synthesis

A narrative synthesis will examine the included systematic reviews. The data will be reported and organized in tables in a narrative form. Important data, such as study characteristics, findings, and key conclusions will be compiled into tables. Furthermore, a narrative synthesis will be carried out to provide a thorough description of the outcomes.

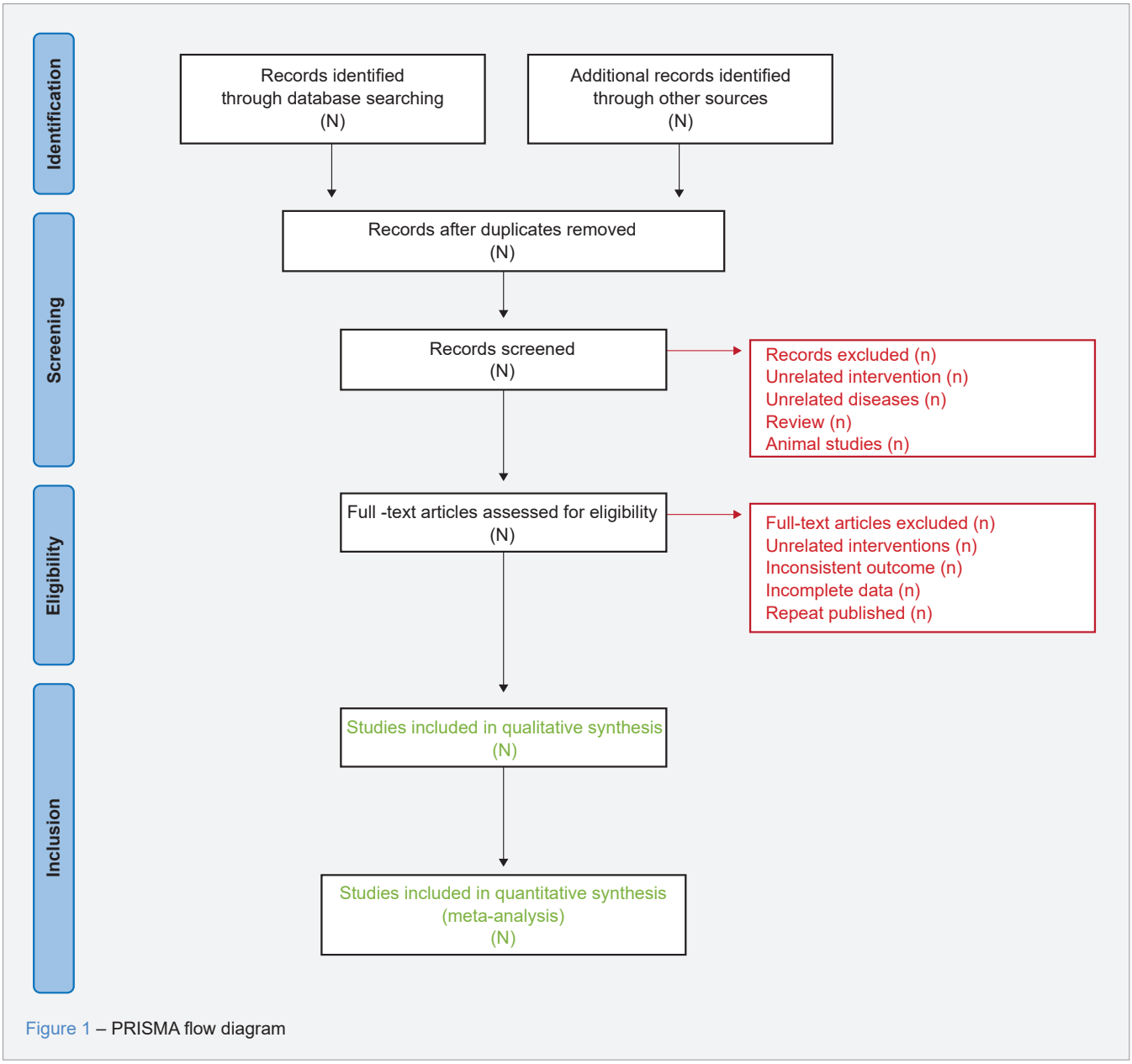

Figure 1 – PRISMA flow diagram

Meta-bias(es)

To determine whether reporting bias is present, we will determine whether the protocol of the reviews was published before the study was started. We will evaluate whether selective reporting of outcomes is present (outcome reporting bias).

Confidence in cumulative evidence

The quality of evidence for all outcomes will be judged using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group methodology. The quality of evidence will be assessed across the domains of risk of bias, consistency, directness, precision and publication bias. Additional domains may be considered where appropriate. Quality will be adjudicated as high (further research is very unlikely to change our confidence in the estimate of effect), moderate (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate), low (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate), or very low (very uncertain about the estimate of effect).

Table 4 – Proposed data extraction template, indicating domains for which reviewers will extract data

Research objective	Data extraction domains
To characterize the extent, range, and nature of evidence synthesis on climate change and MBD in the temperate region	• Name of record • Year of publication • Countries covered characterized by (i) name, (ii) continent, (iii) income, (iv) health system type and coverage, (v) literacy rate, (vi) % urban population, (vii) international arrivals, (viii) crop production • MBD • Mosquito species • Review methodology (systematic, meta-analysis) • Number of database searched • Date range of database searched • Date range of included primary studies • Type of primary studies included in the review (quantitative, qualitative, mixed-methods, other) • Number of primary research records reviewed • Aim of the study
To analyze the connections between climate change in the temperate regions and MBD	• Relationships examined between concepts (e.g., climate change broadly AND (re-)emergence of MBD in countries of the temperate region; increase temperature AND emergence of dengue in Portugal) and rationale for this examination • Proximal impact(s), if applicable • Intermediate impact(s), if applicable • Distal impact(s), if applicable • Specific climate change (e.g., rainfall, humidity, temperature, extreme events) • Scale of impact (e.g., sporadic vector findings, vector introduction, outbreaks, endemic) • Key findings about the relationships studied • Any further relevant data
To explore, if any, the strategies to mitigate the (re-)emergence of MBD	• Recommend strategies to address impacts, when possible, categorized as: (i) community-level or population-level; (ii) Regional-level or global-level; (iii) policy responses; (iv) future research
To explore, if any, the health burden	• Incidence and prevalence • Mortality rates • DALYs • QALYs
To explore, if any, the economic impact	• Direct medical costs • Indirect medical costs • Intangible costs • Economic impact on healthcare systems • Macroeconomic impact

DISCUSSION

This protocol is an important starting point for performing an umbrella review to identify the impact of climate change on the emergence and reemergence of diseases transmitted by mosquitoes in temperate zones. The publication of this protocol before carrying out the umbrella review enables a peer-review evaluation to improve the quality to the planned review.

The epidemiology of MBD is traditionally associated with environmental conditions, complicated by anthropological factors, which makes their control challenging.[19] To effectively address public health concerns, lower the burden of disease, and enhance the health and well-being of populations worldwide, stakeholders must have a thorough understanding of emergent and reemergent mosquito-borne diseases.[12]

This work is timely, given the growing body of literature on the relationship between health and climate change and the urgent need for synthesized data to guide international policies. Awareness of (re)emergent mosquito-borne diseases allows stakeholders to take immediate preventive actions. A thorough understanding of newly emerging diseases helps to set up a reliable surveillance system for early detection and to allocate resources effectively.[12]

There are some limitations, namely the fact that only systematic reviews and meta-analysis are going to be considered, and the quality of this umbrella review will ultimately reflect the quality of the underlying systematic reviews included.[30] However, the umbrella review presented in this protocol will provide one of the highest levels of evidence and a comprehensive summary regarding the impacts of climate change on the emergence and reemergence of diseases transmitted by mosquitoes in temperate zones in a transparent and structured format, allowing the detection of possible research gaps which will inform policymakers of the countries in the temperate zones on how to timely adapt to the diseases that are endemic in countries from the tropical and subtropical region areas. Furthermore, this research study will bring updated information about this topic to the scientific community, highlight methodological flaws in the previous studies, and highlight areas that require more investigation.

CONCLUSION

Mosquito-borne diseases represent a global public health concern, mainly because of the diversity of diseases that can be transmitted. Since many mosquito species have undergone a dramatic global expansion and are expected to persist in dispersing beyond their present geographic range, a transparent and systematic summary of the existing evidence is needed to assist the relevant stakeholders from the countries in the temperate zones.

The relevance of investigating this subject arises from the need to have a comprehensive overview of the growing literature required for policy action to tackle this emerging problem. It will represent an innovative study in the sense that it is the first umbrella review on this topic and the first review to include all temperate zones.[31]

ACKNOWLEDGMENTS

We are very grateful for the expertise and enthusiasm of Teresa Alves, retired geography professor from the Center of Geographical Studies at the Institute of Geography and Spatial Planning at the University of Lisbon.

AUTHOR CONTRIBUTIONS

All authors contributed equally to this manuscript and approved the final version to be published.

COMPETING INTERESTS

SD has received consulting fees from Transmissible Public Health Consultancy (Q3/4 2022) for the development of Early Warning System prototype (unrelated to manuscript).

CM is supported by the NIHR Global Health Research Centre on NCDs and Environmental Change (NIHR203247).

All other authors have declared that no competing interests exist.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Gender Disparities in the Academic Performance of Neurology Residents in Portugal

Disparidade de Género nas Classificações dos Médicos Internos de Neurologia em Portugal

Filipa LADEIRA✉*[1], Patrícia FAUSTINO*[2], Mafalda SOARES*[2], Vanessa CARVALHO*[3]
Acta Med Port 2024 Sep;37(9):634-637 ▪ https://doi.org/10.20344/amp.21637

ABSTRACT

Implicit bias has been linked to gender disparities in medical careers, impacting not only access to leadership positions but also early career opportunities. We aimed to evaluate if there were differences in the assessment of Neurology residents according to gender. We collected publicly available grades and rankings of two major evaluations that residents are submitted to, one at the beginning and another at the end of the neurology residency program, the National Board Exam and neurology examination, respectively. The National Board Examination is a multiple-choice gender-blinded evaluation, while the neurology examination is an oral gender-unblinded evaluation. We found that 36.5% of women and 21.6% of men were in the first quartile of the National Board Examination ranking, which reflects a similar representation among top classifications when assessed through a gender-blinded examination. On the other hand, the percentage of men who were in the top classification of NE, a gender-unblinded evaluation, was more than twice as high compared to women (37.8% *vs* 18.3%, $p < 0.05$). The findings of the present study may imply that there could be a disparity in women's career progression among neurology residents in Portugal, although the recruitment seems balanced between genders.
Keywords: Gender Equity; Internship and Residency; Neurologists; Neurology; Physicians, Women; Portugal; Sexism

RESUMO

O preconceito implícito tem sido associado a disparidades de género nas carreiras médicas, influenciando o acesso a cargos de liderança e oportunidades ao longo da carreira. Pretendeu-se avaliar se existiriam diferenças na avaliação de médicos internos de neurologia de acordo com o género. Foram comparadas as classificações disponíveis publicamente de dois momentos de avaliação aos quais os médicos internos de neurologia são submetidos, no início e final do internato de neurologia, respetivamente: a Prova Nacional de Acesso à Formação Especializada e o exame final de neurologia. A Prova Nacional de Seriação é uma avaliação de escolha múltipla, com ocultação de género na atribuição da classificação. O exame final de neurologia é uma avaliação oral sem ocultação de género na atribuição da classificação. Verificou-se que 36,5% das mulheres e 21,6% dos homens estavam no quartil superior de classificação na Prova Nacional de Seriação, o que reflete uma representação semelhante entre classificações superiores quando a avaliação é dependente de um exame com ocultação de género. Pelo contrário, a percentagem de homens no quartil superior de classificação no exame final de neurologia, uma avaliação sem ocultação de género, foi mais do dobro das mulheres (37,8% *vs* 18,3%). Os resultados do presente estudo podem implicar que existe uma disparidade na progressão na carreira das mulheres entre os médicos internos de neurologia em Portugal.
Palavras-chave: Equidade de Género; Internato e Residência; Médicas; Neurologia; Neurologistas; Portugal; Sexismo

INTRODUCTION

Implicit bias may mediate unconscious discriminatory behaviors toward women in STEMM (science, technology, engineering, mathematics, and medicine) sciences. From the beginning of medical history, most clinicians were men, and until the nineteenth century, women were often vetoed from practicing medicine.[1] More recently, there has been a shift in the gender distribution of physicians, which might be too recent to overcome gender bias in medicine. The internalized stereotype of the male physician may contribute to an underestimation of women's skills usually associated with the male gender, such as productivity, leadership potential, and quality of work.[1] The gender bias might contribute to a gender gap and glass ceiling effect which prevents minorities to achieve leadership roles in medical careers. Monitoring the structure and processes of medical departments is key to acknowledging the gender gap, which might lead to the implementation of strategies to reduce it.

Recently, studies evaluating career progression in medical specialties reported conflicting results regarding gender-based disparities.[2-4] Regarding Neurology careers, there is evidence that access to leadership positions is still a challenge for women at a late-career stage.[5]

We aimed to evaluate the gender distribution of the top-ranked performers in two national examinations performed in Portugal – the National Board Examination (NBE) and the neurology examination (NE) – to understand if there were gender-based disparities during the early years of the medical career among neurologists.

METHODS

Publicly available academic milestone ratings of neurology residents in Portugal [references available in Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/21637/15457)] were

* Shared first co-authorship.
1. Multiple Sclerosis Centre of Integrated Responsibility. Unidade Local de Saúde São José. Lisbon. Portugal.
2. Neurology Department. Unidade Local de Saúde São José. Lisbon. Portugal.
3. Neurology Department. Unidade Local de Saúde Santa Maria. Lisbon. Portugal.
✉ **Autor correspondente:** Filipa Ladeira. filipaladeira@msn.com
Recebido/*Received*: 05/04/2024 - **Aceite/*Accepted*:** 21/06/2024 - **Publicado *Online*/*Published Online*:** 12/07/2024 - **Publicado/*Published*:** 02/09/2024

compared according to gender.

All neurology residents who completed their training between 2019 and 2022 were included. This timeframe was chosen since there was a change in the structure and scoring of the NBE after 2019, and therefore scores from previous years could not be compared. The following scores were collected:

- Score 1: NBE grade. In Portugal, the selection of medical graduates into residency programs is dependent upon the grade of a yearly, standardized, gender-blinded nationwide multiple-choice test. All neurology residents that completed their Neurology training between 2019 and 2022, performed the NBE at least five years before (before 2017). Before 2019, the NBE test was based on a single Internal Medicine Medicine Book (Harrison's Principles of Internal Medicine)[6,7] and evaluated the candidate's knowledge of internal medicine focusing on the following areas: pulmonology, cardiology, nephrology, hematology and gastroenterology. The final score varied between 0 - 100. The average classification might differ according to yearly variation in the examination assessment framework.
- Score 2: NBE ranking. According to the National Ranking Test, a list ordered according to the National Ranking Test grade assigns a position that defines the priority to select the specialty/department where the candidate intends to complete his/her residency. The position of the candidate is independent of the yearly variation in the examination and is gender-blinded.
- Score 3: NE grade. After concluding the five years of residency, the residents perform a final neurology examination evaluating the portfolio, the supervisor rating, and neurology knowledge through a gender-unblinded oral examination. The examination takes place in a small number of neurology departments, other than the candidate's own department. The average classification might vary according to the assessment framework and local evaluators. Although the classification might vary between 0 – 20.00, since 2019 no candidate has had a classification lower than 18.00. We used a transformed variable: final classification -18 x 100 to improve the normality of the distribution.
- Score 4: NE ranking. According to the NE grade, a list of ranked candidates is published, that assigns neurologists a priority to select the department where they wish to develop their activity as specialists. The order is independent of the year of conclusion of the residency. We compared the gender distribution in the highest (first) quartile of each classification.

Gender was defined as the gender reported in the official reports of both examinations (NBE and NE), although this often refers to the biological sex of the individual and not to their gender identity.

A baseline analysis was performed using descriptive statistics, namely mean or median and standard deviation or interquartile range for continuous variables and absolute numbers and percentages for categorical variables. We used the chi-square test to compare percentages of categorical variables, and the Mann-Whitney test to compare continuous variables with normal distribution.

Since we analyzed only data that was available in the public domain, approval by an ethics committee was not required.

RESULTS

We evaluated scores from 108 neurology residents, of which 71 (65.7%) were women. The distribution of candidates according to the year of NE exam was the following: 29 (26.9%) candidates in 2022; 28 (26.0%) in 2021; 21 (19.5%) in 2020; 30 (27.7%) in 2019 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/21637/15457). The median absolute and first quartile scores according to gender distribution are presented in Tables 1 and 2 respectively.

The null hypothesis that the proportion of women and men in the first quartile of the NE classification over the study period did not differ significantly was rejected. In the gender-unblinded NE ranking, the proportion of women that achieved the top classifications was lower: 18.3% *vs* 37.7%, *p*-value = 0.035

On the other hand, the null hypothesis that the proportion of women and men in the first quartile of the NBE ranking did not differ significantly was not rejected. In the gender-blinded NBE ranking, the proportion of women and men that achieved the first quartile of classification was similar: nearly one quarter of the female and male total sample.

Table 1 – Descriptive data of the study population by absolute score values

Score		All residents	Male residents	Female residents
Gender-blinded scores	NBE grade, median (IQR)	83.0 (10.0)	82.0 (12.5)	84 (10.5)
	NBE ranking, median (IQR)	243.5 (289.3)	252.0 (266.0)	237.0 (296.0)
Gender-unblided scores	NE grade, median (IQR)	177.0 (12.0)	178.0 (13.5)	177 (13.0)
	NE ranking median (IQR)	8.0 (8.8)	7.0 (9.5)	8.0 (9.0)

IQR: interquartile range; NBE: National Board Examination; NE: national examination

Table 2 – Descriptive data of the study population by superior quartiles of each score

Score		Male residents	Female residents
Gender-blinded scores	NBE grade superior quartile ≥ 88, n (%)	10 (27.0)	22 (31.9)
	NBE ranking, superior quartile ≤ 108.5, n (%)	8 (21.6)	19 (36.5)
Gender-unblided scores	NE grade, superior quartile ≥ 182, n (%)	12 (32.4)	18 (25.3)
	NE ranking, superior quartile ≤ 3.25, n (%)	14 (37.8)	13 (18.3)*

NBE: National Board Examination; NE: national examination
*: *p*-value < 0.05 in Q-square test

DISCUSSION

Before the neurology residency, close to one-quarter of male and female candidates were in the first quartile of the NBE, a gender-blinded evaluation. This reflects a proportional gender representation in the highest ranking of classifications.

After concluding the neurology residency, 37.8% of men were in the gender-unblinded NE ranking first quartile *versus* 18.3% of women. The proportion of male neurologists in the first quartile was more than twice that of women's.

Also, the top classifications were attributed to 36.5% of women at the start of neurology residency; however, after completing residency, the proportion of women in the top classifications dropped to 18.3%. With men, we observed the opposite: 21.6% of men occupied the higher ranking at the beginning of the neurology residency, but the proportion increased to 37.8% by the end of training.

Since NBE and NE grades are influenced by factors such as the yearly and/or local variations of the examinations, the ranking might be a more accurate measure to perceive gender differences in the milestones of a neurology resident's career.

Our findings suggest that women may have equal opportunities when evaluated through gender-blinded evaluations. The same group of candidates, however, performed worse and was underrepresented in the top classifications of the final neurology examination, a gender-unblinded examination. The differences in gender rankings may reflect differences in resident performance; however, the same group of candidates was evaluated at two different stages of their careers, and women's baseline medical knowledge was equivalent to men's.

We must acknowledge that we are comparing two different types of evaluations: one that evaluates a wide range of topics and one that evaluated solely the trainee's knowledge in neurology. Furthermore, while one is only dependent on theoretical knowledge, the other also evaluates clinical and communication skills. However, such a stark difference between genders and their representation in the top quartiles of the rankings is unlikely solely due to the worse performance of female trainees in clinical and communication tasks.

The findings of the present study may imply that there could be a disparity in women's career-perceived knowledge and clinical ability among neurology residents in Portugal when evaluated through a gender-unblinded examination, although their performance did not differ from their male peers when evaluated with a gender-blinded methodology. Further studies evaluating the existence of gender discrimination in the neurology career in Portugal are needed, and the implementation of gender equity strategies should be considered.

KEY MESSAGES

- Implicit bias has been linked to gender disparities in medical careers. We aimed to evaluate gender disparities among neurology resident classifications in Portugal.
- The proportion of men/women among the top classifications assessed through a gender-blinded examination was similar.
- The percentage of male residents in the top classification of a gender-unblinded evaluation was more than twice that of women.
- These findings may imply that there could be disparities in women's career progression among Neurology residents in Portugal.

AUTHOR CONTRIBUTIONS

All authors contributed equally to this manuscript and approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

FL received consulting fees from Novartis and Merck; received payment or honoraria from Novartis, Biogen, Merck, Sanofi-Genzyme, Roche and AstraZeneca for lectures, presentations, speakers bureaus, manuscript writing or educational events; received payment from Novartis, Merck and Roche for expert testimony; received support from Roche, Merck, Teva, Jansen and Sanofi-Genzyme for attending meetings and/or travel; participated in Data Safety Monitoring Boards or Advisory Boards for Merck, Novartis and Roche.

MS received payment or honoraria from Merck and Novartis for lectures, presentations, speakers' bureaus, manuscript writing or educational events; received support from Janssen, Merck, Pfizer and Roche for attending meetings and/or travel; participated in Advisory Boards for Roche; is a member of the Portuguese Committee of Neurology Residents and Young Specialists and a resident and research fellow of the European Academy of Neurology.

VC received payment or honoraria from Bial for lectures, presentations, speakers' bureaus, manuscript writing or educational events; received support from Bial for attending meetings and/or travel; is a resident and research fellow of the European Academy of Neurology.

PF received support from Biogen, BMS, Janssen, Merck, Roche and Sanofi for attending meetings and/or travel; is a resident and research fellow of the European Academy of Neurology.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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ACTA MÉDICA PORTUGUESA
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The Red Reflex Test and Leukocoria in Childhood

O Teste do Reflexo Vermelho do Olho e a Leucocória na Criança

Joana SANTOS-OLIVEIRA✉[1], Sara CATARINO[2], Augusto MAGALHÃES[1,3], Gustavo ROCHA[4], Renato SANTOS SILVA[1,5]
Acta Med Port 2024 Sep;37(9):638-646 ▪ https://doi.org/10.20344/amp.21367

ABSTRACT

The red reflex test, performed using a direct ophthalmoscope, serves as a critical diagnostic tool in identifying various ocular conditions. These conditions encompass retinal anomalies (such as retinoblastoma, Coats disease, retinopathy of prematurity, familial exudative vitreoretinopathy, myelinated nerve fibers, ocular toxocariasis, ocular toxoplasmosis, retinochoroidal coloboma, astrocytic, and combined hamartoma), vitreous abnormalities (including persistent fetal vasculature), lens issues (like cataract), anterior chamber and corneal conditions (comprising dysgenesis of the anterior segment, congenital glaucoma, birth trauma), and tear film disturbances. During this examination, the presence of leukocoria, characterized by a white pupillary reflex, can suggest the presence of underlying conditions. Any suspicion of an abnormal red reflex test warrants immediate evaluation by a qualified ophthalmologist. This article primarily underscores the paramount importance of the red reflex examination, not only to identify potential sight-threatening but also life-threatening conditions. It delves into the most common causes of leukocoria in childhood and offers insights into a comprehensive diagnostic approach. The target audience for this article includes pediatricians, primary care clinicians, and ophthalmologists, all of whom play a pivotal role in the early detection and intervention of these critical eye disorders.
Keywords: Child; Pupil Disorders/diagnosis; Reflex, Pupillary; Retinoblastoma/diagnosis

RESUMO

O teste do reflexo vermelho, realizado usando um oftalmoscópio direto, é uma ferramenta de diagnóstico crucial na identificação de várias doenças oculares. Estas podem abranger anomalias da retina (como retinoblastoma, doença de Coats, retinopatia da prematuridade, vitreorretinopatia exsudativa familiar, fibras nervosas mielinizadas, toxocaríase ocular, toxoplasmose ocular, coloboma corioretiniano, astrocitoma e hamartoma combinado), anomalias do vítreo (incluindo vasculatura fetal persistente), alterações do cristalino (como catarata), irregularidades na câmara anterior e córnea (compreendendo disgenesia do segmento anterior, glaucoma congénito, trauma associado ao parto) e distúrbios no filme lacrimal. Durante este exame, o reflexo pupilar branco é classificado como leucocória. Qualquer suspeita de alteração do reflexo vermelho requer uma avaliação urgente por um oftalmologista qualificado. Este artigo enfatiza principalmente a importância primordial do exame do reflexo vermelho como um meio de identificar doenças que ameaçam não só a visão, mas também a vida. Explora as causas mais prevalentes de alteração do reflexo vermelho em crianças e oferece informações sobre uma abordagem diagnóstica e terapêutica abrangente. O público-alvo deste artigo inclui pediatras, médicos de medicina geral e familiar e oftalmologistas – especialidades que desempenham um papel fundamental na deteção precoce e intervenção destas doenças oculares críticas.
Palavras-chave: Criança; Distúrbios Pupilares/diagnóstico; Reflexo Pupilar; Retinoblastoma/diagnóstico

INTRODUCTION

The red reflex is a fascinating optical phenomenon occurring when light traverses the pupil, reflects off the retina, and then returns through the pupil, manifesting as a reddish-orange glow. This coloration aligns with the natural hue of healthy choroidal vasculature, as all the optical structures within a normal eye, such as the tear film, cornea, lens, and vitreous are transparent.[1] This remarkable occurrence can even be unintentionally observed in everyday life, often appearing in flash photographs.

Abnormal findings in the red reflex, such as dark spots, a weakened reflex, a white reflex, or asymmetry between the reflexes, often indicate irregularities in the transparency of the ocular structures or changes in the coloration of the retina or choroid. It is worth noting that changes in the reflex may be intermittent and contingent on gaze direction, particularly if induced by a localized retinal lesion, often located in the peripheral fundus.[1,2]

Conducting the red reflex examination, also known as the Bruckner test, entails a semi-darkened room where the ophthalmoscope's light is projected onto the patient's eyes from approximately 50 cm away. The direct ophthalmoscope should be set to a lens power of zero and held near the observer's eyes. Dimming the room lights, if applicable, can facilitate the examination by enlarging the pupillary diameter.[1,2]

The American Academy of Pediatrics currently advocates that pediatricians or primary care clinicians proficient in this technique perform a red reflex examination on all neonates, infants, and children. This evaluation should occur before discharge from the neonatal nursery and be repeated during routine health supervision visits.[2]

The term 'leukocoria' is derived from the Greek words '*leukos*' (white) and '*kore*' (pupil) and describes the clinical observation of a white pupillary reflex. Leukocoria is a

1. Department of Ophthalmology. Unidade Local de Saúde de São João. Porto. Portugal.
2. Pediatrics Department. Unidade Local de Saúde de São João. Porto. Portugal.
3. Reference Centre of Inherited Metabolic Diseases. Pediatrics Department. Unidade Local de Saúde de São João. Porto. Portugal.
4. Department of Neonatology. Unidade Local de Saúde de São João. Porto. Portugal.
5. Department of Surgery and Physiology. Faculdade de Medicina. Universidade do Porto. Porto. Portugal.
✉ **Autor correspondente:** Joana Santos Oliveira. u016825@chsj.min-saude.pt
Recebido/*Received*: 13/02/2024 - **Aceite/*Accepted*:** 20/05/2024 - **Publicado *Online*/*Published Online*:** 29/07/2024 - **Publicado/*Published*:** 02/09/2024

paramount indicator of retinoblastoma, the most prevalent malignant intraocular tumor in childhood. This seemingly innocuous white pupil reflex is, in fact, a critical red flag that demands immediate attention.[3]

This article's main objective is to underscore the importance of the red reflex examination in identifying potential vision-impairing and even life-threatening ailments. Furthermore, it elucidates the most common causes of leukocoria and other changes of the red reflex in childhood and offers insights into diagnostic approaches. The intended audience comprises pediatricians, primary care clinicians, and ophthalmologists.

Abnormal red reflex test

Any modification that alters the transparency of the optical medium or changes the natural coloration of the retina or choroid can lead to an abnormal outcome in the red reflex test. These causative factors may be categorized anatomically, ranging from posterior to anterior ocular structures (Table 1).[2,4,5]

Retinal causes

Retinoblastoma (RB), the most prevalent malignant intraocular tumor in childhood, stems from mutations in the retinoblastoma gene (*RB1*) located on chromosome 13q14.2. This condition arises due to the inactivation of both alleles of the RB tumor suppressor gene, resulting in a malfunctioning protein that disrupts the cell cycle and triggers uncontrolled cell proliferation. Inheritance patterns include autosomal dominant transmission in 30% to 40% of instances (hereditary RB), while the remaining 60% to 70% are categorized as sporadic cases without a familial inheritance pattern (non-hereditary RB). Typically, diagnosis occurs before the age of five, with the majority presenting before the age of three, although neonatal diagnosis is less common. Leukocoria manifests as the initial sign in 60% of cases, while strabismus, often associated with a macular lesion, ranks as the second most common early indicator of RB (Fig. 1A).[6,7]

It is important to note that even unilateral disease does not exclude the presence of a germline mutation, underscoring the need for genetic testing in all RB cases to guide future tumor surveillance. Moreover, RB can exhibit an additional, more complex facet. It may manifest not only in both eyes but also as an intracranial midline primitive neuroectodermal tumor, which is most commonly found within the pineal gland. This unique presentation is referred to as trilateral RB.[6,7]

In severe cases, this tumor can lead to death if metastasis occurs, typically via the optic nerve. Additionally, the risk

Table 1 – Causes of an abnormal red reflex test

Retina	Vitreous	Lens	Anterior chamber and cornea	Tear film
Retinoblastoma	Persistent fetal vasculature	Cataract	Dysgenesis of the anterior segment	Mucus
Coats disease	Endophthalmitis	Anterior/Posterior lenticonus	Congenital glaucoma (striae or corneal edema)	Foreign bodies
Retinopathy of prematurity	Vitritis		Leukoma	
Familial exudative vitreoretinopathy			Hypopyon	
Myelinated nerve fibers			Pupillary membrane persistence	
Ocular toxocariasis				
Ocular toxoplasmosis				
Retinochoroidal coloboma				
Astrocytic and combined hamartoma				
Retinal detachment				
Cytomegalovirus retinitis				
Herpes simplex retinitis				
Endophthalmitis				
Morning Glory anomaly				
Norrie disease				
Incontinentia pigmenti				
Commotio retinae				

of second primary tumors, with osteogenic sarcoma being the most prevalent, further complicates the prognosis.[6,7]

Early detection and treatment, overseen by a multidisciplinary specialty team, offer the best chance for survival and preservation of ocular function and vision while minimizing the adverse effects of treatment. The standard practice now includes testing for mutations in the *RB1* gene, accompanied by screening and genetic counseling recommendations for affected families.[8]

Coats disease is a retinal vascular disorder characterized by retinal telangiectasia, accompanied by intraretinal and/or subretinal exudation, with all occurring without significant retinal traction (Fig. 1B). This condition is typically sporadic and non-hereditary, without associated systemic

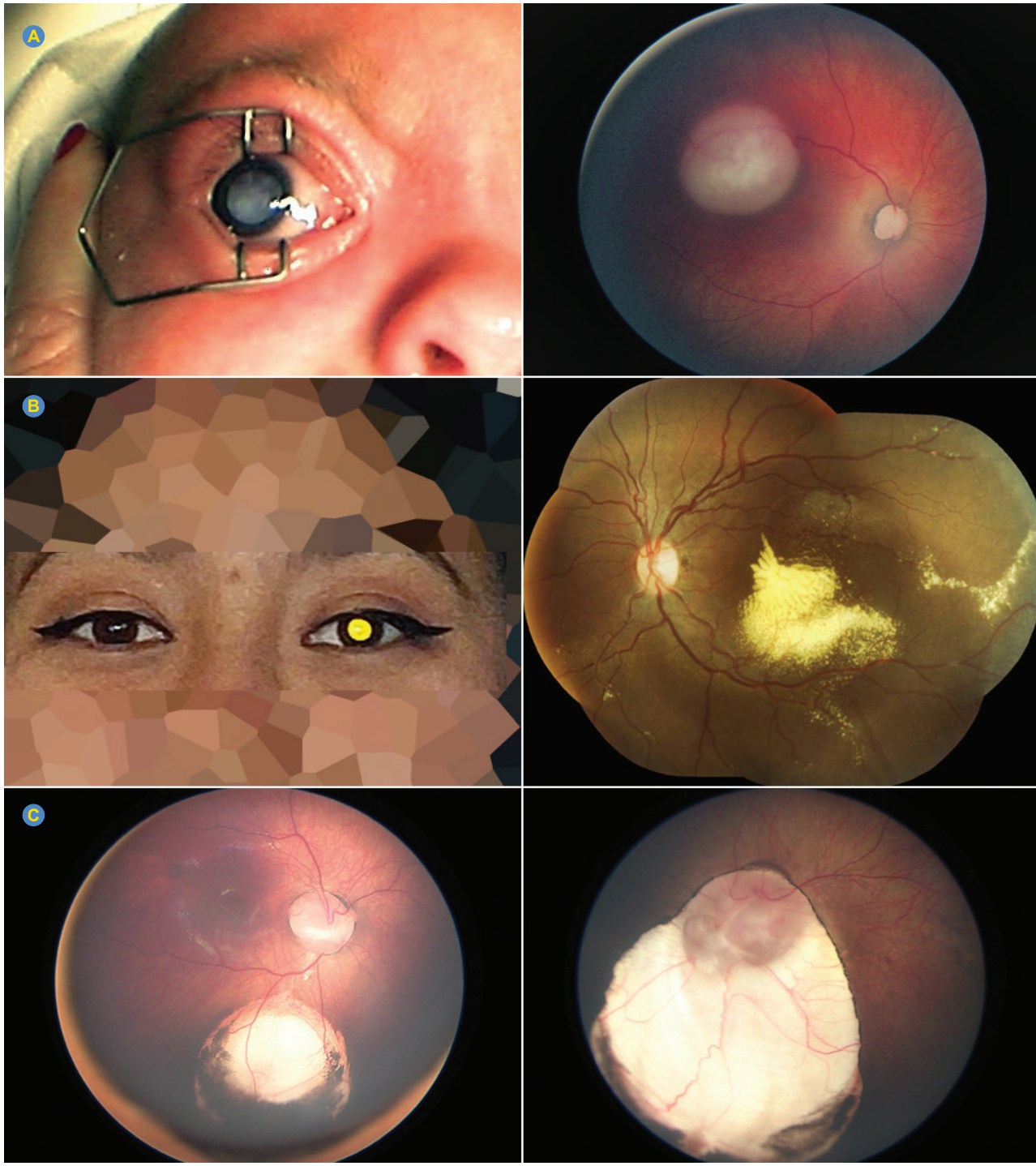

Figure 1 – Retinoblastoma (A); Coats disease (B); retinochoroidal coloboma (C)

abnormalities or racial predilection. It most commonly unfolds unilaterally in young males, with diagnoses predominantly occurring during the initial two decades of life. Therefore, it has a later onset compared to RB patients.

Patients with Coats disease may present with visual loss, strabismus, xanthocoria (manifesting as a yellowish reflex), or nystagmus. Notably, the red reflex observed in this condition often exhibits a distinctive yellowish tinge, attributable to the presence of subretinal lipids.[9]

While Coats disease typically presents in childhood and adolescence, it is worth noting that, although rare, cases have been documented in the neonatal period.[10]

Retinochoroidal coloboma is a congenital ocular anomaly of the intricate process of eye formation. It begins with the development of the optic vesicle, an outgrowth from the forebrain. This vesicle subsequently undergoes invagination, giving rise to the double-layered optic cup. The inner layer of the optic cup evolves into the neural retina, while the outer layer, derived from the proximal portion of the optic vesicle, transforms into the retinal pigment epithelium (RPE). During the embryonic stage, a crucial event known as the optic, choroidal, or fetal fissure emerges, allowing mesenchymal tissue to ingress into the optic cup through invagination along the optic cup and optic stalk. Ordinarily, this fissure undergoes a gradual closure process, typically finalizing by the fifth to seventh week of gestation, with the inferonasal part being the last to seal.

However, when this closure process encounters aberrations or interruptions, it results in the formation of a coloboma. The term 'typical coloboma' is employed to describe the defects predominantly observed in the inferonasal region of the retina, whereas defects occurring in other areas are referred to as 'atypical colobomas' (Fig. 1C).

When light enters the eye and hits the abnormal area of the retina where the coloboma is present, it can scatter or reflect differently compared to the healthy parts of the eye. This can result in an irregular or white appearance of the pupil when observed with an ophthalmoscope or in photographs, leading to the characteristic white or grayish reflex seen in leukocoria.

It is worth noting that in certain medical conditions like the CHARGE syndrome, colobomas can be accompanied by a spectrum of other anomalies, encompassing heart defects, choanal atresia, nervous system abnormalities, genital or urinary tract anomalies, or ear malformations.[5,11]

Retinopathy of prematurity (ROP) is a proliferative retinal vascular disorder that impacts premature infants, particularly those born before 32 weeks of pregnancy and/or with a birth weight lower than 1500 g. The intricate process of retinal angiogenesis commences at around 16 weeks of gestation, gradually extending from the optic disc towards the nasal ora serrata by 36 weeks and reaching the temporal ora serrata (the serrated junction between the choroid and the ciliary body) by 40 weeks of gestation. Consequently, premature infants are born with underdeveloped retinal vascularization.

The delicate balance of this vascularization process can be disrupted, leading to abnormal fibrovascular proliferation at the retinal periphery. In severe cases, this can progress to retinal detachment due to traction, posing a significant risk of blindness.[12]

Leukocoria manifests in ROP only in its severe forms, particularly when it results in tractional retinal detachment.[13]

Familial exudative vitreoretinopathy (FEVR) is an inherited vitreoretinopathy characterized by abnormal retinal vascularization (Fig. 2A). This genetic disorder can manifest in different inheritance patterns, including autosomal dominant (involving *FZD4* or *LRP5* genes), recessive (involving *LRP5* gene), or X-linked (involving the *NDP* gene), depending on the specific gene involved.

A defining feature of FEVR is the presence of an avascular peripheral retina, most notably visible in the temporal periphery, often forming a distinctive V-shaped pattern. In moderate to severe cases, this condition may progress to retinal neovascularization and fibrosis, particularly at the junction between vascular and avascular regions of the retina. Such progression can lead to the traction of the macula and retinal vessels, resulting in varying degrees of macular ectopia, tractional retinal detachment, and impaired vision. In the most severe instances, this traction can culminate in complete retinal detachment.[7,14]

Myelinated nerve fibers manifest, in fundoscopy examinations, as distinctive gray-white patches with irregular, frayed borders on the anterior surface of the retina. The reflection of light from these gray-white nerve fibers gives rise to leukocoria (Fig. 2B).

During typical prenatal development, myelination of the optic nerve commences at the lateral geniculate body, progresses towards the eye, and concludes posterior to the lamina cribrosa (a sieve-like portion of the posterior sclera) before birth. Nevertheless, in some cases of developmental abnormalities, myelination extends further, anterior to the lamina cribrosa, affecting the nerve fibers within the optic nerve head and retina.

It is important to note that these myelinated nerve fibers are generally considered benign and nonprogressive lesions.[15]

Ocular toxocariasis is a relatively rare infection caused by the larvae of the nematode parasite *Toxocara canis*, commonly found in dogs. Human infection occurs incidentally when individuals ingest infective eggs present in contaminated soil or from paratenic hosts. Once ingested, these eggs hatch, and the larvae penetrate the intestinal wall, entering the bloodstream and subsequentl

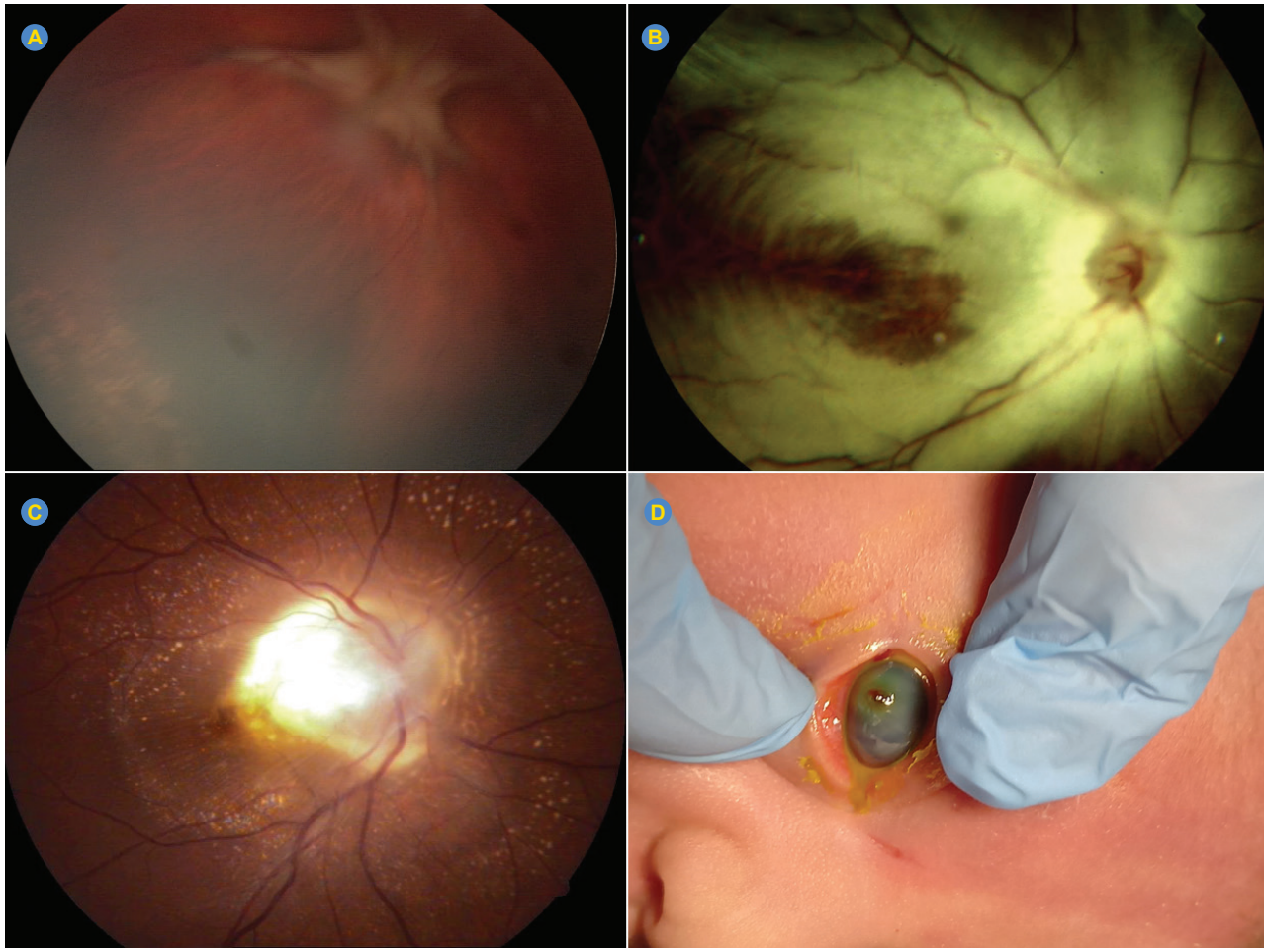

Figure 2 – Familial exudative vitreoretinopathy (A); myelinated nerve fibers (B); ocular toxocariasis (C); birth trauma with forceps (D)

disseminating to various organs, including the liver, heart, lungs, brain, muscles, and eyes. Ocular toxocariasis primarily manifests in two clinical forms: visceral larva migrans and ocular larva migrans. In the latter, a common presentation involves the formation of granulomas within the retina, often accompanied by varying degrees of vitritis. Key symptoms of this condition encompass decreased vision, ocular pain, photophobia, and the perception of floaters.[16] Remarkably, ocular toxocariasis has even been documented in preterm neonates (Fig. 2C).[17]

Ocular toxoplasmosis arises from an infection with the protozoan parasite *Toxoplasma gondii* and is one of the most prevalent causes of posterior uveitis worldwide. Cats serve as the definitive hosts for *T. gondii*. The classic form of this disease is recurrent posterior uveitis, characterized by the development of unilateral, necrotizing retinitis accompanied by secondary choroiditis. These inflammatory changes are typically located adjacent to a pigmented retinochoroidal scar and are often associated with retinal vasculitis and vitritis. In affected children capable of vocalizing their discomfort, symptoms may include complaints of reduced vision or ocular pain, while parents may observe signs such as leukocoria or strabismus. Ocular toxoplasmosis represents a significant clinical concern due to its potential for vision-threatening complications.[18]

Astrocytic hamartomas represent benign glial tumors originating from astrocytes within the nerve fiber layer of the retina. Although they are classically linked to systemic phacomatoses like tuberous sclerosis complex and neurofibromatosis, these lesions can also emerge as incidental discoveries in otherwise healthy individuals. They exhibit a wide range of locations within the retina, spanning from the optic disc to the periphery. Ophthalmoscopically, they typically manifest as raised growths with well-defined borders, sporting a distinctive 'mulberry' appearance characterized by multiple lobules. Fortunately, complications are rare in cases of astrocytic hamartomas, underscoring their benign nature.[19]

Combined hamartoma of the retina and retinal pigment epithelium represents a benign and pigmented

elevation within the retinal and retinal pigment epithelial layers. It is presumed to be congenital. The most prevalent presentation is painless, progressive vision loss, with a higher incidence observed in macular lesions.[20]

Vitreous causes

Early in embryonic development, the intraocular fetal vascular system plays a pivotal role in shaping the lens, vitreous, and retina. This vascular network originates from the optic nerve head, traverses the central vitreous, envelopes the maturing crystalline lens, and ultimately nourishes the anterior segment of the eye. Crucially, the timely regression of this fetal vascular system is essential for establishing a clear optical medium.

However, **persistent fetal vasculature** (PFV) represents a congenital ocular anomaly wherein this vascular network does not regress as expected, either partially or entirely, for reasons that remain elusive. Diagnosis of PFV typically occurs shortly after birth, highlighting the significance of early recognition. Traditionally, PFV could be divided into three categories based on the location of the vascular abnormalities: purely anterior, purely posterior, and combined PFV. Purely anterior PFV is relatively common and is characterized by cataract, posterior crystalline lens, a shallow anterior chamber and elongation of ciliary processes. Purely posterior PFV mainly involves the vitreous and the retina and it may manifest as a stalk from the optic nerve, retinal proliferative membrane, retinal fold, retinal detachment, or optic nerve hypoplasia. Combined PFV, involving both the anterior and posterior segments, is the most common type, and accounting for about 60% of all cases (Figs. 3A and 3B).[21]

Endophthalmitis is a serious ophthalmological condition characterized by infectious involvement of the vitreous, bearing devastating consequences for vision. In the pediatric population, the severity of this disorder escalates, as children may struggle to articulate or identify their symptoms, potentially leading to diagnostic delays. Clinical manifestations of endophthalmitis encompass a red eye, diminished visual acuity, eyelid edema, ocular discomfort, excessive tearing, or photophobia. This affliction can be categorized as exogenous when pathogens directly enter the eye through mechanisms such as intraocular surgery, penetrating trauma, or contiguous spread from adjacent tissues. Acute postoperative endophthalmitis typically manifests within one to two weeks following surgery. Alternatively, it may manifest as endogenous when infectious agents disseminate hematogenously into the eye from a distant source of infection.[22]

Vitritis denotes inflammation of the vitreous humor. In pediatric patients, it most frequently occurs in conditions such as pars planitis, sarcoidosis, toxocariasis, toxoplasmosis, tuberculosis, Behçet's disease, or tubulointerstitial nephritis and uveitis (TINU).[23]

Lens causes

A **cataract** is a condition characterized by an opacity of the lens. If not diagnosed and treated promptly, it can lead to partial or total vision loss. In infants and toddlers, cataracts can manifest across a wide spectrum, ranging from subtle anterior polar cataracts that appear as small opacities in the red reflex to dense, white nuclear cataracts that give rise to a white pupil – a true leukocoria. It is important to note that only white cataracts result in leukocoria, while others may not display this telltale sign but instead attenuate the passage of light through the pupil, thereby reducing the red reflex (Figs. 3C and 3D).

Cataracts in children may manifest in isolation or in conjunction with various underlying conditions. These include chromosomal abnormalities such as trisomy 13, 18, and 21, systemic syndromes like Alport syndrome and Lowe syndrome, as well as diseases like Fabry disease, galactosemia, diabetes mellitus, and Wilson disease. Infections such as cytomegalovirus, rubella, syphilis, toxoplasmosis, and chickenpox, as well as instances of trauma and radiation exposure, can also contribute to cataract development. It is worth noting that cataracts associated with systemic diseases typically affect both eyes in nearly all cases.

The timing of congenital cataract detection plays a pivotal role in shaping post-surgical visual outcomes. Early therapeutic intervention, specifically before six weeks of age for unilateral cases and eight weeks for bilateral cataracts, has been linked to the most favorable visual results.[24]

Anterior chamber and corneal causes

While anterior chamber and corneal conditions can indeed manifest with white color anomalies, it is essential to distinguish them from true leukocoria. In these cases, the white appearance does not originate from the pupil itself or the passage of light through it. Instead, it results from the presence of white structures anterior to the pupil.

Dysgenesis of the anterior segment of the eye represents a complex spectrum of congenital abnormalities affecting the structures at the front of the eye, including the cornea, iris, and lens. These abnormalities arise during embryonic development, leading to structural irregularities and malformations. This group of disorders includes aniridia (partial or complete absence of the iris), Axenfeld-Rieger anomaly, Peter's anomaly, sclerocornea, and primary congenital glaucoma.[25] Peter's anomaly, sclerocornea, and congenital glaucoma may present with white opacifications of the cornea.

Peter's anomaly is a congenital disorder that primarily affects the anterior segment of the eye. It is characterized

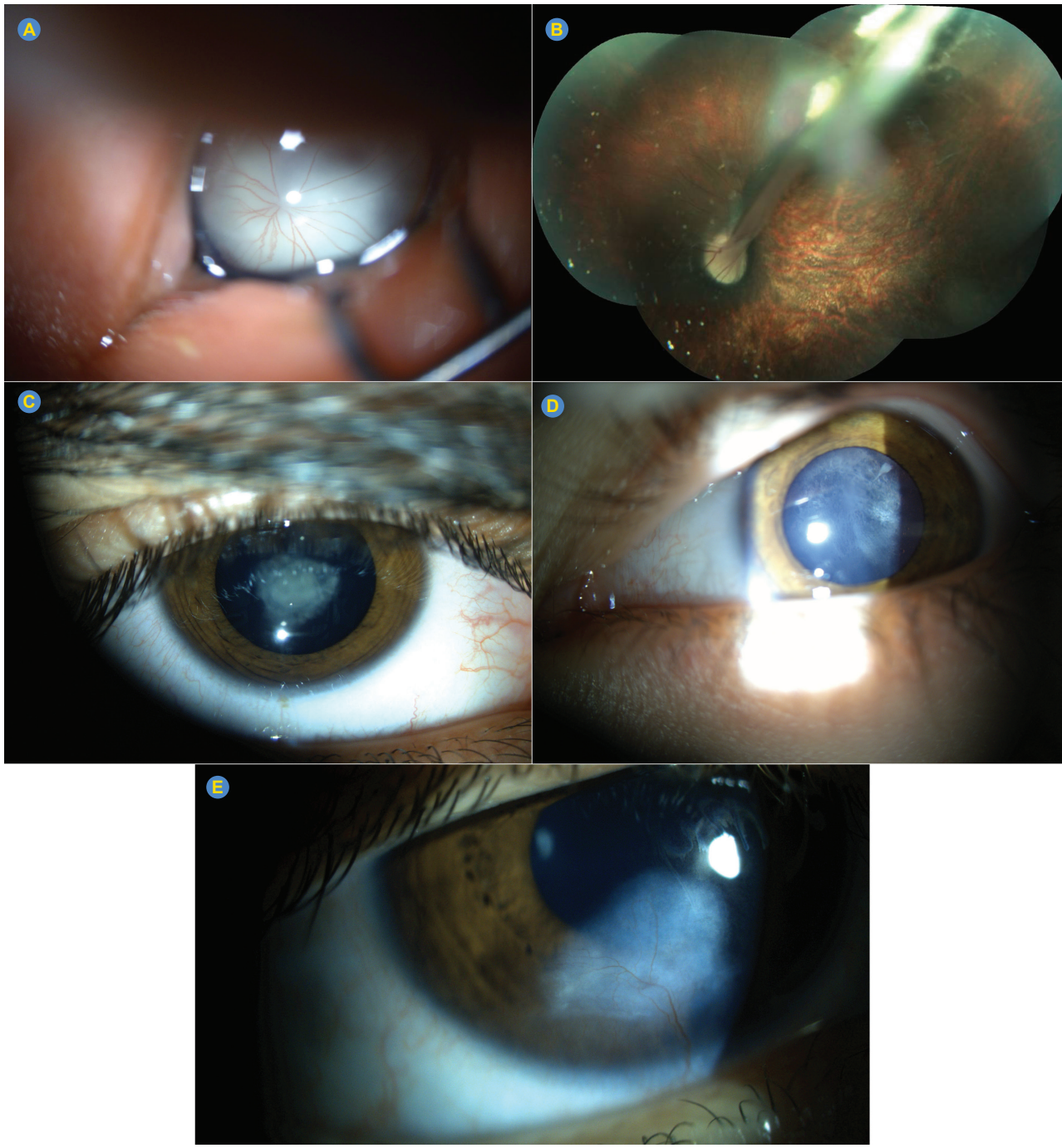

Figure 3 – Persistent fetal vasculature (A, B); cataract (C, D); corneal leukoma (E)

by a central corneal opacity and is often associated with other ocular defects such as thinning of the cornea, iridocorneal adhesions, and cataract.[26]

Sclerocornea is a rare, non-inflammatory condition characterized by the partial or complete opacification of the cornea, which has a sclera-like appearance. This congenital anomaly is typically bilateral and involves the peripheral cornea, although it can sometimes affect the entire cornea. Management may involve supportive care or surgical intervention, such as a corneal transplant, in certain cases.[26]

Congenital glaucoma is a severe condition that is characterized by elevated intraocular pressure, leads to optic nerve damage, and is associated with symptoms such as photophobia, epiphora, and blepharospasm. Clinical

characteristics often include an increase in corneal diameter, corneal edema, and breaks in Descemet's membrane, known as Haab's *striae*. These breaks can cause corneal edema leading to secondary opacification and a whiter color of the cornea.[27,28]

Corneal opacities that present as a white or grey color of the cornea may also be acquired either by infections, trauma, inflammatory or metabolic conditions. Infections such as herpes zoster, rubella, or *Chlamydia trachomatis* may lead to corneal scarring.[29-31] Interstitial keratitis, a non-infectious inflammation of the corneal stroma may also present as a whitish cornea.[32] Birth trauma (Fig. 2D), accidental or surgical trauma produces corneal injury that leads to scarring and leukoma (Fig. 3E).[33,34] In rare metabolic diseases such as mucopolysaccharidosis corneal clouding may appear by deposition of glycosaminoglycans.[35] Severe vitamin A deficiency may produce xerophthalmia and subsequent corneal scarring.[36]

Pseudoleukocoria

An abnormal red reflex test may originate from various ocular conditions affecting the retinal, vitreous, lens, anterior chamber, corneal, or tear film structures.[2,4] It is imperative to differentiate leukocoria from pseudoleukocoria. The latter may occur when a child fixates off-axis, resulting in an abnormal light reflex from the optic nerve in the affected eye or in a child with strabismus, where the fundus reflex of the fixing eye appears darker while that of the non-fixing eye appears brighter and lighter.[1]

Pseudoleukocoria can also be caused by anisometropia (significant difference in refractive error between the two eyes). In this case, the eye with greater axial length (more myopic) will have a reduced bright reflection. This change in brightness can be difficult to assess in clinical practice by untrained clinicians.[1]

Medical history and physical examination

Upon suspicion of an abnormal red reflex, a comprehensive medical history should be compiled, encompassing prenatal, birth, and postnatal history, with a focus on exposures and complications that might be associated with specific causes. Examples include exposure to corticosteroids (which can induce cataracts), congenital infections like cytomegalovirus, toxoplasmosis, or rubella (which can cause chorioretinitis and/or cataracts), and preterm birth (associated with ROP). A meticulous history of medical conditions and medications (e.g., corticosteroids), time course, exposure to puppies or kittens, as well as a history of pica or geophagia (associated with toxocariasis or toxoplasmosis) and detailed ophthalmological family history (e.g., RB, congenital cataract and FEVR) should also be obtained.[37]

The physical examination should meticulously assess dysmorphic features and growth parameters, including head circumference, and evaluate the skin for signs of coagulopathy, trauma, or neurocutaneous disorders.[39] During the ophthalmology consultation, a thorough ophthalmologic examination should be conducted according to the child's age, encompassing visual acuity testing in each eye, intraocular pressure measurement, pupillary reflex testing, sensorimotor examination, anterior segment examination, dilated fundus examination, and cycloplegic refraction.[3] Parents of these children should also undergo an ophthalmologic evaluation, as they often exhibit similar conditions, albeit in a milder form, as frequently observed in cases of congenital cataracts.[10]

Changes in the visual axis invariably affect visual function. However, changes in the extra-macular retina could result in modifications in the red reflex under certain gaze positions and may not necessarily impact visual acuity. Decreased or lost visual stimuli can disturb efferent pathways, leading to changes in ocular motility and subsequently causing strabismus.

PROGNOSIS AND CONCLUSION

The prognosis of an abnormal red reflex test depends on its etiology. While cases of RB may be life-threatening, contemporary advancements have enabled survival rates to exceed 95% to 98% in industrialized countries. Conversely, these conditions may compromise future visual acuity by inducing amblyopia.[6]

In conclusion, the red reflex test should be performed on all newborns and children during routine health surveillance visits. Detecting an abnormal red reflex can be pivotal for identifying diseases that threaten sight and even life. Any suspicion requires an expedited evaluation by an ophthalmologist.

AUTHOR CONTRIBUTIONS

JSO, RSS: Data collection, writing and critical review of the manuscript.

SC, GR: Critical review of the manuscript.

AM: Data collection, critical review of the manuscript.

All authors approved the final version to be published.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Bipolar Camouflage: A Cerebellar Cognitive Affective Syndrome Case Report

Camuflagem Bipolar: Um Caso de Síndrome Cognitiva Afetiva do Cerebelo

Teresa REYNOLDS DE SOUSA✉[1], Miguel SCHÖN[2], Pedro ALVES[3,4], Filipa NOVAIS[1,5,6], Tiago MENDES[5,7]
Acta Med Port 2024 Sep;37(9):647-651 ▪ https://doi.org/10.20344/amp.21593

ABSTRACT

The cerebellar cognitive affective syndrome is a neuropsychiatric syndrome composed of affective (anxiety, depression, euphoria, and emotional lability) and cognitive symptoms (executive, attentional, and visuospatial deficits) that was described in the 1990s. We present the case of a 49-year-old woman with a history of an acute neurological episode at the age of 28, after which she reported a change in personality, brief and alternating periods of depression, hypomania, and mixed episodes, and cognitive impairment that had a major impact on her personal and occupational level of functioning. She was initially diagnosed with bipolar disorder, but a clinical, neuropsychological, and imaging re-evaluation prompted a diagnostic reconsideration in favor of a cerebellar cognitive affective syndrome. This enabled therapeutical and prognostic refinement. Here, we discuss the diagnostic challenges of this syndrome and the implications that an accurate diagnosis has for patients.
Keywords: Cerebellar Diseases; Cognition Disorders; Mood Disorders

RESUMO

A síndrome cognitiva afetiva do cerebelo é uma síndrome neuropsiquiátrica descrita na década de 1990 caracterizada pela presença de sintomas afetivos (ansiedade, labilidade, depressão ou elação do humor) e cognitivos (défices executivos, atencionais, visuoespaciais) associados a lesões cerebelosas. Apresentamos o caso de uma mulher de 49 anos, com história de um episódio neurológico agudo aos 28 anos, após o qual apresentou um quadro de alteração da personalidade, períodos breves alternantes de depressão, hipomania e episódios com características mistas, bem como alterações cognitivas, com impacto significativo sobre as esferas pessoal e laboral. Foi inicialmente diagnosticada com perturbação afetiva bipolar, mas, após reavaliação clínica, neuropsicológica e avaliação imagiológica, o diagnóstico foi revisto para síndrome cognitiva afetiva do cerebelo. Este facto permitiu um refinamento do plano terapêutico e da perspetiva prognóstica. Neste artigo, discutimos os desafios diagnósticos desta síndrome e as implicações que o correto diagnóstico acarreta para os doentes.
Palavras-chave: Doenças do Cerebelo; Perturbações da Cognição; Perturbações do Humor

INTRODUCTION

Until the 1990s, the cerebellum was associated exclusively with motor coordination and balance. In that decade, Jeremy Schmahmann studied a group of patients with lesions confined to the cerebellum and noticed that they exhibited a set of other deficits, both cognitive and affective in nature, which allowed the identification and description of the cerebellar cognitive affective syndrome (CCAS).[1]

It consists of a neuropsychiatric syndrome resulting from cerebellar lesions of diverse etiologies, including degenerative and vascular origins. From a clinical perspective, CCAS is characterized by: 1) cognitive symptoms, including executive dysfunction, attentional control deficits, visuospatial impairments, and language disturbances[2]; 2) affective symptoms such as blunted affect, emotional lability, anxiety, dysphoria, or depression; 3) impairments in theory of mind; 4) behavioral disturbances such as disinhibition or ritualized behaviors (often associated with ruminative or obsessive thoughts).[3,4] Typically, CCAS presentations correlate with lesions affecting the posterior cerebellar regions.

Even though it is an uncommon condition,[5] CCAS remains underdiagnosed and is frequently misdiagnosed as another neurological or psychiatric condition. This is especially true when its presentation is predominantly affective/behavioral and has significant implications in terms of therapeutic efficacy and iatrogenesis. In this article, the authors present a case of CCAS that was initially diagnosed as bipolar affective disorder (BD), exploring its presentation and evolution over time and reinforcing the therapeutic and prognostic implications that the correct diagnosis determined.

CASE REPORT

We report the case of a 49-year-old woman, divorced, with a 20-year-old son, entitled to a disability pension since she was 30 years old. She had a medical history of hypertension, type 2 diabetes, and obstructive sleep apnoea syndrome. There was no family history of psychiatric illness. She was referred to the Psychiatry clinic by the family

1. Psychiatry and Mental Health Department. Unidade Local de Saúde Santa Maria. Lisbon. Portugal.
2. Neurology Department. Unidade Local de Saúde Santa Maria. Lisbon. Portugal.
3. Language Study Unit. Egas Moniz Centre. Faculdade de Medicina. Universidade de Lisboa. Lisbon. Portugal.
4. Stroke Unit. Neurology Department. Unidade Local de Saúde Santa Maria. Lisbon. Portugal.
5. Psychiatry and Psychology Department. Faculdade de Medicina. Universidade de Lisboa. Lisbon. Portugal.
6. Environmental Health Institute (ISAMB). Faculdade de Medicina. Universidade de Lisboa. Lisbon. Portugal.
7. Molecular Medicine Institute (IMM). Faculdade de Medicina. Universidade de Lisboa. Lisbon. Portugal.
✉ **Autor correspondente:** Teresa Reynolds de Sousa. teresareynoldsdesousa@gmail.com
Recebido/*Received*: 27/03/2024 - **Aceite/*Accepted*:** 09/05/2024 - **Publicado *Online*/*Published Online*:** 17/07/2024 - **Publicado/*Published*:** 02/09/2024

physician due to loss of psychiatric follow-up and as she had been previously diagnosed with type I BD.

At the age of 28, she was hospitalized for an acute episode of visual, verbal articulation and balance disturbances that lasted less than 12 hours. Before that, she had not had any affective episodes, namely of the depressive type. Since the hospitalization, she describes a personality change with increased impulsivity and disinhibition, and mood swings. She presented brief (lasting a few days) and alternating episodes of depression (sadness, depressive thoughts, psychomotor retardation, social isolation, anhedonia, hypersomnia, neglect of hygiene and household chores), hypomania (increased energy, elevated mood, talkativeness, increased goal-directed activity, decreased need for sleep), and mixed feature episodes (dysphoria, marked emotional lability), accompanied by intense anxiety. Initially, there were no periods of time free of affective symptoms, but these came later on and gradually lasted longer. The patient also reported cognitive changes that manifested simultaneously, characterized by difficulties in planning and attentional control. In particular, she described having difficulties in figuring out how to execute tasks involving multiple steps (e.g., sorting the laundry by colour), no longer being able to pay attention to two stimuli at the same time, and having to make a tremendous effort to be able to focus and perform simple tasks (e.g., calculating the change of a small purchase). This condition radically altered the patient's personal and work functioning, leading to her inability to maintain employment for more than two months and ultimately resulting in disability retirement.

In this context, she was prescribed various psychotropic drugs, having had sequential medication trials and adjustments. In the last years of her previous follow-up, she had been maintained on sodium valproate 500 mg daily, topiramate 300 mg daily, pregabalin 225 mg daily, and trazodone extended release 300 mg at bedtime, and she reported having greater clinical stabilization but still experiencing some affective episodes. Over the years, there has been a gradual fading of affective symptoms as the described affective episodes became subtler, and the patient reported a slight and progressive improvement in cognitive functioning.

She had her first medical appointment in our psychiatry

Table 1 – Detailed results of the neuropsychological assessment

	Test	Raw score	z-score
Attention, processing speed and immediate memory	Letter cancellation ("A")	16/16; 39 s	-1.6
	Trail Making Test part A	59 s	-1.0
	Toulouse-Pieron test – Work efficiency	89	-1.9
	Toulouse-Pieron test – Dispersion index	34%	-1.7
	Stroop test - words	72	-0.68
	Stroop test - colours	36	-1.5
	Digit span forward	5	-0.5
Orientation	Space, time and person	15/15	NA
Executive functions	Digit span backwards	2	-1.8
	Trail Making Test part B	260	-2.4 (score B-A)
	Stroop test interference	7	-1.5 (interference score)
	Phonemic verbal fluency ("P")	6	-1.3
	Semantic verbal fluency ("animals")	18	0
	Graphomotor alternation	2/2	NA
	Proverb interpretation	8	0.8
	Raven's Progressive Matrices	4	-5.1
Memory	Logical memory – immediate recall	8.5	-1.2
	Verbal Paired Associates Test	14	-0.3
	Information (remote memory)	16	-2.1
Visuoperceptual, visuospatial and visuoconstructive abilities	Copy of cube	3	1.2
	Clock drawing	3	0.6
	Incomplete Letters (VOSP subtest)	20/20	NA
	Dot counting (VOSP subtest)	10/10	NA
Calculus	Written calculus	13	-0.9

NA: not applicable.

clinic in January 2021, and by then she had already had three years of pharmacological non-compliance due to a loss of follow-up. She had not presented major affective episodes during this period, but maintained rapid and frequent mood swings that had no apparent correlation with life events, as well as pervasive anxiety. That day, she presented with difficulties in sustaining attention, disinhibition, expansive gesturing, a pressured, loud, but organized speech, digressive thinking, a slightly depressed mood, emotional lability, fragmented sleep, and good insight regarding both the psychopathology she presented and the cognitive deficits, which she described with accuracy and detail.

On neurological examination, she was alert, without nystagmus, and without appendicular or gait ataxia.

We performed a neuropsychological assessment (NPA), which confirmed the presence of a cognitive impairment predominantly concerning attentional and executive domains (Table 1). The NPA documented: a marked impairment in non-verbal abstraction reasoning; moderate deficits in divided attention and ability to alternate between two sets of stimuli; a mild impairment in sustained attention for short and long periods of time, selective attention and inhibitory control, working memory, and phonemic verbal fluency.

We requested a cranial magnetic resonance imaging (MRI), which showed a bilateral lesion of the posterior paravermis, suggestive of a chronic ischemic lesion, and a mild bilateral frontotemporal and cerebellar atrophy (Fig. 1).

Given the likely association between the lesion found in the MRI and the clinical episode reported at 28 years of age, the temporal relationship between this clinical episode and the onset of cognitive-affective symptoms, and the patient's neuropsychological profile, we revised the patient's diagnosis to CCAS.

After pharmacological adjustments, and for the last two years, the patient remained stabilized on sodium valproate 750 mg and escitalopram 10 mg daily, without mood swings and without significant anxiety. Despite her disability pension and some persisting difficulties, she has been able to maintain a job as a waitress.

DISCUSSION

Typically, the diagnosis of CCAS is considered in the presence of a cerebellar ataxic syndrome associated with executive and visuospatial cognitive dysfunction and affective symptoms, along with the finding of structural cerebellar lesions. The absence of coordination symptoms can pose difficulties to the diagnostic process,[3] as we observed in the current case, where the predominant neuropsychiatric symptoms mimicked BD. However, the late onset of the psychiatric presentation, its abrupt onset, and the early cognitive dysfunction prompted a differential diagnosis with neurological diseases involving the central nervous system.[6] The progressive attenuation of affective symptoms and cognitive dysfunction over time is also suggestive of CCAS. In his initial description,[1] Schmahmann described a consistent improvement leading to the remission of cognitive and affective symptoms over several months or a few years. However, numerous cases have been reported where this does not occur.[3,5] Our patient showed gradual improvement, but an unusual duration of affective and cognitive symptoms. We expect that, in the future, she will

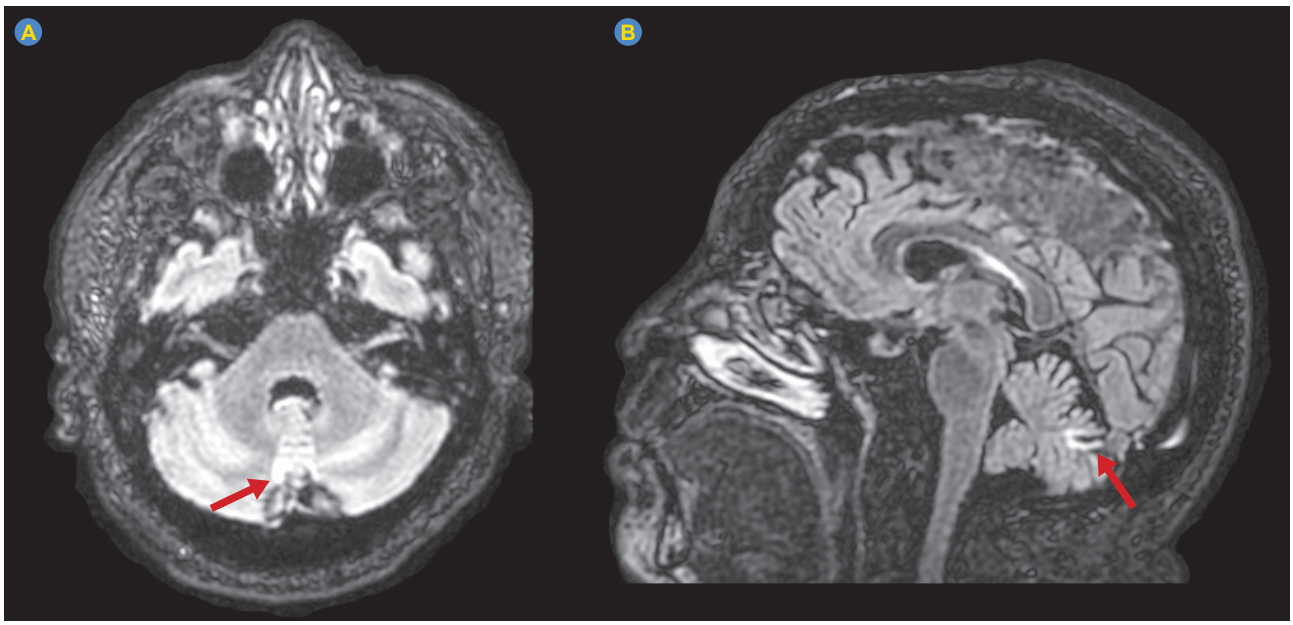

Figure 1 – T2/FLAIR sequence showing an hyperintensity in the paravermian region bilaterally, suggestive of an ischemic lesion

display further progressive attenuation of her affective and cognitive symptoms.

Bilateral cerebellar lesions, as opposed to unilateral ones, seem to correlate with greater clinical severity, and lesions in the vermis have been linked to cases with predominant affective manifestations.[3] It is important to note that the MRI revealed a pattern of mild atrophy in the frontotemporal region. This pattern did not worsen in subsequent imaging scans and may be explained by diaschisis of cerebellar projections into the frontal and temporal cortices.[3]

Schmahmann's group developed a diagnostic tool consisting of a set of cognitive tests combined with a questionnaire that assesses the patient's emotional expression.[7] This tool is useful for screening patients with suspected or confirmed cerebellar injury; however, it has not yet been validated in the Portuguese population.[8]

From a pharmacological standpoint, there is no specific treatment for this condition, and therefore, the patient was treated symptomatically with a mood stabilizer and an antidepressant. It is worth noting that the dosage of the mood stabilizer used in this case is lower than what is typically required for the treatment of bipolar disorder, and in line with what is expected in a neuropsychiatric syndrome.

Appropriate rehabilitation, not only targeting coordination symptoms, if present, but also cognitive symptoms is recommended and can offer some benefit. Cognitive deficits should be explained in order to enable the patient to deliberately overcome them using compensatory cognitive strategies.[3]

We acknowledge that the absence of detailed clinical and imaging data about the patient's initial hospitalization, at the age of 28, is a substantial limitation of this report.

This case report emphasizes the need to consider CCAS in the differential diagnosis of atypical affective and/or cognitive presentations, even in the absence of coordination and balance disturbances. Neuropsychological assessment and cranial MRI are useful diagnostic tools in investigating CCAS. The presence of CCAS has pharmacological implications, in particular, because its treatment requires lower-than-usual doses of psychotropic drugs, and prognostic implications such as a progressive attenuation of symptoms over time.

PREVIOUS AWARDS AND PRESENTATIONS

A different and simplified version of this clinical case was presented as an oral communication by the author Teresa Reynolds de Sousa (together with three other colleagues) at the XV National Congress of Psychiatry 2021. No prior submission or publication was made in another scientific journal.

AUTHOR CONTRIBUTIONS

TRS, MS: Literature review, writing of the manuscript.

PA, FN: Writing and critical review of the manuscript.

TM: Literature review, writing and critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

FN received consulting fees from Guidepoint and IQVIA; received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Lundbeck and Tecnifar; received support from Angellini, Lundbeck and Viatris for attending meetings and/or travel.

The authors have declared that no competing interests exist.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

COL4A1 and Intraventricular Hemorrhage

COL4A1 e Hemorragia Intraventricular

Laura LEITE DE ALMEIDA✉[1,2], Ana GRANGEIA[2,3], Luísa SAMPAIO[2,4], Ana VILAN[2,5]
Acta Med Port 2024 Sep;37(9):652-653 ▪ https://doi.org/10.20344/amp.20515

Keywords: Cerebral Hemorrhage/genetics; Collagen Type IV/genetics; Fetal Diseases/genetics; Infant, Newborn
Palavras-chave: Colagénio Tipo IV/genética; Doenças Fetais/genética; Hemorragia Cerebral/genética; Recém-Nascido

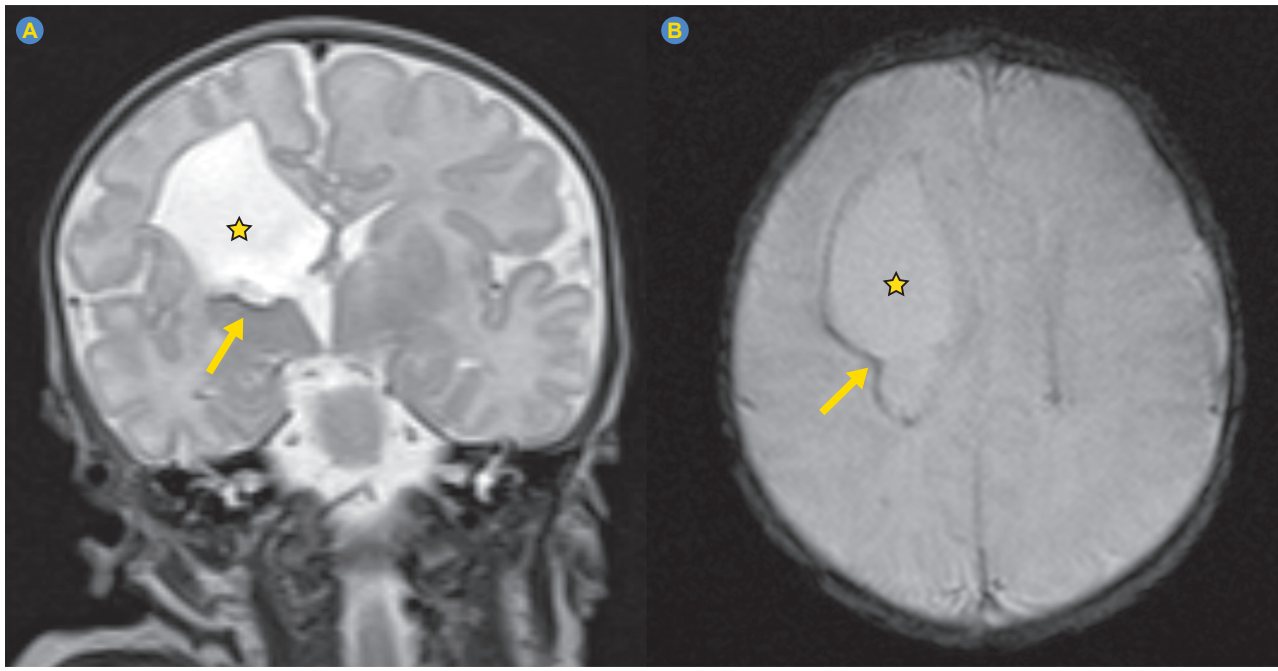

Figure 1 – Brain MRI. Coronal T2 weighted-image (WI) (A) and axial T2*-WI (B), depicting right frontal porencephalic cavity (star) with peripheral hemorrhagic residues (arrow)

A healthy primigravida with a 36-week gestation presented with fetal right ventriculomegaly. Magnetic resonance imaging (MRI) showed an encephaloclastic porencephaly and residual hemorrhagic components. Trauma, hypertension, TORCH infection and alloimmune thrombocytopenia were excluded. A caesarean section was planned and a term boy with normal platelet count and coagulation tests was delivered. Brain MRI confirmed the previous findings (Fig. 1). *A* heterozygous pathogenic variant (c.518G>A, p.Gly173Asp), maternally inherited, was identified in the *COL4A1* gene. Abdominal and cardiac ultrasound were normal. At three years old the child presented left hemiparesis, inaugural epilepsy, and strabismus with no retinal arterial tortuosity or cataract.

Collagen type IV alpha 1 (*COL4A1*) is a structural component of the vascular basement membrane of many tissues. Its fragility can trigger rupture and intrauterine intraventricular hemorrhage, leading to porencephaly and neurological symptoms, like hemiparesis and epilepsy, which were previously unexplained.[1-3] Early diagnosis allowed an appropriate follow-up and genetic counseling.

AUTHOR CONTRIBUTIONS

LLA: Data collection, literature search and drafting of the manuscript.

AG: Critical review of the manuscript.

1. Serviço de Pediatria. Centro Hospitalar Universitário de São João. Porto. Portugal.
2. Faculdade de Medicina. Universidade do Porto. Porto. Portugal.
3. Serviço de Genética Médica. Centro Hospitalar Universitário de São João. Porto. Portugal.
4. Serviço de Neurorradiologia. Centro Hospitalar Universitário de São João. Porto. Portugal.
5. Serviço de Neonatologia. Centro Hospitalar Universitário de São João. Porto. Portugal.
✉ **Autor correspondente:** Laura Leite de Almeida. analauramlalmeida@gmail.com
Recebido/*Received*: 21/08/2023 - **Aceite/*Accepted*:** 06/12/2023 - **Publicado *Online*/*Published Online*:** 29/05/2024 - **Publicado/*Published*:** 02/09/2024

LS: Data collection and analysis.

AV: Data collection, literature search and critical review of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

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PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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ACTA MÉDICA PORTUGUESA
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Recomendações para a Redução do Impacto Ambiental dos Inaladores em Portugal: Documento de Consenso

Recommendations for Reducing the Environmental Impact of Inhalers in Portugal: Consensus Document

Luis CAMPOS[1,2], Paula ROSA[3,4,5], Pedro CARREIRO MARTINS[6,7,8], Bilhota XAVIER[9,10], Pedro LEUSCHNER[11,12,13], Maria Inês M. MARQUES[14,15], José ALBINO[16], Carlos ROBALO CORDEIRO[5,17,18]
Acta Med Port 2024 Sep;37(9):654-661 ▪ https://doi.org/10.20344/amp.22062

RESUMO

Este documento de consenso aborda a redução do impacto ambiental dos inaladores em Portugal. Foi elaborado pelo Conselho Português para a Saúde e Ambiente e pelas sociedades que representam as especialidades com maior volume de prescrição destes medicamentos, nomeadamente a Sociedade Portuguesa de Pneumologia, a Sociedade Portuguesa de Alergologia e Imunologia Clínica, a Sociedade Portuguesa de Pediatria, a Sociedade Portuguesa de Medicina Interna e a Associação Portuguesa de Medicina Geral e Familiar em conjunto com uma associação de doentes, a Associação Respira. Reconhece-se o impacto significativo dos inaladores pressurizados doseáveis nas emissões de gases com efeito de estufa e a necessidade de transição para alternativas mais sustentáveis. Calculou-se a pegada de carbono dos inaladores pressurizados doseáveis e dos inaladores de pó seco em Portugal e estimou-se o nível de literacia dos médicos prescritores relativamente a este tema. Finalmente, foram elaboradas recomendações com o objetivo de acelerar a redução da pegada ecológica dos inaladores.
Palavras-chave: Administração por Inalação; Gases de Efeito Estufa; Inaladores de Dose Calibrada; Inaladores de Pó Seco; Nebulizadores e Vaporizadores; Pegada de Carbono; Portugal

ABSTRACT

This consensus document addresses the reduction of the environmental impact of inhalers in Portugal. It was prepared by the Portuguese Council for Health and the Environment and the societies representing the specialties that account for these drugs' largest volume of prescriptions, namely the Portuguese Society of Pulmonology, the Portuguese Society of Allergology and Clinical Immunology, the Portuguese Society of Pediatrics, the Portuguese Society of Internal Medicine, the Portuguese Association of General and Family Medicine and also a patient association, the Respira Association. The document acknowledges the significant impact of pressurized metered-dose inhalers on greenhouse gas emissions and highlights the need to transition to more sustainable alternatives. The carbon footprint of pressurized metered-dose inhalers and dry powder inhalers in Portugal was calculated, and the level of awareness among prescribing physicians on this topic was also estimated. Finally, recommendations were developed to accelerate the reduction of the ecological footprint of inhalers.
Keywords: Administration, Inhalation; Carbon Footprint; Dry Powder Inhalers; Greenhouse Gases; Metered Dose Inhalers; Nebulizers and Vaporizers; Portugal

INTRODUÇÃO

Em 28 de julho de 2022, a Assembleia Geral das Nações Unidas reconheceu um novo direito humano: o direito a um ambiente limpo, saudável e sustentável.[1] No entanto, as determinantes ambientais da saúde – tais como a superpopulação, as alterações climáticas, a degradação dos ecossistemas, a perda da biodiversidade e o esgotamento dos recursos naturais – têm conhecido um agravamento acelerado que compromete esse direito.[2]

Atualmente, os fatores ambientais já são responsáveis por cerca de 13 milhões de mortes, correspondendo a 20% da mortalidade global.[3] Em todo o mundo, nove em cada dez pessoas respiram ar que contém níveis de poluentes

1. Hospital CUF Tejo. Lisboa. Portugal.
2. Conselho Português para a Saúde e Ambiente. Lisboa. Portugal.
3. Serviço de Pneumologia. Hospital de Vila Franca de Xira Unidade Local de Saúde Estuário do Tejo. Vila Franca de Xira. Portugal.
4. Hospital CUF Descobertas. Lisboa. Portugal.
5. Sociedade Portuguesa de Pneumologia. Lisboa. Portugal.
6. Serviço de Imunoalergologia. Hospital Dona Estefânia. Unidade Local de Saúde São José. Lisboa. Portugal.
7. NOVA Medical School. Universidade NOVA de Lisboa. Lisboa. Portugal.
8. Sociedade Portuguesa de Alergologia e Imunologia Clínica. Lisboa. Portugal.
9. Sociedade Portuguesa de Pediatria. Lisboa. Portugal.
10. Secção Pediátrica da Qualidade e Segurança. Sociedade Portuguesa de Pediatria. Lisboa. Portugal.
11. Serviço de Medicina Interna. Centro Hospitalar Universitário de Santo António. Porto. Portugal.
12. Instituto de Ciência Biomédicas Abel Salazar. Porto. Portugal.
13. Sociedade Portuguesa de Medicina Interna. Lisboa. Portugal.
14. Unidade de Saúde Familiar Reynaldo dos Santos. Unidade Local de Saúde Estuário do Tejo. Vila Franca de Xira. Portugal
15. Associação Portuguesa de Medicina Geral e Familiar. Lisboa. Portugal.
16. Associação Respira. Lisboa. Portugal.
17. Serviço de Pneumologia. Centro Hospitalar Universitário de Coimbra. Unidade Local de Saúde de Coimbra. Coimbra. Portugal.
18. Faculdade de Medicina. Universidade de Coimbra. Coimbra. Portugal.

✉ **Autor correspondente:** Luis Campos. luis.campos@cpsa.pt
Recebido/*Received*: 10/07/2024 - **Aceite/*Accepted*:** 20/08/2024 - **Publicado/*Published*:** 02/09/2024

acima das diretrizes da Organização Mundial da Saúde.[3]

As alterações climáticas e a degradação ambiental estão a provocar uma transição epidemiológica, com o aumento do risco de eventos extremos e inesperados, incluindo a possibilidade de novas pandemias. As doenças respiratórias e alérgicas – como a asma e a doença pulmonar obstrutiva crónica (DPOC) – são das mais afetadas pelo impacto dos fatores ambientais em consequência do aquecimento global, da poluição do ar,[3] de mudanças nos padrões de polinização, de alterações na qualidade do ar interior e de eventos climáticos extremos.[1,4]

De acordo com o relatório da Health Care Without Harm,[5] 4,8% das emissões anuais de gases com efeito de estufa (GEE) em Portugal são geradas pelo sector da saúde (0,35 tCO_2-eq/capita, num total de 3,61 $MtCO_2$-eq), um valor acima da média global de 4,4%.[5] Para captar os gases da atmosfera libertados pelo sector da saúde em Portugal seria necessário plantar mais de 148 milhões de árvores anualmente.

Os inaladores pressurizados doseáveis (pMDI) contribuem para estas emissões porque utilizam GEE, designadamente hidrofluoroalcanos (HFA), como propelentes comprimidos para a geração de aerossóis, que facilitam a inalação e o transporte do fármaco até aos pulmões. Os principais HFA utilizados nos inaladores pMDI são o HFA-134a (tetrafluoroetano) e o HFA-227ea (heptafluoropropano).[6]

No início de 2024, o Conselho Europeu adotou regulamentos que visam a eliminação progressiva dos gases fluorados (HFC) e especificamente dos HFA, devido ao seu alto potencial de aquecimento global.[7] Esses regulamentos terão impacto sobre a produção de inaladores de dose calibrada (IDC), que utilizam uma quantidade significativa de HFC, promovendo alternativas com gases de baixo potencial de aquecimento global. A transição será gradual, com as quotas atuais de HFC para IDC mantidas até 2026, mas eliminando-as até 2030.

Algumas sociedades e outras organizações, a nível internacional, têm elaborado normas para a redução do impacto ambiental dos inaladores, particularmente na redução da prescrição de pMDI.[8-12]

O objetivo deste documento foi consensualizar recomendações para a redução do impacto ambiental dos inaladores em Portugal. Estas recomendações foram desenvolvidas pelo Conselho Português para Saúde e Ambiente e pelas sociedades que representam as especialidades com maior volume de prescrição destes medicamentos, nomeadamente a Sociedade Portuguesa de Pneumologia, a Sociedade Portuguesa de Alergologia e Imunologia Clínica, a Sociedade Portuguesa de Pediatria, a Sociedade Portuguesa de Medicina Interna e a Associação Portuguesa de Medicina Geral e Familiar em conjunto com uma associação de doentes, a Associação Respira. Para obter uma compreensão mais aprofundada da situação atual em Portugal, foi também calculada a pegada de carbono da terapêutica inalatória associada aos dois tipos de dispositivos mais utilizados: os pMDI e os inaladores de pó seco (DPI). Foi ainda realizado um inquérito para avaliar o grau de consciencialização dos prescritores sobre o impacto ambiental dos inaladores.

MÉTODOS

A metodologia para o cálculo da pegada carbónica em Portugal teve por base uma revisão inicial da literatura publicada até novembro de 2023, da qual se releva a escassez de artigos focados em Portugal. O cálculo da pegada de carbono da terapêutica inalatória em Portugal baseou-se no artigo de Alzaabi *et al*,[13] que quantifica a pegada de carbono dos inaladores em diferentes países. As emissões de carbono são estimadas através da métrica CO_2-eq, que tem em conta os ingredientes ativos, a classe de inalador e o tipo de dispositivo. Em conformidade com o mesmo artigo, as emissões anuais de GEE foram expressas em CO_2-eq, considerando o ciclo de vida completo de cada inalador. Estas emissões foram quantificadas de acordo com o SimaPro *Life Cycle Assessment software*; bases de dados Ecoinvent; a informação disponível em artigos científicos[14-19]; e o potencial de aquecimento global dos HFC. Considerou-se um período de 100 anos, com base no *Intergovernmental Panel on Climate Change Fifth Assessment Report*.

Para melhor compreensão da quota de mercado de cada tipo de dispositivo de terapêutica inalatória, foram igualmente tidos em consideração os dados de vendas da IQVIA entre os anos 2018 e 2022.

De seguida, foi calculado o impacto ambiental de cada dispositivo comercializado em território nacional para estimar a pegada de carbono referente à terapêutica com recurso a pMDI e DPI. Foi possível identificar a pegada de 14 dispositivos pMDI e de 38 dispositivos DPI que representam, respetivamente, 84% e 91% das vendas unitárias totais de cada tipo de inalador.

A pegada de cada tipo de inalador (pMDI e DPI) foi depois extrapolada linearmente para o total de vendas. Atribuiu-se um valor médio aos inaladores cujos dados relativos à pegada ecológica não estavam disponíveis.

Uma vez que Portugal não produz inaladores, a fase inicial do ciclo de vida destes dispositivos não foi considerada, focando os cálculos apenas nas fases de utilização, reciclagem e eliminação dos resíduos. O peso de cada uma das fases para a pegada foi baseado na literatura científica existente.

Depois da revisão da literatura e da atribuição de valor à pegada carbónica referente à utilização de dispositivos de

terapêutica inalatória pMDI e DPI, foram realizadas duas sessões presenciais de trabalho com todos os membros envolvidos no projeto, de forma a definir e priorizar as recomendações tendo em vista a aceleração da mudança pretendida.

A definição e priorização das recomendações teve em consideração as experiências publicadas de outros países. Destas, a que melhor descreve as ações implementadas e os respetivos resultados obtidos foi a do National Health Service, do Reino Unido.

Em 2021, as NICE *Guidelines NG80* foram atualizadas com a introdução do *Decision Aid*,[20] documento simplificado para auxiliar os doentes que necessitam de terapêutica inalatória a escolher o inalador mais adequado e com o menor impacto ambiental possível. Em outubro de 2021, foi elaborado um guia para facilitar a escolha, pelos profissionais de saúde,[21] da terapêutica inalatória a prescrever, priorizando a otimização dos cuidados para a asma e a DPOC, e contribuindo para a redução da pegada carbónica. Também em outubro de 2021, o grupo de trabalho sobre inaladores do NHS England and NHS Improvement (NHSEI) criou um boletim que permite aos utilizadores comparar o impacto de qualquer mudança de inalador, tanto a nível da pegada de carbono como a nível dos custos quer para o utilizador quer para o sistema de saúde.[22]

Apesar de não ser possível identificar o impacto isolado de cada uma destas iniciativas, o lançamento, em janeiro de 2022, de uma plataforma *online* que permite o livre acesso aos dados da pegada de carbono da terapêutica inalatória no país veio facilitar a análise da evolução da prescrição de inaladores com base numa série de comparadores pré-definidos.[23]

Entre as diferentes métricas disponíveis nesta plataforma, é relevante destacar que no período entre janeiro 2022 e dezembro de 2023 a percentagem de prescrição de inaladores dosimetrados de aerossol agonistas beta-2 de curta duração (SABA MDI) com menor pegada de carbono como percentagem do total de prescrições de inaladores SABA MDI subiu de 8,7% para 43,4%, ou seja, a utilização de inaladores SABA MDI com menor pegada passou a ser quase cinco vezes mais elevada em apenas dois anos. No mesmo período, a prescrição de inaladores de manutenção com elevada pegada ecológica desceu dos ~56% para os ~53%.

Estes resultados demonstram a potencial dificuldade e demora destas alterações até produzirem efeitos práticos, o que reforça a relevância e urgência da implementação das recomendações descritas neste documento em Portugal.

Para avaliação das recomendações por impacto e facilidade de execução, foram realizadas duas rondas Delphi após a primeira sessão de trabalho, que envolveram representantes do Conselho Português para a Saúde Ambiente e de cada uma das sociedades signatárias deste documento de consenso.

Com base nesses resultados, foram identificadas e acordadas as recomendações mais relevantes, e reformuladas a sua descrição e nomenclatura, por forma a serem usadas como recomendações de sustentabilidade ambiental em saúde.

Foi ainda avaliado o grau de conhecimento do impacto ambiental dos inaladores entre uma amostra de médicos prescritores através de um inquérito *online*, anonimizado, realizado entre os dias 24 de maio e 23 de junho. O inquérito foi divulgado pelas sociedades subscritoras, tendo sido obtido um total de 348 respostas. A amostra do estudo foi composta maioritariamente por participantes do sexo feminino (65%). No que respeita às especialidades médicas, 38% dos participantes eram de Pneumologia, 22% de Medicina Interna, 20% de Medicina Geral e Familiar, 15% de Imunoalergologia e 6% pertenciam a outras especialidades. Relativamente à faixa etária dos participantes, 20% tinham menos de 24 anos, 43% estavam entre os 35 e 49 anos, 19% tinham entre 50 e 64 anos, e os 18% restantes tinham 65 anos ou mais.

RESULTADOS

De acordo com os dados de vendas da IQVIA analisados (Fig. 1), em 2022 foram vendidos em Portugal 1 692 633 dispositivos pMDI e 2 408 761 dispositivos DPI. Verificou-se também que, apesar de haver um maior volume de vendas de DPI, as vendas e a quota de mercado de pMDI têm vindo a aumentar ao longo dos anos. Os pMDI prevalecem na terapêutica de alívio, enquanto os DPI são mais utilizados na terapêutica de manutenção. Esta última, por ser a mais utilizada, foi analisada com maior detalhe.

Desta forma, constatou-se que, no período entre 2018 e 2022, o impacto ambiental da terapêutica de manutenção aumentou 16% por ano, o que corresponde a um aumento de 7990 tCO_2-eq em 2018 para 14 344 tCO_2-eq em 2022. Verifica-se que, para este tipo de terapêutica, embora haja uma maior venda de dispositivos DPI, os dispositivos pMDI têm vindo a ganhar importância no mercado (taxa de crescimento anual composta de 12,9%, comparativamente a apenas 2,7% nos DPI). Com o aumento do volume de vendas dos inaladores pMDI, aumenta também o seu impacto ambiental. Considerando o mesmo período, denota-se um crescimento das emissões de carbono totais (pMDI + DPI) de 8,1%, motivado principalmente pelo aumento das emissões relativas aos dispositivos pMDI (8,3%), enfatizando o seu contributo para a pegada carbónica total da terapêutica inalatória.

Os cálculos revelaram que os inaladores pMDI são responsáveis por aproximadamente 95% da pegada de

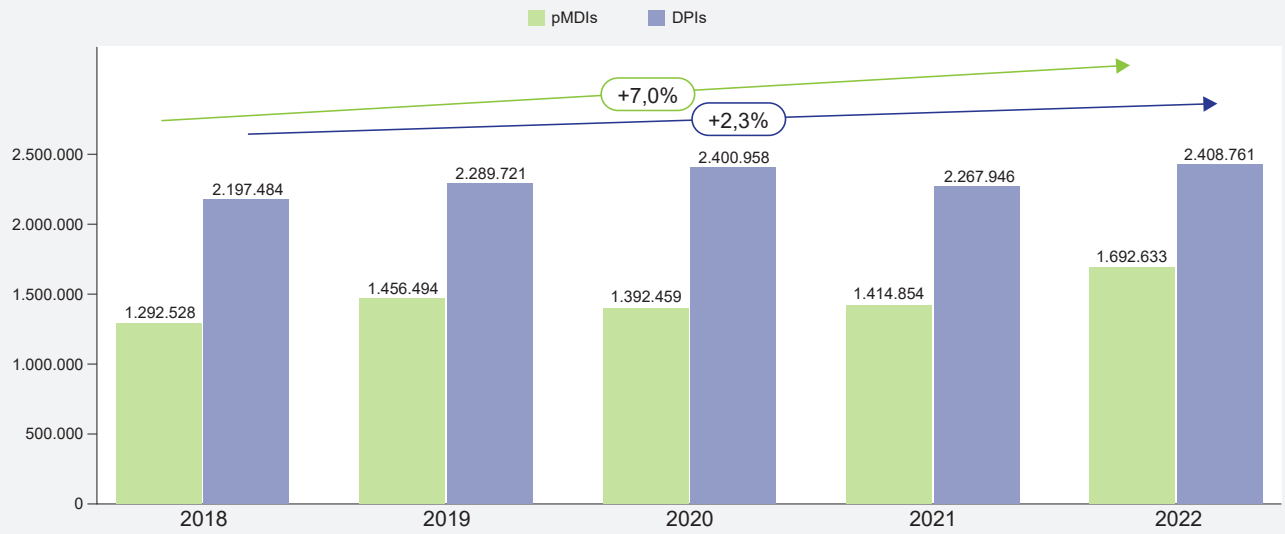

Figura 1 – Volume de vendas pMDI *versus* DPI – dados IQVIA *Sell-in*, vendas em unidades, 2018 - 2022, Portugal

carbono da terapêutica inalatória em Portugal no ano de 2022, emitindo 30 665,6 tCO2-eq, sendo os DPI responsáveis pela emissão de apenas 1594,6 tCO_2-eq.

Focando exclusivamente os inaladores pMDI, dada a sua maior pegada de carbono e disponibilidade de dados, foram realizados dois ajustes ao valor calculado.

Em primeiro lugar, o valor obtido foi calculado tendo em conta 84% das unidades pMDI vendidas em Portugal. Assim sendo, assumiu-se uma pegada média equivalente e linear para os restantes 16% de unidades vendidas, resultando numa estimativa total de 35 572 tCO2-eq para a pegada de carbono total dos pMDI.

No sentido inverso, e considerando que a análise foi feita com base no cálculo da pegada de carbono durante todo o ciclo de vida dos inaladores, ajustaram-se os resultados anteriores para os inaladores pMDI, considerando apenas as fases de utilização, reciclagem e eliminação dos resíduos, cuja representatividade é superior a 85% do total do ciclo de vida dos pMDI.[24] Assim, a estimativa para os valores da pegada dos inaladores pMDI em Portugal reduz-se a 30 236 tCO2-eq. Para compensar estas emissões, seria necessário plantar mais de 1,3 milhões de árvores anualmente.

Para poder aferir o impacto dos inaladores no sector da saúde e a urgência que existe em priorizar ações na redução da sua pegada, comparou-se o peso ambiental e o peso financeiro no total do sector da saúde. Tendo como referência o valor das emissões de carbono totais para o sector da saúde de 3,61 $MtCO_2$-eq,[5] verifica-se que os inaladores pMDI representam 0,84% dessas emissões. Como ponto de comparação, o peso económico dos inaladores pMDI (tendo em conta a despesa com as vendas destes inaladores sobre o total da despesa do sistema de saúde), é de 0,098%,[11,24] ou seja, o seu impacto ambiental é quase nove vezes superior ao seu impacto económico.

O questionário dirigido aos médicos prescritores permitiu estimar o seu grau de conhecimento sobre a pegada ecológica dos inaladores (Fig. 2). Como se pode verificar, apenas 52,3% dos médicos prescritores admitiu ter conhecimento sobre este assunto. Este défice é mais acentuado entre os 25 e os 34 anos, faixa etária onde apenas 42,9% dos médicos admitem ter conhecimento. É também relevante destacar que 15% dos inquiridos identificou erradamente os inaladores DPI como sendo os mais poluentes e mais de 70% não tem em consideração aspetos ambientais na hora de prescrever inaladores.

Perante esta evidência sobre o impacto ambiental dos inaladores, especialmente dos pMDI, e dado o nível de desconhecimento dos médicos prescritores, formulou-se uma série de recomendações a serem implementadas. Estas foram projetadas para envolver todos os intervenientes com impacto direto ou indireto na redução da pegada ecológica dos tratamentos respiratórios, desde profissionais de saúde até decisores políticos, visando a sua implementação conjunta e transversal com o objetivo de alcançar uma prática médica mais sustentável e eficiente.

Recomendações para a redução do impacto ambiental dos inaladores

Estas recomendações têm como objetivo ajudar os diferentes intervenientes a adotar e implementar práticas com impacto imediato ou a médio prazo na redução da pegada

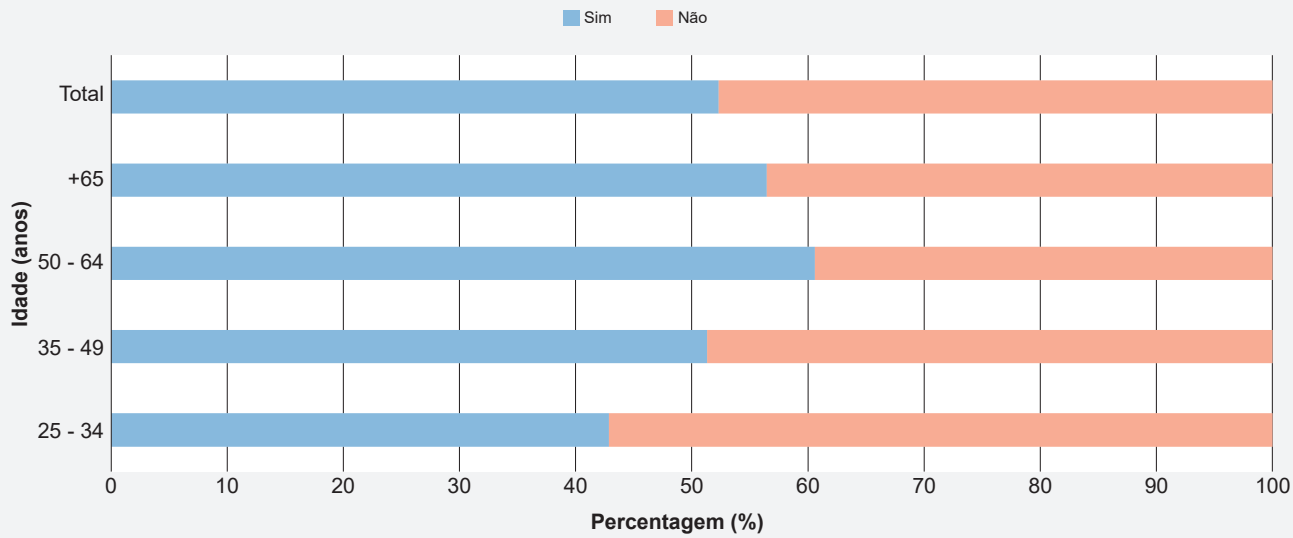

Figura 2 – Nível de conhecimento sobre a pegada ecológica dos inaladores, por parte dos médicos prescritores (por idades)

ambiental associada aos inaladores em Portugal:

1. Na prescrição de inaladores, sempre que haja uma alternativa terapêutica, em termos de efetividade e segurança, os DPI, devem ser preferidos aos pMDI. Quando os pMDI são necessários, devem-se escolher inaladores com menor volume de HFA (Tabela 1)[6,24];
2. Deve ser introduzido um mecanismo de alerta sobre a pegada ecológica de cada inalador nas plataformas de prescrição, com base num sistema de cores;
3. Devem ser implementadas estratégias para incentivar a devolução dos dispositivos usados nas farmácias e para otimizar o reaproveitamento destes dispositivos;
4. Devem ser definidos indicadores para monitorizar o impacto da implementação de medidas para a redução da pegada ecológica dos inaladores, e os respetivos resultados devem ser inseridos no Observatório Português da Saúde e Ambiente;
5. Os temas da sustentabilidade ambiental e da pegada ambiental do sector da saúde devem ser introduzidos nas reuniões científicas das associações e sociedades com responsabilidade na produção, prescrição, utilização e eliminação de inaladores;
6. Deve ser produzida uma declaração dirigida aos decisores políticos para que a sustentabilidade ambiental em saúde seja uma prioridade política e um critério em todas as decisões a todos os níveis no sector da saúde;
7. Devem ser introduzidos critérios de emissões líquidas de GEE tendencialmente nulas nas compras, contratações e adjudicações públicas;
8. Deve ser introduzido o tema das determinantes ambientais e o seu impacto na saúde na formação pré e pós-graduada de todas as profissões da área da saúde;
9. Devem ser divulgadas iniciativas e exemplos de boas práticas de sustentabilidade ambiental na saúde a nível nacional e internacional;
10. Deve ser incrementada a literacia ecológica dos doentes e público em geral, envolvendo e integrando as associações de doentes no processo.

Estas recomendações serão apresentadas e discutidas detalhadamente com os demais intervenientes, por forma a assegurar o seu entendimento e aprovação, e assim garantir a sua implementação de forma eficiente.

Além disso, as tabelas produzidas pelo NHS em Inglaterra com a identificação da pegada por inalador [21] foram adaptadas para produzir a Tabela 1, para que os prescritores tenham maior facilidade em identificar a pegada carbónica dos diferentes inaladores, conforme consta na recomendação 1 e como um primeiro passo para a recomendação 2.

DISCUSSÃO

Existem inúmeras combinações de fármaco/dispositivo no mercado em Portugal, o que permite que os diferentes perfis de doentes possam ter acesso ao fármaco correto, no inalador mais apropriado. Em termos clínicos, parecem não existir diferenças significativas na efetividade de uso de pMDI ou DPI,[24-26] desde que os dispositivos sejam utilizados corretamente e que a técnica de inalação seja adequada. Logo, a substituição de alguns pMDI por DPI constituiria uma redução de GEE com benefício ambiental relevante. Assim sendo, deve considerar-se esta transição

Tabela 1 – Nível da pegada ambiental dos diferentes tipos de inaladores em Portugal

Nome	Tipo de inalador	Tipo de terapêutica	Nível de pegada
AIRFLUSAL FORSPIRO	DPI	Manutenção	
ANORO ELLIPTA	DPI	Manutenção	
ASMANEX TWISTHALER	DPI	Manutenção	
ASMATIL	DPI	Manutenção	
ASMO-LAVI	DPI	Manutenção	
ASSIEME TURBOHALER	DPI	Manutenção	
ATROVENT	MDI	Alívio	
BECLOTAIDE	MDI	Manutenção	
BEVESPI AEROSPHERE	MDI	Manutenção	
BIRESP SPIROMAX	DPI	Manutenção	
BR IPRATROPIO BUP	MDI	Alívio	
BRETARIS GENUAIR	DPI	Manutenção	
BRICANYL	DPI	Alívio	
BRIMICA GENUAIR	DPI	Manutenção	
BRISOMAX	DPI	Manutenção	
BRISOVENT DISKUS	DPI	Manutenção	
BRISOVENT INALADOR	MDI	Manutenção	
BROPAIR SPIROMAX	DPI	Manutenção	
BUFOMIX EASYHALER	DPI	Manutenção	
DUAKLIR GENUAIR	DPI	Manutenção	
DUORESP SPIROMAX	DPI	Manutenção	
EKLIRA GENUAIR	DPI	Manutenção	
ELEBRATO ELLIPTA	DPI	Manutenção	
FLIXOTAIDE DISKUS	DPI	Manutenção	
FLIXOTAIDE (AEROSSOL)	MDI	Manutenção	
FLUTIC+SALMET CCL	MDI	Manutenção	
FLUTIC+SALMET GES	DPI	Manutenção	
GIBITER EASYHALER	DPI	Manutenção	
INCRUSE ELLIPTA	DPI	Manutenção	
INHALOK AIRMASTER	DPI	Manutenção	
LAVENTAIR ELLIPTA	DPI	Manutenção	
MAIZAR	DPI	Manutenção	
QVAR	MDI	Manutenção	
RELVAR ELLIPTA	DPI	Manutenção	
REVINTY ELLIPTA	DPI	Manutenção	
SALBUTAM NOVOLIZER	DPI	Alívio	
SALBUTAMOL MG GPO	MDI	Alívio	
SALBUTAMOL MG SDZ	MDI	Alívio	
SALFLUMIX EASYHALE	DPI	Manutenção	
SEEBRI BREEZHALER	DPI	Manutenção	
SEFFALAIR SPIROMAX	DPI	Manutenção	
SERATAIDE DISKUS	DPI	Manutenção	
SERATAIDE INALADOR	MDI	Manutenção	
SERKEP	MDI	Manutenção	
SYMBICORT TURBOHALER	DPI	Manutenção	
SYMBICORT	MDI	Manutenção	
TOVANOR BREEZHALER	DPI	Manutenção	
TRELEGY ELLIPTA	DPI	Manutenção	
ULTIBRO BREEZHALER	DPI	Manutenção	
VENTILAN	MDI	Alívio	
VERASPIR	DPI	Manutenção	
XOTERNA BREEZHAL	DPI	Manutenção	

Verde: nível baixo ou menos que 2 $kgCO_2e$ por inalador; Amarelo: nível alto ou menos de 20 $kgCO_2e$ por inalador; Vermelho: nível muito alto ou mais de 20 $kgCO_2e$ por inalador.

em doentes de baixo risco, com a patologia controlada, sem exacerbações e com suficiente débito inspiratório, tentando adequar o inalador ao doente, tendo sempre em conta o seu consentimento.[27] De notar que o mau controlo da asma e da DPOC pode advir duma técnica inalatória incorreta, pelo que será sempre preferencial a utilização de dispositivos com menor número de passos e menor complexidade de manuseio.

A redução de erros na utilização de qualquer tipo de inalador depende da promoção da literacia, nomeadamente do ensino e treino regular da técnica inalatória.[28] Uma técnica adequada assegura um melhor controlo da doença,[25] contribuindo para a redução da utilização da medicação de alívio e, consequentemente, para a redução das emissões de GEE. A disponibilização de dados sobre a pegada de carbono dos inaladores permitirá que os doentes e os profissionais de saúde tomem decisões informadas sobre o dispositivo a utilizar.

Não temos dados que nos permitam explicar o aumento das vendas de inaladores pMDI em Portugal nos últimos anos, que poderá ter origem no aumento da necessidade de terapêutica de alívio no pós-pandemia. De qualquer forma, a aparente falta de conhecimento sobre o impacto ambiental dos inaladores de quase metade dos médicos inquiridos e, por outro lado, a falta de consideração dos aspetos ambientais na hora de prescrever, terão seguramente contribuído para este aumento. É urgente trabalhar estes eixos para que os médicos possam ter ao seu dispor todos os dados necessários para uma tomada de decisão consciente.

A principal limitação do cálculo da pegada carbónica dos inaladores resulta da falta de detalhe dos dados disponíveis na bibliografia consultada. Este estudo teve em conta a pegada ecológica média de cada inalador, mas apenas foi possível identificar a pegada ecológica para 84% do volume de vendas de pMDI e 91% para DPI. Apesar desta limitação metodológica, a principal mensagem deste artigo – que os inaladores pMDI têm, ao dia de hoje, um peso desproporcionalmente elevado na pegada ecológica do sector da saúde – iria manter-se independentemente do impacto dos inaladores que não foram incluídos nesta contabilização.

Uma limitação adicional foi o facto de o cálculo da pegada de carbono ter sido realizado com base no ciclo de vida completo do inalador, sendo posteriormente ajustado para excluir os valores referentes à fase de produção do dispositivo e do ingrediente ativo. Contudo, é relevante referir que a estimativa da pegada ecológica total do sector da saúde em Portugal[5] incluiu a fase de produção, ainda que esta ocorra fora do território nacional. Tal facto implica uma subestimação do peso dos inaladores na pegada ecológica total do sector da saúde.

O défice de informação que dificultou a realização dos estudos que precederam as recomendações torna evidente a necessidade de quantificar e caracterizar os processos que conduzem a uma tão elevada pegada ecológica do setor da saúde, identificar as melhores práticas para mitigar este impacto e aplicar a ciência da implementação para mudar os comportamentos das pessoas e das organizações.

CONCLUSÃO

Durante este processo, que juntou peritos de diversas áreas, foi consensual que existe um grave problema ambiental global, e que o sector da saúde tem um contributo relevante para o mesmo.

Presentemente, os inaladores pressurizados, por utilizarem gases fluorados, têm uma pegada de carbono maior quando comparados com os inaladores de pó seco. É, por isso, importante sensibilizar os prescritores para a pegada carbónica dos inaladores, reconhecendo que, atualmente, os DPI apresentam um perfil ambiental mais favorável. No entanto, à medida que forem desenvolvidos novos inaladores pressurizados sem gases fluorados, é essencial que estes sejam também incluídos como uma alternativa sustentável.[9]

Para mitigar o impacto ambiental da nossa prática médica, as recomendações de sustentabilidade ambiental em saúde destacadas neste documento devem ser implementadas de forma coordenada por todos os intervenientes em Portugal. Estas representam passos essenciais para alinhar o sector da saúde com as metas globais de sustentabilidade. A sua adoção por todos os intervenientes reduzirá a pegada ecológica e melhorará a qualidade de vida dos doentes e a eficiência dos tratamentos, alinhando assim a prática médica com os imperativos globais de sustentabilidade.

Apesar de os inaladores representarem uma pequena parte do impacto ambiental do sector da saúde, este consenso é uma iniciativa exemplar do que tem de ser feito globalmente pelo Sistema de Saúde em Portugal. Só assim será possível mitigar este impacto ambiental e aumentar a consciencialização dos profissionais de saúde em relação a este desafio.

Os profissionais de saúde têm o dever ético de participar ativamente na luta contra as alterações climáticas e a degradação ambiental, e pela redução da pegada ecológica do sector da saúde, não só como cuidadores, mas também como 'defensores' dos doentes. Algumas sociedades científicas têm vindo a apelar a este envolvimento.[29,30]

AGRADECIMENTOS

Os autores gostariam de agradecer à MOAI Consulting pelo apoio de revisão bibliográfica, consultoria e *medical writing*, e à IQVIA pela disponibilidade para a utilização dos dados de venda para o cálculo da pegada ecológica dos inaladores em Portugal.

CONTRIBUTO DOS AUTORES

LC: Definição da metodologia do projeto, desenho e elaboração do artigo, análise e interpretação dos dados, redação do manuscrito, revisão crítica do conteúdo, aprovação da versão final.

PR, JA, CRC: Desenho e elaboração do artigo, análise e interpretação dos dados, redação do manuscrito, revisão crítica do conteúdo, aprovação da versão final.

PCM: Redação do manuscrito, revisão crítica do conteúdo, aprovação da versão final.

BX, PL, MIMM: Redação do manuscrito, revisão crítica do conteúdo, aprovação da versão final.

PROTEÇÃO DE PESSOAS E ANIMAIS

Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial atualizada em 2013.

CONFIDENCIALIDADE DOS DADOS

Os autores declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação de dados.

CONFLITOS DE INTERESSE

PCM recebeu honorários de consultoria da Bial e da AstraZeneca; recebeu pagamentos ou honorários por palestras, apresentações, gabinetes de oradores, redação de manuscritos ou eventos educativos da Bial, Medinfar, Jaba Recordati e GSK; recebeu apoio para participar em reuniões e/ou viagens da Medinfar e da Bial.

CRC recebeu honorários de consultoria da Boheringer Ingelheim, MSD, GSK e Pfizer.

MIMM recebeu apoio da Associação Portuguesa de Medicina Geral e Familiar (APMGF) para participação em reuniões e/ou deslocações.

PR recebeu pagamentos da Jaba Recordati pelo seu testemunho de perito.

PL recebeu honorários de apresentação e de gabinete de oradores da GSK, AstraZeneca e Bial; participou num conselho consultivo da GSK; é coordenador da organização sem fins lucrativos Núcleo de Estudos de Doenças Respiratórias da Sociedade Portuguesa de Medicina Interna.

Os restantes autores declaram não ter conflitos de interesse relacionados com o presente trabalho.

FONTES DE FINANCIAMENTO

As reuniões de discussão, cujos resultados serviram de

base a este artigo de perspetiva, foram financiadas pela GSK. Contudo, a GSK não teve qualquer influência nas conclusões que surgiram das mesmas nem no conteúdo e escrita deste artigo de perspetiva.

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What is Needed for Parents to Work Together with Primary Care Physicians in Dealing with Childhood Obesity and Overweight?

O que É Necessário para Pais e Médicos dos Cuidados de Saúde Primários Abordarem a Obesidade Infantil e o Excesso de Peso?

Keywords: Child; Family Practice; Health Knowledge, Attitudes, Practice; Overweight; Parents; Pediatric Obesity
Palavras-chave: Conhecimentos, Atitudes e Prática em Saúde; Criança; Excesso de Peso; Medicina Geral e Familiar; Obesidade Pediátrica; Pais

Dear Editor,

Parents' inaccurate perception of their children's weight, on which the study by Rodrigues *et al*[1] was focused, seems to us to be a key determinant of the difficulties experienced by primary care physicians (PCP) in preventing and treating childhood obesity. Parents may underestimate their children's weight, especially if their children are overweight or obese, which is more common in families with a low socioeconomic status.[1,2] Rodrigues *et al*[1] reported that parents' inability to detect obesity in their children increased by around 50% in 2016 - 2017 compared with 2009 - 2010.[1] These results are particularly worrying in a post-pandemic world in which the prevalence of obesity and overweight has increased again, contrary to the downward trend that had been seen since 2008 in Portugal and many other countries.[3]

Parents are the main source of influence on their children. Their perception of their children's weight and their beliefs about health and illness are influenced by cultural and ethnic factors and are often distorted by the media,[1] which adds critical challenges to PCP activity in today's multicultural society.

As some parents do not consider their children's overweight to be a health problem,[2] they do not seek medical advice regarding this issue.[4]

When analyzing the barriers identified by both parents[4] and PCPs[5] to manage childhood obesity (Table 1), they seem to almost mirror each other and to mainly stem from problems in the doctor-parent-child communication.

To prevent and treat childhood obesity, it is necessary to invest in an effective relationship in this triad, respect cultural differences and provide tools to improve parental perception of their children's weight, in order to encourage their children to adopt healthy lifestyle behaviors. Health education in schools and in the community must be maintained, and advertisements promoting healthy eating choices and physical activity in-between children's television programs should be introduced as they positively influence the whole family. It would be important for Primary Health Care to start raising awareness of childhood obesity during antenatal visits and childbirth preparation programs. Additionally, for parents who are overweight or obese themselves, PCPs should address the problem early on and implement measures to address it effectively.

Above all, there is an urgent need to implement patient-centered strategies during visits to the PCP, namely motivational interviewing, in order to adapt the management of childhood overweight and obesity to the stage of health behavior change that the parents are in, as well as to aggregate social, economic, and political efforts to effectively tackle childhood obesity.[1,2]

Table 1 – Barriers identified in the management of childhood obesity in primary care

By parents	• Lack of knowledge and resources of PCPs to treat childhood obesity. • Focus of visits only on the child's weight. • Concern about being blamed by the PCP for their child's weight. • Fear of social services involvement. • Restricted PCP time spent with parents and child. • Limited accessibility for both initial contact and follow-up visits. • Fear of a negative impact of the appointment on the child's mental well-being. • Unhelpful or judgmental advice from PCPs. • Lack of comprehension by the PCPs regarding economic difficulties in buying healthy food.
By primary care physicians	• Lack of appropriate training in management of childhood obesity. • Lack of confidence in their ability to work with parents and motivate them to change family lifestyles. • Lack of scheduling and consultation time. • Fear of triggering psychological problems in the child. • Fear of damaging the doctor-patient relationship. • Discomfort with parents' reactions. • Cultural factors that influence parents' beliefs about health and illness. • Communication problems and language barriers with parents from other cultures. • Inconsistent messages from different sources about lifestyle changes received by parents. • Perceived lack of parental motivation and resistance to change. • Powerlessness and inefficacy of their efforts. • Complex family situations, including low socio-economic status and overweight problems of parents themselves.

PCP: primary care physician

AUTHOR CONTRIBUTIONS

BNS, LASQ: Literature review and writing of the manuscript.

AM, AB: Critical review of the manuscript.

All authors approved the final version to be published.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Beatriz NICOLAU SOARES✉[1], Luís António SOUSA QUEIRÓS[2], Álvaro MENDES[1], Alcina BASTOS[2]

1. Unidade de Saúde Familiar 3 Rios. Unidade Local de Saúde Tâmega e Sousa. Penafiel. Portugal.
2. Unidade de Saúde Familiar Hygeia. Unidade Local de Saúde Tâmega e Sousa. Penafiel. Portugal.

✉ **Autor correspondente:** Beatriz Nicolau Soares. beatriznicolau.med@gmail.com

Recebido/*Received*: 10/04/2024 - **Aceite/*Accepted*:** 06/04/2024 - **Publicado/*Published*:** 02/09/2024

https://doi.org/10.20344/amp.21656

Endobronchial Obstruction by an Inflammatory Myofibroblastic Tumor

Obstrução Endobrônquica por um Tumor Miofibroblástico Inflamatório

Keywords: Airway Obstruction; Bronchial Neoplasms; Bronchoscopy; Myofibroblasts
Palavras-chave: Broncoscopia; Miofibroblastos; Neoplasias Brônquicas; Obstrução das Vias Aéreas

Dear Editor,

Inflammatory myofibroblastic tumors (IMT) are rare benign neoplasms comprised of myofibroblasts associated with a polymorphic inflammatory stromal infiltrate[1]; they may occur in different organs/structures[2] and mostly affect young individuals, up to forty years old.[3]

We present a case of a 26-year-old woman who attended the emergency department with a two-day history of fever and a dry cough; she also noted mild fatigue with approximately three weeks duration. At presentation she was tachypneic and hypoxemic; pulmonary auscultation showed decreased lung sounds in the lower left hemithorax. A chest radiograph documented lower left lobe atelectasis. Her condition deteriorated rapidly during the next 24 hours, with development of severe respiratory failure; a second chest radiograph now showed total left lung atelectasis. Computerized tomography (CT) (Fig. 1A) confirmed the atelectasis,

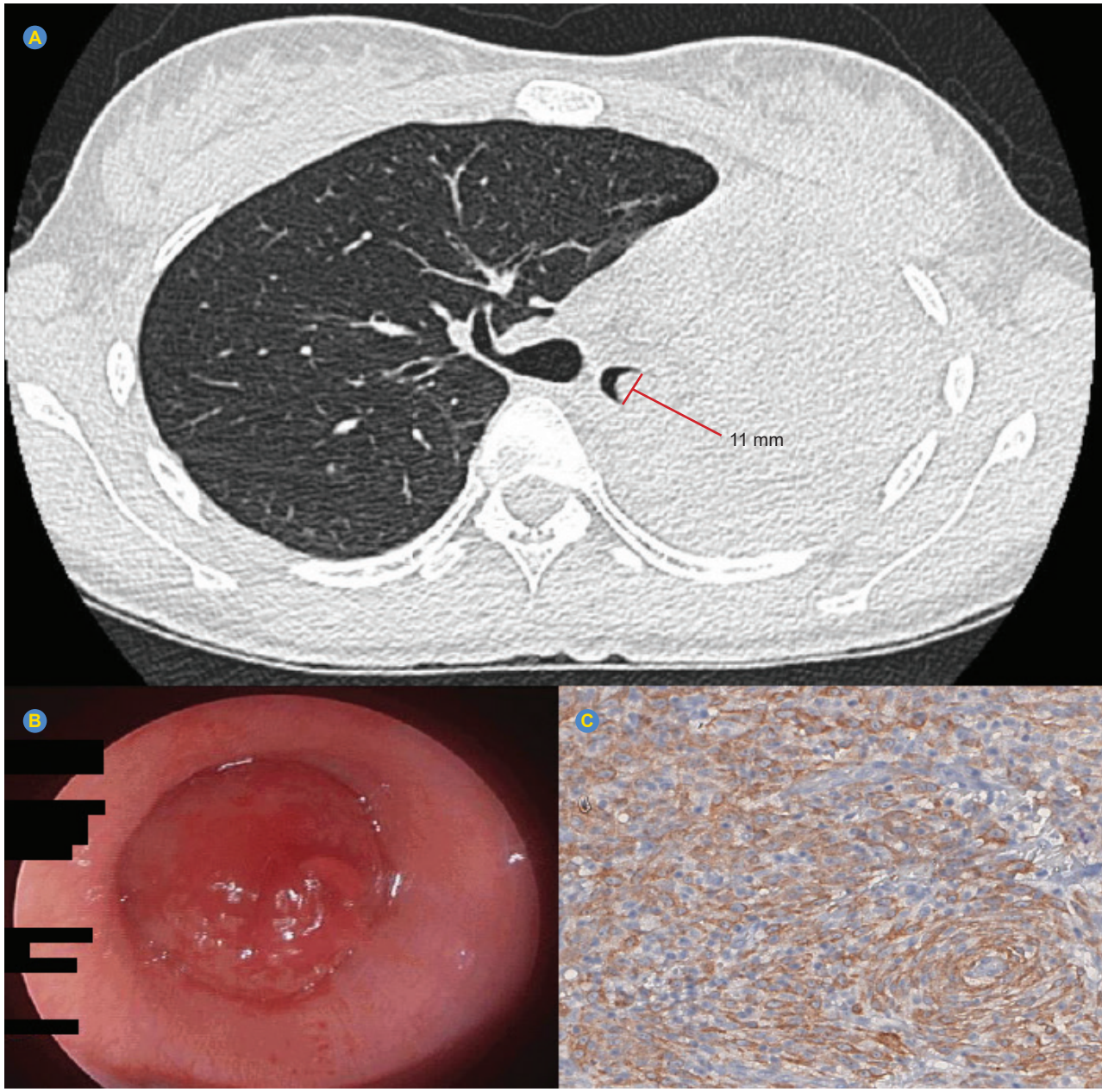

Figure 1 – Computerized tomography with total left lung atelectasis, showing endoluminal lesion (A); Endobronchial image obtained via rigid bronchoscopy, showing an obstructive, highly vascularized lesion in the left main bronchus (B); Immunohistochemical exam, with positive staining for cytoplasmatic ALK expression (C).

and an expansive lesion in the left main bronchus (LMB) was noted. Rigid bronchoscopy was performed, showing a highly vascularized, smooth tumor, causing total occlusion of the LMB (Fig. 1B). Laser photocoagulation and mechanical debulking were performed; there was severe bleeding, which was controlled with cold saline, topical adrenaline, and tranexamic acid. The tumor was totally removed, and the complete patency of the left bronchial tree was documented. Respiratory failure was completely resolved after the procedure. The patient is currently doing well and is being followed with regular bronchoscopies and CT scans. A positron emission tomography has also been performed which excluded the presence of any tumor with metabolic activity.

Microscopically, the tumor was composed of spindle to epithelioid myofibroblasts arranged in fascicular and storiform patterns, accompanied by inflammatory infiltrate composed of lymphocytes, plasmacytes, eosinophils and neutrophils. Necrosis was absent and mitotic activity was evaluated as low-to-moderate, with five mitoses in 10 high power fields. Immunohistochemical study demonstrated cytoplasmic expression of anaplastic lymphoma kinase (ALK) (Fig. 1C) and no immunoexpression for desmin and CK8/18. The histopathologic characteristics favored the diagnosis of IMT.

Inflammatory myofibroblastic tumors rarely manifest in the lung or bronchus (0% - 12%)[3] and are a rare cause of lung tumors (0.04% - 1%), which reinforces the rarity of this case. Although they are benign, they may have an aggressive course, with a risk of local progression, relapse (up to 37%)[3] and metastasis (up to 11%),[3] highlighting the importance of being aware of this entity and considering it in the differential diagnosis of rapidly growing endobronchial tumors. In this case, due to rapid patient deterioration, emergent treatment was required. Although surgical excision is considered the best treatment,[3,4] bronchoscopic intervention has been used, with comparable success to surgery and the benefit of being more readily available. In cases of relapsing or metastatic disease, which is more likely if the resection is incomplete, the role of medical treatment remains understudied.[4,5] It has been shown that overexpression of ALK (which is present in up to 60% of IMT[4]) may be a therapeutic target, with the possibility of treatment with crizotinib or ceritinib.[3] Current evidence suggests that, in patients with advanced disease who are not surgical candidates, crizotinib may be an interesting option, with response rates of up to 50% in ALK-positive patients, which favors considering its use in this subset of patients as standard treatment; further studies should be undertaken to better understand the role of ALK inhibitors, both as a complement and as an alternative to local excision.

AUTHOR CONTRIBUTIONS

BSS, MLS: Data collection, writing of the manuscript.
HNB: Critical review of the manuscript.
All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Bruno S. SILVA✉[1,2], Maria Luísa SACRAMENTO[3], Hélder NOVAIS E BASTOS[4,5,6]
1. Pulmonology Department. Unidade Local de Saúde de Santo António. Porto. Portugal.
2. Instituto de Ciências Biomédicas Salazar. Universidade do Porto. Porto. Portugal.
3. Pathology Department. Unidade Local de Saúde de São João. Porto. Portugal.
4. Pulmonology Department. Unidade Local de Saúde de São João. Porto. Portugal.
5. Faculdade de Medicina. Universidade do Porto. Porto. Portugal.
6. Instituto de Biologia Molecular e Celular. Instituto de Investigação e Inovação em Saúde (IBMC/i3S). Universidade do Porto. Porto. Portugal.
✉ **Autor correspondente:** Bruno S. Silva. brunosilva.pneumologia@chporto.min-saude.pt
Recebido/*Received*: 13/04/2024 - **Aceite/*Accepted*:** 12/06/2024 - **Publicado *Online*/*Published Online*:** 24/07/2024 - **Publicado/*Published*:** 02/09/2024

https://doi.org/10.20344/amp.21664

Anesthetic Management of Labor in a Woman with Hereditary Angioedema

Gestão Anestésica de uma Mulher Grávida com Angioedema Hereditário

Keywords: Analgesia, Obstetrical; Anesthesia, Obstetrical; Angioedemas, Hereditary
Palavras-chave: Analgesia Obstétrica; Anestesia Obstétrica; Angioedemas Hereditários

Hereditary angioedema (HAE) is a rare genetic disorder marked by recurrent swelling episodes in the skin and mucous membranes due to C1 inhibitor (C1-INH) deficiency or malfunction, leading to bradykinin overproduction.[1,2] This condition poses significant challenges during pregnancy,[2] and requires proper anesthetic management during labor.

We describe a case of a 30-year-old primigravida with HAE and normal C1-INH levels who experienced recurrent angioedema episodes since a young age, occasionally affecting the glottis, and which responded to frozen fresh plasma. Multidisciplinary collaboration was essential, requiring delivery at a facility with plasma-derived human C1-INH concentrate (PdhC1INH). During pregnancy, despite having discontinued treatment with danazol, the frequency of angioedema decreased, with only mild episodes in the third trimester.

At 38 weeks and four days, she underwent induction of labor, receiving short-term prophylaxis with PdhC1INH infusion one hour before the epidural catheter placement. An experienced anesthesiologist used ultrasound to locate the cricothyroid membrane. A vacuum-assisted delivery was performed, resulting in a healthy newborn. The patient was monitored in the high-dependency unit (HDU) for 24 hours and discharged after two uneventful days.

This case illustrates the successful management of HAE during labor and postpartum. HAE, affecting approximately 1 in 50 000 individuals worldwide,[1] involves recurrent edema formation in various body sites. Types 1 and 2 involve C1-INH deficiency or dysfunction, respectively, while normal C1-INH levels characterize type 3, posing challenges during pregnancy due to estrogen susceptibility.[3]

Plasma-derived human C1-INH concentrate is preferred for acute treatment and short or long-term prophylaxis during pregnancy and labor.[1] According to the literature, routine prophylaxis before uncomplicated vaginal deliveries is not recommended, but otherwise advised before forceps or vacuum extraction, or cesarean delivery.[1,4] The multidisciplinary team decided to administer PdhC1INH since the patient had angioedema crises during the third trimester,[1] no long-term prophylaxis was administered during the pregnancy, and had a known history of multiple laryngeal attacks.[4] Epidural analgesia might avoid airway complications, especially during cesarean delivery.[1] Prompt identification of potential airway compromise is crucial, considering the risk of laryngeal edema, since it may not respond to standard treatments.[4,5] The postpartum period requires close monitoring in the HDU due to potential crises in the first 72 hours, which can be treated with PdhC1INH when necessary.[4]

Effective management of pregnant women with HAE requires a multidisciplinary approach, individualized labor plans, and proactive measures to address potential complications. Prophylactic PdhC1INH and epidural analgesia are pivotal in preventing HAE attacks during labor and delivery, thus ensuring favorable outcomes.

AUTHOR CONTRIBUTIONS

IPR: Study design, data acquisition and analysis.

MMA, LM: Study design, critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Inês P. RODRIGUES✉[1], Maria M. ARMINDO[1], Luísa MARINHO[1]
1. Anesthesiology Department. Hospital Pedro Hispano. Unidade Local de Saúde de Matosinhos. Porto. Portugal.
✉ **Autor correspondente:** Inês Portugal Rodrigues. inesp_rodrigues@hotmail.com
Recebido/*Received*: 25/03/2024 - **Aceite/*Accepted*:** 17/06/2024 - **Publicado/*Published*:** 02/09/2024

https://doi.org/10.20344/amp.21580

Strongyloides stercoralis in Low-Income Immigrants from Portuguese Speaking African Countries in Lisbon, Portugal

Strongyloides stercoralis em Imigrantes de Baixo Rendimento Oriundos de Países Africanos de Língua Oficial Portuguesa em Lisboa, Portugal

Palavras-chave: Africa; Emigrantes e Imigrantes; Estrongiloidíase/diagnóstico; Estrongiloidíase/epidemiologia; Portugal/epidemiology; *Strongyloides stercoralis*
Keywords: Africa; Emigrants and Immigrants; Portugal/epidemiology; *Strongyloides stercoralis*; Strongyloidiasis/diagnosis; Strongyloidiasis/epidemiology

Strongyloides stercoralis is a soil-transmitted helminth (geohelminth) with fecal-oral transmission and autoinfection,[1] and through solid organ transplant,[2] although dogs can act as reservoirs.[3] Prevalence can be high in low-income countries.[1] Infection in susceptible individuals may lead to a superinfection syndrome or disseminated strongyloidiasis with a high mortality rate.[1]

With the aim of estimating the prevalence and characterizing the population and risk factors for strongyloidiasis in a community of low-income immigrants from Portuguese-speaking African countries in Portugal, we conducted a cross-sectional study, with non-random convenience sampling, that included an epidemiological questionnaire applied between April and June of 2022 to adult users of Centro Padre Alves Correia, a non-profit institution that provides immigrants with medical care, food and other support.

Ethical approval was granted by the Instituto de Higiene e Medicina Tropical Ethics Committee (ref. 6.22, 25-04-2022).

A total of 150 people answered the questionnaire and provided stool samples, with a 92.6% response rate. Most participants were female, between 18 and 76 years old (average 42.7), from Guinea-Bissau or São Tomé and Príncipe, 94% lived in an urban environment before settling in Portugal, and 86% had been in Portugal for less than 10 years (47.3% under five years). Direct parasitological diagnosis of intestinal helminths was made with the Willis and Telemann-Lima methods,[4] and *S. stercoralis* larvae culture on Koga Agar were negative. However, in three samples an 18S fragment was amplified by the polymerase chain reaction (PCR) (Fig. 1),[5] with sequence TAGCTTACATTGATTACGTCCCTGCCCTTTGTACACACCGCCCGTCGCTGCCCG (Sanger sequencing), confirmed by a Basic Local Alignment Search Tool (BLAST) search as genus *Strongyloides*. This corresponds to a 2% infection prevalence rate (0.68% - 5.7%, 95% confidence interval). All detected cases, to whom treatment was offered, were present in women aged between 40 and 60, from São Tomé and Príncipe or Guinea-Bissau, who used a shared family bathroom. Among the three cases, one reported sometimes walking barefoot before moving to Portugal, one reported not always washing her hands after using the toilet, and one reported some gastrointestinal symptoms, but none reported any rashes.

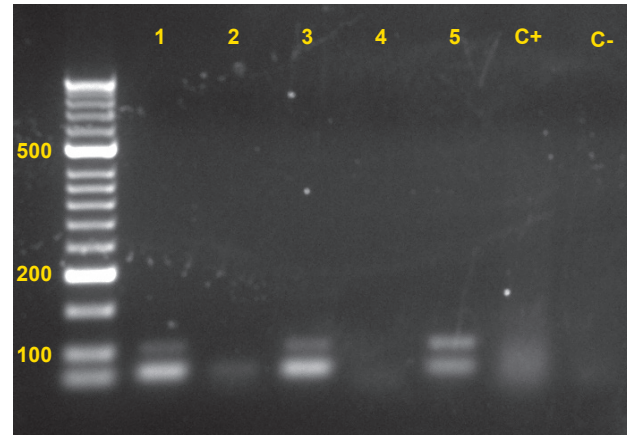

Figure 1 – PCR amplification results of *S. stercoralis* 18S. Agarose (1.5%) gel electrophoresis at 100 V, stained with ethidium bromide. 1 - 5: samples 158, 181, 205, 206 and 244, respectively; C+: *S. stercoralis* positive control; C-: negative control; molecular marker: 50 bp HyperLadder™ (Meridian Bioscience) with band sizes indicated in base pairs (bp).

Although a low *S. stercoralis* prevalence rate was found in this migrant population, it is recommended that further studies, with larger samples, be conducted to evaluate if and what control strategies should be implemented, including further diagnostic tests. Although it has been suggested that the most cost-effective strategy could be to preventatively treat all immunosuppressed immigrants from endemic regions, or even all migrants from endemic regions,[6] there is no evidence from clinical studies so far. We recommend increasing awareness among clinicians of strongyloidiasis in immigrant populations from endemic areas, along with improvements in Ivermectin accessibility for clinical use, recognized as the most effective treatment for this infection.

PREVIOUS AWARDS AND PRESENTATIONS

This study is part of Diamarize Carinton's master's thesis.

AUTHOR CONTRIBUTIONS

All authors contributed equally to this manuscript and approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

IM is a paid section editor for Gene (Elsevier) and the coordinator of the MulhereSTrop network.

All other authors have declared that no competing interests exist.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors, but the authors acknowledge “Fundação para a Ciência e a Tecnologia” for funds to GHTM - UID/04413/2020 and LA-REAL – LA/P/0117/2020.

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Diamarize CARINTON[1], Rosa TEODÓSIO[2], Silvana BELO[3], Isabel L. MAURÍCIO✉[3]

1. Instituto de Higiene e Medicina Tropical (IHMT). Universidade NOVA de Lisboa. Lisboa. Portugal.
2. Unidade de Ensino e Investigação de Clínica Tropical. Global Health and Tropical Medicine (GHTM). Associate Laboratory in Translation and Innovation Towards Global Health (LA-REAL). Instituto de Higiene e Medicina Tropical (IHMT). Universidade NOVA de Lisboa. Lisboa. Portugal.
3. Unidade de Ensino e Investigação de Parasitologia Médica. Global Health and Tropical Medicine (GHTM). Associate Laboratory in Translation and Innovation Towards Global Health (LA-REAL). Instituto de Higiene e Medicina Tropical (IHMT). Universidade NOVA de Lisboa. Lisboa. Portugal.

✉ **Autor correspondente:** Isabel L. Maurício. isabel.mauricio@ihmt.unl.pt

Recebido/*Received*: 07/05/2024 - **Aceite/*Accepted*:** 18/06/2024 - **Publicado/*Published*:** 02/09/2024

https://doi.org/10.20344/amp.21782

Diabetes Tipo 2: (Não Tão) Novas Estratégias

Type 2 Diabetes: (Not So) New Strategies

Palavras-chave: Comportamento Alimentar; Diabetes Mellitus Tipo 2; Dieta; Hábitos Alimentares; Portugal
Keywords: Diabetes Mellitus, Type 2; Diet; Feeding Behavior; Portugal

Caro Editor,

O artigo publicado pela Acta Médica Portuguesa em janeiro de 2024 intitulado "Hábitos Alimentares das Pessoas com Diabetes Mellitus Tipo 2 em Portugal: Um Estudo Transversal"[1] da autoria de Correia Rodriguez *et al*, incide sobre o papel fundamental da alimentação como terapêutica principal da doença, e nos dados preocupantes que resultam do seu incumprimento.[1]

Em 2021, a nível global, estimou-se que 529 milhões de pessoas vivem com diabetes. Dessas, 96% têm diabetes *mellitus* tipo 2 (DM2) associada a fatores de risco tais como índice de massa corporal elevado (52,2%) e a hábitos alimentares de risco (25,7%).[2] Todas as evidências apontam para um aumento da prevalência desta doença, que deve ser encarada como um problema grave e urgente de saúde pública mundial, pelo que o foco dos clínicos deveria centrar primeiramente as intervenções no estilo de vida, nomeadamente na alimentação, com o objetivo principal de perda de peso mesmo que coexista a necessidade de terapêutica farmacológica.

O estudo DiRECT-Aus mostrou que a remissão da doença ocorreu após 12 meses em 56% dos casos,[3] em resultado de um programa de substituição total da dieta durante 13 semanas, seguido de reintrodução alimentar e manutenção de peso.[3] Por outro lado, o estudo *Look AHEAD (Action for Health in Diabetes)* alcançou maior perda de peso no grupo com DM2 aleatorizado para intervenções intensivas no estilo de vida em comparação com o grupo de controlo que recebeu educação para a diabetes (diferença de -7,9% em um ano e -3,9% em quatro anos).[4] Apenas 2% do grupo de controlo alcançou remissão, mas 11,5% e 7,3% dos participantes na intervenção de estilo de vida intensiva alcançaram remissão em um e quatro anos, respetivamente.[4] Durante os primeiros 12 meses de remissão, a massa de células beta funcional máxima retorna completamente ao normal e permanece assim por pelo menos 24 meses, consistente com a recuperação da função secretora de insulina das células beta, que antes se desdiferenciaram devido ao excesso calórico crónico.[5] A probabilidade de alcançar a remissão após 15% de perda de peso foi demonstrada principalmente pela duração da doença, verificando-se mais facilmente na diabetes de curta duração pela melhor função basal da célula beta.[5]

Apesar de diversas normas de orientação clínica existentes indicarem, na sua maioria, a necessidade de uma intervenção no estilo de vida, esta não é efetivamente levada a cabo, o que poderá dever-se à pouca formação na área de nutrição durante o curso de medicina, à escassez de recursos humanos (médicos, enfermeiros, nutricionistas, etc.) e também à própria dificuldade da mudança de hábitos culturais e pessoais. Assim, é urgente a consciencialização da sociedade e dos decisores das consequências desta doença, mas, principalmente, dos benefícios do seu adequado controlo e remissão.

CONFLITOS DE INTERESSE

AM recebeu apoio da Menarini para participar no congresso de 2022 da Sociedade Portuguesa de Medicina Interna – Congresso Nacional de Medicina Interna.

FONTES DE FINANCIAMENTO

Este trabalho não recebeu qualquer tipo de suporte financeiro de nenhuma entidade no domínio público ou privado.

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Ana MORGADO✉[1]
1. Serviço de Medicina Interna. Hospital de Faro. Unidade Local de Saúde do Algarve. Faro. Portugal.
✉ **Autor correspondente:** Ana Morgado. amargarida.marcelo@gmail.com
Recebido/*Received*: 08/03/2024 - **Aceite/*Accepted*:** 24/06/2024 - **Publicado/*Published*:** 02/09/2024

https://doi.org/10.20344/amp.21370

Palliative Care in Portugal: Are we "Choosing Wisely"?

Cuidados Paliativos em Portugal: Estamos a Escolher Criteriosamente?

Keywords: Attitude of Health Personnel; Palliative Care; Portugal
Palavras-chave: Atitude do Pessoal de Saúde; Cuidados Paliativos; Portugal

Dear Editor,

The 'Choosing Wisely' campaign, which originated in April 2012 as an initiative of the American Board of Internal Medicine, has garnered widespread adoption.[1] Over 80 specialty medical colleges and consumer groups have joined, advocating for a paradigm shift in medicine: moving from a foundation of trust and steering away from defensive practices.[1] By promoting informed decision-making, the campaign aims to improve patient care while reducing healthcare spending and potential harm from overuse of medical interventions.[1]

In Portugal, the campaign's influence is evident through the adoption of 200 recommendations by the Portuguese Medical Association, known as "*Escolhas Criteriosas em Saúde*".[2] Within the comprehensive document collating recommendations from 38 medical specialties, the term 'palliative care' (PALC) appears twice, underscoring its importance in healthcare decision-making. Might it be timely to revisit the initiative 'Choosing Wisely' in Portugal, and focus specifically on the role of PALC?

Under the initiative's umbrella, support has been garnered from 30 Portuguese scientific societies and 36 patient associations and other entities,[3] which raised questions about their advocacy efforts and the impact achieved in promoting PALC. For example, the American College of Emergency Physicians, emphasized, as early as in 2013, the importance of early engagement with palliative and hospice care services, highlighting potential benefits for patients' quality and quantity of life.[4]

A decade ago, during the 67th World Health Assembly, resolution 67.19 recognized the moral imperative of integrating PALC into healthcare systems.[5] In Portugal, this recognition materialized in Law No. 52/2012, known as the "Basic Law for Palliative Care", stating citizens' rights to access PALC and establishing the "National Palliative Care Network", operating under the authority of the Ministry of Health.[6] Interestingly, the 'Choosing Wisely' initiative and Law No. 52/2012 of the Portuguese Republic were launched in the same year. Law No. 52/2012 includes provisions that resonate with the ethos of the 'Choosing Wisely' initiative, striving to prevent low-value care and asserting that therapeutic obstinacy amounts to clinical malpractice.

As the projected increase in terminally ill patients underscores the importance of prioritizing people-centered care, the need for informed decision-making in end-of-life care becomes increasingly critical.[7] Ensuring access to quality palliative and end-of-life care is imperative, especially given the projected increase – from 6.3 million in 2017 to 9.7 million in 2050 – in the number of individuals who will require such services.[7]

There are several barriers to PALC in Portugal due to myths and knowledge gaps. This was reported in an online survey with 592 participants (152 healthcare professionals and 440 laypersons) who responded to an anonymous questionnaire focused on PALC goals and purposes.[8] Laypersons revealed several misconceptions: PALC is only for those dying (67.0%), provided only in hospitals (60.2%), and only for cancer patients (32.5%). Additionally, they thought accessing PALC required stopping other treatments (53.4%), and believed referring doctors were giving up on patients (39.3%). They also thought PALC was for those not requiring specialized care (33.2%), equated it with having "nothing left to do" (31.1%), believed it accelerated death (41.8%), and thought PALC professionals promoted euthanasia (26.1%). Healthcare professionals (doctors, nurses, physiotherapists, and occupational therapists) had their own misconceptions: they believed PALC is not for everyone regardless of age (55.9%), thought PALC is for patients with a life expectancy of fewer than six months (47.4%) or in the process of dying (25.0%), and believed it accelerates death (17.1%). Additionally, they believed pain in PALC is normal and inevitable (17.1%), and it is only treated with addictive drugs (55.9%).[8] Raising public awareness and educating both the community and healthcare professionals about PALC should occur alongside the establishment of new PALC services. Prioritizing education and awareness campaigns for PALC is essential for public health.[9]

In light of these aspects, it is pertinent to reassess the 'Choosing Wisely Portugal' initiative's stance on PALC and evaluate its alignment with evolving healthcare needs and priorities.

AUTHOR CONTRIBUTIONS

CR: Literature search, writing of the manuscript.

PRP: Literature search, writing and critical review of the manuscript.

All authors approved the final version to be published.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Cristiana ROLÃO✉[1,2], Paulo REIS-PINA[3,4]
1. Emergency Department. Unidade Local de Saúde Santa Maria. Lisboa. Portugal.
2. General Inpatient Unit. Pulmonology Department. Unidade Local de Saúde Santa Maria. Lisboa. Portugal.
3. Palliative Medicine Center. Faculty of Medicine. Universidade de Lisboa. Lisbon. Portugal.
4. Bento Menni Palliative Care Unit. Casa de Saúde da Idanha. Sintra. Portugal.
✉ **Autor correspondente:** Cristiana Rolão. cristianarolao@gmail.com
Recebido/*Received*: 16/05/2024 - **Aceite/*Accepted*:** 10/07/2024 - **Publicado/*Published*:** 02/09/2024

https://doi.org/10.20344/amp.21838

Recovery como Objetivo Terapêutico na Esquizofrenia: O Dever de Oferecer Mais

Recovery as a Therapeutic Goal in Schizophrenia: The Duty to Offer More

Palavras-chave: Esquizofrenia; Psicologia do Esquizofrénico; Reabilitação Psiquiátrica
Keywords: Psychiatric Rehabilitation; Schizophrenia; Schizophrenic Psychology

Caro Editor,

Percorremos um longo caminho até à compreensão atual da esquizofrenia, paradigma de doença mental grave, como perturbação multidimensional resultado de complexas interações entre fatores biológicos, psicológicos e socioculturais, que determinam a evolução e grau de funcionalidade. O mesmo não pode ser dito relativamente ao tratamento que, na prática clínica, se mantém assente em intervenções maioritariamente farmacológicas que focam o controlo sintomático, não contemplando a heterogeneidade interindividual de funcionalidade, resultando na revalidação da esquizofrenia entre as três patologias neuropsiquiátricas mais impactantes em termos de incapacidade a nível global.[1]

A insatisfação com o tratamento psicofarmacológico, que possibilita a recuperação de funcionalidade em apenas um a cada sete doentes tratados,[2] resultou na redefinição do objetivo terapêutico, para '*recovery',* um conceito mais amplo e complexo que o de remissão, ainda que esta se mantenha como pré-requisito essencial.

Recovery define-se como um constructo multidimensional, que integra, além da dimensão clínica, uma dimensão funcional, pessoal e social, e uma dimensão subjetiva, que designa o processo, trajeto pessoal de se estabelecer como individuo com papel ativo na comunidade, com objetivos e expectativas relativamente ao futuro, e a si próprio.[3] Isso não significa a restituição do funcionamento pré-mórbido, mas a aquisição de novos recursos pessoais que capacitem estes indivíduos para a participação plena na comunidade e nos seus cuidados de saúde, tendo em conta implicações impostas pela condição da doença, que inevitavelmente passa a fazer parte de si.

A conceptualização do *recovery* como meta realista coloca os holofotes sobre a reabilitação psicossocial como forma de intervenção, reinventando-a, e impõe a restruturação da organização dos serviços de saúde mental, para um modelo comunitário, aspeto já integrado nas políticas reformistas de saúde mental em Portugal.[4] Passam a ser contemplados os aspetos habitacionais, ocupacionais, psicoeducacionais e socioculturais, sendo os objetivos terapêuticos obtidos através do sentido de pertença e participação nos contextos comunitários, constituindo eles próprios recursos e oportunidades de integração e autonomização do doente.

Neste processo, o doente participará ativamente definindo expectativas e o momento do tratamento, e os profissionais de saúde assumirão um papel de facilitadores, idealmente partilhado com os familiares tidos como fonte de apoio moral, prático e força motivadora essenciais[5] para a re-significação da vida depois da doença.

Além da necessária restruturação dos serviços e escassez de recursos, a estigmatização[3] e postura dos profissionais envolvidos constituem, talvez, as principais barreiras ao *recovery*. É imprescindível que estes, mais do que o próprio utente, valorizem e maximizem o seu potencial, ao invés de focarem e trabalharem os défices.

A promessa de que "a Saúde do meu Doente será a minha primeira preocupação" e o dever de oferecer o melhor tratamento devem orientar a prática diária. No caso da esquizofrenia, implica abandonar o modelo biomédico e a resignação com o controlo sintomático, e oferecer mais.

CONTRIBUTO DOS AUTORES

MJA: Planeamento e conceção do trabalho, redação e revisão crítica do manuscrito.

PPP: Revisão crítica do manuscrito.

Todas as autoras aprovaram a versão final a ser publicada

CONFLITOS DE INTERESSE

As autoras declaram não ter conflitos de interesse relacionados com o presente trabalho.

FONTES DE FINANCIAMENTO

Este trabalho não recebeu qualquer tipo de suporte financeiro de nenhuma entidade no domínio público ou privado.

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Maria João AMORIM✉[1], Patrícia PERESTRELO PASSOS[1]
1. Departamento de Psiquiatria e Saúde Mental. Unidade Local de Saúde do Alto Minho. Viana do Castelo. Portugal.
✉ **Autor correspondente:** Maria João Amorim. juamorim2005@hotmail.com
Recebido/*Received*: 09/05/2024 - **Aceite/*Accepted*:** 12/07/2024 - **Publicado/*Published*:** 02/09/2024

https://doi.org/10.20344/amp.21804

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