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Special Issue Reprint

Healthy and Safe Environments Across Occupational and Environmental Contexts

Edited by
Carlos Alberto Alves Carvalhais, Joana Carvalho dos Santos
and Cristiana Maria Matos da Costa Pereira

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About the Editors

Carlos Alberto Alves Carvalhais

Carlos Alberto Alves Carvalhais holds a degree in Environmental Health from the School of Health of the Polytechnic Institute of Porto (ESS|P.Porto), a master's degree in Occupational Safety and Hygiene Engineering from the Faculty of Engineering of the University of Porto, and a PhD in Occupational Health and Safety from the University of Porto. He also has postgraduate experience in Radiation Protection and Safety from University College of Dublin and ESS|P.Porto and postgraduate experience in Chemical Toxicology from the Polytechnic University of Catalunia (Spain). After graduating, he developed professional and scientific activity in occupational and environmental health in the Air and Occupational Health Unit of the National Institute of Health Dr. Ricardo Jorge. He also has experience in the area of quality, environment and safety management in the industry. Currently, he is an Assistant Professor at ESS|P.PORTO, teaching in the Environmental Health BSc degree program and in the Safety and Hygiene in Organizations master's degree program. He has also supervised several master's and doctoral research projects in his field. He is an integrated researcher at the RISE - Health Research Network, specifically at the Center for Translational Health and Medical Biotechnology Research (T.BIO), and a collaborator researcher at the HBMEx: Human biomonitoring for Environmental Exposure and Risk Lab from ITR. He has been developing research on topics related to occupational health and safety, indoor environments and OSHE management, of which results have been awarded. He is the author of several publications, articles published in international journals with peer reviews, book chapters, and full articles in international indexed conference proceedings. He also has several communications that have been presented at national and international conferences.

Joana Carvalho dos Santos

Joana Carvalho dos Santos is currently a Professor at the Environmental Health Department of the School of Health, Polytechnic University of Porto (ESS|P. PORTO). She is presently the coordinator of the Bachelor's degree in Environmental Health and the President of the Pedagogical Council of ESS|P.PORTO. She is also a researcher at the Center for Translational Health and Medical Biotechnology Research, ESS | P. PORTO, and at the Biomechanics and Health Unit of the Institute of Science and Innovation in Mechanical and Industrial Engineering (INEGI/LAETA). She received her PhD in Occupational Health and Safety from the Faculty of Engineering, University of Porto (Cum Laude distinction), with a thesis focused on understanding the development of fatigue (including mental fatigue) in real work conditions (assembly work). Her scientific research has been developed in the domains of Ergonomics and Human Factors, Occupational Fatigue, Occupational Health, Safety and Hygiene. Currently, her main interest is the risk management and health outcomes of human–robot collaboration (HRC) workplaces. She has been a principal investigator and team member in several research projects (e.g., WINWORL [Interreg fund]; ActionSAFE [FCT funded], ASA [Contract funded], NeoNoise, PELE project, COBOSHe, among others) and has published papers in international peer-reviewed journals, book chapters, and conference proceedings. Over the years, her research has been awarded, and in 2023 her scientific merit was publicly recognized by the Polytechnic University of Porto through the PAPRE program. She has also supervised and co-supervised several MSc and PhD theses.

Cristiana Maria Matos da Costa Pereira

Cristiana Maria Matos da Costa Pereira is a researcher with expertise in environmental health, microbiology, toxicology, and public health. She graduated in Biology from the University of Porto in 1998 and obtained her PhD in Metabolism—Clinic and Experimentation from the Faculty of Medicine of the University of Porto in 2017, with distinction, with a thesis on oxidative stress and DNA damage as contributors to inflammatory bowel disease. She was an Auxiliary Researcher at the National Institute of Health Dr. Ricardo Jorge (INSA) and currently works at the Environmental Hygiene and Human Biological Monitoring Unit, Department of Health Protection from Laboratoire National de Santé (Luxembourg), and has been an integrated researcher at the Institute of Public Health of the University of Porto (ISPUP) since 2012. Her career includes previous roles in clinical microbiology, quality control, and virology research. Her scientific activity spans a broad range of topics, with a particular focus on indoor air quality and its impact on respiratory health, microbiological risk assessment, the development of self-disinfecting surfaces, and the role of oxidative stress and DNA damage in chronic diseases. She has published more than 30 peer-reviewed articles in specialized journals and contributed as co-author to numerous collaborative studies with national and international partners. She has also supervised master's and doctoral research projects. Cristiana has been actively involved in national and European research projects, including participation in COST Actions and international scientific networks, enhancing the dissemination and impact of her work. She has received several distinctions for her research, notably the Arnaldo Sampaio Award for the best public health investigation in Portugal (2014–2016) and the Young Investigator Award in 2005.

Preface

This Reprint brings together contributions that address the complex interactions between occupational and environmental health, with the shared goal of promoting safe and sustainable living and working conditions. Its scope spans diverse contexts, from industrial settings to community environments, highlighting both traditional hazards and emerging risks that affect human well-being.

The purpose of this Reprint is to provide readers with an integrated view of how scientific evidence can inform practice and policy in order to reduce exposures, prevent disease, and foster resilience. Motivated by the growing convergence of occupational and environmental challenges, the collection underscores the value of cross-disciplinary perspectives, innovative research, and applied solutions.

The Reprint is intended for a broad audience, including researchers, practitioners, and policymakers who are engaged in public health, and environmental and occupational health and safety. It may also serve as a reference for educators and students seeking to understand the evolving landscape of risks and interventions in this field.

By gathering these studies under a unified framework, we hope to contribute to a better understanding of how shared determinants of health can be addressed collectively, and to inspire new collaborations that strengthen the link between evidence and action.

Carlos Alberto Alves Carvalhais, Joana Carvalho dos Santos, and
Cristiana Maria Matos da Costa Pereira
Guest Editors

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Editorial

Healthy and Safe Environments Across Occupational and Environmental Contexts: A Holistic Perspective

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Introduction

According to the World Health Organization (WHO), “good health depends on clean air, a stable climate, and a preserved natural environment, as well as access to adequate water, sanitation, and hygiene. It also requires protection from harmful radiation, unsafe chemical management, and unhealthy working conditions. A healthy environment could prevent nearly a quarter of the global disease burden” [1]. In line with this, environmental health is defined as the science that “addresses all the physical, chemical, and biological factors external to a person, and all the related factors impacting behaviors. It encompasses the assessment and control of those environmental factors that can potentially affect health. It is targeted towards preventing disease and creating health-supportive environments” [2].

Complementing this perspective, occupational health is defined as “an area of work in public health to promote and maintain the highest degree of physical, mental, and social well-being of workers in all occupations” [3]. Achieving safe and healthy workplaces requires sustained interaction between scientific evidence and policymaking. To illustrate this, the International Labour Organization (ILO) and the WHO outline five major categories of occupational risks: biological; physical; ergonomics and work design; psychosocial factors and job-related stress; and chemical hazards [4].

In recent years, however, shifts in the nature of work have generated new risks that impact both physical and mental health, while also deepening health inequalities within and between nations [5]. Although occupational health historically developed as a separate domain from environmental health, growing evidence highlights their convergence. In many cases, hazards in the workplace and in the general environment stem from the same sources, making common approaches to risk control both feasible and effective [6,7]. Indeed, environmental and occupational health hazards—whether biological, chemical, physical (including radiological), biomechanical, or psychosocial—share the potential to cause severe consequences, from injuries and acute toxic exposures to chronic conditions such as cancer, respiratory, and cardiovascular diseases [6,7].

The convergence of these challenges has never been more evident. Climate change, industrial development, and urbanization have intensified exposures that affect not only workers but also entire communities, underscoring the urgency of integrated approaches to environmental and occupational health [8]. This Special Issue, "Healthy and Safe Environments across Occupational and Environmental Contexts", was conceived as a timely response to these challenges—aiming to promote a cross-sectoral dialogue and evidence-based strategies for protecting human health in a wide variety of settings.

This Special Issue is a valuable opportunity to reflect on the overarching theme and to share our perspective as Guest Editors. Our primary intention was to provide a platform for advancing research that bridges the boundaries between occupational safety and environmental health. We encouraged submissions that embraced innovation, explored interconnections across disciplines, and addressed real-world complexities in exposure assessment, risk communication, health promotion, and policy design.

We are pleased to present eight high-quality contributions that illustrate the thematic richness and relevance of this Special Issue.

Several papers deepen our understanding of the subtle, long-term health effects of environmental pollutants. In their umbrella review, Fiore et al. examine the link between air pollution and breast cancer, revealing consistent associations with NO_2 and particulate matter exposures and reinforcing the urgency of integrating cancer prevention strategies into environmental health policy. Similarly, Badanta et al. focus on sustainability in healthcare systems, highlighting hospitals not only as care providers but also as potential sources of environmental degradation. Their review proposes pathways toward greener, more resilient healthcare infrastructure.

Two other studies explore the implications of endocrine-disrupting chemicals (EDCs) on women's health. Moon et al. present a prospective cohort study linking EDC exposure to perinatal depression, while Caporossi et al. provide case–control evidence of associations between phthalates, bisphenol A, and infertility, particularly in relation to endocrine dysfunction and recurrent pregnancy loss. These studies remind us that environmental exposures are intimately connected to reproductive and mental health, and that vulnerable populations—especially women—require targeted protection.

The occupational dimension of this Special Issue is equally compelling. In an industrial context, Carvalhais et al. identify stress vulnerability and perceived occupational noise as significant predictors of burnout, calling for integrated psychosocial and physical risk management approaches. Worker safety in highly specialized environments is addressed by Flori et al., who examine the unique exposure risks in high-field nuclear magnetic resonance spectroscopy laboratories—a less studied but growing concern in scientific and research institutions.

Health promotion is also explored from an organizational and cultural perspective. Garzillo et al. assesses the adherence to healthy lifestyles among young workers in a Mediterranean context and underscores the need for differentiated interventions, particularly addressing nutritional education and gender-sensitive approaches to physical activity, to improve long-term well-being and reduce health risks. Meanwhile, Saccardo et al. presents a retrospective study examining the relationship between air quality and Ear, Nose, and Throat (ENT) emergencies during the COVID-19 pandemic, revealing the persistent impact of environmental factors even amid heightened public health protections.

Altogether, the studies featured in this Special Issue illustrate the diversity of environmental and occupational contexts, the variety of health outcomes they affect, and the range of scientific methodologies being applied to study them. What binds them together is a shared recognition: that ensuring healthy and safe environments requires interdisciplinary collaboration, systems thinking, and a proactive approach to both research and intervention.

Looking forward, we recommend that future research continue to explore synergistic effects across occupational and environmental exposures, particularly in underrepresented populations and emerging sectors. It is also essential to strengthen surveillance systems and harmonize exposure assessment methodologies to enable comparability and to support effective policy implementation. Bridging the gap between scientific evidence and actionable policy must remain a key priority. We hope this Special Issue will serve as a reference and stimulus for both established and early-career researchers committed to advancing health, equity, and sustainability across disciplines.

Conflicts of Interest: The authors declare no conflict of interest.

List of Contributions:

1. Badanta, B.; Porcar Sierra, A.; Fernández, S.T.; Rodríguez Muñoz, F.J.; Pérez-Jiménez, J.M.; Gonzalez-Cano-Caballero, M.; Ruiz-Adame, M.; de-Diego-Cordero, R. Advancing Environmental Sustainability in Healthcare: Review on Perspectives from Health Institutions. *Environments* **2025**, *12*, 9. https://doi.org/10.3390/environments12010009.
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Systematic Review

Air Pollution and Breast Cancer Risk: An Umbrella Review

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Abstract: Breast cancer (BC) is a major global health challenge, responsible for one in four cancer diagnoses and one in six cancer-related deaths worldwide. It is the most frequently diagnosed cancer among women and the primary cause of cancer-related deaths in most countries. Recent studies have suggested a potential link between exposure to ambient air pollutants—such as nitrogen dioxide (NO_2) and particulate matter (PM_{10} and $PM_{2.5}$)—and an increased risk of breast cancer. However, the existing evidence remains inconclusive. This umbrella review, conducted according to PRISMA guidelines, aimed to evaluate the strength and reliability of epidemiological evidence concerning this association. All seven meta-analyses included in this review reported a relative risk greater than 1 for exposure to the three pollutants, though findings varied in terms of heterogeneity and publication bias. Notably, the overall analysis indicates that exposure to both NO_2 and $PM_{2.5}$ may be associated with an increased risk of breast cancer incidence, while the evidence linking $PM_{2.5}$ exposure to breast cancer mortality appears to be weaker. The most vulnerable groups were identified as premenopausal European women exposed to NO_2 and PM_{10}, as well as individuals in developed countries exposed to $PM_{2.5}$. Further research is necessary to examine PM composition and refine exposure assessment methodology. Given the widespread impact of breast cancer as the most common invasive malignancy, incorporating this outcome into environmental health research on air pollution is essential. A clearer understanding of these associations could support more targeted environmental interventions. Importantly, the available evidence suggests that breast cancer prevention can be addressed not only through personal lifestyle changes but also through broad public health policies focused on reducing NO_2, PM_{10} and $PM_{2.5}$ levels.

Keywords: air pollution; female breast cancer; particulate matter; nitrogen dioxide

1. Introduction

Breast cancer (BC) continues to represent a significant public health concern due to its high prevalence, accounting for roughly 11.6% of all cancer diagnoses worldwide [1,2]. The development of BC is influenced by a complex interplay of factors, as there are several types of breast cancer, each with different pathophysiological mechanisms [3,4]. Epidemiological studies have reported various risk factors associated with the development or progression of BC. These include hereditary and genetic factors, such as an individual or family history of BC and/or ovarian cancer, and inherited mutations (i.e., BRCA1, BRCA2, and other BC susceptibility genes). Other important risk factors include early age at menarche, late age at menopause, nulliparity, late age at first birth, obesity, and smoking [5,6], while breastfeeding and physical activity are recognized as protective factors [7–9]. Additionally, the International Agency for Research on Cancer (IARC) has highlighted some environmental and lifestyle-related risk factors, such as alcohol consumption, diethylstilbestrol exposure, hormonal therapies (including combined estrogen–progestin contraceptives and menopausal treatments), and ionizing radiation (X-rays and gamma rays) [10]. Recent studies have increasingly associated environmental pollutants—particularly endocrine-disrupting chemicals (EDCs) like dioxins and phthalates—with early breast development, breastfeeding difficulties, and a heightened risk of breast cancer due to their ability to interfere with the endocrine system and mammary gland development [11–15].

An emerging area of investigation is the potential relationship between ambient air pollution and breast cancer. While current findings vary across studies [16–25], a notable increase in BC cases in U.S. women between 1986 and 2002 has been partly attributed to greater exposure to emissions from traffic and industrial sources [26]. The biological plausibility of a potential connection between air pollution and BC is supported by the International Agency for Research on Cancer (IARC)'s classification of outdoor air pollution as a human carcinogen [27]. Given that approximately 80% of the global urban population is exposed to air pollution levels that exceed the recommended limits set by the World Health Organization (WHO) [28], further exploration of this potential association is crucial. Research has primarily concentrated on three pollutants—nitrogen dioxide (NO_2), and particulate matter (PM_{10} and $PM_{2.5}$)—as potential contributors to BC risk. This work aims to systematically assess the available literature using the umbrella review approach, which synthesizes findings from existing reviews to clarify areas of agreement, identify methodological limitations, and highlight directions for future investigation [29,30].

2. Materials and Methods

2.1. Umbrella Review Methods

Umbrella reviews, as described by Aromataris et al. [29], aggregate and re-analyze findings from existing systematic reviews to identify potential biases, areas of consensus, and gaps in the literature. As noted by Fusar-Poli [30], this approach offers a higher-level synthesis that enhances the interpretation and relevance of evidence, supporting more informed clinical and policy decisions.

The current umbrella review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [31,32], in line with a priori protocol agreed upon by all authors and registered in PROSPERO (CRD42023395494).

2.2. Objective, Inclusion Criteria, and Exclusion Criteria

2.2.1. Review Question

This review seeks to determine whether exposure to air pollution is associated with an increased risk of BC incidence and mortality. Specifically, it examines the potential association between BC risk and exposure to nitrogen dioxide (NO_2) and to particulate matter (PM_{10} and $PM_{2.5}$).

2.2.2. Objective

The primary objective of this review is to assess the quality and reliability of existing evidence pertaining to the associations between exposure to NO_2, PM_{10}, and $PM_{2.5}$ and the risk of BC incidence and mortality.

2.2.3. Inclusion Criteria

Meta-analyses investigating the association between air pollution exposure and BC incidence or mortality in women, based on observational studies, were considered. The inclusion criteria were structured according to the Population, Exposure, Comparator, and Outcome (PECO) framework. The specific PECO criteria used for selecting meta-analyses are detailed below.

Participants:

Women in the general population who are at risk of developing BC.

Exposures and comparator:

Meta-analyses considering the exposure to the three pollutants PM_{10}, $PM_{2.5}$, and NO_2, using various exposure assessment models, and comparing different concentration levels.

Outcomes:

Incidence and mortality risks reported using statistical measures such as the pooled relative risk (RR).

2.2.4. Exclusion Criteria

The following types of studies were excluded: commentary, letters, non-English language studies, studies that did not report relevant BC outcomes, and studies that did not include a meta-analysis.

A study was classified as a meta-analysis if it met the following criteria:

- It clearly detailed the methodology used for systematic review;
- It provided details on the search strategy employed;
- It identified relevant primary studies from at least one database (e.g., PubMed OR Embase);
- It performed a quality appraisal of the include primary studies.

2.3. Search Strategy and Data Extraction

A comprehensive search was conducted in the PubMed (MEDLINE) and Embase databases from inception to December 2024. The search strategy was designed around the key terms "breast cancer" and "air pollutants" and was limited to meta-analyses with a search filter in the title or abstract fields. Table S1 provides the detailed search strategy.

Study selection was independently performed by two authors (CM and CAM), ensuring a rigorous screening process, while data extraction was performed in pairs by all authors (CM and MPo, MPa and MF, LM and SC, EF and CM, and CaM and GT). Extracted data included the following variables: first author, year of publication, study design, total population, number of events, age of the participants, country, confounders, pollutant increase, effect size with the corresponding 95% confidence interval (CI), exposure models, pollutants, exposure time, heterogeneity, and publication bias. We also discuss histological type, TNM stage, hormonal receptors, and menopausal status in the selected studies. To assess the extent of overlap among primary studies listed in each review, a citation matrix was constructed, and the Corrected Covered Area (CCA) was calculated. This metric quantifies the proportion of shared studies across various meta-analyses, providing a standardized measure of redundancy [33]. The formula for the CCA is as follows:

$$CCA = (N - r)/(rc - r)$$

where N represents the total number of citations of primary studies (including repeated citations), r is the count of primary studies, and c is the number of meta-analyses considered. The CCA is then classified as minimal (<5%), moderate (5–10%), or high (>10%), based on the proportion of overlap among studies [33].

2.4. Meta-Analytical Methods Used by the Authors of the Included Studies

To ensure a thorough assessment of the methodologies employed in the meta-analyses included in this umbrella review, we examined several key aspects: stated objectives and research questions, search strategy, eligibility criteria, data extraction process, quality assessment, statistical analysis (effect size measurement, model selection, heterogeneity, and publication bias), sensitivity analysis, registration and protocol adherence, PRISMA reporting, and ethical considerations.

2.5. Quality of Assessment

Two researchers (MP and MF) evaluated the methodological quality of each included meta-analysis using the AMSTAR 2 tool [34]. This 16-item checklist assesses key aspects of meta-analysis, with seven items, marked with an asterisk, designated as critical domains due to their significant impact on overall validity (Table S2). These items may be modified by the authors according to their perspectives on the article under review. In particular, we decided to classify domain 8 (Did the review authors describe the included studies in adequate detail) as 'critical', instead of domain 7 (Did the review authors provide a list of excluded studies and justify the exclusions?) of the original list, considering domain 8 a more appropriate measure of the quality of the studies.

Each criterion was evaluated based on whether it was fully met or only partially met. The overall assessment of methodological quality was determined by considering the extent to which criteria were satisfied. If a review exhibited multiple non-critical weaknesses, confidence in its findings was considered lower, which could result in a reclassification from moderate to low confidence. The confidence ratings are summarized in Table 1 [34].

Table 1. Rating overall confidence in the results of the review [34].

Rating	Description
High	No or one non-critical weakness: the meta-analysis provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.
Moderate	More than one non-critical weakness *: the meta-analysis has more than one weakness but no critical flaws; it may provide an accurate summary of the results of the available studies that were included in the review.
Low	One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest.
Critically low	More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.

* Multiple non-critical weaknesses diminish confidence in the review, and it is appropriate to move the overall appraisal down from moderate to low confidence.

2.6. Evaluation of the Strength of Evidence

The strength of the evidence was initially classified into four categories—strong, moderate, modest, and weak—based primarily on the percentage of meta-analyses reporting positive associations, grouped as follows: strong: ≥75%; moderate: ≥50–75%; modest: ≥25–50%; and weak: <25% [35].

This initial classification was then subject to potential downgrading by 1 level based on 3 additional criteria: number of cases (less or greater than 1000); level of heterogeneity, measured using the I^2 statistic (with thresholds at 40%, 60%, and 80% for increasing heterogeneity); and presence of publication bias, assessed via Egger's test ($p > 0.10$ = low risk; p = 0.05–0.10 = moderate risk; and $p < 0.05$ = high risk) or using the trim-and-fill method. Criteria are summarized in Table 2.

Table 2. Criteria used to evaluate the strength of evidence.

Evidence	Positive Association	Cases	Heterogeneity I^2	Publication Bias
Strong	≥75%	>1000	0–40%	Absent: Egger's test $p > 0.10$ or Negligible difference in case of trim-and-fill
Moderate	≥50–75%	>1000	41–60%	Possible: Egger's test p = 0.05–<0.10
Modest	≥25–<50%	<1000	61–80%	High: Egger's test $p \leq 0.05$
Weak	0–<25%	<1000	81–100%	High: Egger's test $p \leq 0.05$

The strength of the association was based on the pooled relative risks (RRs) from multiple meta-analyses and classified as follows: very strong (RR > 5), strong (RR > 2), moderate (RR > 1.5), modest (RR > 1.2), and weak (RR > 1). In accordance with the American Statistical Association's recommendations, a positive relative risk (RR) with a lower confidence interval limit between 0.70 and 1.00 was considered a potential trend warranting further investigation [36–38].

3. Results

3.1. Search Strategy Outcome

The complete process of article collection, screening, and eligibility assessment is shown in Figure 1. The initial search identified 40 studies. After eliminating duplicates, 34 studies remained and were screened based on their title and abstract. Of these, 15 were excluded for not meeting the inclusion criteria, leaving 19 full-text articles that were considered potentially eligible for inclusion. Of these, eight studies were not meta-analyses, one study was a mapping review, two studies had no inherent topic, and one study had no data stratified for sex. Finally, seven meta-analyses were included in this umbrella review: [39–45]. Excluded articles and the reasons for exclusion are reported in Table S3.

3.2. Quality Assessment and Bias

The seven studies evaluated received scores ranging from 10.5 to 14 based on the number of positive/yes ratings. Specifically, five studies were classified as having "moderate" quality, one as "low" quality, and another as "critically low" quality (Table 3). Additionally, all confounding factors considered within each study were analyzed and systematically categorized (Table S4). Regarding publication bias, Gabet et al., 2021 [39], Guo et al., 2021 [40], and Wei et al., 2021 [43] used a funnel plot, an Egger's test and trim-and-fill analysis to investigate publication bias. Zhang et al., 2019 [41], Praud et al., 2023 [44], and Arif et al., 2024 [45] used a funnel plot and an Egger's test, while Yu et al., 2021 [42] used only a funnel plot.

3.3. Associations Between NO_2, PM_{10}, and $PM_{2.5}$ Exposure and Breast Cancer

Tables 4 and 5 summarize the key characteristics of the seven studies examining the associations between exposure to these three pollutants and breast cancer incidence and mortality, respectively. Table S5 summarizes the primary studies included in each meta-analysis for individual pollutants and outcomes, along with their corresponding CCA index. Tables S6–S8 provide a summary of the increases in pollutant levels, the exposure assessment models used, sensitivity analyses, heterogeneity, and potential publication bias for the meta-analyses included in this umbrella review, categorized by NO_2, $PM_{2.5}$, and PM_{10}, respectively.

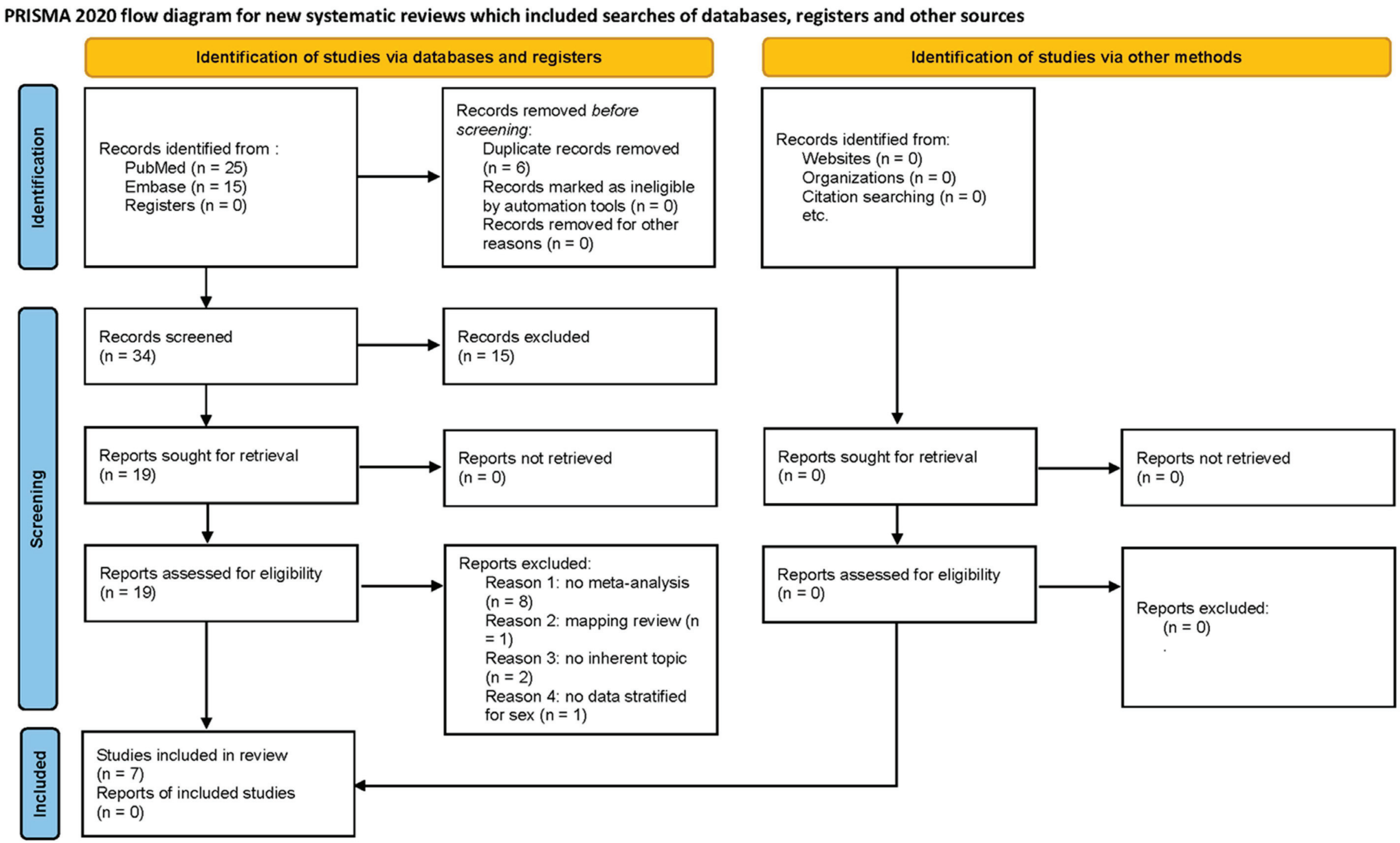

Figure 1. PRISMA flow chart describing the selection of included articles. Adapted by Page et al. 2021 [32].

Table 3. Quality assessment and risk of bias in meta-analysis using AMSTAR 2 [34].

	Gabet et al., 2021 [39]	Guo et al., 2021 [40]	Zhang et al., 2019 [41]	Yu et al., 2021 [42]	Wei et al., 2021 [43]	Praud et al., 2023 [44]	Arif et al., 2024 [45]
1. Did the research questions and inclusion criteria for the review include the components of PICO/PECOS?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. * Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	Yes	Yes	Partial Yes	Yes	Yes	Partial Yes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	No	Yes	Yes	Yes	Yes	Yes
4. * Did the review authors use a comprehensive literature search strategy?	No	Yes	Yes	Yes	Yes	Yes	Yes
5. Did the review authors perform study selection in duplicate?	Yes	No	No	Yes	Yes	Yes	Yes
6. Did the review authors perform data extraction in duplicate?	No	Yes	Yes	Yes	No	No	No
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	No	No	No	No	No	No
8. * Did the review authors describe the included studies in adequate detail?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. * Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	Yes	Yes	Yes	Yes	Yes	No	No
11. * If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. * If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	Yes	Yes	Yes	Yes	Yes	No
13. * Did the review authors account for RoB in primary studies when interpreting/discussing the results of the review?	Yes	Yes	Yes	Yes	Yes	Yes	No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Yes	Yes	No	Yes	Yes	Yes
15. * If they performed quantitative synthesis, did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	No	No	No	No	No	Yes	Yes
Total of yes	13/16 (81.2%)	13/16 (81.2%)	14/16 (87.5%)	14/16 (87.5%)	14/16 (87.5%)	13/16 (81.2%)	10.5/16
Rating overall confidence	Low	Moderate	Moderate	Moderate	Moderate	Moderate	Critically low

The domains considered critical are identified using an asterisk.

Table 4. Associations between NO_2, PM_{10}, and $PM_{2.5}$ exposure and BC incidence.

Pollutant	Author, Year	Design of Included Studies	Total Population	Age (Years)	Country	Effect Size RR (95% CI)	Heterogeneity I^2 *	Publication Bias **
NO_2	Gabet et al., 2021 [39]	6 cohort, 4 case-control	3,914,690	25–75	1 Germany, 2 Sweden, 5 Canada, 2 Denmark, 2 France, 1 Netherlands, 1 UK, 1 Spain, 2 Italy, 1 Norway, 2 USA, 1 Austria	1.03 (1.01–1.05)	24	0.018
	Wei et al., 2021 [43]	11 cohort, 3 case-control	4,002,546	35–85	3 Denmark, 4 USA, 1 Europe, 1 Germany, 1 Israel, 5 Canada	1.02 (1.01–1.04)	46.8	0.024
	Praud et al., 2023 [44]	8 cohort, 5 case-control	128,618	Not reported	3 USA, 5 Canada, 1 Denmark, 2 France, 1 Germany, 1 Europe	1.02 (1.00–1.03)	16.9	0.27
PM_{10}	Zhang et al., 2019 [41]	8 cohort	592,369	25–65+	5 USA, 2 Denmark, 1 Netherlands, 1 UK, 1 Italy, 1 Norway, 1 Germany	1.05 (0.98–1.12)	72.7	Not Reported
	Yu et al., 2021 [42]	4 cohort	2,107,018	0–90	1 Denmark, 1 USA, 1 Germany	1.05 (0.93–1.19)	68	0.030
	Gabet et al., 2021 [39]	1 case-control, 5 cohort	1,326,524	0–90	1 France, 1 Germany, 1 Sweden, 2 Denmark, 1 Netherlands, 1 UK, 1 Italy, 1 Norway, 3 USA, 1 Austria	1.06 (0.99–1.13)	27.6	0.41
	Guo et al., 2021 [40]	1 case-control, 8 cohort	2,552,761	0–90	5 USA, 1 Canada, 2 Denmark, 1 Italy	1.03 (0.98–1.09)	65.1	0.009
	Wei et al., 2021 [43]	7 cohort	2,290,241	0–90	4 USA, 1 Germany, 1 Denmark, 1 Europe	1.04 (0.98–1.10)	70.3	0.06
	Arif et al., 2024 [45]	10	Not reported	Not reported	4 Europe, 4 Americas	1.14 (0.97–1.30)	84.0	0.00
$PM_{2.5}$	Yu et al., 2021 [42]	6 cohort	2,871,705	25–85	1 Denmark, 1 USA, 3 Canada	1.03 (0.93–1.13)	63	0.020
	Wei et al., 2021 [43]	11 cohort	11,755,200	0–90	2 Denmark, 6 USA, 1 Europe (Sweden, Norway, Italy, UK, Netherlands, Austria), 3 Canada	1.03 (0.99–1.06)	8.2	0.00023
	Gabet et al., 2021 [39]	1 case-control, 6 cohort	2,848,486	25–85	1 France, 1 Sweden, 2 Canada, 2 Denmark, 1 Netherlands, 1 UK, 1 Italy, 1 Norway, 3 USA, 1 Austria	1.01 (0.93–1.11)	37.4	0.72
	Guo et al., 2021 [40]	11 cohort, 1 case-control, 1 ecological, 1 cross-sectional	6,643,972	25–85	7 USA, 2 Canada, 2 China, 2 Denmark, 1 Italy, 1 Japan	1.04 (0.98–1.10)	17,4	0,293
	Zhang et al., 2019 [41]	11 cohort, 2 ecological	994,551	25–>65	1 Canada, 6 USA, 1 Sweden, 2 Denmark, 1 Netherlands, 1 UK, 1 Austria, 1 France, 3 Italy, 1 Spain, 1 Germany, 1 China, 1 Puerto Rico, 1 Taiwan, 1 Japan	1.02 (0.93–1.11)	30.6	0.218
	Arif et al., 2024 [45]	14	Not reported	Not reported	4 Europe, 7 Americas	1.05 (0.98–1.12)	55.7	0.00

* I^2 test interpretation: 0–40%: might not be important, 41–60%: may be moderate, 61–80%: may be substantial, 81–100%: may be considerable. ** Egger's test *p*-value: *p*-value < 0.05 indicates the presence of publication bias.

Table 5. Associations between PM_{10} and $PM_{2.5}$ exposure and BC mortality.

Pollutant	Author, Year	Study Design	Total Population (nr)	Cases	Age (Years)	Country	Effect Size RR (95% CI)	Heterogeneity I^2 *	Publication Bias **
$PM_{2.5}$	Yu et al., 2021 [42]	4 cohort	756,393	7895	0–90	3 USA, 1 Hong Kong	1.18 (0.81–1.73)	70	0.02
	Zhang et al., 2019 [41]	5 cohort, 2 ecological	913,779	5439	25–65+	1 Canada, 6 USA, 1 Sweden, 2 Denmark, 1 Netherlands, 1 UK, 1 Austria, 1 France, 3 Italy, 1 Spain, 1 Germany, 1 China, 1 Puerto Rico, 1 Taiwan, 1 Japan	1.17 (1.05–1.30)	73.1	0.122
	Guo et al., 2021 [40]	3 cohort, 1 case-control, 1 ecological, 1 cross-sectional	692,257	51,661	25 to 85	7 USA, 2 Canada, 2 China, 2 Denmark, 1 Italy, 1 Japan	1.20 (0.92–1.48)	52.5	0.12
	Arif et al., 2024 [45]	Not reported	Not reported	Not reported	Not reported	Not reported	1.17 (1.07–1.27)	55.2	0.04
PM_{10}	Zhang et al., 2019 [41]	cohort/case-control	264,064		25–55+	USA	1.11 (1.02–1.21)	0.0	
	Guo et al., 2021 [40]	cohort/case-control	264,064		25–55+	USA	1.07 (0.93–1.20)	56.4	Not NA

* I^2 test interpretation: 0–40%: might not be important, 41–60%: may be moderate, 61–80%: may be substantial, 81–100%: may be considerable. ** Egger's test *p*-value: *p*-value < 0.05 indicates the presence of publication bias.

3.3.1. NO_2 Exposure and BC Incidence

The association between NO_2 exposure and BC incidence is addressed in only three of the seven selected studies: Gabet et al. [39], Wei et al. [43], and Praud et al. [44]. All three studies reported a positive association with relative risks (RRs) of 1.03 (95% CI: 1.01–1.05), 1.02 (95% CI: 1.02–1.04), and 1.015 (95% CI: 1.003–1.028), respectively, per 10 $\mu g/m^3$ NO_2 increase. The meta-analyses included 16 primary studies [46–61] showing a very high level of overlap (CCA = 66%) [33] and heterogeneity ranging from 16% to 46.8%.

Wei et al. [43] conducted four subgroup analyses based on study design, geographical region, menopausal status, and estrogen/progesterone receptor (ER/PR) status. Risk was higher in case-control studies and among Asian populations. No differences in risk were observed based on hormonal receptor status. In other subgroup analyses, risk estimates remained unchanged, while heterogeneity was lower among studies conducted in North America and Europe, as well as in postmenopausal women and receptor-positive and receptor-negative groups. Gabet et al. [39] also conducted multiple subgroup analyses, showing stable association across study design, population characteristics, level of adjustment, and analytical approaches. Variations emerged depending on how exposure was characterized. Risk estimates ranged from 1.01 in studies using residential history for exposure assessment to 1.06 in studies involving participants recruited from 2000 onward and were higher in premenopausal women (1.04, 95% CI 0.94–1.16). Regarding hormone receptor status, the relative risk (RR) was 1.045 (0.980–1.114) for estrogen-receptor-positive/progesterone-receptor-positive (ER+/PR+) tumors and 0.987 (0.885–1.101) for estrogen-receptor-negative/progesterone-receptor-negative (ER–/PR–) tumors. Similarly, Praud et al. [44] found an increased risk among European populations and ER+/PR+ tumors, with negligible heterogeneity. Sensitivity analyses are detailed in Table S6.

The overall findings suggest a moderate positive association between NO_2 exposure and BC incidence, despite substantial study overlap.

3.3.2. PM_{10} Exposure and BC Incidence

The association between PM_{10} exposure and BC incidence is addressed in six studies. The reported relative risks (RRs) across studies were as follows: 1.06 (95% CI: 0.99–1.13) [39], 1.03 (95% CI: 0.98–1.09) [40], 1.05 (95% CI: 0.98–1.12) [41], 1.05 (95% CI: 0.93–1.19) [42], 1.04 (95% CI: 0.98–1.10) [43], and 1.14 (95% CI: 0.97–1.30) [45]. All six meta-analyses reported a positive association with the lower confidence interval limit exceeding 0.93, well above the 0.70 threshold suggested by the American Statistical Association to indicate a positive trend [36]. The meta-analyses included nine primary studies [25,46,47,49,52,56,58,62,63] showing a very high level of overlap (CCA =56%) [33] and high heterogeneity (from 27.6% to 84.0%). Five studies conducted subgroup analyses to explore heterogeneity (Table S7). Zhang et al. [41] performed three subgroup analyses, adjusting for invasive breast cancer and estrogen/progesterone receptor status. No significant differences in risk estimates were observed, though heterogeneity decreased across all subgroups. Wei et al. [43] analyzed factors such as study design, geographic location, menopausal status, and estrogen/progesterone receptor status, with the European population showing higher risk (RR = 1.16, 95% CI: 1.07–1.25). Gabet et al. [39] performed extensive subgroup analyses, noting reductions in both risk estimates and heterogeneity when considering major reproductive factors, residential history, hormone-receptor-positive cases, menopausal status, North American cohorts, and studies using home addresses for exposure assessment. Increased heterogeneity was reported for hormone-receptor-negative cases. Studies published since 2000, and those using modelling for exposure assessment, reported higher risk estimates alongside increased heterogeneity. Guo et al. [40] observed higher risk estimates in studies with follow-up periods shorter than 11 years and greater heterogeneity in studies conducted in North America, and in those published before 2017. Arif et al. [45] reported a higher risk measure in European studies compared to those from the Americas with low heterogeneity (<0.01%). Yu et al. [42] did not perform subgroup analyses. The overall findings suggest a weak positive trend between PM_{10} exposure and BC incidence, highlighting the necessity of further research.

3.3.3. $PM_{2.5}$ Exposure and BC Incidence

The association between $PM_{2.5}$ exposure and BC incidence is addressed in six of the seven selected meta-analyses. These studies reported relative risk (RR) estimates of 1.03 (95% CI: 0.93–1.13) [39], 1.01 (95% CI: 0.93–1.11) [40], 1.042 (95% CI: 0.987–1.108) [41], 1.02 (95% CI: 0.93–1.11) [42], 1.03 (95% CI: 0.99–1.06) [43], and 1.05 (95% CI: 0.98–1.12) [45]. All studies reported a positive association, with the lower bound of the confidence interval exceeding 0.93—well above the 0.70 threshold suggested by the American Statistical Association [36]. The meta-analyses included 18 primary studies [22,25,46–49,56,58–60,62–68] showing high overlap (CCA = 38%) and heterogeneity between 8.2% and 55.7%.

Five studies conducted subgroup analyses (Table S7). Zhang et al. [41] performed three subgroup analyses, examining invasive breast cancer and estrogen/progesterone receptor status. Their results indicated similar risk estimates across subgroups, with a reduction in heterogeneity. Wei et al. [43] conducted four subgroup analyses, considering study design, geographic region, menopausal status, and receptor type. While risk estimates remained stable, heterogeneity decreased in some cases, particularly among European populations and receptor status subgroups. Gabet et al. [39] reported lower risk estimates and reduced heterogeneity for reproductive factors, residential history, hormonal status, and North American populations. Both risk estimates and heterogeneity increased in studies conducted in Europe and in those using exposure modeling and home address data. Guo et al. [40] analyzed subgroups based on follow-up duration (greater or less than 11 years), geographic region, and publication period (before or after 2017). They found no significant changes in risk estimates but observed lower heterogeneity in studies with follow-up periods exceeding 11 years, those conducted in North America, and those published before 2017. Arif et al. [45] reported lower risk estimates in the Americas but higher heterogeneity compared to Europe. Yu et al. [42] did not perform any subgroup analyses. The overall findings suggest a positive moderate potential trend between $PM_{2.5}$ exposure and BC incidence, pointing to the need for additional studies and more in-depth analysis in future work.

3.3.4. $PM_{2.5}$ Exposure and BC Mortality

The association between $PM_{2.5}$ exposure and BC mortality is addressed in only four of the seven selected studies [40–42,45]. The meta-analyses reported relative risk (RR) estimates of 1.20 (95% CI: 0.92–1.48) [40], 1.17 (95% CI: 1.05–1.30) [41], 1.18 (95% CI: 0.81–1.73) [42], and 1.17 (95% CI: 1.07–1.27) [45]. Two meta-analyses reported a positive association, with the lower bound of the confidence interval exceeding 1. In the other two studies, the lower bounds exceeded 0.81—higher than the threshold of 0.70 suggested by the American Statistical Association [36]. The meta-analyses included 10 primary studies, [49,63,69–76] with high overlap (CCA = 30%) and heterogeneity from 52.5% to 73.1%.

Subgroup analyses were conducted in only two studies [41,42] and details are reported in Table S7. Zhang et al. [41] found increased risk in cohort studies and higher exposure levels, though heterogeneity remained high (Table S4). Guo et al. [40] reported higher risk in studies with shorter follow-up periods and in developing countries, while heterogeneity increased with longer follow-up durations (>11 years), older publications, and in Asian cohorts and research from developing countries. Yu et al. [42] and Arif et al. [45] did not conduct subgroup analyses.

Overall, findings suggest a positive modest trend between $PM_{2.5}$ exposure and BC mortality, highlighting the necessity for additional studies.

3.3.5. PM_{10} Exposure and BC Mortality

Only two meta-analyses [40,41] evaluated the relationship between PM_{10} exposure and BC mortality, both including the same two primary studies [69,70], but assigning them different weights in the pooled relative risk estimates. The two meta-analyses reported an RR of 1.11 (95% CI: 1.02–1.21) with no heterogeneity (I^2 = 0%) and an RR of 1.07 (95% CI: 0.93–1.20) with moderate heterogeneity (I^2 = 56.4%), respectively. The association between PM_{10} exposure and BC mortality was classified as "weak". Guo et al. [40] performed subgroup analyses, noting higher risks with shorter follow-up periods and earlier publication dates, but found no major differences in other subgroups. Zhang et al. [41] did not perform subgroup analyses due to lack of heterogeneity. Given the limited number of studies, further investigation is needed.

4. Discussion

This umbrella review synthesizes evidence on the associations between exposure to nitrogen dioxide (NO_2), fine particulate matter ($PM_{2.5}$), and coarse particulate matter (PM_{10}) and the risk of breast cancer (BC) incidence and mortality in women. All included meta-analyses reported pooled relative risks (RRs) greater than 1 for each pollutant–outcome pair, with lower bounds of confidence intervals (CIs) exceeding 0.70, although with varying levels of heterogeneity. Among the pollutants examined, NO_2 showed sufficiently conclusive evidence of a weak positive association with BC incidence. For $PM_{2.5}$ and PM_{10}, the findings suggest a positive trend for both incidence and mortality outcomes, with the trend being more pronounced for $PM_{2.5}$ and incidence. The most vulnerable groups included premenopausal European women exposed to NO_2 and PM_{10} and individuals in developed countries exposed to $PM_{2.5}$. A recent cohort study in the U.S. study [77] found an 8% increase in estrogen-receptor-positive BC per 10 μg/m^3 increase in $PM_{2.5}$.

The carcinogenic effects of NO_2 may be driven by both direct and indirect mechanisms. NO_2 exposure has been associated with reduced DNA methylation, which can alter gene expression and contribute to genomic instability—a key factor in cancer progression [78]. Epigenomic studies have identified lower DNA methylation levels in blood samples years before BC diagnosis [79]. Additionally, as a major component of vehicle emissions and other high-temperature fossil fuel combustion, NO_2 can be a marker of traffic-related and industrial air pollution, including harmful substances like heavy metals, PAHs, and benzene, which have known genotoxic, mutagenic, and endocrine-disrupting effects [80–88], supporting the association between NO_2 exposure and breast cancer risk. Accordingly, the IARC classifies diesel emissions as carcinogenic (Group 1) and gasoline exhaust as possibly carcinogenic (Group 2B) [89]. The carcinogenic potential of particulate matter (PM) is less defined due to variations in composition and particle size, which depend on emission sources and regional air quality [90]. Certain PM components—black carbon, elemental carbon, and sulfates—are recognized as risk factors [65,91,92], along with airborne metals like mercury, cadmium, and lead, which are linked to increased postmenopausal BC risk [93–95].

Epidemiological and toxicological studies suggest two key mechanisms for PM-related cancer risk: (1) oxidative stress from reactive oxygen species (ROS), causing DNA damage [96,97] and (2) inflammation, with the release of cytokines like TNF-α and IL-1α that may promote tumor progression [98]. Furthermore, evidence indicates a dose–response relationship between PM exposure, elevated C-reactive protein (CRP) levels, and breast cancer risk [99]. Finally, BC mortality is influenced not only by environmental exposures but also by healthcare-related factors such as delays in diagnosis, limited treatment access, and barriers to early detection.

Strengths and Limitations

This umbrella review presents several strengths. To our knowledge, a comprehensive synthesis evaluating the links between NO_2, $PM_{2.5}$, and PM_{10} exposure and breast cancer risk has not yet been conducted. By providing a broad perspective on air pollution as a public health concern, this review highlights its potential role in breast cancer, the most commonly diagnosed malignancy worldwide, with incidence peaking between the ages of 60 and 70. A rigorous methodology was applied, including a structured literature search across two scientific databases, independent study selection and data extraction by two researchers, and quality assessment using AMSTAR 2.

However, some limitations exist. First, the included meta-analyses exhibited considerable heterogeneity, which weakens causal inferences. This variability stems from differences in geographic regions, time periods, data collection methods, and exposure assessments. While subgroup analyses attempted to address this issue, they remained limited by their reliance on general study characteristics. More refined stratifications—such as histologic and molecular subtypes, mammographic breast density, occupational history, and individual-level exposure data—were unavailable, as these factors were not considered in the original studies. This heterogeneity is further complicated by physiological changes that occur during critical periods of mammary tissue development and hormone signaling, such as puberty, pregnancy, and menopause. These stages, known as windows of susceptibility (WOS), may represent heightened vulnerability to chemical exposures. Assessing the impact of such exposures during these critical windows is essential for accurately evaluating their contributions to breast cancer risk [100–104]. Understanding pollutant impacts during these periods is essential for effective prevention [99–104]. A further limitation is the high overlap among the included meta-analyses, as reflected by the high Corrected Covered Area (CCA) index (30–66%). This overlap indicates that the synthesized evidence is not entirely independent. Although alternative methods like network meta-analysis or excluding redundant reviews are suggested [105], we included all of them due to their unique subgroup analyses. Still, this highlights the need for more primary studies.

Another concern pertains to how exposure is measured. Estimating individual exposure to air pollution is a key challenge in environmental health research, especially in regions with multiple pollution sources and uneven pollutant distribution. The accuracy of these estimates can vary depending on the method used—for instance, whether data come from air quality monitoring stations, land-use regression (LUR) models, or other modeling techniques. In addition, differences in the length and timing of exposure assessments between studies can introduce inconsistencies. These variations may lead to exposure misclassification, which can influence the reliability of the results and complicate comparisons across studies [106]. Many studies assessed only one pollutant, ignoring potential combined effects, and few analyzed PM composition, even though toxicity varies by component [107,108]. Furthermore, most meta-analyses assumed a linear relationship between air pollution and BC risk, without exploring potential nonlinear effects. Residual confounding is also a concern, as not all studies adjusted for socioeconomic, behavioral, or genetic factors. Lastly, publication bias may influence results. Although funnel plots and Egger's tests were used, three authors also applied trim-and-fill methods, excluding smaller studies to estimate adjusted summary effects based on larger ones [39,40,43].

5. Conclusions

This umbrella review highlights the growing evidence that air pollution, particularly exposure to nitrogen dioxide (NO_2), fine particulate matter ($PM_{2.5}$), and coarse particulate matter (PM_{10}), may increase the risk of both breast cancer incidence and mortality in women, though findings varied in terms of heterogeneity and publication bias. The most vulnerable groups were identified as premenopausal European women exposed to NO_2 and PM_{10}, as well as individuals in developed countries exposed to $PM_{2.5}$.

Given that breast cancer remains the most frequently diagnosed invasive malignancy and the second leading cause of cancer-related deaths among women worldwide, it is imperative that future environmental epidemiological research prioritize breast cancer as a critical health outcome when assessing the effects of air pollution.

In particular, further studies are needed to investigate the impact of multi-pollutant exposures and their combined effects on breast cancer risk. Additionally, identifying specific components of PM, such as black carbon, elemental carbon, and various metals, that may drive carcinogenic risks, is crucial. It is also important to assess breast cancer risk across different histologic and molecular subtypes, as the effects of environmental pollutants may vary in their carcinogenicity across different types of cancer. Furthermore, the existing evidence base is adequate to support breast cancer prevention strategies encompassing both individual lifestyle modifications and public health policies and environmental regulations designed to decrease NO_2, $PM_{10,}$ and $PM_{2.5}$ concentrations.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/environments12050153/s1: Table S1: Search strategy in PubMed and Embase; Table S2: AMSTAR2 check list. Table S3: Excluded articles and reasons. Table S4: Confounders included in the study analysis. Table S5: Primary studies included in each review. Table S6: Sensitivity analysis and publication bias for NO_2 exposure. Table S7: Sensitivity analysis and publication bias for PM2.5 exposure. Table S8: Sensitivity analysis and publication bias for PM10 exposure.

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Abbreviations

The following abbreviations are used in this manuscript:

BC	Breast cancer

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MDPI

Systematic Review

Advancing Environmental Sustainability in Healthcare: Review on Perspectives from Health Institutions

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Abstract: Hospitals play a key role in promoting sustainable and healthy living. Few studies have taken this perspective into account. Therefore, we explored the role of hospital institutions in the development and implementation of sustainability strategies linked to the provision of health services. Applying the PRISMA guidelines, we conducted a systematic review of the PubMed, Scopus, CINAHL, PsycINFO and Web of Science databases and the references of the resulting articles in Mendeley Desktop v1.19.8. Articles peer-reviewed between 2016 and 2023 were eligible if they analyzed sustainable healthcare, activities derived from services provided and professional involvement. From the 27 articles that constituted the final sample, two themes were identified: (a) environmental sustainability in healthcare and (b) involvement of healthcare professionals in environmental sustainability. Proposals for sustainable actions to reduce the environmental impact of healthcare related to the use of natural resources, sustainable food, sustainable transport and waste management were reviewed. The role of healthcare workers, their attitudes and perceptions of sustainability and global health improvement were investigated. Reducing health pollution involves addressing excessive or inappropriate consumption of resources and minimizing the environmental footprint of healthcare activities. The different contexts reveal the heterogeneity of the sustainability interventions existing in the healthcare industry, both in terms of subject matter and in terms of the number of publications from each country.

Keywords: development strategies; green hospital; healthcare sector; sustainable development

1. Introduction

The World Health Organization (WHO) has declared that climate change presents a threat to human health in terms of death and illness from increasingly extreme weather events, such as heatwaves, storms and floods; the disruption of food systems and an increase in vector-borne diseases. Between 2030 and 2050, climate change is expected to cause approximately 250,000 additional deaths per year from undernutrition, malaria, diarrhea and heat stress alone. Furthermore, it is undermining many of the social determinants of good health, such as livelihoods, equality, access to healthcare and functioning of health systems and social support structures [1]

Healthcare and, more specifically, hospitals, play a crucial role in contributing to environmental deterioration, since they generate pathological, pharmaceutical, chemical and radioactive waste, posing significant health risks [2]). Health activities in Western countries such as Canada emit thousands or millions of tons of greenhouse gases and other pollutants each year, which has resulted in the annual loss of 23,000 disability-adjusted life years [3].

The future quality of health services in terms of climate resilience and environmental sustainability is directly related to support health systems to leapfrog to cheaper, cleaner and more reliable solutions, while decarbonizing high-emitting health systems [1].

Some strategies to mitigate the environmental and health impact generated by the provision of health services are being carried out in several dimensions. Firstly, it is worth highlighting the modernization of facilities with new technologies and the design and construction of ecological hospitals through thermal (electrical energy savings and solar protection), acoustic (patient comfort and no noise pollution) and lighting strategies (i.e., openings in building facades) [4]. Several studies have determined that the introduction of elements to provide greater interior thermal comfort (i.e., an increase in relative humidity) reduces the load on air conditioning systems [5,6]). In fact, the results of the first study reflected that increasing indoor relative humidity by 10% reduced the cooling load and energy consumption by 24.9% in green hospitals compared to conventional hospitals.

Secondly, the implementation of sustainable measures can be driven by political and management commitments. In fact, new business models are emerging for pharmaceutical companies, where innovation is a key element in improving sustainable development, especially in the field of green technologies [7]. To achieve this, regulatory frameworks and management plans as well as awareness among managers and health professionals are necessary. Results from several studies show that the corporate responsibility of a proactive manager or leader with high environmental values positively influences (39%) the pro-environmental behavior of healthcare professionals [8,9]). In addition, various authors support training in sustainable development, climate change or gas emissions, among others, to increase knowledge that can be reflected in the clinical practice of health professionals, in the generation of scientific data and in the proposal of new policies [10,11]

Finally, healthcare sustainability science also explores dimensions of resource consumption and environmental emissions associated with healthcare activities. Previous studies have shown that some proposals include the inclusion of new forms of care, such as telemedicine, which would contribute to a reduction in carbon emissions [12,13], the development of life cycle inventory databases for medical devices and drugs and revision of infection control standards driving non-evidence-based uptake of single-use disposable devices [14]. More simply, health education can itself be an ally of sustainability. In this way, advising more physical activity in parks, bicycling or walking, as well as reducing the consumption of prepared foods not only encourages more healthy active lifestyles but could also help reduce air pollution and the use of plastics.

Reducing pollution from healthcare involves addressing excessive or inappropriate consumption of resources and minimizing the environmental footprint of healthcare activities. Efforts to achieve these measures will result in higher-value care and better population health [15]. Therefore, given the active role that hospital institutions must develop to achieve global health and the direct relationship between sustainability initiatives and the well-being of the population, this work aims to explore the role of hospital institutions in the development and implementation of sustainability strategies linked to the provision of health services.

2. Materials and Methods

2.1. Study Design

A systematic review following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [16] (Supplementary Materials) was conducted using five electronic databases: PubMed, Scopus, CINAHL, PsycINFO and Web of Science. The searches were performed by two researchers independently between December 2023 and January 2024, using the following Boolean expression, slightly adapted for each database: ("green hospital" OR "healthcare sector" OR "healthcare institution*" OR "sustainable hospital*") AND ("agenda 2030" OR "eco-friendly" OR "pro-environmental" OR "sustainable development" OR "sustainability development goals" OR "sustainability strategy" OR sustainab*).

2.2. Inclusion and Exclusion Criteria

Articles were included if they investigated sustainability issues related to healthcare and were (a) peer-reviewed articles published between 2016 and 2023 and (b) quantitative, qualitative or mixed-design studies. No language restrictions were applied. Articles were excluded if they were editorials, conference proceedings, opinion essays, literature reviews or books or if they did not address environmental sustainability in the healthcare sector. Studies that focused on policies and regulations regarding health environmental sustainability, as well as sustainability measures applied to health infrastructures, were also excluded.

2.3. Study Selection and Data Extraction

After the search, 1575 publications matching the search criteria were included as references in the software Mendeley Desktop v1.19.8. The screening procedure was carried out by two researchers independently, aiming to identify relevant studies based on the inclusion and exclusion criteria. First, duplicate publications were removed (n = 548); then, the reviewers screened 1027 articles by title and abstract. Two hundred and twenty-four full-text articles were screened by two researchers, and if there was a disagreement, another reviewer was consulted. After reading the full-text articles, our final sample included 27 studies. The flowchart is included in Figure 1.

Finally, the following items were extracted for each study: authors, country, year of publication, study objective, research design, sample characteristics and major findings (Appendix A). The summary tables were thoroughly reviewed by all reviewers independently, with critical discussions of the extracted data.

To develop the themes for this systematic review, a thematic analysis approach was used [17]. Two reviewers involved in the searches, screening, article evaluation and data extraction organized descriptive labels, focusing on emerging or persistent concepts and similarities or differences in the role of hospital institutions in the development and implementation of sustainability strategies linked to health service delivery. The coded data from each paper were examined and compared with the data from all the other studies. Finally, the different categories were gathered (grouped) into the following two themes: (a) environmental sustainability in healthcare and (b) engaging health professionals in environmental sustainability.

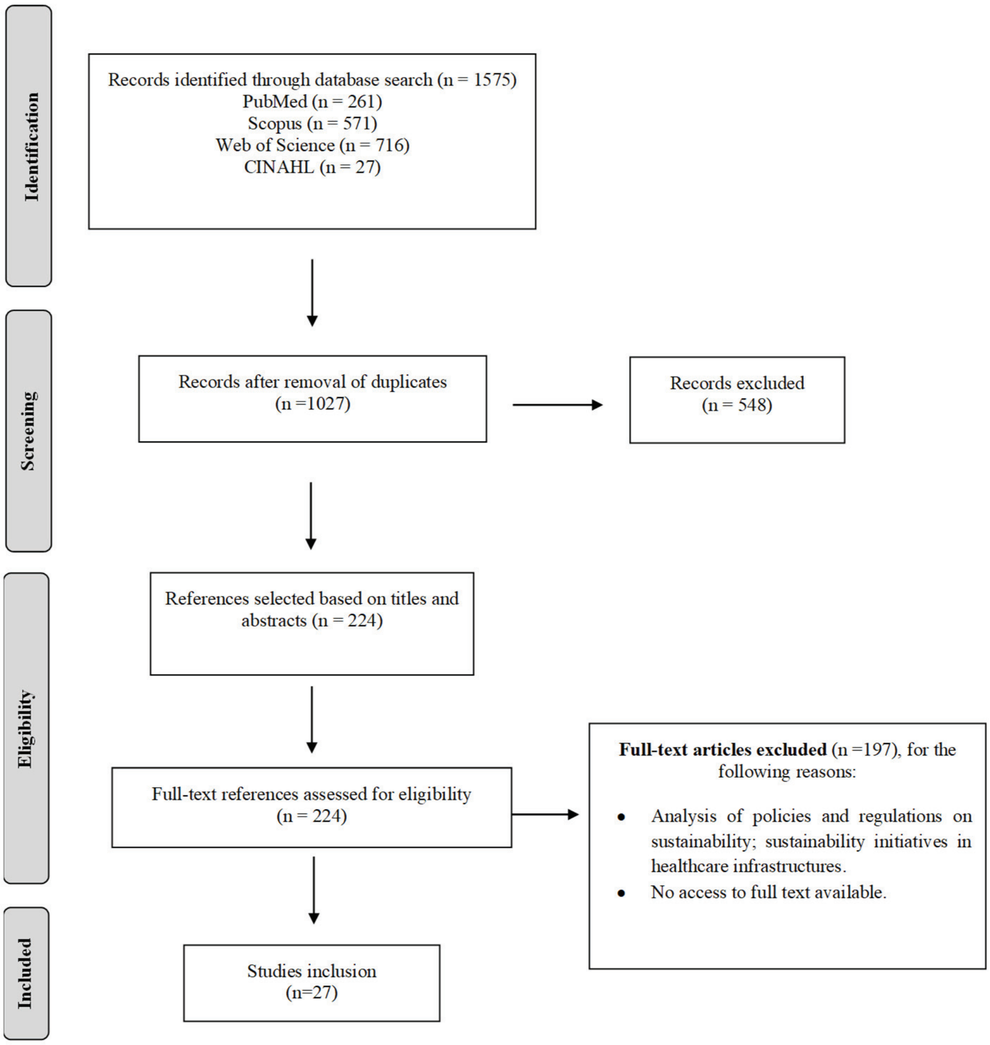

Figure 1. Flowchart for article selection in this systematic review. From Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit www.prisma-statement.org (accessed on 10 June 2024) [16].

3. Results

The results below show the main characteristics of the studies included in this review, as well as a qualitative analysis of the content based on the themes established by the authors.

Characteristics of the Included Studies

A total of 27 articles were included in the final step of the systematic review; 70% of them were published in the last three years (*n* = 19). Seventy percent of the studies were conducted in Europe and Asia (*n* = 10; 37% and *n* = 9; 33%), followed by the Americas (*n* = 4; 14%) and Australia (*n* = 2; 8%).

Most of the articles selected for this review investigated sustainability strategies in healthcare systems (*n* = 14; 51.8%). In addition, some publications focused on analyzing environmental damage caused by healthcare activity and identified facilitators and barriers to the implementation of sustainability measures (*n* = 9; 33.3%), and some addressed the role of healthcare professionals in the implementation of these measures (*n* = 8; 29.6%). Most studies' respondents were healthcare workers from public hospitals (*n* = 15; 68%), of those studies, four (18%) included management and leadership professionals. Other participants were medical students, food chain staff and health industry workers (n = 3; 13%). The full characteristics of the selected studies are shown in Appendix A; a scheme (Figure 2) reflecting the dynamics of environmental impact of medical activities and proposed measures to reduce such impact, as well as a qualitative analysis of the results, are presented below.

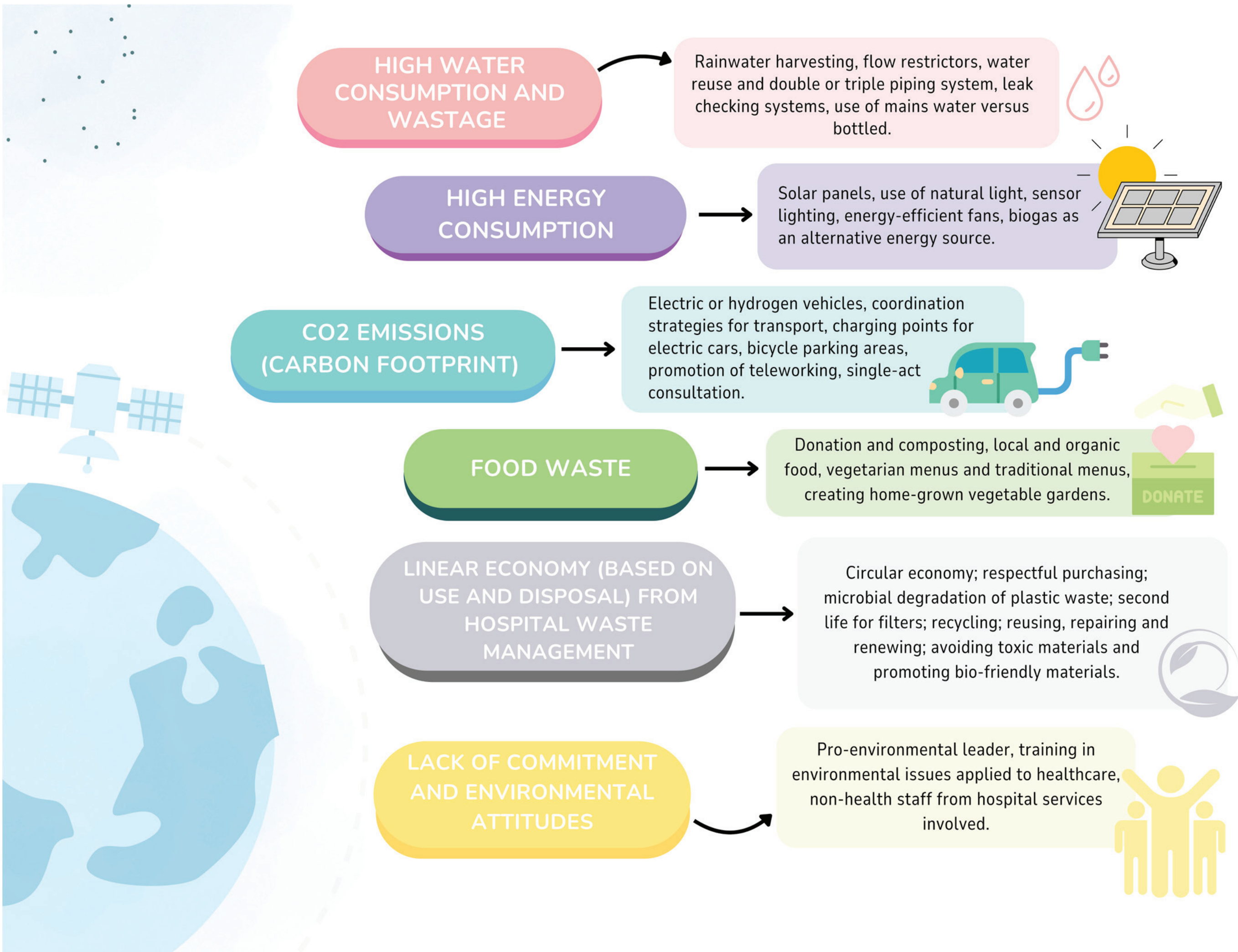

Figure 2. Dynamics of environmental impact of medical activities and measures to reduce it.

Theme 1. Environmental sustainability in healthcare

The detection of a greater environmental impact of the activities of healthcare institutions has been linked to air conditioning; the use of electromedical material for diagnosis; surgical procedures; pharmaceutical products and single-use products such as sterile gloves, gowns, masks or syringes, as well as the transfer of patients themselves to receive healthcare [18,19]. Based on analyses of these forms of damage, various actions in favor of sustainable healthcare stand out.

Promoting sustainable practices in the use of energy and natural resources and in reducing the carbon footprint: Using solar panels and natural light, sensor lighting, energy-efficient fans, biogas and biodiesel, rainwater collection and water treatment were different strategies implemented to achieve a reduction of up to 30% in hospital consumption [20]. Other measures also stand out: checking for leaks in the piping system, using flow restrictors, recycling water and using a double or triple piping system (cold water, hot water and reticulation of non-potable water) [21]. Finally, a study also showed that patient care procedures such as anesthesia could in-corporate climate benefits in pediatrics [22].

Encouraging sustainable transport: Some hospitals have opted to use electric or hydrogen vehicles instead of diesel, create a transport coordination role, install charging points in parking lots for electric cars and create better and larger bicycle parking areas. In addition, the promotion of teleworking has been analyzed as a measure to limit travel and pollution, and to this end, awareness of the importance of sustainable transport for staff and patients has been promoted [23] This is also helped by single-act consultations, where the patient is seen by all professionals involved on the same day (decreasing transport and therefore up to 35% of emissions) [24].

Sustainable food: On the one hand, this review highlights the waste of food in health services and the need to create measures to avoid food waste, such as the reduction of waste by reusing both edible and inedible waste (i.e., donation) [25] and composting. On the other hand, the consumption of local and organic food is encouraged [25,26], as well as implementing vegetarian menus and traditional menus, creating home-grown vegetable gardens [26] and using mains water instead of bottled water in canteens [21]. As an example, the cost of bottled water consumption in a hospital canteen for about 200 people is about €14,000. In contrast, the installation of a microfiltration system in the drinking water supply network plus the water consumed would cost €2800, which would translate into savings of around €11,200 per year [21].

Adopting sustainable practices in waste management: According to some authors [21,27], one hospital produces about 10.58 kg/person/month of non-hazardous waste and 5.26 kg/month of potentially infectious waste. Of this, 62% is not segregated (40% textiles, 20% paper, 17% plastic). It is therefore necessary to promote the separation of waste in order to recycle; promote respectful purchasing (i.e., avoiding composite packaging of needles reduces unsorted waste by 3%); encourage a change in clinical practice to reduce the use of materials [21,28].; reuse, repair and renew (bases of the circular economy) [29]; avoid toxic materials and promote bio-friendly materials and renewable sources [28].

Currently, the linear economy (based on use and disposal) is the most widespread [27]. Achieving a circular economy will require measures such as changes in protocols; staff training; clear instructions from companies on how to recycle material after use; smaller and more recyclable packaging [21,27] or promotion of the segregation of waste in a way that allows its subsequent reuse. A proposed example of creating strategies that include members of society in the functioning of the hospital circular economy consists of cooperatives that allow citizens to take charge of the segregation and sorting of materials, so that they can use them to create recycled objects such as purses, bags or packages, which they can then display or sell at a craft fair [30].

Another specific strategy contemplates microbial degradation as the most sustainable and economical option for the treatment of plastic waste [31] or the possibility of giving a second life to dialysis filters, which can be used as water filters [25]

Theme 2. The involvement of healthcare professionals in environmental sustainability

The studies included in this review have analyzed different attitudes and perceptions of health professionals towards sustainability as well as factors that influence them.

Deng et al. [8] observed that healthcare staff with pro-environmental values significantly tended to favor reducing hospitals' carbon footprint through actions such as the rational use of energy, switching off electrical equipment that is not being used or using recyclable materials. According to Xu et al. [32], the figure of a pro-environmental and sustainability-minded leader could have an influence of around 40% on workers. In addition to this, this leader figure also had a mediating character between the pro-environmental attitudes of healthcare workers and corporate social responsibility in 47% of cases [8], highlighting the positive moderation of female leaders [33]. Another study states that a leader with strong environmental values favors better management of energy expenditure by workers during their clinical activity. For example, up to 90% of the costs of air conditioning can be reduced [9].

In this way, knowledge acquired through training is highlighted as a key factor [8,34–36], which can be extrapolated to future professionals, that is, nursing and medical students. As an example, students from a medical school in Bristol were sent to a SusQI (sustainability in quality improvement) workshop, with the aim of identifying challenges in translating knowledge into practice. Institutional inertia was found to affect their confidence in suggesting changes, and only a minority perceived sustainable healthcare as more than their professional role [37].

Despite the interest of healthcare providers in promoting sustainable measures, several perceived barriers were mentioned, of which the following should receive particular attention: lack of interest on the part of the healthcare facility, difficulty and effort involved in implementing strategies, cost and lack of training [26,27,38]. Regarding renewables, they mentioned that the major impediment to increasing the supply of renewables consisted of the limitations due to the state-level electricity contract and the prices/costs of renewables [39]. However, decreasing the environmental footprint, improving community health, reducing costs, composting and involving non-health staff from other hospital services are perceived as enablers.

4. Discussion

To evaluate the contribution of this review, an analysis of existing similar works was conducted beforehand. The review of other systematic review studies did not reveal a perspective equivalent to that addressed in this work, which has focused on offering a comprehensive literature review to provide a broad perspective on the current state of knowledge, specifically centered on the attitude of healthcare institutions towards implementing environmental care measures within their organizations and the importance of the involvement of healthcare professionals in the application of such measures. This review paper specifically aims to synthesize the state of knowledge concerning the role of hospital institutions in the development and implementation of sustainability strategies related to healthcare service delivery and reducing pollutant emissions such as chemical, radioactive or greenhouse gases and other harmful substances. It also explores the extent to which hospital management prioritizes environmental harm reduction through facility design, technology adoption and the influence of an environmentally oriented organizational culture within the healthcare sector.

Although certain reviews have addressed issues related to the role of healthcare managers, such as those by van Schie [40] and McCauley et al. [41], these studies lack the broad, synthesizing approach undertaken in this review. The systematic reviews published in recent years, although abundant, primarily focus in most cases on environmental improvements in the management of specific healthcare services, such as surgery [42], radiology [43], gastroenterology [44] or radiology departments [45].

Regarding the included works, it is noteworthy that 70% of the papers included in the review were published in the last three years, predominantly in Europe, indicating the cultural influence underlying the prevalence of such policies. Furthermore, the reviewed literature reveals no controversies or opposing viewpoints regarding the necessity of implementing measures to improve hospital management practices. However, while studies such as those of Barbero and Pallaro [25], Cakmak and Yol [46] and Dagenais et al. [38] highlighted the importance of organizational involvement, others, such as that of Boussuge-Roze et al. [27], revealed that healthcare professionals surveyed across

42 countries perceived a lack of interest from the hospitals (59%) and insufficient training (37%) in the implementation of new procedures. The relevance of programs involving staff in environmental care is underscored by other systematic literature reviews with a narrower focus on specific services, such as the review by Huo et al. [47], which pertains to surgical services.

An intriguing aspect regarding potential areas for knowledge expansion lies in the economic evaluation of the benefits derived from implementing waste reduction strategies and improving environmental management in healthcare facilities. While the reviewed studies mention economic advantages, including those from a circular economy perspective, no comprehensive economic analysis supporting these claims has been conducted. This topic is only partially addressed in the literature review conducted by Davies et al. [48].

Implications for Clinical Practice

The results of this study provide a starting point to help create a model for healthcare facility management that contributes to global health and the development of green hospitals. For nurses, in particular, this review is a call to action within the decision-making competencies of the management bodies of healthcare institutions and health systems. Considering the breadth of services offered by nurses, proposals for environmentally sustainable healthcare can emerge. Furthermore, the results highlight the need for sustainability training from academic to continuing education courses and multidisciplinary collaborative work.

Another implication would be the possibility of involving other managers and policymakers in refining regulations that motivate the environmental participation of the centers, that is, that the people who provide healthcare would have the political and regulatory support needed to contribute to the achievement of the 2030 Agenda.

Finally, we must address the implications for citizens. Firstly, by reducing environmental pollution and promoting the use of preventive and health-promoting practices, sustainable practices can help prevent disease and improve the quality of life of the population. Secondly, reducing resource consumption and improving efficiency in service delivery can make health services more accessible and affordable to society. Lastly, reducing energy and water consumption contributes to a healthier and safer environment. In other words, the implementation of sustainable healthcare systems has important implications in terms of improving the quality of healthcare, reducing healthcare costs and environmental impact and promoting a culture of sustainability.

5. Limitations

The present review has some limitations that should be highlighted. It is possible that not all available information has been found, as many hospital sustainability initiatives or approaches may be part of hospital policies, regulations and/or projects that have not been disseminated at a scientific level. However, very broad descriptors and five electronic databases were applied to ensure the greatest number of available resources. A broader review of the gray literature, as well as a review of calls for projects and data from ministries related to health and the environment or from healthcare organizations or systems themselves, would likely be productive in future lines of research. Finally, although this work highlights the assessment of unexplored aspects of the problem, it has the limitations of a review, that is, the absence of proven novelties. To this end, this group of authors, as part of the SUSTAinsHealth project, is carrying out interviews with a qualitative approach regarding environmental sustainability strategies in the health sector that could be replicated in different countries.

6. Conclusions

The health system is increasingly adopting 'green' hospital services, which emphasize the environmental and social impacts of institutional operations. Hospitals play a pivotal role in evaluating and mitigating the environmental footprint of healthcare activities. This study identified a range of sustainable initiatives grounded in a circular economy framework, encompassing sustainable practices in energy and natural resource use, eco-friendly transport solutions, sustainable food procurement and comprehensive waste management strategies. Furthermore, the findings underscore the critical role of committed leadership and the pro-environmental attitudes of managers and healthcare professionals, which act as catalysts to foster more sustainable and environmentally conscious healthcare practices. This highlights the necessity of integrating environmental stewardship into the strategic and operational frameworks of healthcare systems, positioning hospitals as key players in promoting ecological sustainability within their communities.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/environments12010009/s1.

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Data Availability Statement: The data that support the findings of this study are available upon request from the corresponding authors.

Conflicts of Interest: The authors declare no conflicts of interest.

Appendix A

Table A1. Results of the Systematic Review.

Reference	Objective	Methodology	Main Findings	Theme
Abhilash, 2022 [31] (India)	To analyze the means of treatment and/or disposal of plastic waste in the hospital setting during the COVID-19 pandemic.	Qualitative narrative analysis of degradation methods for plastic polymers.	The microbial degradation of plastic waste (degradation of plastic polymers and production of bio-based polymers) was found to be the most cost-effective and least ecotoxic method compared to other methods such as chemical disinfection; dissolution of plastic polymers to recover pigments or other polymers and thermal processes, most notably pyrolysis (use of thermal energy to break the chemical bonds in polymers).	Environmental sustainability in healthcare

Table A1. *Cont.*

Reference	Objective	Methodology	Main Findings	Theme
Barbero and Pallaro, 2017 [25] (Italy)	To discuss the potential of applying a systemic design (SD) approach for sustainable healthcare.	Qualitative study using a systemic design (SD) approach	The SD methodology is presented for enhanced material and energy production processes in the healthcare industry, thus reducing energy expenditure. Several examples of the use of this system include "communication design" (e.g., raising awareness about local food consumption, improving the circular economy, and protecting the environment), "NUF portable filters" (reusing dialysis filters to purify water in other low-income countries), "recovery of hospital food waste" (preventing food waste generation and promoting its reuse in hospitals by educating staff and users) and "eco-dialysis" (exploring the relationship between the components of dialysis devices to optimize material and energy flow, thus creating an efficient and sustainable system adapted to patient needs).	Environmental sustainability in healthcare
Boussuge-Roze et al., 2022 [27] (Various countries)	To investigate the current practice and expectations of European cardiac electro-physiology (EP) centers in terms of environmental sustainability, with a focus on EP catheters.	Quantitative study (online survey) Sample: N = 278 public hospital workers from 42 countries. Gender: 76% men Average age: 43 years.	A total of 72% of the healthcare professionals surveyed say that a linear economy of disposable catheters and packaging is still in place. Possible solutions include changes through protocols, educating professionals, clear instructions from companies after use of the material for recycling, reusing catheters after the necessary regulatory measures and using recyclable and smaller packaging. Overall, 82% of respondents showed interest in performing sustainable work, identifying the main barriers as the lack of interest from the hospital (59%), the complexity of the measures (48%), the effort required to change practices (47%), cost (33%) and lack of training (37%).	Engaging health professionals in environmental sustainability
Burch and McGain, 2021 [39] (Australia)	To identify points of view of healthcare leaders about the carbon footprint, sources of energy and barriers in the field of health.	Qualitative study (interviews) Sample: N = 13 Victorian public healthcare chief executive officers	Most participants acknowledged the importance of climate change and were cognizant of its negative impact. In addition, they had a consensus regarding the significant role of leadership in prompting environmental sustainability in the health public sector. Currently, however, support for renewable electricity is, for the most part, an aspiration and not perceived as a priority, although electricity accounts for 7% of total carbon emissions in Australia. The main perceived barriers to increasing renewable energy supply were limitations due to state-level electricity contracts and the costs of renewable energy resources.	Engaging health professionals in environmental sustainability

Table A1. *Cont.*

Reference	Objective	Methodology	Main Findings	Theme
Cakmak and Yol, 2019 [46] (Türkiye)	To create awareness of optimizing energy while maintaining quality in the provision of health services in medical devices.	Quantitative study calculating the energy density of hospital equipment. Sample: N = 1 hospital in Turkey	The medical devices that consume the most energy were radiological imaging, angiography, nuclear medicine, biosafety cabinets, autoclaves, incubators and operating rooms. The majority of this consumption was due to laser devices. Large medical imaging equipment accounted for 38% of the hospital's energy consumption, followed by nuclear medicine at 15%. Energy-saving strategies include reducing standby power levels, using hibernation and shortening startup times on high-power devices.	Environmental sustainability in healthcare
Carino et al., 2021 [26] (Various countries)	To explore the perspectives of hospital food supply chain staff on sustainable practices in food provision, identifying existing barriers and enablers and gathering recommendations for future implementation of sustainable foodservice practices.	Qualitative (semi-interview structure) Sample: N = 46 participants from across the food supply chain for patients Gender: 65% women	Strategies were identified to achieve sustainable food services, such as purchasing organic and local food, composting, vegetarian menus, use of traditional foods and creation of vegetable gardens. Innovation, education of society and environmental professionals and the creation of government regulations were highlighted as facilitators for sustainable food practices. Barriers included strict infection control standards and requirements, restrictions in current waste disposal contracts and the lack of a food sustainability policy.	Environmental sustainability in healthcare
Cockrell et al., 2022 [13] (USA)	To evaluate the environmental impact of implementing telehealth.	Quantitative (Retrospective cohort study at a pediatric surgical care center) Sample: N = 60,773 face-to-face meetings and 10,626 telehealth meetings	The incorporation of telehealth in preanesthesia and pediatric surgery clinics resulted in significant reductions in CO_2 emissions. Telehealth resulted in 1477 patient-km saved and a 312-ton reduction in CO_2 emissions. It was also shown that the greater the distance from home to the hospital, the greater the use of telehealth.	Environmental sustainability in healthcare

Table A1. *Cont.*

Reference	Objective	Methodology	Main Findings	Theme
Dagenais et al., 2022 [38] (Canada)	To analyze the barriers and facilitators to implementing sustainable menu practices (SMPs) in Quebec healthcare institutions.	Qualitative study (interviews) Sample: N = 17 foodservice managers from healthcare institutions	The barriers encountered were perceived to a greater extent than the facilitators. These include the complexity of implementation due to the lack of adaption to all institutional contexts, which is related to the lack of support from these organizations and the perception of high cost. This highlights the need for greater collaboration and communication between all actors in the hospital food system. The highlighted facilitators include a reduction in the ecological footprint, contribution to improving community health, the possibility of composting, cost reduction, a reduction in subcontracting, centralization of the kitchen and the involvement of kitchen staff in sustainable development.	Environmental sustainability in healthcare
Deng et al., 2022 [8] (Pakistan)	To examine the relationship between a hospital's corporate social responsibility (CSR) initiatives and employees' pro-environmental behavior with the mediating effect of environmentally specific transformational leadership (ESTL).	Quantitative study (self-administered survey) Sample: N = 239 employees of the Lahore Hospital (39% position) leadership and 66% between 1 and 5 years of work experience). Gender: 58.39% men Age: 89% between 22 and40 years	Leaders embracing environmental sustainability and CSR have a transformational role and significantly influence the pro-environmental attitudes of healthcare workers (manifested as pro-environmental behavior, or PEB), thus facilitating the development of sustainability measures. The ESTL not only directly influences PEB but also acts as a mediator between the PEB and CSR of healthcare workers in 47% of cases. Furthermore, a positive relationship was observed between altruistic values and greater involvement of staff in the initiatives. Thus, the promotion of these values through training was recommended.	Engaging health professionals in environmental sustainability
Eckelman et al., 2018 [3] (Canada)	To estimate the life cycle emissions and associated environmental impacts and secondary health damage produced by the Canadian healthcare system.	Qualitative study Economic–environmental–epidemiological analysis to compare medical expenses with emissions of greenhouse gases and other pollutants.	Greenhouse gas emissions in the Canadian health industry are mainly due to hospital activities, pharmaceutical products and medical services. Canadian healthcare activities accounted for 33 million tons of greenhouse gas emissions and more than 200,000 tons of other pollutant emissions, resulting in an estimated annual loss of 23,000 disability-adjusted life years due to exposure to these pollutants.	Environmental sustainability in healthcare

Table A1. *Cont.*

Reference	Objective	Methodology	Main Findings	Theme
Fang et al., 2022 [34] (China)	To review the experiences acquired in nosocomial environments around the world related to healthcare waste management.	Quantitative study (survey) Sample: N = 416 Hospital workers and managers in Shanghai.	A key factor in achieving sustainable waste management is environmental education of staff. Other strategies include conducting an orderly environmental inventory, planning and executing the placement of materials with reuse of everything possible, reducing wastage of energy (turning off electrical appliances when not in use, rational use of air conditioning) and materials and reducing power systems (electrical, thermal, etc.).	Environmental sustainability in healthcare
Geethika and Devi, 2022 [20] (India)	To measure the ecological costs, using carbon foot-printing and operational costs, of a 250-bed multi-specialty hospital with basic green hospital compliance.	Mixed study Participant observation, discussion groups and data obtained from the hospital database. Sample: N = 250-bed multi-specialty hospital	The service with the highest cost and energy consumption (up to 80%) for any hospital is air conditioning. The factors that generate the largest carbon footprint during hospital practices are electricity consumption (17,000 tons of CO_2/year) and the biomedical waste generated (723 tons of CO_2). Some sustainable ecological tools that have been used are as follows: - Use of solar energy (145 solar panels) and natural light; - Combined heat and power system; - Low-consumption ceiling fans; - Motion-sensor lighting; - Local suppliers; - Use of biogas and biodiesel; - Rainwater harvesting and on-site water treatment. These measures reduced the hospital's operating costs by 30%.	Environmental sustainability in healthcare
Hunfeld et al., 2023 [19] (Netherland)	To perform a material flow analysis in an academic intensive care unit and to obtain information on mass, carbon footprint, agricultural land occupation and water usage and to determine so-called "environmental hotspots" in the ICU.	Mixed study Material flow analysis by combining data analysis, measurements, desk research and interviews with staff members Sample: N = 1 ICU at Erasmus MC hospital in Rotterdam (56 mixed surgical and non-surgical beds)	The environmental impact per patient admitted to the ICU was 17 kg of solid waste, 12 kg of CO_2 eq, 300 L of water use and 4 m^2 of agricultural land occupation per day. Five single-use products were identified as the elements with the greatest environmental impact in terms of resource use and waste generation: non-sterile gloves, isolation gowns, bed protectors, surgical masks and syringes (including packaging).	Environmental sustainability in healthcare

Table A1. *Cont.*

Reference	Objective	Methodology	Main Findings	Theme
Irianti, 2016 [29] (Australia)	To gain information about methods and technology used in hospital waste management that can be adopted by Indonesian hospitals.	Qualitative study In-depth interviews and observation Sample: Hospital personnel of HWM practices in The Royal Brisbane and Women's Hospital (Australia).	The proposed hospital waste management is based on the division of waste into four groups (clinical, cytotoxic, recyclable and general waste) and focuses on the incorporation of the '3 Rs' (reduce, recycle and reuse), the segregation of sources, color-coded collection to minimize the production of medical waste and the development of a leadership figure to minimize illnesses and accidents related to waste management.	Environmental sustainability in healthcare
Marsden et al., 2021 [37] (United Kingdom)	To evaluate a training workshop on improving sustainability for clinical practice.	Qualitative study (5 focus groups) Sample: N = 17 third-year medical students at Bristol Medical School who participated in a SusQI (sustainability in quality improvement) workshop	Although the workshop motivated students and gave them skills they wanted to use in the future to improve quality, they expressed that there were multiple barriers to translating what they had learned into actual practice. Thus, although the workshop was successful in restructuring students' perceptions of sustainability, it was not enough, as some students were constrained by the social and cultural contexts of their clinical practice settings. Medical students who applied their learning to the clinical workplace were internally motivated and self-determined but needed time and opportunities to complete projects. Other students were cautious about disrupting established hierarchies and practices or were frustrated by institutional inertia. These barriers impacted their confidence in suggesting or achieving change. A minority saw sustainable healthcare as beyond their professional role.	Engaging health professionals in environmental sustainability
Narayanan et al., 2022 [22] (UK)	To compare the differences in the carbon footprint of inhalational anesthesia and total intravenous anesthesia (TIVA) when used in children.	Quantitative study Mathematical simulation models to compare four pediatric anesthesia techniques in children weighing 5, 10, 20, 30, 40 and 50 kg	TIVA with propofol and remifentanil had a smaller carbon footprint during a typical 60 min anesthetic process (1.26 kg of carbon dioxide equivalents [CO_2 eq] for a 20 kg child) than IV induction. followed by maintenance by inhalation (2.58 kg CO_2 eq) and inhalation induction and maintenance (2.98 kg CO_2 eq). Inhalation induction followed by IV maintenance alone had a lower carbon footprint than inhalation induction and maintenance when used in longer procedures (>77 min for children 5–20 kg; >105 min for children 30–50 kg). All in all, IV anesthesia had climate benefits in pediatrics. However, when used after inhalation induction, the benefits were only achieved in longer procedures.	Environmental sustainability in healthcare

Table A1. *Cont.*

Reference	Objective	Methodology	Main Findings	Theme
Peng et al., 2022 [9] (Pakistan)	To improve the energy-specific pro-environmental behavior (EPEB) of hospital employees in an environmentally specific servant leadership (ESL) framework.	Quantitative study Surveys where the variables ESL, EPEB, GSE and GPOS were measured by adapting items from different sources Sample: N = 316 healthcare professionals. Sex: 63% males Age: between 22 and 65 years	The statistical results of the study showed that a servant leadership style with high environmental values (i.e., leaders who prefer environmental benefits to economic ones) has a positive influence on pro-environmental behavior specifically related to energy use by healthcare professionals during the performance of their duties, as employees learn from their leadership and improve their attitudes toward the environment due to the greater perception of support from the organization for implementing ecological initiatives (for instance, without this influence, the energy consumption due to air conditioning increases by 90%). Similarly, the energy consumption behavior of hospital employees improved due to different organizational factors, including leadership style and support for green initiatives.	Engaging health professionals in environmental sustainability
Power et al., 2021 [24] (Ireland)	To estimate the carbon footprint of a single intravitreal injection in a hospital-based intravitreal service.	Quantitative study Calculation of greenhouse gas emissions using the hybrid lifecycle analysis technique (Data on materials procurement, patient travel to and from the hospital and building energy use were used for this calculation)	The carbon emissions associated with an intravitreal injection were 13.68 kg CO_2 eq. This equates to 82,100 kg CO_2 eq annually per ophthalmological service. - Patient journeys: 10.49 kg CO_2 eq per injection (77% of emissions); - Materials procurement: 2.54 kg CO_2 eq (19%); - Building energy use: 0.65 kg CO_2 eq (4% of total emissions). Several aspects were identified that could help reduce emissions, such as bilateral injections on the same day, which would reduce emissions by 35% (less patient travel). Eliminating items considered dispensable from injection packs (povidone–iodine forceps, hand towels, 2 mL syringe, etc.) would reduce emissions by approximately 0.56 kg per injection, i.e., an annual saving of 3360 kg CO_2 eq for an average hospital. No savings were identified in energy use.	Environmental sustainability in healthcare

Table A1. *Cont.*

Reference	Objective	Methodology	Main Findings	Theme
Puška et al., 2022 [23] (Bosnia and Herzegovin)	To suggest a model for the selection of healthcare waste incinerators in secondary healthcare institutions in Bosnia and Herzegovina.	Qualitative study Study in four phases: selection of experts to create a questionnaire to evaluate incinerator alternatives, establishing the weight of the criteria selected in the previous phase, ranking of incinerators and sensitivity analysis and examination of the results. Sample: N = 3 experts examined 6 incinerators	Based on fuel consumption and environmental impact, alternative A2 (I8-M50) best meets the objectives, followed by alternative A1 (I8-M40). Small incinerators have less impact on the environment than larger ones because they consume less fuel and destroy less waste. Their community acceptance is better; they take up less space and are less expensive compared to large incinerators. They can also be installed in populated areas because they do not generate significant air pollution. The study showed that the most important criterion according to the experts' assessment is the technical criterion, followed by the economic and environmental criteria, with the social criterion (acceptance of the incinerator by the community) being the least important.	Environmental sustainability in healthcare
Ryan-Forgarty et al., 2016 [36] (Ireland).	To explain and evaluate a systems-based action framework designed to create synergies between both regulatory requirements and voluntary initiatives, supported by government agencies and NGOs, so as to best meet environmental impact mitigation objectives.	Qualitative study Review of programs and actions on waste management and energy consumption. Sample: Cork University Hospital Programs: Green Campus; Eco-Schools; EPA Green Health; Global Network of Green Hospitals Healthy; Public Sector Energy Efficiency Program	This implementation resulted in the mitigation of existing impacts and a commitment to continuous improvement. Environmental education programs, especially action- and reward-based programs, proved successful in providing a systematic approach that facilitates environmental action and education. The researchers acted as advisors and highlighted the seven steps of the program, namely, creating an environmental committee, conducting an environmental study, developing an action plan, monitoring and evaluation (using sustainability indicators), reporting and engagement, linking to on-campus learning and developing a green charter (to ensure continuity).	Environmental sustainability in healthcare

Table A1. *Cont.*

Reference	Objective	Methodology	Main Findings	Theme
Simpson et al., 2022 [35] (United Kingdom)	To scope, identify and appraise the effectiveness of proposed actions relevant to air quality across all areas of operational management at the Queen Elizabeth Hospital Birmingham.	Mixed study Semi-structured interviews and questionnaire to score 79 actions identified in the qualitative phase Sample: 32 experts in areas of interest for the project	The actions with the greatest impact on improving air quality were as follows: - Improve the efficiency of activities that are executed remotely; - Create the role of transportation coordinator to help reduce the impact of employee travel and transportation; - Convert the fleet to electric or hydrogen fuel to replace diesel trucks and vans; - Establish real optimal levels of teleworking and guide the sustainable use of transport to establish new habits; - Implement 'auto-off' periods for non-essential information technology equipment; - Incorporate sustainability into procurement processes by rewarding low-impact and low-emission supply chains; - Install charging points for electric vehicles in the parking lot; - Evaluate the capacity of bicycle courier logistics; - Collect patient and visitor travel data through registration systems; - Integrate sustainable transportation into the patient mindset; - Create and promote a 'sustainability in health management' module with the education department; - Create more and better secure bicycle storage.	Environmental sustainability in healthcare
Scavarda et al., 2019 [30] (Brazil)	To analyze the central sterilization department and the storage of materials in the health supply chain in a Brazilian private health institution and propose a management framework.	Literature review and analysis of the supply chain of materials that make up surgical kits in a healthcare institution (observing the processing of approximately 400 surgical kits from 50 hip arthroplasty surgical procedures). Sample: private health institution in Rio de Janeiro with 200 beds and 11 operating rooms	The proposed healthcare supply chain management framework addresses four materials. It advocates strategies to sell cardboard for packaging to recycling cooperatives, which could save USD 132,000 at the end of one year. Paperboard also provides craftsman cooperatives with other possibilities for conversion into several other products, such as earring, bracelet and necklace boxes. In relation to plastics, a reduction in their use is encouraged, including incineration, reducing the release of toxins. Furthermore, the sale of plastic may reduce the costs of nonwoven sterile barrier systems, thereby allowing reverse logistics of these products to be implemented in the supply chain.	Environmental sustainability in healthcare

Table A1. *Cont.*

Reference	Objective	Methodology	Main Findings	Theme
Vaccari et al., 2017 [21] (Italy)	To examine approaches to more sustainable management of waste and water consumption in a healthcare facility.	Quantitative study Sample: N = 1, Gardone Val Trompia Hospital in Brescia, Italy.	Some of the highlighted proposals are as follows: - Technological practices: modification of plants or supply procedures. - Behavioral practices: changing staff and patient water usage habits (i.e., using fresh water instead of bottled water in the dining room). - Healthcare solid waste management: the hospital produces 10.58 kg/person/month of non-hazardous waste and 5.26 kg/month of potentially infectious waste. A high level of unsorted waste was observed (62%), mainly textiles (40%), paper (20%) and plastics (17%). Given the high consumption of paper and plastics, there is a possibility of recovering their value provided they can be segregated, waste can be selectively collected, and recycling is increased. On the other hand, efforts must be made to change clinical practices by using fewer materials and incorporating the use of environmentally friendly materials.	Environmental sustainability in healthcare
Vishwakarma et al., 2022 [28] (India)	To investigate the relationship among the indicators of stakeholder involvement, sustainable supply chain practices, sustainable performance and the circular economy and its effect on attaining sustainability at large.	Quantitative study Questionnaires to identify SHSCP, HSI, SHP and CHE practices. Sample: N = 145 participants (60.68% hospital staff and 39.32% healthcare industry stakeholders)	A positive relationship was confirmed among the circular economy, the supply chain, the participation of people interested in healthcare and sustainability measures (statistically significant relationships between HSI and SHSCP; HSI and SHP; SHSCP and SHP; SHSCP and CHE and SHP and CHE. Some of the proposals include repairing, reusing and renewing resources; reducing biomedical waste and the use of toxic materials; extending the useful life of products; and making greater use of bio-friendly products and renewable sources. In addition, the circular economy was promoted as a mechanism to streamline consumption and increase digitalization.	Engaging health professionals in environmental sustainability

Table A1. *Cont.*

Reference	Objective	Methodology	Main Findings	Theme
Wei et al., 2021 [33] (China, Pakistan and Romania)	To reduce the environmental footprint of a hospital by promoting its employees' environment-specific behavior via corporate social responsibility (CSR) and ethical leadership (EL).	Quantitative study Survey Sample: N = 489 staff surveys from the hospital (61.76% health workers and 38.24% general administration) Gender: 56.85% men Age: 42.55% from 20 to 30 years, 46.01% from 31 to 50 and 11.6% over 50	The respondents confirmed that they were motivated to participate in different activities related to environmental behavior in response to the commitment to corporate social responsibility (CSR) by this organization ($\beta1 = 0.426$; $p < 0.05$). Therefore, to reduce the environmental footprint of institutions, policies are needed that redefine the CRS of institutions, and they need to understand the importance of CRS. A positive relationship was observed between EL and CRS ($\beta2 = 0.388$; $p < 0.05$), as well as between EL and employee pro-environmental behavior ($\beta3 = 0.32$; $p < 0.05$). An ethical leader must communicate to the employee the importance of improving the environmental footprint. The overall environmental performance of organizations is enhanced through the voluntary commitment of their employees. In the presence of such leadership, employees increase their environmental commitment to a higher level, stimulating their pro-environmental behavior ($\beta4 = 0.128$, $p < 0.05$). Finally, both male and female leaders positively moderated the indirect relationship between CSR and pro-environmental behavior, but this moderation was stronger among female leaders.	Engaging health professionals in environmental sustainability
Weisz et al., 2020 [18] (Austria and Germany)	To identify areas for sustainability improvement in healthcare systems and break down carbon emissions attributable to this care.	Quantitative study Multi-regional input–output analysis for carbon emissions by healthcare providers. Sample: healthcare systems in Austria and Germany	Austria's healthcare carbon footprint was 6.8 million tonnes of CO_2 in 2014 (14% less than in 2005, thanks to the use of renewable energy). Hospitals contributed 32% of emissions, with 48 tCO_2 per bed per year. Emissions were mainly produced by purchases of medical goods and services (36%), pharmaceuticals (19%) and energy consumption (31%). CO_2 emissions from patient transport also increased by 15%, demonstrating the need for improved planning. The six main areas of intervention in sustainability are direct energy use, product alternatives, prevention of inefficiencies in the health system (e.g., rational use of pharmaceuticals), changes in medical treatments, changes in national planning of health service delivery and transformation of the healthcare system towards promotion.	Environmental sustainability in healthcare

Table A1. *Cont.*

Reference	Objective	Methodology	Main Findings	Theme
Xu et al., 2022 [22] (Pakistan)	To analyze the attitude and the pro-environmental behavior (PEB) of healthcare professionals through corporate social responsibility (CSR) and green organizational practices in the health sector of an emerging economy.	Quantitative study Survey Sample: N = 441 health professionals Sex: 58% men (256) and 42% women (185) Age: from 18 to 65 years	CSR activities were shown to positively influence employees' pro-environmental behavior (β1 = 0.493; $p < 0.01$) and promote the adoption of green practices in organizations (β2 = 0.362; $p < 0.01$). Furthermore, the results indicated that the implementation of green organizational practices fosters employees' green behavior (β3 = 0.183; $p < 0.01$). Healthcare professionals with pro-environmental, altruistic values favor a reduction in the carbon footprint of a hospital (β4 = 0.276, $p < 0.01$) through actions such as rational energy use, turning off electrical equipment when not in use and using recyclable and reusable materials. Therefore, it was suggested that the hospital re-evaluate its hiring procedure to select these types of professionals, as they will help the hospital's sustainability to a greater extent. Similarly, HE demonstrates the importance of personal values and the corporate responsibility of managers to be proactive in environmental sustainability.	Engaging health professionals in environmental sustainability

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Associations of Exposure to 24 Endocrine-Disrupting Chemicals with Perinatal Depression and Lifestyle Factors: A Prospective Cohort Study in Korea

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Abstract: During pregnancy, reproductive hormonal changes could affect the mental health of women, such as depression and anxiety. Previous studies have shown that exposure to endocrine disrupting chemicals (EDCs) is significantly associated with mental health symptoms; however, the results were inconsistent. We aimed to examine the association between 24 endocrine-disrupting chemicals (EDCs) in maternal urine and perinatal depression and their association with dietary and lifestyle factors. Participants were recruited from the "No Environmental Hazards for Mother–Child" cohort in Korea. Structured questionnaires asking dietary and lifestyle factors and evaluation of depressive symptoms were administered during antepartum (14 weeks of gestation) and postpartum (within four weeks after birth) periods. Urine samples were collected from 242 and 119 women during antepartum and postpartum periods, respectively. To assess perinatal depression, we used the Center for Epidemiological Studies-Depression Scale and the Edinburgh Postnatal Depression Scale. Antepartum depression and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP) (1.50, 1.01–2.23) and 1-hydroxypyrene (1-OHP) (0.05, 0–0.89) showed significant positive association. Additionally, postpartum depression showed significant associations with mono(2-ethyl-5-oxohexyl) phthalate (MEOHP) (2.78, 1.00–7.70), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) (2.79, 1.04–7.46), 2-hydroxynaphthalene (2-NAP) (7.22, 1.43–36.59), and 2-hydroxyfluorene (2-FLU) (<0.01, 0–0.004). Some dietary factors (consumption of fish, fermented foods, cup noodles, and popcorn) and consumer product factors (use of skin care, makeup, perfume, antibiotics, sunscreen, nail polish, new furniture, plastic tableware, detergent, polish, paint, and pesticide) were associated with the concentration level of chemicals. We found that exposure to several EDCs during pregnancy and the postpartum period was associated with perinatal depression and dietary–lifestyle factors. Women in childbirth need to actively seek out information about exposure to EDCs and make efforts to avoid them for their own and fetal health.

Keywords: perinatal depression; endocrine disrupting chemical; dietary factor; lifestyle factor

1. Introduction

The endocrinology of pregnancy is related to physiological changes during fetal development and growth [1]. During the perinatal period, when a woman is pregnant and gives birth, she undergoes significant hormonal changes. For example, as the placenta develops, the levels of human chorionic gonadotropin (hCG) and placental lactogen, which provide nutrients to the fetus, increase, as do the levels of estrogen and progesterone, which are essential for maintaining pregnancy [2]. However, after birth, the placenta, which secretes reproductive hormones, is expelled, and the levels of these hormones drop rapidly [2]. The concentration of thyroid-stimulating hormone (TSH) in early pregnancy temporarily decreases due to the lowering effect of thyroid function caused by increased hCG levels and then begins to increase again [3]. This thyroid hormonal fluctuation may influence physiological changed that could be associated with mental health, including postpartum depression (PPD) [3]. In addition, pregnancy increases cardiac output and respiratory rate by approximately 30–40%, constituting a physical burden for women [2]. Due to these physical changes and fluctuations in reproductive hormones, women experience mental health symptoms such as anxiety, stress, and depression during the perinatal period [4–6]. Perinatal depression is defined as the occurrence of major depressive episodes, either during pregnancy (antenatal depression, AD) or within the first four weeks of postpartum (PPD). Exposure to EDCs in pregnant women can lead to endocrine disruptions, including immune activation and inflammatory responses [4]. According to a systematic review study, the biological and psychosocial predictors of PPD include hormonal dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, inflammatory processes, genetic vulnerabilities, severe life events, chronic stress, and social support [7]. Among these, exposure to EDCs has been identified as a biologically significant factor [4,7]. The relationship between EDC concentrations in biological samples reflecting internal exposure in pregnant women and PPD has been the focus of recent research. A study conducted in Korea observed an association between EDC concentrations in breast milk and postpartum depression, underscoring the need for further research [8].

Phthalates, bisphenols, parabens, polycyclic aromatic hydrocarbons (PAHs), and volatile organic compounds (VOCs) are endocrine-disrupting chemicals (EDCs) that people may be ubiquitously exposed to in daily life through oral ingestion, dermal absorption, and inhalation [9,10]. These non-persistent chemicals are characterized by short half-lives ranging from 6 to 24 h, which leads to rapid metabolism and large within-person variability over time [9]. Despite their fast turnover, these chemicals are found consistently in human samples, such as urine or breast milk, indicating that most individuals face regularly daily exposure [4,11]. Although the mechanisms underlying the increased risk of perinatal depression following exposure to non-persistent EDCs are unclear, some possible explanations have been suggested. EDCs have estrogenic effects on the hippocampus and amygdala, regulating the hypothalamic–pituitary–adrenal axis (HPA) or influencing changes in neurotransmitters, causing anxiety and depressive behavioral disorders [12–14]. EDCs may cause depression by interfering with the production, transport, and release of neurotransmitters such as dopamine, causing synaptic plasticity [15,16]. Another mechanism is that EDCs act like fake thyroid hormones, which can induce thyroid dysfunction or hypothyroidism and cause psychopathological effects [4]. In other words, if exposed in early pregnancy, EDCs can interfere with thyroid function, reducing the fetus' neurological development and the mother's metabolic function [17,18]. Other possible mechanisms include elevated proinflammatory cytokine levels, oxidative stress, and epigenetic gene expression [19,20]. Epidemiological studies linking exposure to diverse EDCs and psychosocial disorders, such as depression and anxiety, have been reported in various populations, but the results are inconsistent [9,11,21–28]. Previous epidemiological studies have reported that exposure to phthalates and bisphenols increased the risk of postpartum depression by 1.03 (95% CI: 0.07, 1.99) times with bisphenol A (BPA) and bisphenol F (BPF) [11], 1.22 times (95% CI: 1.00–1.48) with mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), 1.33 times (95% CI: 1.14–1.54) with mono-N-butyl phthalate (MnBP), 1.23 times (95% CI: 0.99–1.51) with mono-isobutyl phthalate (MiBP), and 1.29 times (95% CI: 1.00–1.67) with monobenzyl phthalate (MBzP) [24]; in contrast, several epidemiological studies reported that there was no significant difference between exposure to phthalates, bisphenols, and parabens and postpartum depression [9,11,24]. Although women are vulnerable to depression and anxiety during pregnancy, few studies have reported on perinatal depression. Therefore, the purpose of this study was to determine the level of exposure to EDCs during pregnancy and the postpartum period and to determine the relationship between exposure to EDCs and ante- and postpartum depression. Additionally, we explored the relationship between pregnant women's diet, lifestyle habits, and exposure to 24 selected EDCs.

2. Materials and Methods

2.1. Study Design and Population

The No Environmental Hazards for Mother–Child (NoE-MoC) study is a prospective birth cohort in Korea established from the 1st trimester of pregnancy to three years after childbirth. Pregnant women were recruited from 2022 to 2023 in five hospitals in Korea (three in Seoul, one in Gyeonggi-do, and one in Gangwon-do) if they met the following inclusion criteria: (1) healthy Korean pregnant women at least 18 years of age; (2) 14 weeks of gestation (1st trimester of pregnancy); (3) receiving regular prenatal care from an obstetrician; (4) singleton pregnancy; (5) not taking any medications for mental health symptoms such as depression or anxiety; (6) not having any underlying disease such as hypertension, diabetes mellitus, thyroid, etc. All the participants were Koreans of the same ethnicity, maintained national insurance coverage, and lived with their husbands. They were invited to submit urine samples and answer a structured questionnaire covering sociodemographic and obstetric characteristics, dietary factors, consumer product factors, fetal growth records with ultrasonography, and depression symptoms when they visited the hospital for a medical checkup (1st, 2nd, and 3rd trimesters of pregnancy and within 4 weeks after childbirth). Considering the short half-life of EDCs, we investigated whether the study participant used food and personal care products within one to two days. We simultaneously conducted a structured questionnaire, urine collection, and assessment of depressive symptoms. Structured questionnaires and evaluation of depressive symptoms were conducted during pregnancy (around 14 weeks) and postpartum (within four weeks after birth), and urine samples were collected from 242 and 119 women, respectively, during each period. A total of 242 eligible pregnant women were enrolled in this cohort, and 197 were subsequently followed up, of whom 119 submitted postpartum depression scores. Written consent was obtained after participants received detailed explanations regarding this study from qualified nurses at the first visit. This study was approved by the Ethics and Human Committees of Kyung Hee University (KHSIRB-21-598) and Kangwon National University Hospital (KNUH-2022-02-001-001).

2.2. Perinatal Depression Assessment

Maternal ante- and postpartum depressive symptoms were assessed using a self-administered questionnaire, employing the Korean version of the Center for Epidemiological Studies-Depression Scale (CES-D) [29–31] for antepartum depression and the Korean version of the Edinburgh Postnatal Depression Scale (K-EPDS) [31,32] for postpartum depression. The Korean version of the CES-D consists of 20 items covering depressive mood, guilt, lack of self-valuation, hopelessness, and sleep disturbance. The total score ranges from 0 to 60, with a higher score indicating more depressive symptoms. A four-point Likert scale (0–3) was used, with 0 indicating "not at all" and 3 "severely". A total $\leq$ 20 was classified as "normal" and $\geq$21 was classified as "at risk, abnormal" based on the validated cut-off point for Korean women [30]. The K-EPDS consists of 10 items covering depressive mood, anxiety, hopelessness, and irritability. The total score ranges from 0 to 22, with a higher score indicating more depressive symptoms. The same four-point Likert scale was used, with a total $\leq$ 9 being classified as "normal" and $\geq$10 as "at risk, abnormal" based on the validated cut-off point for postnatal Korean women [32]. Standardized z-scores were calculated and used to compare and analyze EPDS and CES-D scores.

2.3. Dietary and Lifestyle Factors Assessment

The questionnaire administered to pregnant women included items on sociodemographic and health information (gestational age, weight, height, marital status, educational level, monthly household income, occupation, residence, medical history, obstetric history, alcohol use, and smoking); dietary factors; and consumer product factors. All items in the dietary and consumer product questions were chosen based on a literature review that showed a significant association with exposure to EDCs. This questionnaire was validated by exposure assessment experts and used in our previous research [12]. Participants were required to indicate the frequency of food consumption and daily life product usage from the past 1 day to 4 weeks. Dietary factors consisted of meat with fat tissue, fish, dairy products, shellfish, fermented food, fried food, fast food, frozen food, cup noodles, ice cream, canned food, vinyl-packed food, and popcorn. Consumer product factors consisted of skincare products, makeup products, hair products, manicures, perfumes, antibiotics, sunscreen, new furniture, plastic bowls, disposable dishware, dishwasher, detergent, polish, water-proofing products, air freshener, glue, insect repellent, and mosquito repellent. Responses were recorded using a nine-point Likert scale interpreted as follows: 1 (none or rarely), 2 (once a month), 3 (2–3 times a month), 4 (once a week), 5 (2–4 times a week), 6 (5–6 times a week), 7 (once a day), 8 (twice a day), and 9 (3 times or more a day). All scores were added to calculate the total score in each domain.

2.4. Analysis of 24 Non-Persistent Chemicals in Urine Samples

We collected 20-mL maternal spot urine samples in polypropylene cups during each follow-up visit, which were directly stored at −80 °C until analysis. We measured the concentrations environmental pollutant chemicals, including nine phthalate metabolites (MnBP, MEP, MCPP, MBzP, MMP, MEOHP, MEHHP, MECPP, and MiBP) [8,10–12,14,21]; five phenols (BPA, BPF, BPS, TCS, and BP-3) [8,10–13,17,18]; four parabens (MP, EP, BP, and PP) [8,11,12,17]; four PAHs (1-OHP, 2-NAP, 1-PHE, and 2-FLU) [23,24,27,28]; and two VOCs (t, t-MA and BMA) [22,26] in the urine samples. The full names of these chemicals and the limit of detection (LOD) are presented in Table 1.

Detailed procedures for sample preparation, quality assurance, and quantification have been previously described [8,33]. Briefly, LC-MS/MS and the Thermo Scientific™ Vanquish™ ultra-high-performance liquid chromatography (UHPLC) system (Thermo Finnigan, San Jose, CA, USA) were used in the chemical analysis employing an ACE Excel 2 C18-AR column (150 mm × 2.1 mm I.D.; Advanced Chromatography Technology, Aberdeen, UK) and a TSQ Altis triple-quadrupole mass spectrometer (Thermo Finnigan) equipped with an electrospray ionization (ESI) source. The mobile phase consisted of water with 0.1% formic acid (solvent A) and acetonitrile with 0.1% formic acid (solvent B), with a gradient elution program optimized for target analytes. The spray voltage was 4500 V in the positive mode and 3500 V in the negative mode. The ion transfer tube temperature was 320 °C, and the vaporizer temperature was 340 °C in both modes. The column temperature was maintained at 35 °C. All experiments were performed in time-dependent reaction monitoring mode for simultaneous analysis. All chemicals used in this study were purchased from Sigma-Aldrich (St. Louis, MO, USA), Merck (Darmstadt, Germany), or Burdick and Jackson (Muskegon, MI, USA). *E. coli* β-glucuronidase (140 U/mg at 37 °C) was purchased from Roche (Mannheim, Germany). Standard reference materials (SRMs) 3672 and 3673 were purchased from the National Institute of Standards and Technology (NIST, Gaithersburg, MD, USA).

Table 1. Creatinine adjusted urinary concentration of chemicals in the ante- and postpartum periods (µg/g creatinine).

Groups	Analytes	Antepartum (14 Weeks of Gestation, n = 242)							Postpartum (One Month after Delivery, n = 119)						*t*-test *	*p*-Value
		DF (%)	LOD (µg/L)	GM	25th	50th	75th	Max	DF (%)	GM	25th	50th	75th	Max		
Phthalates	MnBP	100	0.11	14.45	7.72	15.34	26.11	232.82	100	24.95	14.51	22.33	39.44	192.25	−5.430	**<0.001**
	MEP	73.6	0.07	1.23	<LOD	1.80	6.35	684.50	100	3.28	1.11	2.52	8.04	711.64	−2.166	**0.031**
	MCPP	97.1	0.06	0.44	0.30	0.42	0.66	10.31	97.6	0.46	<LOD	0.49	0.63	3.14	−0.461	0.645
	MBzP	90.9	0.04	0.21	0.11	0.22	0.40	7.30	94.4	0.19	0.12	0.16	0.35	8.00	1.120	0.263
	MMP	100	0.01	0.33	0.17	0.33	0.62	11.51	37.3	0.03	<LOD	<LOD	0.21	79.21	2.019	**0.045**
	MEOHP	100	0.03	2.55	1.48	2.61	4.67	34.58	96.0	2.76	1.77	3.02	6.72	84.02	−1.958	0.052
	MEHHP	100	0.03	4.24	2.48	4.40	7.51	55.02	97.6	4.06	2.57	4.27	9.14	125.91	−0.640	0.523
	MECPP	92.1	0.03	3.40	2.48	5.08	10.32	53.47	98.4	8.87	5.63	8.65	18.24	196.18	−6.100	**<0.001**
	MiBP	98.8	0.07	5.35	2.54	5.69	12.00	178.70	82.5	3.34	1.01	5.32	18.30	300.41	0.288	0.774
Bisphenols	BPA	78.5	0.12	0.64	0.36	0.61	1.06	22.7	99.2	0.87	0.50	0.83	1.48	21.34	−5.118	**<0.001**
	BPF	42.1	0.08	0.47	0.09	0.26	2.48	19.9	48.4	0.11	<LOD	<LOD	0.19	2.78	4.100	**<0.001**
	BPS	98.8	0.01	0.30	0.13	0.25	0.63	22.1	100	0.77	0.37	0.64	1.74	86.62	−5.168	**<0.001**
Phenols	TCS	71.5	0.04	0.28	0.13	0.27	0.63	3.11	22.2	0.74	0.48	0.48	0.48	25.12	−6.855	**<0.001**
	BP-3	71.5	0.10	0.43	0.14	0.30	0.93	341	69.8	0.25	<LOD	0.15	0.52	156.64	0.022	0.983
Parabens	MP	100	0.15	6.70	2.77	4.82	9.07	1390	64.3	1.93	<LOD	1.81	13.90	682.09	2.307	**0.022**
	EP	99.6	0.14	32.80	10.2	40.30	126	2900	90.5	29.14	10.50	48.08	168.23	2492.72	−0.431	0.667
	PP	31	0.21	1.99	0.34	0.93	12.7	250	69.8	0.64	<LOD	0.32	1.44	303.40	−2.129	**0.034**
	BP	100	0.07	0.78	0.48	0.70	1.09	23.8	100	1.11	0.73	0.96	1.53	12.52	−3.567	**<0.001**
PAHs	1-OHP	85.5	0.03	0.14	0.07	0.13	0.23	4.08	98.4	0.10	0.07	0.11	0.15	0.97	2.652	**0.008**
	2-NAP	100	0.05	2.39	1.24	2.07	3.96	84.1	99.2	2.06	1.01	1.82	3.67	76.89	0.667	0.505
	1-PHE	77.3	0.02	0.07	0.04	0.06	0.09	37.0	84.9	0.05	0.03	0.05	0.08	0.53	2.077	**0.039**
	2-FLU	95	0.01	0.13	0.08	0.14	0.22	9.10	92.9	0.11	0.07	0.13	0.21	2.43	0.094	0.925
VOCs	t,t-MA	99.6	0.58	45.20	21.40	44.80	92.0	554	100	48.75	28.81	43.56	72.59	395.46	−0.869	0.386
	BMA	99.6	0.04	2.87	1.49	2.49	4.67	10100	99.2	5.57	3.24	5.21	9.43	791.21	−5.2132	**<0.001**

DF, detection frequency; LOD, limit of detection; GM, geometric mean; Min, minimum; Max, maximum; MnBP, mono-N-butyl phthalate; MEP, mono ethyl phthalate; MCPP, Mono(3-carboxypropyl) phthalate; MBzP, monobenzyl phthalate; MMP, mono(2-methylpropyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MiBP, mono-isobutyl phthalate; BPA, Bisphenol A; BPF, Bisphenol F; BPS, Bisphenol S; MP, Methylparaben; EP, Ethylparaben; BP, Butylparaben; PP, Propylparaben; TCS, Triclosan; BP-3, Benzophenon-3; 1-OHP, 1-hydroxypyrene; 2-NAP, 2-hydroxynaphthalene; 1-PHE, 1-hydroxyphenanthrene; 2-FLU, 2-hydroxyfluorene; t,t-MA, trans, trans-muconic acid; BMA, benzylmercapturic acid; * *t*-test after natural log transformation; bold values are statistically significant ($p < 0.05$).

For quality control, a standard calibration curve with a regression coefficient > 0.99 was generated for all curves using 30% methanol in aqueous solution. The standard calibration curve ranged between 0.005 and 20 ng/mL. Urine samples were spiked with isotope-labeled standard material. The signal-to-noise ratio of the matrix used in this analysis was three. The average recovery rate for all targets in the matrix spike sample ranged between 86 and 105%, and the relative standard deviation ranged between 11 and 17%. Matrix spike urine samples with known concentrations (1, 10, and 20 ng/mL) and randomly selected procedural blank samples were used for experimental verification. No target analytes were detected in the blank sample. To evaluate the intra-day precision, the standard solution evaluated six times a day was compared with the target solution, and the inter-day precision was evaluated against the standard solution measured six days in a row. The overall quality and accuracy of the described analysis method were monitored through an interlaboratory comparison program.

2.5. Statistical Analyses

All chemicals were detected in >30% of urine samples. Values below the LOD were substituted with LOD/$\sqrt{2}$ [34]. The urinary creatinine levels were adjusted to reflect changes in the intra- and inter-subject variability in renal filtration dynamics [35]. Demographic characteristics were described as the mean, standard deviation, median, and minimum–maximum for continuous variables and numbers and percentages for categorical variables. A normality test (Kolmogorov–Smirnov test) was conducted for all data; because the level of chemical concentration in urine samples showed a right-skewed distribution, a natural log transformation was performed. The mean differences between the chemicals in both the ante- and postpartum periods were compared using a Student's *t*-test. Pearson's correlation coefficients were used to identify correlations among chemicals, depression scores, and dietary and lifestyle factors. To examine the association between each analyte (phthalates, phenols, parabens, PAHs, and VOCs) and ante- and postpartum depression, multiple logistic regression with the entry method was used to estimate odds ratios (ORs) and 95% confidence intervals. To confirm the association between each analyte and dietary and consumer product factors, bivariate linear regression was used. To evaluate the mixture effect between urinary chemicals and the perinatal depression score, we used Bayesian Kernel Machine Regression (BKMR). BKMR is a reliable method frequently used in the environmental health research field in which non-linear, non-additive, and mixture interaction effects of all substances are considered [36]. The overall cumulative mixture effects and dose–response effects of each of 24 urinary chemicals were evaluated in relation to the antepartum and postpartum depression scores. Subsequently, we evaluated the mixture effect of each chemical on the depression score by dividing the chemicals into subgroups according to phthalates, bisphenols, parabens, PAHs, and other chemicals. Maternal age, early pregnancy body mass index (BMI), education, income, parity, cotinine level in the urine, and neonatal sex were adjusted for as covariates following the previous studies [8,9,11,12]. Statistical significance was evaluated at $p < 0.05$. All statistical analyses were performed using R 4.1.0 (R Development Core Team, Vienna, Austria) and SPSS 28.0 (IBM SPSS Statistics, Armonk, NY, USA).

3. Results

3.1. Study Participants

The mean maternal age at the first visit was 33.8 years (range 21–42 years), and the mean early pregnancy BMI was 23.2 kg/m^2 (Table 2). Over 81% of the participants had a college or higher educational level, over 51% reported a more than 5000 USD household income monthly, about 65% were employed and lived in metropolitan areas, and over

57% were primipara mothers. The mean maternal urinary cotinine level was 25.4 μg/g creatinine. The mean cotinine level of non-smokers was 0.89 μg/g creatinine, while the mean cotinine level of six possible smokers was 995.76 μg/g creatinine (ranged from 544.88 to 1720 μg/g creatinine). The mean score of antepartum depression was 16.5 (range 1–36), and 23.6% of participants were classified as abnormal, with a score $\geq$ 21. The mean score of postpartum depression was 8.9 (range 0–22), and 45.4% of participants were classified as abnormal, with a score $\geq$ 9.

Table 2. Socioeconomic characteristics and ante- and postpartum depression of participants (n = 242).

Variables	Categories	n/M	%/SD	Median	Min	Max
Age (years)		33.8	4.0	34.0	21.0	42.0
Early-pregnancy BMI (kg/m^2)		23.2	4.2	22.5	14.8	40.2
Education	<college	44	18.2			
	$\geq$college	198	81.8			
Household income ($/month)	$\leq$5000	124	51.2			
	>5000	118	48.8			
Employment status	Yes	157	64.9			
	No	85	35.1			
Residence area	Metropolitan	155	64.0			
	Non-metropolitan	87	36.0			
Parity	Primipara	139	57.4			
	Multipara	103	42.6			
Cotinine level (μg/g creatinine) *		0.31	186.46	0.22	0.04	1720
Antepartum depression score		16.5	6.1	15.5	1	36
	Low ($\leq$20)	185 (76.4)				
	High ($\geq$21)	57 (23.6)				
Postpartum depression score (n = 119)		8.9	3.6	8	0	22
	Low ($\leq$9)	65 (54.6)				
	High ($\geq$10)	54 (45.4)				

M, mean; SD, standard deviation; Min, minimum; Max, maximum; BMI, body mass index; * detection frequency of cotinine was 84.3%.

3.2. Non-Persistent Urinary Chemical Concentrations in the Ante- and Postpartum Periods

Table 2 shows the detailed results for each tested chemical in 242 antepartum and 119 postpartum urine samples. The detection frequency, LOD, geometric mean (GM), median, minimum, and maximum values are shown. The detection frequency ranged from 22.2% for TCS in the postpartum period to 100% for MnBP, MMP, MEOHP, MEHHP, MP, BP, and 2-NAP in the antepartum period and for MnBP, MEP, BPS, BP, and t,t-MA during the postpartum period. Significant mean differences between the ante- and postpartum periods were present in MnBP, MEP, MMP, MECPP, BPA, BPF, BPS, TCS, MP, PP, BP, 1-OHP, 1-PHE, and BMA, with urinary concentrations decreasing from antepartum to postpartum (Figure 1). Each subject's urinary chemical concentration changes between ante the partum and postpartum periods are presented as line graphs (Figure 2). Some chemicals, including MEOHP, MEHHP, MECPP, BPA, BPS, TCS, and BMA, generally showed an increasing tendency, while BPF and 1-PHE showed a decreasing pattern in the postpartum period compared to antepartum period.

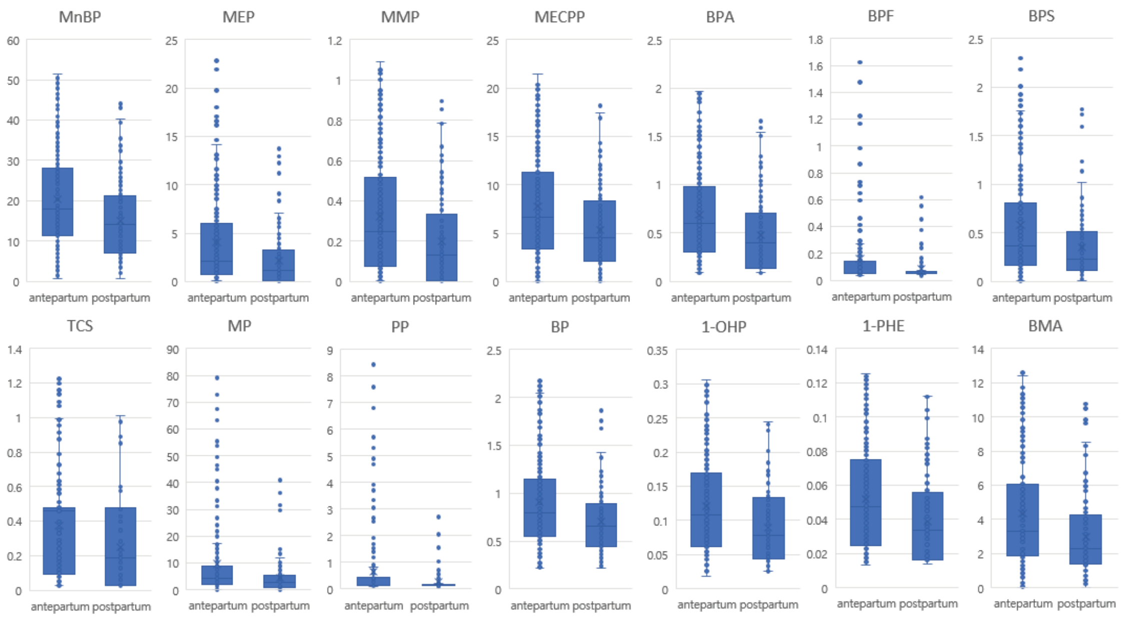

Figure 1. Concentration changes of chemicals in the ante- and postpartum periods. All boxplots show statistically significant higher median, mean, IQR, minimum, maximum, and outliers of chemicals in the antepartum period versus postpartum period. MnBP, mono-N-butyl phthalate; MEP, mono ethyl phthalate; MMP, mono(2-methylpropyl) phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; BPA, Bisphenol A; BPF, Bisphenol F; BPS, Bisphenol S; TCS, Triclosan; MP, Methylparaben; PP, Propylparaben; BP, Butylparaben; 1-OHP, 1-hydroxypyrene; 1-PHE, 1-hydroxyphenanthrene; BMA, benzylmercapturic acid. Extreme outliers (<Q1 − 5*IQR, >Q3 + 5*IQR) have been omitted.

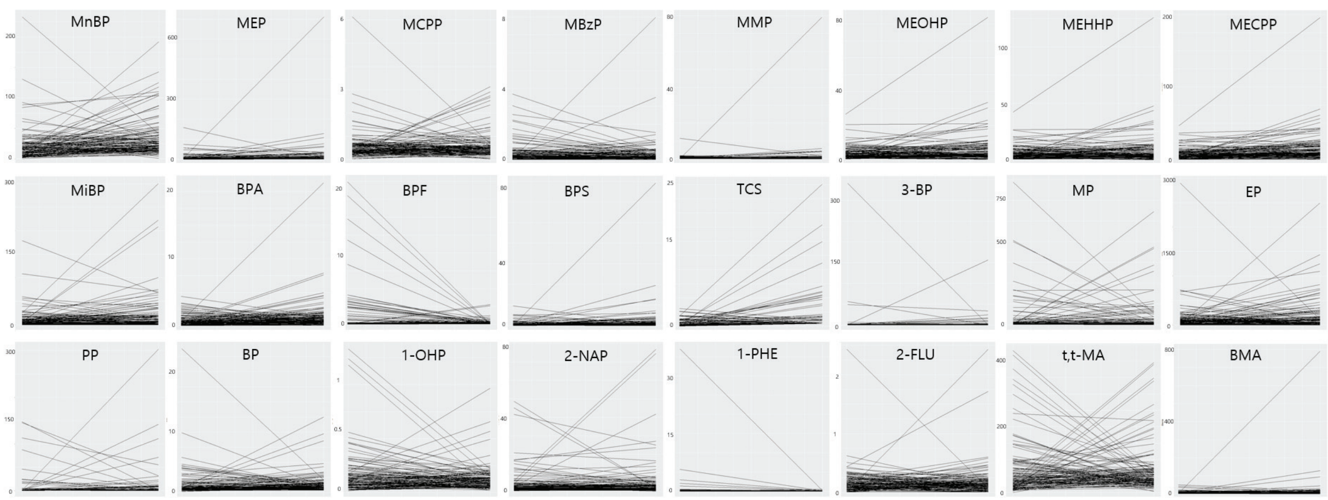

Figure 2. Difference of 24 non-persistent endocrine disrupting chemicals (EDCs) in maternal urine at the points of the 1st trimester and one month after delivery (n = 119). MnBP, mono-N-butyl phthalate; MEP, mono ethyl phthalate; MCPP, Mono(3-carboxypropyl) phthalate; MBzP, monobenzyl phthalate; MMP, mono(2-methylpropyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MiBP, mono-isobutyl phthalate; BPA, Bisphenol A; BPF, Bisphenol F; BPS, Bisphenol S; MP, Methylparaben; EP, Ethylparaben; BP, Butylparaben; PP, Propylparaben; TCS, Triclosan; BP-3, Benzophenon-3; 1-OHP, 1-hydroxypyrene; 2-NAP, 2-hydroxynaphthalene; 1-PHE, 1-hydroxyphenanthrene; 2-FLU, 2-hydroxyfluorene; t,t-MA, trans, trans-muconic acid; BMA, benzylmercapturic acid.

3.3. Association Between Urinary Chemical Concentration and Ante- and Postpartum Depression

In the antepartum period, the depression score of mothers was statistically significantly correlated with MCPP ($r = -0.18$), MBzP ($r = -0.11$), MEHP ($r = -0.07$), and PP (r = −0.06). In the postpartum period, some chemicals showed slight positive correlation with depression score, but there was no statistical significance at the significance level $p < 0.05$. The distribution of each depression score at the antepartum and postpartum periods is presented as scatter plots (Supplementary Figure S1).

In the adjusted multiple logistic regression model with covariates of maternal age, early pregnancy BMI, education, income, parity, gestational age, urine cotinine level, and neonatal sex, we observed a significant association with antepartum depression scores in MECPP (aOR = 1.50, 95% CI = 1.010–2.227) and 1-OHP (aOR = 0.05, 95% CI = 0.003–0.888) (Table 3). In the postpartum period, the antepartum depression score was adjusted with other covariates. Several phthalates and PAHs were significantly associated with maternal postpartum depression scores. In the phthalate group, this consisted of MEOHP (aOR = 2.78, 95% CI = 1.004–7.700) and MEHHP (aOR = 2.79, 95% CI = 1.040–7.459) and, in the PAH group, of 2-NAP (aOR = 7.22, 95% CI = 1.426–36.593) and 2-FLU (aOR <0.01, 95% CI = 0–0.004).

Table 3. Multiple logistic regression of the association between 24 chemicals and antepartum and postpartum depression.

		Antepartum Depression (n = 242)			**Postpartum Depression (n = 119)**		
Groups	**Chemical**	**aOR**	***p*-Value**	**95% CI**	**aOR**	***p*-Value**	**95% CI**
Phthalates	MnBP	0.97	0.863	0.682–1.379	0.46	0.185	0.144–1.455
	MEP	0.79	0.081	0.603–1.030	1.03	0.936	0.536–1.970
	MCPP	0.27	0.065	0.064–1.088	0.30	0.562	0.005–17.788
	MBzP	0.38	0.130	0.113–1.325	9.92	0.307	0.121–NA
	MMP	0.67	0.473	0.217–2.031	<0.01	0.180	0–NA
	MEOHP	1.04	0.874	0.645–1.675	**2.78**	**0.049**	**1.004–7.700**
	MEHHP	1.09	0.710	0.697–1.700	**2.79**	**0.042**	**1.040–7.459**
	MECPP	**1.50**	**0.045**	**1.010–2.227**	2.73	0.056	0.973–7.641
	MiBP	1.09	0.604	0.797–1.477	1.08	0.749	0.668–1.751
Bisphenols	BPA	0.87	0.731	0.400–1.901	1.00	1.000	0.106–9.446
	BPF	0.82	0.467	0.475–1.407	0.02	0.326	0–49.044
	BPS	0.99	0.984	0.523–1.886	0.41	0.296	0.078–2.174
Phenols	TCS	0.96	0.944	0.320–2.890	0.77	0.805	0.100–5.983
	BP-3	0.90	0.642	0.589–1.386	0.94	0.947	0.168–5.314
Parabens	MP	0.85	0.222	0.660–1.102	0.77	0.335	0.448–1.315
	EP	1.03	0.725	0.865–1.232	0.89	0.506	0.622–1.264
	PP	0.91	0.562	0.671–1.242	0.64	0.399	0.228–1.801
	BP	1.00	0.993	0.439–2.294	0.06	0.087	0.002–1.511
PAHs	1-OHP	**0.05**	**0.041**	**0.003–0.888**	0.01	0.511	0–NA
	2-NAP	1.10	0.660	0.727–1.654	**7.22**	**0.017**	**1.426–36.593**
	1-PHE	0.27	0.355	0.016–4.364	<0.01	0.144	0–NA
	2-FLU	0.37	0.423	0.032–4.217	**<0.01**	**0.017**	**0–0.004**
VOCs	t,t-MA	1.08	0.621	0.796–1.466	0.68	0.442	0.250–1.832
	BMA	0.97	0.852	0.691–1.356	0.67	0.603	0.148–3.027

Multiple logistic regression results adjusted for maternal age, early-pregnancy body mass index, education, income, parity, gestational age, and maternal urine cotinine level. Postpartum pregnancy depression score was adjusted for antepartum depression score and neonatal sex; bold characters indicate statistical significance ($p < 0.05$). MnBP, mono-N-butyl phthalate; MEP, mono ethyl phthalate; MCPP, Mono(3-carboxypropyl) phthalate; MBzP, monobenzyl phthalate; MMP, mono(2-methylpropyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MiBP, mono-isobutyl phthalate; BPA, Bisphenol A; BPF, Bisphenol F; BPS, Bisphenol S; MP, Methylparaben; EP, Ethylparaben; BP, Butylparaben; PP, Propylparaben; TCS, Triclosan; BP-3, Benzophenon-3; 1-OHP, 1-hydroxypyrene; 2-NAP, 2-hydroxynaphthalene; 1-PHE, 1-hydroxyphenanthrene; 2-FLU, 2-hydroxyfluorene; t,t-MA, trans, trans-muconic acid; BMA, benzylmercapturic acid; aOR, adjusted odds ratio; CI, confidence interval.

We used the BKMR method to assess the mixture effects of 24 non-persistent EDCs on antepartum (Figure 3a) and postpartum (Figure 3d) depression. The overall effect regression models were adjusted for maternal age, early-pregnancy BMI, education, income, parity, gestational age, maternal urine cotinine level, and neonatal sex. Both antepartum and postpartum depression scores showed no statistically significant association between urinary chemicals in terms of overall mixture effect when other chemical levels were fixed at similar percentiles from the 10th to 90th. Figure 3b,e show the dose–response relationship for the association between each non-persistent chemical level and antepartum and postpartum depression scores, with other chemical levels fixed at their median. Each chemical showed different dose–response results, including positive, negative, and non-linear patterns. Figure 3c,f show the estimated effect and 95% confidence intervals of interquartile change of each chemical and antepartum and postpartum depression scores after fixing the other chemical levels at their 25th (red), 50th (green), and 75th (blue) percentiles. No individual chemical showed a statistically significant interquartile change effect in this analysis.

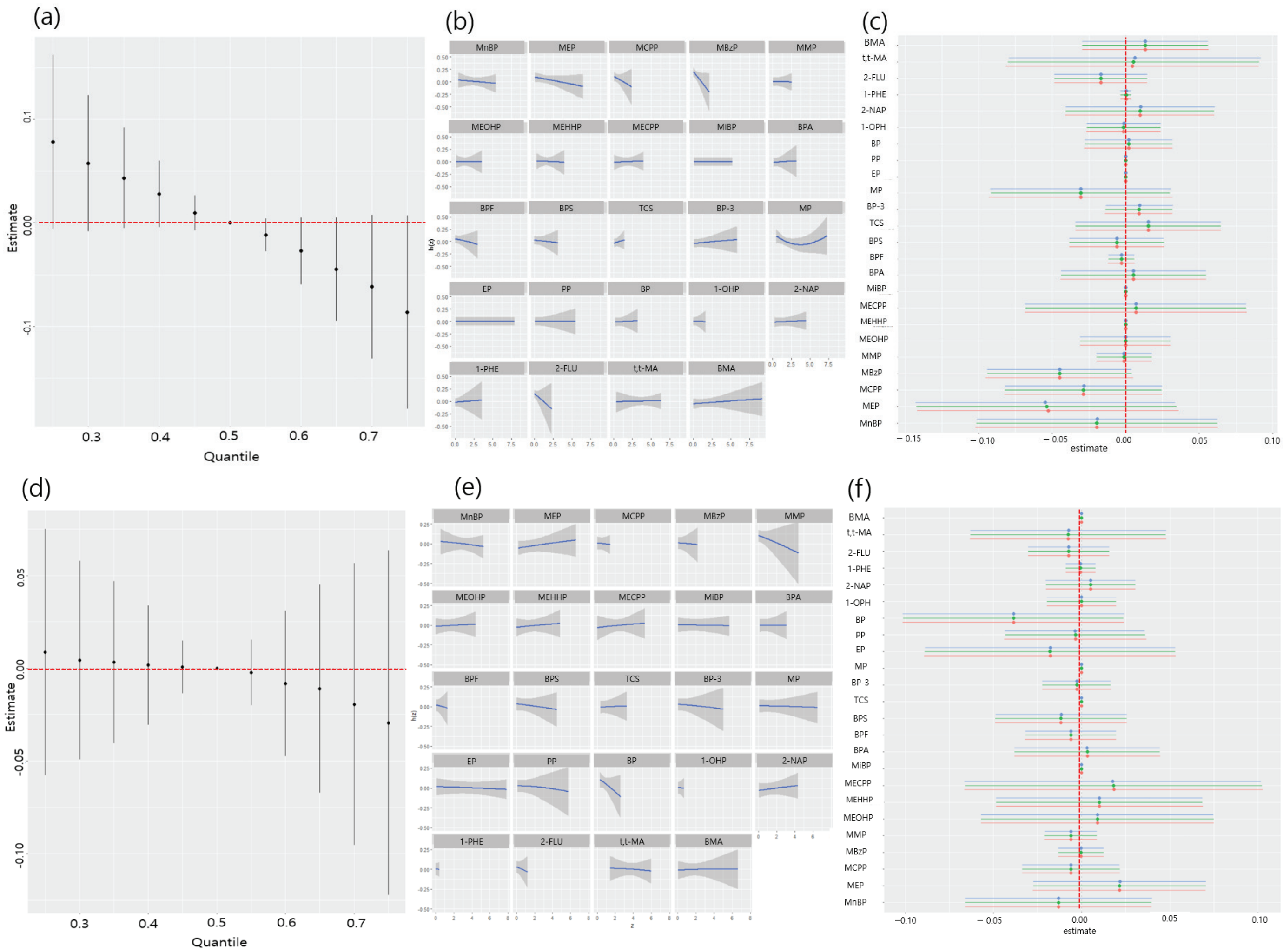

Figure 3. Bayesian Kernel Machine Regression between phthalates, bisphenols, parabens, PAHs, and other chemicals and antepartum and postpartum depression scores. (**a**) The overall effects of bisphenols; parabens; polycyclic aromatic hydrocarbons (PAHs); and other chemicals (TCS, BP-3, and VOCs) on the antepartum depression score were estimated using the Bayesian Kernel Machine Regression (BKMR) adjusted for maternal age, early-pregnancy body mass index, education, income, parity, gestational weeks, maternal urine cotinine level, and neonatal sex; ln: natural log. (**b**) Exposure–response relationship for the association between each chemical and antepartum depression score, fixing other chemical levels at their median. (**c**) The red, green, and blue bars and dots shows the estimated effect and 95% confidence intervals of an interquartile range change of each urinary chemical and antepartum depression score when the level of each of the other chemicals was held at

their corresponding 25th, 50th, and 75th percentiles, respectively. (**d**) The overall effects of bisphenols; parabens; polycyclic aromatic hydrocarbons (PAHs); and other chemicals (TCS, BP-3, and VOCs) on the postpartum depression score were estimated using the Bayesian Kernel Machine Regression (BKMR) adjusted for early pregnancy depression score, maternal age, early-pregnancy body mass index, education, income, parity, gestational weeks, maternal urine cotinine level, and neonatal sex; ln: natural log. (**e**) Exposure–response relationship for the association between each chemicals and postpartum depression score, fixing other chemical levels at their median. (**f**) The red, green, and blue bars and dots shows the estimated effect and 95% confidence intervals of an interquartile range change of each urinary chemical and postpartum depression score when the level of each of the other chemicals was held at their corresponding 25th, 50th, and 75th percentiles, respectively.

3.4. Association Between Dietary/Lifestyle Factors and Depression

In this study, the consumption of fish (MiBP), fermented food (MMP), cup noodle (MBzP), and popcorn (MEP) and use of manicure (MBzP), perfume (MiBP), plastic tableware (MMP), paint (MEHHP), and pesticides (MCPPs) were significantly associated with an increase in urinary phthalate concentration in pregnant women during the antepartum and postpartum periods. The increase in bisphenol levels was correlated with the consumption of fish (BPF) and popcorn (BPF) and the use of paint (BPA and BPF). TCS was significantly associated with the consumption of frozen food and use of new furniture. Increased paraben concentrations were significantly correlated with fermented foods (BP), consumption of cup noodles (MP and PP), skincare, makeup, sunscreen (EP), perfumes (PP), pesticides (MP), and the use of polishes (BP). Increased levels of PAHs in urine were significantly associated with the consumption of fermented and frozen foods; use of skin care, perfume, hand washer, and sunscreen products; and use of detergent, polish, air fresheners, and paint. There was a significant increase in VOCs in urine with the use of skincare products and polish (Tables 4 and 5).

Table 4. Associations between chemicals in maternal urine and dietary factors and consumer products in the antepartum period (n = 242).

Chemical		Dietary Factors						Consumer Products Factor											
		Fish	Dairy Products	Fermented Foods	Frozen Foods	Cup Noodle	Popcorn	Skincare Products	Makeup Products	Perfume	Antimicrobial Products	Sunscreen	New Furniture	Plastic Bowl	Detergent	Polish	Air Freshener	Paint	Pesticides
				B									B						
MnBP	beta	0.03	0.01	0.00	−0.06	−0.06	−0.05	−0.01	−0.03	−0.04	−0.02	−0.01	**−0.10 ***	−0.01	−0.02	−0.09	−0.02	0.00	0.00
MEP	beta	0.03	−0.07	0.04	−0.07	−0.11	−0.19	0.06	0.01	0.09	0.00	−0.01	−0.04	−0.02	−0.02	−0.10	0.00	−0.17	0.05
MCPP	beta	0.02	0.00	0.01	−0.01	0.00	−0.01	0.00	−0.01	0.00	0.00	−0.01	−0.02	−0.01	0.00	−0.03	0.00	−0.01	0.00
MBzP	beta	0.02	0.02	0.01	−0.01	−0.01	−0.03	0.01	0.00	−0.01	0.01	0.01	0.00	0.00	0.01	0.01	0.00	0.06	0.02
MMP	beta	0.00	0.00	**0.03 ***	−0.01	−0.01	0.00	0.01	−0.01	0.00	0.00	0.00	0.00	**0.02 ***	0.01	−0.01	0.01	0.02	0.00
MEOHP	beta	0.05	0.03	0.01	0.02	−0.01	−0.02	0.01	−0.01	−0.04	0.01	−0.01	−0.01	0.00	0.02	0.00	−0.02	0.14	−0.01
MEHHP	beta	0.05	0.04	0.00	0.02	−0.01	0.01	0.01	−0.01	−0.04	0.01	−0.02	−0.01	0.00	0.01	0.04	−0.03	**0.23 ***	0.01
MECPP	beta	0.05	0.05	0.00	0.02	−0.01	0.00	0.03	−0.01	−0.05	0.01	−0.02	−0.04	0.00	0.02	−0.01	−0.03	0.18	0.01
MiBP	beta	**0.15 ***	0.02	−0.05	0.02	0.06	0.06	−0.01	−0.01	−0.07	0.00	0.02	−0.08	−0.01	−0.04	−0.12	−0.05	−0.09	0.02
BPA	beta	0.03	0.01	0.03	0.01	−0.01	0.04	0.02	0.00	0.01	0.00	0.02	0.00	0.01	0.00	0.04	0.00	**0.12 ***	0.00
BPF	beta	**0.07 ***	0.04	−0.02	0.00	−0.01	0.05	0.02	−0.02	−0.01	−0.01	−0.02	−0.04	−0.03	−0.01	0.06	−0.02	**0.18 ***	0.01
BPS	beta	0.00	0.01	−0.02	0.03	−0.04	0.03	0.00	−0.01	0.01	0.01	−0.01	**0.05 ***	0.01	0.01	0.00	0.00	0.10	−0.01
TCS	beta	−0.01	0.00	0.00	**0.03 ***	0.02	−0.02	0.00	0.01	0.01	0.00	0.00	**0.02 ***	0.02	0.00	−0.02	0.00	0.04	0.01
BP-3	beta	0.03	−0.04	0.02	0.00	−0.04	−0.03	0.01	−0.02	0.06	0.00	0.02	0.03	0.02	−0.01	0.05	0.00	0.20	0.07
MP	beta	0.05	0.03	0.00	0.08	−0.17 *	0.10	0.06	0.02	0.00	−0.02	0.00	0.05	0.02	−0.01	−0.01	0.01	−0.13	**0.21 ***
EP	beta	0.08	0.03	0.04	0.02	−0.07	−0.01	**0.14 ***	**0.10 ***	0.08	0.03	**0.09 ***	0.04	−0.04	0.04	−0.11	0.00	−0.46	0.04
PP	beta	−0.02	0.06	−0.01	0.01	−0.10 *	−0.03	0.04	0.00	0.00	0.00	−0.01	0.04	0.01	0.03	−0.12	0.01	−0.05	0.10
BP	beta	−0.01	0.00	**0.04 ***	0.00	0.00	0.03	−0.01	0.00	0.00	0.01	0.01	**0.03 ***	0.01	0.01	0.04	0.01	−0.06	0.01
1-OHP	beta	0.01	0.00	**0.02 ***	0.01	0.00	0.00	**0.02 ***	0.00	**0.02 ***	**0.01 ***	**0.01 ***	0.00	0.00	0.01	**0.04 ***	**0.01 ***	**0.10 ***	−0.01
2-NAP	beta	0.00	−0.01	0.04	**0.07 ***	0.00	0.07	0.02	0.00	0.02	0.02	0.03	−0.01	−0.01	**0.06 ***	−0.04	**0.05 ***	0.01	−0.02
1-PHE	beta	0.03	−0.01	0.02	−0.01	0.00	−0.03	0.00	−0.01	−0.01	−0.01	0.00	−0.01	0.01	0.00	−0.02	−0.01	−0.01	0.00
2-FLU	beta	0.00	0.00	**0.02 ***	0.01	−0.01	0.01	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.00	−0.01	0.01	0.00	0.00
t,tMA	beta	0.01	0.00	0.05	0.04	0.05	0.09	**0.07 ***	0.03	0.05	0.04	0.01	0.01	0.00	−0.03	−0.05	0.00	0.20	−0.02
BMA	beta	−0.03	−0.04	0.05	−0.02	0.04	0.08	−0.04	0.00	0.02	−0.02m	0.00	−0.05	−0.03	−0.02	−0.02	0.02	0.02	0.05

Multiple linear regression results adjusted for maternal age, early-pregnancy body mass index, education, income, parity, gestational age, and maternal urine cotinine level after natural log transformation for chemical concentrations; *p*, *p*-value; bold and asterisk (*) characters indicate a statistically significant positive association ($p < 0.05$). MnBP, mono-N-butyl phthalate; MEP, mono ethyl phthalate; MCPP, mono(3-carboxypropyl) phthalate; MBzP, monobenzyl phthalate; MMP, mono(2-methylpropyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MECPP, Mono(2-ethyl-5-carboxypentyl) phthalate; MiBP, mono-isobutyl phthalate; BPA, Bisphenol A; BPF, Bisphenol F; BPS, Bisphenol S; MP, Methylparaben; EP, Ethylparaben; BP, Butylparaben; PP, Propylparaben; TCS, Triclosan; BP-3, Benzophenon-3; 1-OHP, 1-hydroxypyrene; 2-NAP, 2-hydroxynaphthalene; 1-PHE, 1-hydroxyphenanthrene; 2-FLU, 2-hydroxyfluorene; t,t-MA, trans, trans-muconic acid; BMA, benzylmercapturic acid.

Table 5. Associations between chemicals in maternal urine and dietary factors and consumer products in the postpartum period (n = 119).

Chemical		Dietary Factors						Consumer Products											
		Fish	Dairy Products	Fermented Foods	Frozen Foods	Cup Noodle	Popcorn	Skincare Products	Makeup Products	Manicure	Perfume	Antimicrobial Products	Sunscreen	New Furniture	Plastic Bowl	Detergent	Polish	Air Freshener	Pesticide
		B										B							
MnBP	beta	0.020	−0.009	0.023	−0.023	−0.016	0.097	−0.056	−0.007	−0.204	0.114	0.004	−0.043	−0.008	−0.033	−0.037	0.031	−0.027	0.058
MEP	beta	0.067	−0.003	−0.011	0.027	0.063	**0.258** *	0.051	0.150	0.780	0.016	0.024	0.087	0.138	−0.037	0.009	−0.048	0.000	0.212
MCPP	beta	−0.001	0.016	0.002	−0.004	−0.005	0.011	−0.004	0.007	0.051	0.024	−0.006	−0.011	−0.022	0.003	0.003	−0.034	−0.009	**0.068** *
MBzP	beta	−0.011	0.016	0.011	−0.004	**0.053** *	0.053	0.018	0.030	**0.227** *	−0.003	0.004	0.006	−0.022	−0.004	0.012	−0.040	0.007	−0.016
MMP	beta	0.014	−0.021	0.021	−0.012	−0.051	0.038	−0.020	−0.023	−0.164	0.045	−0.003	−0.032	0.024	0.012	−0.014	−0.075	−0.044	0.004
MEOHP	beta	0.01	−0.01	0.01	−0.01	0.02	−0.04	−0.01	0.04	−0.40	0.25	0.03	−0.04	−0.08	0.00	−0.01	−0.20	0.00	0.02
MEHHP	beta	0.02	−0.01	0.01	0.00	0.05	−0.04	−0.01	0.03	−0.38	0.21	0.03	−0.05	−0.08	0.01	0.00	−0.27 *	−0.01	0.01
MECPP	beta	0.02	0.02	0.04	0.02	0.06	0.04	−0.02	0.05	−0.11	0.23	0.05	−0.06	−0.10	0.01	−0.02	−0.23 *	0.00	0.04
MiBP	beta	0.03	−0.02	0.06	0.07	0.03	0.19	0.00	0.03	−0.68	**0.47** *	−0.01	0.00	−0.03	0.05	0.00	−0.16	−0.07	0.12
BPA	beta	−0.04	0.02	−0.02	−0.05	−0.06	0.07	0.02	−0.01	−0.02	0.07	−0.02	−0.01	−0.02	0.00	0.02	0.04	−0.03	−0.05
BPF	beta	−0.01	0.00	−0.01	−0.01	−0.01	**0.09** *	−0.01	−0.02	−0.04	−0.01	0.00	0.00	0.01	−0.01	−0.01	−0.03	0.00	−0.02
BPS	beta	0.01	−0.07	−0.03	−0.01	0.05	−0.02	−0.01	0.06	0.05	0.07	0.02	0.03	−0.02	−0.01	−0.02	−0.03	0.00	−0.03
TCS	beta	−0.08 *	−0.03	−0.08 *	−0.06	−0.11 *	−0.04	0.03	0.02	−0.18	0.15	0.02	−0.01	−0.01	−0.02	0.02	0.02	−0.04	−0.07
BP-3	beta	−0.08 *	−0.03	−0.08 *	−0.06	−0.11 *	−0.04	0.03	0.02	−0.18	0.15	0.02	−0.01	−0.01	−0.02	0.02	0.02	−0.04	−0.07
MP	beta	−0.13	0.00	−0.06	−0.04	−0.07	0.11	0.13	0.08	−0.21	0.57	0.04	0.05	0.06	−0.10	−0.03	−0.05	−0.01	0.18
EP	beta	0.01	0.03	−0.24 *	−0.27 *	−0.26	−0.34	0.06	−0.09	0.06	0.20	−0.08	0.00	−0.01	−0.11	−0.05	0.18	0.03	−0.01
PP	beta	−0.07	0.01	−0.02	−0.01	−0.09	0.00	0.07	0.14	0.00	**0.37** *	0.02	0.06	0.01	−0.07	−0.04	−0.02	−0.06	0.10
BP	beta	0.00	0.01	0.01	−0.01	0.01	0.05	0.01	0.01	0.16	−0.01	0.01	0.00	0.01	0.00	0.00	**0.14** *	0.01	0.00
1-OHP	beta	0.00	0.01	0.01	−0.01	0.01	0.05	0.01	0.01	0.16	−0.01	0.01	0.00	0.01	0.00	0.00	**0.14** *	0.01	0.00
2-NAP	beta	0.00	0.01	0.01	−0.01	0.01	0.05	0.01	0.01	0.16	−0.01	0.01	0.00	0.01	0.00	0.00	**0.14** *	0.01	0.00
1-PHE	beta	0.00	0.01	0.01	−0.01	0.01	0.05	0.01	0.01	0.16	−0.01	0.01	0.00	0.01	0.00	0.00	**0.14** *	0.01	0.00
2-FLU	beta	0.00	0.01	0.01	−0.01	0.01	0.05	0.01	0.01	0.16	−0.01	0.01	0.00	0.01	0.00	0.00	**0.14** *	0.01	0.00
t,tMA	beta	0.00	0.01	0.01	−0.01	0.01	0.05	0.01	0.01	0.16	−0.01	0.01	0.00	0.01	0.00	0.00	**0.14** *	0.01	0.00
BMA	beta	0.05	0.02	0.04	−0.06	−0.06	0.07	−0.01	−0.08	0.04	0.15	−0.02	−0.07	−0.02	−0.02	−0.05	0.00	−0.05	0.18

Multiple linear regression results adjusted for maternal age, early-pregnancy body mass index, education, income, parity, maternal urine cotinine level, and neonatal sex after natural log transformation for chemical concentrations; *p*, *p*-value; bold and asterisk (*) characters indicate statistically significant positive association ($p < 0.05$). MnBP, mono-N-butyl phthalate; MEP, mono ethyl phthalate; MCPP, mono(3-carboxypropyl) phthalate; MBzP, monobenzyl phthalate; MMP, mono(2-methylpropyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MiBP, mono-isobutyl phthalate; BPA, Bisphenol A; BPF, Bisphenol F; BPS, Bisphenol S; MP, Methylparaben; EP, Ethylparaben; BP, Butylparaben; PP, Propylparaben; TCS, Triclosan; BP-3, Benzophenon-3; 1-OHP, 1-hydroxypyrene; 2-NAP, 2-hydroxynaphthalene; 1-PHE, 1-hydroxyphenanthrene; 2-FLU, 2-hydroxyfluorene; t,t-MA, trans, trans-muconic acid; BMA, benzylmercapturic acid.

4. Discussion

We found that some phthalates and PAHs in maternal urine were significantly associated with ante- and postpartum depression and confirmed the relationship between dietary and lifestyle factors and depression. However, it is difficult to discuss the relationship between EDC exposure and perinatal depression, because few studies have compared them. Therefore, we compared our results with those of previous studies in other population groups, such as children, adults in general, and the elderly.

In the present study, we found that the secondary metabolites of MEHP (MECPP, MEOHP, and MEHHP) in the maternal urine were significantly associated with ante- and postpartum depression, which is supported by several previous studies [9,11,21,24,25]. A Chinese epidemiological study involving 278 pregnant women reported that exposure to a mixture of phthalates, bisphenols, and parabens resulted in a 1.03-fold increase in postpartum depression [11]. Another Chinese study demonstrated an association (OR = 1.490, 95% CI = 1.051–2.112) and a mediating effect (β = 0.1027, 95% CI = 0.0288–0.1971) between MEHP levels in urine samples from the general elderly population and depressive symptoms [21]. Another study found that MECPP was significantly related to depressive symptoms in American adults [24], and concentrations of DEHP metabolites, including MEOHP, MEHHP, and MECPP, were positively associated with an increased risk of depressive symptoms in a Korean elderly population (OR = 1.92, 95% CI = 1.17–3.13) [25]. In toxicological animal studies, female rats exposed to multiple EDCs showed a multigenerational reduction in maternal behaviors such as nursing, grooming, and licking their babies, which is similar to human postpartum depression symptoms [37]. In another animal study, mice exposed to dibutyl phthalate in the peri-gestational period showed impaired maternal behavior, regarded as typical symptoms in maternal postpartum depression [38].

With respect to the link between PAHs and depression, we found that some PAHs (1-OHP, 2-NAP, and 2-FLU) were significantly associated with ante- and postpartum depression, similar to the results of previous studies [23,27,28]. A recent meta-analysis concluded that prenatal exposure to PAHs can be associated with an increased risk of social behavior (OR = 1.60), attention deficits (OR = 2.99), motor skill deficits (OR = 1.91), and other neurodevelopmental problems (OR = 2.10) in children [27]. In addition, exposure to 2-hydroxyfluorene in the general adult population could increase the risk of depression (OR = 1.43). A study in the US that assessed the association between PAH metabolites and the risk of depression using the National Health and Nutrition Examination Survey (NHANES) [23] revealed positive associations between the urinary 1-NAP (OR = 2.78) and 2-NAP level (OR = 3.17) and depressive symptoms in women within the highest quantile of exposure [28].

However, in our study, there was no significant relationship with perinatal depression for bisphenols, parabens, phenols, and VOCs, with the exception of some phthalates and PAHs. A Chinese birth cohort study found that maternal exposure to BPA and BPF during pregnancy was associated with higher postpartum depression scores, suggesting that pregnancy constituted an important window of vulnerability [11]. Another longitudinal study determined the association between exposure to total volatile organic compounds (TVOCs) by air freshener use and maternal postpartum depression symptoms at 6–8 months after delivery (OR = 1.19) [22]. Environmental tobacco smoke, a complex mixture of nicotine, tar, carbon monoxide, carbon dioxide, and PAHs, represents one of the main pollutants influencing maternal depression [4]. A recent meta-analysis found that perinatal exposure to secondhand smoke in non-smoking women significantly increased the risk of maternal depression symptoms at any time during pregnancy or the postpartum period (OR = 1.77) and increased antenatal suicidal ideation (OR = 1.75) [26]. The range of outcomes in these studies can be understood as differences in populations, sample sizes, mixture effects, time when depression was measured, and research design. While our study measured depression in the first trimester of pregnancy (before the 14 week), a previous study measured depression in the second trimester (14–28 weeks) and focused on twin pregnancies [11]. Differences in the composition of reproductive hormones between these trimesters [2] may also feature here.

To the best of our knowledge, limited studies have reported mixture effects of non-persistent EDC exposure on perinatal depression to date [11]. This implies that the present univariate models may underestimate or overestimate the health effects compared to the more advanced mixture model approach like BKMR. In this study, we evaluated the mixture effect of 24 non-persistent EDCs on antepartum and postpartum depression scores after adjusting covariates. Although no chemicals showed a statistically significant association with the depression score at the significance level of $p < 0.05$ in both periods, a distinct trend difference between two periods was observed. Our result aligns with those of a previous study, which reported weak mixture effects of non-persistent EDCs on anxiety and depression during pregnancy and the postpartum period using BKMR and quantile-based g-computation methodologies [11].

In the present study, the consumption of fish, fermented foods, cup noodles, and popcorn and use of nail polish and perfume, plastic tableware, paint, and pesticides were significantly associated with an increased phthalate urinary concentration in pregnant women. This was consistent with the results of previous studies [12,39–46]. Phthalates are classified into low-molecular-weight types (dimethyl, diethyl, dibutyl, and diisobutyl phthalate) and high-molecular-weight types (di(2-ethylhexyl), diisononyl, and diphenyl phthalate). The former are used as solvents in personal hygiene products, cosmetics, and pharmaceuticals, while the latter are used as plasticizers in PVC products, including medical devices and children's toys [47]. Most environmental phenols are also significantly associated with the consumption of fermented foods; frozen foods; cup noodles; and the use of skin care products, makeup products, sunscreen products, perfumes, and pesticides, as reported in previous studies [12,13,48–52]. Increased PAH levels in urine are significantly associated with the use of detergents, polishes, air fresheners, and paints, as well as the use of personal hygiene products such as skin care, perfume, hand wash, and sunscreen products [53–55]. These are compounds of interest in human biomonitoring because of their potential to bioaccumulate and exert carcinogenic, mutagenic, and teratogenic effects [53]. The most common sources of exposure to PAHs are factory and traffic exhaust derived from gasoline and diesel fuels, residential fossil fuel heating, wood-burning ovens and fireplaces, cigarette smoke, fires, and charcoal-based food smoke [55,56]. The present study confirmed that most exposure to EDCs occurs in everyday life, such as from food commonly consumed by pregnant women, personal hygiene, household products, and automobile exhaust. Therefore, pregnant women who are environmentally vulnerable and sensitive should avoid these products and exposures as much as possible.

This study was subject to some limitations. First, we measured depression levels during the first trimester of pregnancy. However, as pregnancy is a time when reproductive hormones change dramatically depending on the trimester, depression scores from that trimester are not representative for the entire pregnancy period. Secondly, the successful follow-up rate of pregnant women was low at approximately 50%. Third, discrepancies in time point between urine sample collection and food and lifestyle factors were observed. Thirdly, we did not have information on family interactions or social support, such as intimacy with the husband, receiving aid from the mother's family, and relationships with friends, which are known to influence perinatal depression. Fourth, compared to other countries, South Korea exhibits greater homogeneity in factors such as ethnicity, marital status, cohabitation with a spouse, and insurance coverage. This introduces limitations in generalizing or extrapolating the findings from the cohort of pregnant women in this study to populations of pregnant women in other countries or regions. Additionally, it should be noted that many participants in this study were residents of metropolitan areas with relatively higher levels of education and income, which should be considered when interpreting and comparing the results. Despite these limitations, our study targeted hard-to-reach pregnant women and was able to obtain information on EDC exposure and depressive symptoms from the same study participants, both during pregnancy and postpartum. Additionally, we attempted to measure the effects of a mixture of 24 EDCs that can be obtained in everyday life.

5. Conclusions

We observed an association between exposure to non-persistent chemicals and an increased risk of ante- or postpartum depression and its association with dietary and lifestyle factors. Our findings provide meaningful information about the identification of toxic chemicals potentially linked to perinatal depression. It is imperative that clinical obstetricians, psychologists, public health organizations, and harmful chemical regulatory governance provide practical guidelines and counseling to mitigate exposure to toxic chemicals. Pregnant women and their families should also pay attention to reducing their exposure to multiple EDCs that are commonly absorbed through various pathways to help prevent antenatal and postnatal depression.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/environments12010015/s1, Figure S1: Distribution of antepartum and postpartum depression score.

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Data Availability Statement: Data is available on request due to privacy restrictions. The data used in this study contains sensitive pregnancy-related information about the participants and can only be made available upon reasonable request to the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

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Evidence About the Possible Role of Phthalates and Bisphenol A in Recurrent Pregnancy Loss and Endocrine Dysfunctions: A Case–Control Study

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Abstract: Objectives. A case–control study was conducted to investigate the exposure levels to some specific chemicals, in women with infertility issues, compared with fertile women. Methods. A total of 186 cases and 196 controls were recruited. Each participant provided a urine sample for the determination of six phthalate metabolites (mono-ethyl phthalate, MEP; mono-n-butyl phthalate, MnBP; mono-n-ottyl phthalate, MnOP; monobenzyl phthalate, MBzP; and two metabolites of the diethyl-hexyl phthalate (DEHP): mono(2-ethyl-5-hydroxyhexyl) phthalate, MEHHP and mono(2-ethylhexyl) phthalate, MEHP) in addition to bisphenol A, BPA. Each woman also completed a questionnaire. The urine samples were analyzed using HPLC/MS/MS methods. Results. The analysis revealed significantly higher metabolite concentrations in cases than in controls for all metabolites, except MnOP. Stratification based on infertility factors, showed a significant association of MnBP, MBzP, BPA and DEHP with ovulatory and endocrine dysfunctions. Furthermore, higher mean concentrations of MEP and DEHP were observed in women with recurrent pregnancy loss (RPL) and idiopathic infertility, respectively. Conclusion. These findings suggest that some of the analyzed chemicals may play a role in female infertility. Exposure to DEP (diethyl phthalate) and DEHP appears to be associated with RPL and idiopathic infertility. Further investigation is required to explore potential sources of these risks.

Keywords: phthalates; reproduction; women; BPA; endocrine disrupters

1. Introduction

Infertility is defined as the inability to conceive after 12 months, or more, of unprotected sexual intercourse [1]. It has a multifactorial etiology, influenced by a range of risk factors that may affect female reproductive capacity. This risk factor can arise from both personal and occupational exposures [2]. In recent years, increasing attention has been focused on xenobiotics classified as endocrine disruptors, which interact with estrogen and androgen receptors [3–5]. Historically, these chemicals have been widely used [6], notably as additives in plastic materials, solvents and stabilizing agents in cosmetics. They were also present in thermal papers and as coating agents in food cans. Currently, numerous legal restrictions exist, particularly in Europe, to reduce this type of risk.

Phthalates represent a class of structurally similar molecules that have been used industrially since the early 20th century. Their reprotoxicity is well documented in the literature [7]. In vivo studies have demonstrated embryotoxicity and fetotoxicity [8,9] in chronically exposed female mice. In human studies, long-term exposure to phthalates has yielded conflicting results regarding their role in pregnancy loss [10–12]. Moreover, other studies have identified associations between phthalate exposure and reduced follicle numbers [13], as well as a decreased number of retrieved, mature and fertilized oocytes [14,15]. Further investigations have highlighted the potential reproductive toxicity of di-(2-ethylhexyl) phthalate (DEHP), diethyl phthalate (DEP), dibenzyl phthalate (DBzP), di-n-butyl phthalate (DnBP), butylbenzyl phthalate (BBzP), and more recently di-n-octyl phthalate (DnOP) and di-iso-nonyl phthalate (DiNP) [16].

Bisphenol A (BPA), structurally similar to 17-β-estradiol, can bind to estrogen receptors (α and β) [17–19]. Both in vivo and in vitro experimental studies have emphasized the reprotoxic effects of BPA, which result in oocyte aneuploidy [20], chromosome segregation [21] and effects on meiotic segregation [22]. However, results from human studies remain inconclusive. While some studies found BPA levels to be negatively correlated with estradiol levels [23,24] and reduced useful oocyte numbers in assisted reproductive technology (ART) cycles [25], other studies have yielded contradictory findings [26]. Furthermore, BPA has also been shown to exhibit antiandrogenic activity [27]. In vitro and in silico assays have demonstrated that BPA significantly antagonizes the androgen receptor (AR) by 5α-dihydrotestosterone (DHT)-induced AR transcriptional activity [27].

Exposure to these chemicals occurs primarily through inhalation, dermal absorption and ingestion [28,29], particularly via food contamination [30,31]. Phthalates are rapidly metabolized into monoesters and oxidative metabolites [32], which are excreted predominantly in urine. For this reason, measuring urinary metabolites of phthalates and BPA is considered the most reliable method to assess environmental exposure, and such molecules are useful as biomarkers. Complete urinary excretion occurs within 24 h, with a peak in urinary levels approximately 4 h after exposure [33,34].

Given the potential reproductive toxicity of these substances, studying infertile women may provide insights into their heightened vulnerability [35]. Therefore, identifying circumstances under which exposure occurs, whether in the workplace or daily life, could help to clarify the real routes of exposure and promote reproductive health.

The present study was conducted to assess if exposure to phthalates and BPA could be linked with reproductive problems in a population of women with diagnosis of infertility, and to explore possible ways of exposure. The aim of this study is to understand whether the infertile population actually shows, as suggested in the literature, higher exposure values for these substances and whether these exposure levels can be correlated with specific infertility factors.

2. Materials and Methods

2.1. Study Population

This epidemiological study enrolled female users of a fertility center as cases. Inclusion criteria were as follows: age under 43 years, no history of chemotherapy related to genital problems, and no infertility issues related to surgery or anatomical alterations. The minimum age of the sample of infertile women was 34 years, as younger women were not present at the assisted reproduction center during the sampling period. It should be noted that the average age of the first pregnancy in Italy is estimated at 32 years, which may contribute to the likelihood of noticing reproductive issues at an older age.

Urine samples were taken from non-pregnant women diagnosed with infertility at the clinic. In this survey, women were explicitly selected from couples where infertility was exclusively attributed to the female partner, while the semen quality of their partners was analyzed.

Confounding factors considered in the statistical elaboration, prioritized in relation to the studied situation, included body mass index (BMI), smoking habits, alcohol consumption, age between 35 and 43 years, prior chemotherapy treatments (excluding genital treatment), insulin-dependent diabetes [36] and thyroid disorders [37]. A final exclusion criterion was an abnormal urinary creatinine level, based on World Health Organization (WHO) guidelines [38].

The calculation of the sample size useful for the significance of the data was carried out starting from the prevalence of the considered pathology: the prevalence data of female infertility in Italy is equal to 15% [39], and a margin of maximum error of 5% and a confidence level of 95% was set.

After applying all criteria, a total sample of 186 eligible women with infertility issues was identified.

The control group consisted of women who had recently given birth in the same hospital's obstetrics unit, without undergoing hormonal or fertility treatment, and who achieved pregnancy within 12 months. Control samples were collected at least 4 days postpartum, resulting in an overall control sample of 196 female subjects.

The Institutional Review Board of the IRCCS San Raffaele Scientific Institute in Milan approved the investigation protocol, assigning it the identification code 73/INT/2017. All procedures involving human participants were conducted in accordance with the Declaration of Helsinki.

All participants signed an informed consent form and subsequently completed a structured questionnaire to collect data on clinical status, with a focus on endocrine conditions, lifestyles and occupational habits. The questionnaire adopted involved a multidisciplinary team in its drafting, made up of gynecologists expert in assisted reproduction, embryologists, statisticians and experts in chemical risk in living and working environments.

A well-trained researcher assisted in the completion of the clinical anamnesis. The questionnaire's life habits section collected information on smoking, alcohol consumption, the use of plastic containers, the use of cosmetics such as scents, hair sprays and nail polish, and dietary habits.

Every participant provided a random spot urine sample during her morning clinical visit. These urine samples were analyzed for chemicals of interest.

The sampling period extended from October 2017 to June 2019, covering the geographic area of Northen Italy.

2.2. Analytical Procedure

The analytical phase employed previously published HPLC tandem mass spectrometry methods [40,41]. Briefly, for phthalates analysis, urine samples underwent a pretreatment involving enzymatic digestion with β-glucuronidase-from E. Coli, followed by solid-phase extraction (SPE OASIS HBL, 6 cm^3, 200 mg cartridges) before the chromatographic column injection. For BPA analysis, the samples were first incubated at 38 °C for 2 h with β-glucuronidase-arylsulfatase enzyme from Elix Pomatia, followed by acidification with acetic acid 2% (*v*/*v*). The analyte was then extracted using SPE extraction with SPE OASIS HBL (6 cm^3, 200 mg) cartridges, before the HPLC-MS/MS analysis.

The main metabolites of phthalates of interest were analyzed: in detail, mono-ethyl phthalate (MEP) from DEP; mono-n-butyl phthalate (MnBP) from DnBP and BBzP; mono-n-ottyl phthalate (MnOP) from DnOP; monobenzyl phthalate (MBzP) from BBzP and DBzP; two metabolites of the DEHP: mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) and mono(2-ethylhexyl) phthalate (MEHP); and total BPA.

Urinary levels were normalized by dividing by urinary creatinine, obtained using the Jaffè's method [42].

Samples with creatinine levels exceeding 3 g/L or below 0.3 g/L were rejected, following the WHO guidelines [38] and the American Conference of Governmental Industrial Hygienists (ACGIH) recommendation [43]. Values outside this range could indicate kidney issues or other diseases, leading to erroneous results.

2.3. Statistical Elaboration

The SPSS® 25.0 (IBM, Armonk, NY, USA SPSS) software was used for statistical analysis. A preliminary descriptive analysis was conducted to assess the characteristics of the sample population and the distribution of urinary metabolite concentrations. For results below the limit of detection (LOD), values were established to LOD divided by two [44]. Non-parametric methods were employed to analyze the phthalate metabolite concentrations, to discriminate the differences between different groups, including occupational activities, personal habits and demographic categories.

To highlight the differences between cases and controls, the odds ratio was calculated, considering working activities and the daily life habits. Associations between urinary metabolites and infertility factors were assessed using the Kruskal–Wallis test and Dunn post hoc test. The statistical elaboration considered the confounding factors using multivariate logistic regressions.

3. Results

Table 1 shows information about the populations studied, highlighting possible significant differences in specific parameters. The two groups of women display similar characteristics, although infertile women had a higher mean older age and a greater tendency to smoke. Regarding the body mass index, the women controls were asked to indicate their weight before the beginning of the pregnancy.

Table 1. Characteristics of population under study.

	Cases (n = 186)	**Controls (n = 196)**	**p Value**
Age (range)	37.6 (29–43)	33.4 (21–44)	0.000 *
BMI [a] (% of subjects in the class)			
Normal	73.3	59.2	0.101
Overweight	11.3	14.8	
Obese	4.3	8.7	
Underweight	9.1	8.7	
Unknown	1.6	8.7	
Present smokers (%)	16.1	6.1	0.010 *
Previously smokers (%)	23.1	20.4	
Alcohol consumption (%)			
Daily	5.9	7.7	0.000 *
Weekly	44.6	26.0	
Monthly	23.7	28.1	
Never	21.0	37.2	
Missing	4.8	1.0	
Residence area (%)			
Urban	79.0	85.7	0.469
Rural	11.8	9.2	
Coast	2.2	1.0	
Industrial	1.1	0.0	
Urban and industrial	1.1	0.0	

Table 1. *Cont.*

	Cases (n = 186)	Controls (n = 196)	p Value
Other	3.7	0.5	
Missing	1.1	1.5	
Use of plastic containers for fat food storage (%)			
Never	17.2	14.3	0.244
Daily	23.1	21.4	
Weekly	38.2	46.9	
Monthly	18.8	16.8	
Missing	2.7	0.5	
Eating canned food at least weekly (%)	43.5	40.3	0.290
Eating soya products at least weekly (%)	17.8	11.8	0.070
Use of scents at least weekly (%)	80.1	80.7	0.560
Use of nail polishes at least weekly (%)	40.9	32.6	0.148
Use of hair sprays at least weekly (%)	16.6	14.3	0.399
Working activity (%)			
Armed forces	0.5	0.0	0.110
Industrial workers	1.1	2.6	
Education/learning area/ professionals/PC operators	60.7	58.2	
Health workers	8.6	11.7	
Cleaning activity/catering	7.5	6.6	
Trade	8.1	5.6	
Unemployed	2.2	4.1	
Others	11.3	11.2	

[a] BMI: body mass index. * Significant difference; Mann–Whitney test for continuous variables; χ^2 test for qualitative variables.

Table 2 presents the results of the urine sample analysis, detailing the number of samples with metabolites exceeding the limit of detection (LOD) of the methods, and the potential differences highlighted using the Mann–Whitney test. Overall, the results showed significantly higher values in infertile women for all the metabolites, with the only exception being for MnOP. Higher exposure was confirmed by the elevated urinary analyte levels in the cases group.

Table 2. Results (µg/g creatinine) of urinary metabolites of phthalates and BPA.

Parameters	MnBP [1]		MEP [2]		MBzP [3]		MnOP [4]		DEHP [5]		BPA [6]	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
N subjects	186	196	186	196	186	196	186	196	186	196	125	112
Arithmetic mean	25.69	21.76	191.82	101.06	5.53	2.75	2.14	1.86	16.52	11.08	1.73	0.90
Median	16.29	11.55	13.26	28.59	2.62	1.33	1.25	1.03	8.57	5.65	0.57	0.24
Standard deviation	38.39	53.24	762.55	292.23	11.47	3.83	2.69	1.86	24.30	11.08	3.82	4.16
5° percentile	1.25	1.25	0.77	1.50	0.27	0.38	0.08	0.29	1.15	0.92	0.05	0.07
95° percentile	108.39	58.02	635.08	421.62	23.72	9.71	8.44	6.18	58.26	28.52	8.49	2.88
p value (Mann–Whitney test)	0.011 *		0.036 *		0.000 *		0.526		0.000 *		0.000 *	
LOD [7] (µg/L)	0.8		3.0		1.2		0.1		0.15 MEHP [8] 0.05 MEHHP [9]		0.02	
% > LOD	97.3	97.4	62.9	79.1	69.4	51.5	91.4	100.0	99.5	100.0	99.2	100.0

[1] MnBP—mono-n-butyl phthalate; [2] MEP—mono ethyl phthalate; [3] MBzP—monobenzyl phthalate; [4] MnOP—mono-n-octyl phthalate; [5] DEHP—di-(2-ethylhexyl) phthalate, molar sum of two metabolites; [6] BPA—bisphenol A; [7] LOD—limit of detection; [8] MEHP—mono(2-ethylhexyl) phthalate; [9] MEHHP—mono(2-ethyl-5-hydroxyhexyl) phthalate. * Significant value.

MEP levels, despite showing considerable variability, were consistently higher than the concentrations of other phthalates. This may be because DEP is the only compound considered here that is not subject to legal restrictions in Europe [45]. The exposure values were also one or two orders of magnitude higher, with peaks reaching up to 7000 µg/L.

Instead, Table 3 stratifies the data according to the infertility factors reported by the infertile women. Differences among the groups were evaluated using the Kruskal–Wallis test, followed by Dunn's post hoc test for a more detailed analysis of the differences between each infertility factor and the controls. Statistically significant differences, between cases and controls, in urinary levels of MEP MnBP, BPA and DEHP were observed in women with infertility related to ovulatory factors or endocrine dysfunction. MEP levels also differed significantly from controls in women with recurrent pregnancy loss and reduced ovarian reserve. Additionally, DEHP levels were significantly elevated in women with ovulatory, endocrine and idiopathic infertility compared to controls.

DEHP showed higher mean concentration levels, compared with mean value in controls, in all groups of the different infertility factors, except for reduced ovarian reserve, with statistical significance in ovulatory and endocrine dysfunction and idiopathic infertility groups (sine causa infertility). MnBP levels were twice as high in women with ovulatory and endocrine dysfunction, and the same trend was observed for MBzP.

MEP levels were notably higher in women with RPL, with the geometric mean concentration being twice that of the controls. Finally, BPA levels were statistically significantly elevated in women with ovulatory and endocrine dysfunction, and an increasing trend was observed in women with endometriosis (mean value: 0.94 ± 3.93 µg/g creatinine), tubal factors (1.07 ± 5.43 µg/g creatinine) and reduced ovarian reserve (0.61 ± 2.58 µg/g creatinine) compared with controls (0.28 ± 3.06 µg/g creatinine), although these differences were not statistically significant.

Table 3. Phthalates levels with stratification for infertility factors vs. controls.

		µg/g Creatinine (Geometric Mean ± SD [a])					
Infertility Factors	**N**	**MnBP**	**MEP**	**MBzP**	**MnOP**	**DEHP**	**BPA**
Controls	196	9.32 ± 3.76	22.86 ± 6.45	1.49 ± 2.94	1.11 ± 2.48	5.46 ± 2.76	0.28 ± 3.06
Ovulatory and endocrine dysfunctions	30	21.95 ± 3.84 *	10.71 ± 9.08	3.97 ± 3.80 *	0.81 ± 4.27	12.64 ± 3.06 *	0.64 ± 2.31 *
Endometriosis	20	15.07 ± 2.94	29.04 ± 6.02	2.02 ± 3.33	1.14 ± 3.21	8.78 ± 2.43	0.94 ± 3.93
Idiopathic	52	13.44 ± 2.74	19.49 ± 10.81	2.26 ± 3.48	1.38 ± 4.35	9.69 ± 2.99 *	0.44 ± 4.56
Recurrent Pregnancy Losses (RPL)	18	14.52 ± 4.50	40.07 ± 21.03 *	2.38 ± 2.54	0.56 ± 3.25	10.61 ± 2.56	0.41 ± 3.68
Reduced ovarian reserve	50	8.72 ± 3.66	7.67 ± 7.07 *	1.74 ± 3.48	1.02 ± 3.11	5.39 ± 3.50	0.61 ± 2.58
Reduced ovarian reserve + endometriosis	3	14.70 ± 1.08	10.88 ± 7.19	0.57 ± 1.54	1.30 ± 1.51	6.03 ± 1.81	-
Tubal factors	13	13.82 ± 2.73	12.86 ± 8.87	3.31 ± 5.28	1.64 ± 3.50	11.77 ± 3.84	1.07 ± 5.43
p value Kruskal–Wallis		0.027 *	0.021 *	0.001 *	0.135	0.000 *	0.000 *
p value Dunn post hoc test		0.029 *	0.029 * 0.025 *	0.004 *	0.135	0.019 * 0.007 *	0.016 *

[a] SD—geometric standard deviation; * statistically significant ($p < 0.05$).

Tables 4 and 5 show the calculated odds ratio between cases and controls, considering the different occupational activities and daily life habits, respectively.

No specific occupation or habit seems to be of higher concern in our sample, with the only exception being the use of canned food (OR = 2.021, 95% CI 1.022–3.996).

Table 4. Odds ratio for working activity, adjusted for age, BMI, smoke, alcohol and pathologies.

Working Activity	Cases	Controls	OR	95% CI	*p* Value
Soldiers/policewomen	1	0	-	-	-
Industrial workers	2	5	2.307	0.348–15.293	0.386
Teachers/professionals	112	114	0.699	0.412–1.187	0.185
Nurses/doctors/health professionals	16	23	0.759	0.330–1.747	0.517
Cleaning women/caterer	14	13	2.060	0.721–5.887	0.177
Cashier/traders	15	11	2.580	0.870–7.646	0.087
Other	4	8	0.559	0.107–2.919	0.490

Table 5. Odds ratio for life habits, adjusted for age, BMI, smoke, alcohol and pathologies.

Habits	Cases	Controls	OR	95% CI	*p* Value
Use of plastic containers for storage of fat food	147	167	0.930	0.480–1.804	0.830
Use of canned food	155	154	2.021	1.022–3.996	0.043 *
Use of soya products	90	86	1.111	0.669–1.844	0.685
Use of scents	162	180	0.607	0.265–1.387	0.236
Use of nail polish	150	160	0.634	0.327–1.228	0.176
Use of hair spray	51	49	1.357	0.749–2.459	0.313

* Significant value.

4. Discussion

The results of this study suggest a possible association between exposure to phthalates and BPA and certain female infertility factors. Overall, there was a statistically significant difference between cases and controls, with higher levels of all metabolites in the infertile women, except for MnOP.

Data stratified by infertility factors indicated significantly higher concentrations of MnBP, MBzP, DEHP and BPA in women with ovulatory problems and endocrine dysfunctions. Otherwise, MEP levels were particularly elevated in women with RPL and reduced ovarian reserve, while DEHP levels were higher in women with idiopathic infertility.

The interaction between these chemicals and the endocrine system may directly interfere with endocrine function, potentially leading to ovulatory problems, as shown in experimental studies. These chemicals can affect the quality of the oocyte [46], and recently, some authors [47] have demonstrated a direct interference action of phthalates on the key pathways involved in oocyte maturation.

Experimental data support our findings with the group of women with endocrine and ovulatory problems. Many of the chemicals examined interact with estrogenic or androgen receptors, often involving the aryl hydrocarbon receptor in biochemical mechanisms [48]. BPA can interfere, at different stages, with the feedback control system of the hypothalamic–pituitary–gonadal (HPG) axis, contributing to reproductive toxicity by altering the gonadotropin-releasing hormone levels, which affect follicle-stimulating hormone (FSH) and luteinizing hormone (LH) release [49]. Similar mechanisms are supposed to be involved for phthalates through the HPG axis alteration. Although the involved mechanism remains uncertain, phthalates have been shown to either trigger or inhibit receptor activity, inducing both positive or negative responses on androgen and estrogenic receptors [50]. In vivo studies have demonstrated that phthalate exposure can impair oogenesis [51–53] and folliculogenesis [54], causing damage to deoxyribonucleic acid in oocytes and altering steroidogenesis and the expression of gonadotropin and hormone receptor signaling [55]. Some studies [16] have suggested that phthalates may contribute to the onset of endometriosis through the action of phthalates on inflammation, cytokine production, oxidative stress increase and proliferation of endometrial cells, though our results did not confirm this hypothesis.

BPA exposure has been associated with a reduced likelihood of embryo implantation and oocyte counts [56,57], as well as other gynecological disorders [58]. BPA tends to bioaccumulate, promoting nongenomic signaling pathways, altering women's metabolism and reproductive function leading to conditions such as hyperandrogenism, insulin resistance, obesity, dyslipidemia, chronic inflammation, anovulation and polycystic ovary syndrome (PCOS) [59]. A case–control study [60] on 321 women with PCOS and 412 controls revealed an increased odds ratio for bisphenol exposure (OR 1.26, 95%, CI 1.12–1.45). Other authors have confirmed the positive association between blood BPA concentrations and PCOS [61]. The current evidence [60,61] suggests a role for BPA, similar to other plasticizers, in female reproductive health, with mean concentrations ranging from 1.00 to 2.70 μg/g of creatinine. This warrants further investigations into the mechanism of action.

Otherwise, epidemiological studies have also highlighted an association between phthalate exposure and infertility, particularly focused on possible effects on oocyte yield [62]; some authors suggested effects like ovarian failure, anovulation and a decrease in steroidogenesis [53]. Though these results are controversial [24].

Regarding the possible association between phthalate exposure and RPL, different studies have focused mainly on DEP, DEHP and DnBP, either individually or in mixtures. However, the evidence remains inconclusive or conflicting [11,63].

Some authors [52] conducted a case–control study focused on RPL (260 patients and 203 controls), finding significantly higher levels of phthalates in cases, especially DEHP (the highest quartile of concentration was strongly related to RPL). The geometric mean of that group of women was 0.27 μg/L (unfortunately, results were presented without creatinine correction), which is markedly lower than the value found in our population (DEHP 10.61 μg/g of creatinine). Messerlian et al. [64] found a similar correlation between DEHP and RPL. Elevated MEP and DEHP levels have been associated with an increased risk of miscarriage [10] in 3220 pregnant women (OR = 1.99 and OR = 2.19, respectively), particularly during early gestation (6-10 weeks of gestation). In later gestation, an association was found only with MEHHP levels (OR = 2.41). However, other authors [12] have not confirmed these findings.

The present study does not highlight a particular risk for DnBP exposure in women with RPL, though previous studies have suggested such an effect [65], observing a solid significance for DnBP exposure and an elevated risk for RPL, with a less consistent correlation with DEHP and DEP metabolite levels [65]. Comparisons with these studies reveal higher DEHP and DEP exposure levels in our sample, up to two orders of magnitude higher, with similar results for DnBP. Conflicting results could be attributed to the differences in study design, exclusion criteria, or the sample size. A meta-analysis considering data on 4713 women (651 cases and 4062 controls) identified an elevated risk of pregnancy loss for MnBP and DEHP (OR = 1.34 and 1.79, respectively), though the authors advised caution due to limited study numbers (only eight) [66]. These data suggest the need to compare findings coming from similar geographic areas to avoid differences due to lifestyle habits and different laws for consumer protection.

Considerations about exposure to mixtures of compounds are mandatory, because even at low doses, different chemicals could determine the same effect. Precisely, in light of these considerations, in a cohort study on 132 women, MEP, MnBP and MiBP levels were associated with a higher risk of RPL [67]. Comparing these results with the data herein presented a significantly higher geometric mean for MEP (40.07 vs. 13.26 μg/g creatinine).

Epidemiological studies about women undergoing ART are of particular interest for our debate. DEHP confirmed its reprotoxicity, with lower probability of implantation (−22%) and lower possibility of clinical pregnancy (−24%) or the birth of an alive child (−38%) in case of higher concentrations [66]. Higher exposure (to DnBP and DEHP) and exposure to multiple phthalates (DEHP, DiNP, BBzP) led to a significant association with a lower chance of pregnancy [68]. With a female population of 663 subjects, urinary MnBP was negatively correlated with the odds of normal fertilization [15]. Finally, a risk of preterm birth was highlighted in the case of preconception exposure, studying a sample of 386 women, considering DEHP exposure [69].

Our findings strongly suggest a role of DEP exposure in the RPL, endorsing what other authors suggested. Instead, epidemiological investigations carried out to understand the role of phthalates in idiopathic infertility have not been conducted to date, to our knowledge, even though our results showed a possible role of DEHP exposure.

The higher urinary levels of the examined metabolites call for considerations regarding the sources of exposure. The stratification of data in relation to occupational activities was not significant, not allowing us to identify specific workplaces with a higher potential exposure. The difference between cases and controls, however, requires further investigation in daily life habits, as certainly some sources of exposure in the context of life led to higher exposures in the studied infertile women.

Furthermore, data related to DEP exposure are quite interesting, particularly as the DEP is currently not subject to any regulatory restriction in Europe. The mean values of DEP metabolite in cases are twice as high as those of controls, in particular, for women affected by RPL, and at least one order of magnitude higher than the other metabolites.

Limitations

A limitation of this study is the use of random spot urine samples, as these reflect exposure over the 12–24 h preceding sampling. However, as some researchers have observed [70], multiple urinary samples tend to fall within the same quartile of concentrations, possibly due to low variability in the underlined exposure in daily life. In particular, intra-subject variability studies [71–73] have shown that the use of a spot urine sample can be considered moderately representative of exposure to phthalates, with some differences from phthalate to phthalate.

Another potential bias is the possibility that women who had given birth a few days before, a major part of our controls, could have a faster toxicokinetic than other women, and this could, to a certain extent, underestimate the level of exposure. While no specific data exist for phthalates and alkylphenols, pharmacokinetic studies [73] support this possibility. On the other hand, some authors [74–76] indicate that for pregnant women there may be higher values of some phthalates, particularly DEHP, linked to hospitalization and the possible use of drips or catheters. Furthermore, it is documented in the literature how renal clearance is modified during pregnancy [77], and therefore, creatinuria levels generally decrease. It must be said however that in the postpartum days, the levels tend to return to the prepartum ones; therefore, in our case, this specific aspect should not have a significant impact.

There is also the possibility that women during pregnancy have adopted healthier lifestyles which may affect levels of phthalates, even if the questionnaire asked for elements related to possible sources of exposure and many of these do not fall into a bad lifestyle such as makeup or storing fatty foods in plastic containers.

Finally, there are numerous reprotoxic chemicals, and there are further substances that could act on the endocrine system producing adverse effects on reproduction. For this reason, there is an inevitable limitation of the obtained results, even considering the main confounding factors, and there could be exposures due to particular lifestyle habits that could affect the results.

5. Conclusions

The results of this epidemiological study suggest that exposure to DEP and DEHP, among other substances, may play a role in the RPL and idiopathic infertility. Other substances like BPA or DnBP have shown, with different magnitudes, a higher level in women with specific infertility factors, and this calls for further research to better clarify their role.

These findings highlight the urgent need for more epidemiological investigations focused on idiopathic infertility, because of a lack of information in this field and the possible cumulative effects of chemical mixtures on female reproductive health. In fact, the real exposure is hardly to one substance, but usually to a mixture of substances, and these must be taken into consideration for probable cumulative adverse health effects.

Regarding DEP, there is still no sufficient evidence in the scientific literature to support the hypothesis of its role in infertility problems. However, it should be taken in mind that "it is the dose that makes a substance a poison", and since the MEP concentrations found in our samples are very high, more accurate studies should be carried out to exclude or confirm the possible risk due to DEP exposure in women.

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Article

Unveiling Stress Vulnerability and Occupational Noise Perception as Burnout Predictors: Results of an Exploratory Study in Industrial Environments

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Abstract: Burnout is a complex phenomenon influenced by both environmental and individual factors. This pilot study explores the predictive role of occupational noise perception and stress vulnerability on burnout symptoms among industrial workers. A cross-sectional survey was conducted with 119 Portuguese workers exposed to occupational noise. Participants completed validated self-report measures assessing noise perception, stress vulnerability, and burnout. Path analysis revealed that both higher stress vulnerability and greater perceived occupational noise were significant predictors of elevated burnout levels. Furthermore, gender emerged as a relevant predictor, with women reporting significantly higher burnout symptoms than men. Age was inversely related to stress vulnerability, indicating greater resilience among older workers. These findings suggest that individual differences in stress vulnerability and noise perception contribute meaningfully to burnout risk, beyond traditional occupational hazard assessments. The study underscores the need for holistic occupational health strategies, integrating both environmental modifications and psychosocial interventions aimed at enhancing workers' coping capacities. This study contributes novel insights into the interplay between perceived noise and psychological vulnerability in industrial settings, supporting broader preventive measures for work-related mental health outcomes.

Keywords: burnout; occupational noise; stress; industrial workers; psychosocial risks

1. Introduction

Occupational noise exposure is a well-established risk factor for hearing loss and other auditory impairments. However, emerging evidence suggests that its effects may extend beyond auditory damage, potentially contributing to psychological stress and burnout symptoms [1]. While most studies on workplace noise have focused on its impact on hearing, less attention has been given to its influence on other health outcomes such as mental health disorders [2]. Moreover, the experience of noise-related stress may be modulated by individual differences in stress vulnerability [1]. Some evidence indicates that noise contributes to psychological strain among workers exposed to multiple occupational hazards, including both physical (e.g., noise) and chemical agents [3].

1.1. Noise and Noise Perception

Noise can be defined as an unwanted sound that acts as a psychosocial stressor adversely affecting the health and well-being of individuals through the activation of the sympathetic and endocrine systems [4–7]. Evidence shows that noise exposure increases systolic and diastolic blood pressure, changes heart rate, and causes the release of stress hormones (including catecholamines and glucocorticoids) [4,8]. The General Stress Model proposed by Babisch [5] explains the rationale behind these reactions (Figure 1). Potential mechanisms are emotional stress reactions due to perceived discomfort (indirect pathway) and non-conscious physiological stress from interactions between the central auditory system and other regions of the CNS (direct pathway) [5,6].

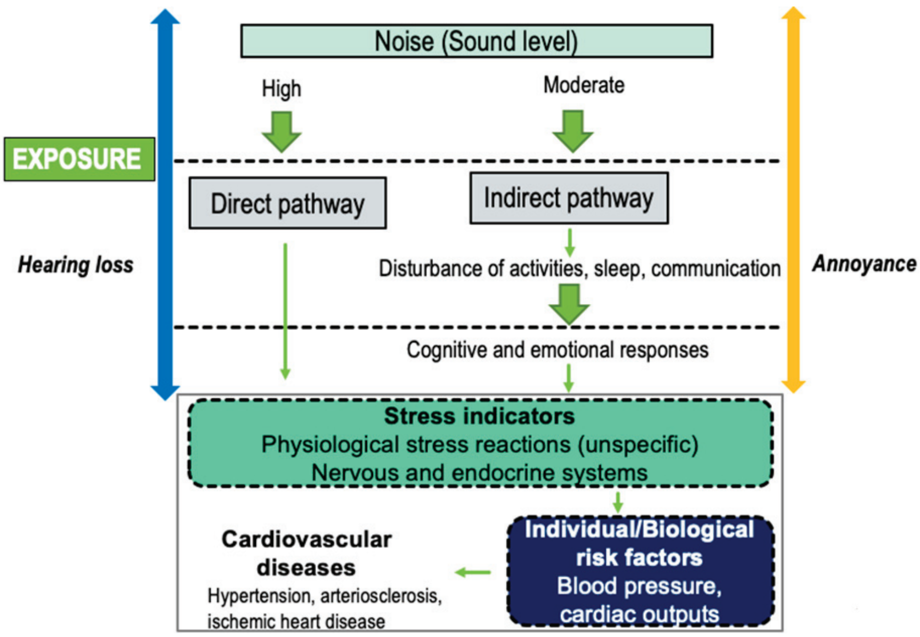

Figure 1. Noise reaction scheme (adapted from Babisch [5]).

High noise perception may contribute to increased stress levels [9]. Noise perception refers to how an individual interprets and responds to auditory stimuli in their environment. In fact, workers' noise perceptions have been studied in several occupational contexts, namely in relation to creating health and safety legislation, so that workers are not exposed to noise that they consider excessive (e.g., patient areas in hospital environments) [10,11].

Noise pollution has emerged as a significant, yet often underestimated, contributor to chronic stress [12]. The incessant exposure to noise—whether from urban traffic, construction, industrial machinery, or the omnipresence of electronic devices—not only affects the auditory system but also impacts cognitive and emotional functioning [13]. Research has increasingly highlighted the adverse effects of noise on human health, with prolonged exposure linked to heightened stress responses, disrupted sleep patterns, and reduced cognitive performance [9]. These effects are particularly relevant in occupational settings, where noise exposure during cognitive tasks can lead to elevated physiological and psychological stress, as well as other non-auditory disorders [3,6,13–17]. Additionally, chronic exposure to psychosocial stressors in the workplace—including noise—has been associated with an increased risk of cardiovascular disease, reinforcing the broader health implications of persistent stressors in the work environment [14].

1.2. Vulnerability to Stress

Vulnerability to stress refers to an individual's susceptibility or predisposition to experience negative effects in response to stressors [18]. Stressors are events, situations, or conditions that can elicit a stress response, which involves the body and mind's efforts to cope with challenges. It can be influenced by various factors, including biological, psychological, and environmental elements [19,20]. An individual's vulnerability to stress significantly shapes their response to environmental stressors. Factors such as sociocultural environment, personal resilience, coping mechanisms, and overall mental health are contributing factors to an individual's profile of stress response [21]. Those already pushing their stress tolerance limit due to work pressures, personal responsibilities, or existing mental health conditions are particularly susceptible to the detrimental effects of noise [21–24]. Recent research has also shown that noise exposure, when combined with high stress from other sources, can lead to severe outcomes such as cardiovascular strain, sleep disturbances, and increased anxiety [22,25,26]. When stress tolerance is already near its limit, the added burden of noise can significantly amplify its harmful effects [8,27].

1.3. Burnout

Burnout is a state of chronic physical and emotional exhaustion, often accompanied by feelings of cynicism and detachment from work [28]. Burnout syndrome is transversal across occupations, since the stressors that can instigate it may be present at any workplace [29]. Consequently, it is expected that burnout has a negative effect on workers' performance, inhibiting creativity and innovation and causing more work-related accidents and absenteeism [30,31]. Both noise perception and vulnerability to stress can be hypothesized as potential predictors of burnout, since, theoretically, individuals with prolonged exposure to noise stressors and higher vulnerability to stress may struggle to cope with yet another work-related challenge [20]. Over time, these heightened stress levels can contribute to burnout [32].

1.4. Rationale and Aim of the Study

Understanding the interaction between environmental stressors and individual psychological traits is essential for developing comprehensive frameworks to address occupational burnout. In particular, the theoretical link between perceived occupational noise (PON) and stress vulnerability (SV) offers valuable insight into the multifaceted nature of burnout. Despite increasing evidence of the impact of occupational stressors on mental health, few studies have integrated both environmental and dispositional variables into explanatory models of burnout.

Perceived occupational noise, a subjective and often underestimated stressor, may play a critical role in the development of burnout, particularly among individuals with high vulnerability to stress. Recognizing the interplay between environmental stimuli and psychological susceptibility underscores the need for holistic approaches to preventing and mitigating burnout. Such approaches should address not only environmental factors, such as noise exposure but also individual factors. This dual perspective may inform the design of more targeted interventions that combine environmental modifications with psychological strategies aimed at enhancing coping mechanisms and reducing vulnerability.

The main aim of this pilot study is to investigate whether noise perception and vulnerability to stress predict burnout symptoms among industrial workers. We also examine the moderating effects of demographic variables, specifically gender and age.

2. Materials and Methods

2.1. Participants

A total of 119 industrial manual workers exposed to occupational noise were recruited through a convenience sampling method from five different industrial settings (metal-working and chemical sectors). This non-probabilistic approach was chosen due to the exploratory nature of the study and the practical accessibility of participants within the selected workplaces. The sample comprised 64 men (54%) and 53 women (45%), while two participants (1%) did not report their gender. The overall response rate was 61.0%. Individuals were aged between 19 and 66 years (M = 34.9, SD = 12.8). Most participants were single (52.1%) or married/living with a partner (37.8%). Only 8 participants (6.7%) were separated/divorced and 4 widowed (3.4%). Regarding education, 59 (49.6%) participants completed 10 to 12 years of education, and 34 (28.6%) completed 9 years or less. Nearly all participants (96.7%) were Portuguese citizens, with the remaining workers originating from Brazil. Seventy-eight (78%) workers reported the need to raise their voice to be able to communicate with their colleagues at the workplace, but just 35 (29.4%) reported using hearing protection devices, at least sometimes. Permission was not obtained to access the noise exposure levels expressed in dB (A).

2.2. Measures

Perception of Occupational Noise (PON): In line with Abbasi et al. [33], who included two standardized items from ISO/TS 15666 [34] to assess noise annoyance in occupational settings, we used the equivalent adapted items from the Portuguese Standard NP 4476 [35], which is based on the first edition of ISO/TS 15666. The questions are as follows: PN1—"Considering the last 12 months, to what extent has the noise at your workplace bothered and disturbed you?", with a 10-point response scale. Higher numbers on the 0–10 scale indicate greater agreement with the statement. PN2—"Considering the last 12 months, indicate from 0 to 10 the extent to which you feel harmed or disturbed by the noise at your workplace". Higer numbers on the scale of 0–10 represent greater reported disturbance.

Stress Vulnerability Scale (23QVS [36]): The Stress Vulnerability Scale is a self-report questionnaire composed of 23 questions used to measure individual vulnerability to stress as a trait. Based on a sample of 368 individuals of the general Portuguese population, the original version had a good internal consistency (Cronbach's $\alpha = 0.83$ for all items). The questionnaire assessed the following seven factors characterizing vulnerability to stress: (i) Perfectionism and Intolerance to Frustration; (ii) Inhibition and Functional Dependence; (iii) Lack of Social Support; (iv) Adverse Life Conditions; (v) Dramatization of Existence; (vi) Subjugation; and (vii) Deprivation of Affection and Rejection. A value of 43 is the cut-off point above which a person is considered to be vulnerable to stress. Appendix A presents an informative English translation of the items included in the 23-item Stress Vulnerability Scale (23QVS), originally validated in Portuguese. This translation is provided for illustrative purposes only.

Shirom-Melamed Burnout Measure (SMBM) [37]: We used the Portuguese version of the SMBM adapted and translated by Gomes [38] to measure Burnout (B). The scale is composed of 14 items assessing feelings of burnout, such as the following: "When I wake up, I feel no energy to go to work"; "I have trouble concentrating at work"; etc. The 14 items are divided into three subscales as follows: (a) Physical Fatigue (6 items), (b) Cognitive Fatigue (5 items), and (c) Emotional Exhaustion (3 items). Respondents rate each item from "never" (1) to "always" (7), with higher scores corresponding to higher levels of burnout. The instrument has shown good psychometric properties in Portuguese samples [38,39].

2.3. Procedure

Questionnaires were distributed at industry sites, mostly in paper format, to facilitate the participation of workers without computer access. Participation was voluntary, and workers were asked to give informed consent with regard to the use of their data for research purposes. All data were confidential and anonymized. The study was approved by the Institutional Ethical Board Committee and was conducted in accordance with the ethical principles of the Declaration of Helsinki. The questionnaire started with a demographic section, followed by the three measures described above. The workers took approximately 10 min to complete the questionnaire. Data were entered into an Excel spreadsheet and further analyzed using R software (version 4.2.3), R Studio Desktop (version 3.6.1), and the R packages "Lavaan" [40] and "semPlot" [41].

3. Results

3.1. Missing Data

There were, in total, five missing values in our data (only two of which were in the same case). The missing pattern was as follows: one missing value each on the variables Age, Stress Vulnerability, and Burnout; two missing values for the variable Sex. Missingness was therefore quite low. Nevertheless, we used both the default ML estimator and listwise deletion for handling missing data. The results of our prediction models were identical, so we present here the ML model only.

3.2. Descriptive Statistics

The means and standard deviations of the variables (by gender) used in the analysis can be seen in Table 1. There were no significant differences between men and women for the variables PN1 (Portuguese Standard item #1), PN2 (Portuguese Standard item #2), and Stress Vulnerability (SV). Men were significantly older than women (t (114) = 3.18, $p < 0.001$), and women had significantly higher levels of Burnout (B) (t (114) = −4.42, $p < 0.001$). Figure 2 shows the separate histograms for the dependent variable Burnout by gender.

Table 1. Means and standard deviations of the variables age, PN1, PN2, Stress Vulnerability (SV), and Burnout (B).

	Female (*n* = 53)	**Male (*n* = 64)**	**Total (*n* = 119)**
	M (SD)	**M (SD)**	**M (SD)**
Age	30.6 (11.12)	37.75 (12.78)	34.92 (12.76)
PN1	5.74 (2.31)	5.86 (2.65)	5.76 (2.53)
PN2	5.55 (2.44)	5.53 (2.57)	5.50 (2.53)
SV	2.42 (0.39)	2.35 (0.51)	2.38 (0.45)
B	3.73 (1.19)	2.68 (1.36)	3.18 (1.39)

Note: There were two individuals who did not indicate their gender.

By analyzing Figure 2, the histogram suggests a tendency for lower burnout levels among men, with a higher concentration of scores in the lower range of the scale. In contrast, women's scores appear more evenly distributed, with a noticeable peak around the mid-range values and a greater proportion reporting moderate to high levels of burnout. This visual pattern may indicate gender-related differences in the experience or perception of occupational burnout within the sample.

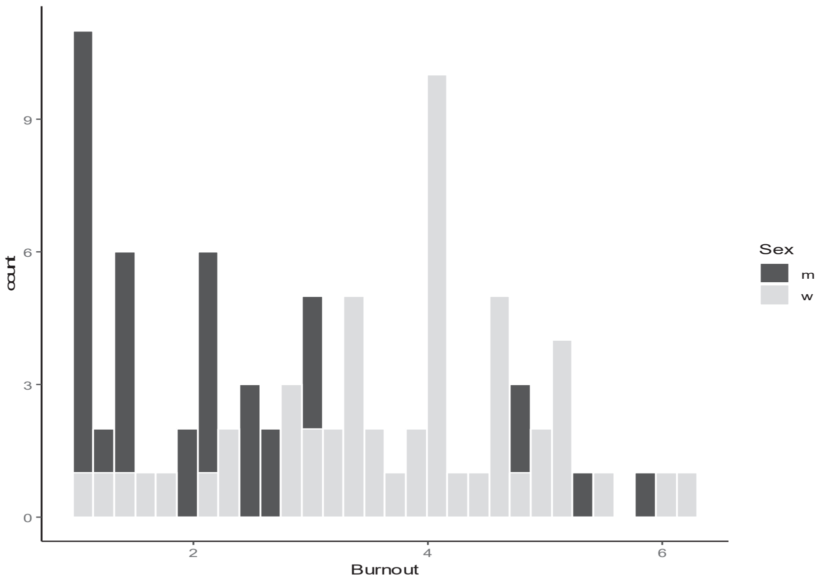

Figure 2. Distribution of burnout scores among male (dark bars) and female (light bars) participants (n = 116). Separate histograms are shown by sex to illustrate differences in the frequency of burnout levels.

3.3. Simple Correlation Analyses

Being male was significantly associated with older age and lower levels of Burnout. There was a significant negative correlation between age and Stress Vulnerability, with older individuals being less vulnerable. The same happened for the relation between age and Burnout: the older the individuals, the lower the burnout levels they reported. As expected, the variables PN1 (Portuguese Standard item #1) and PN2 (Portuguese Standard item #2) referring to the perception of occupational noise in the workplace showed significant positive correlations between them, and both were positively and significantly correlated with reported Burnout. Finally Stress Vulnerability was significantly associated with Burnout levels, with more vulnerable individuals reporting higher levels of Burnout. Table 2 shows the correlation matrix between all variables.

Table 2. Correlation matrix for the variable sex, age, PN1, PN2, Stress Vulnerability (SV), and Burnout (B).

	Sex	Age	PN1	PN2	SV	B
Sex	1					
Age	−0.29 **	1				
PN1	−0.03	0.12	1			
PN2	0.003	0.14	0.87 **	1		
SV	0.08	−0.21 *	0.14	0.16	1	
B	0.38 **	−0.18 *	0.24 **	0.29 **	0.40 **	1

* $p < 0.05$, ** $p < 0.01$ Sex: 0 = male; 1 = female.

3.4. Prediction Models

The main estimation models (displayed as path diagrams) are shown in Figure 3. A latent variable PON (Perception of Occupational Noise) was created with the indicators PN1 and PN2, which consider the two questions included in the Portuguese standard for noise perception, as described in the methods section. The variables SV (Stress Vulnerability) and B (Burnout) are manifest variables and correspond to the total scores obtained from the questionnaire measures 23QVS and SMBM, respectively.

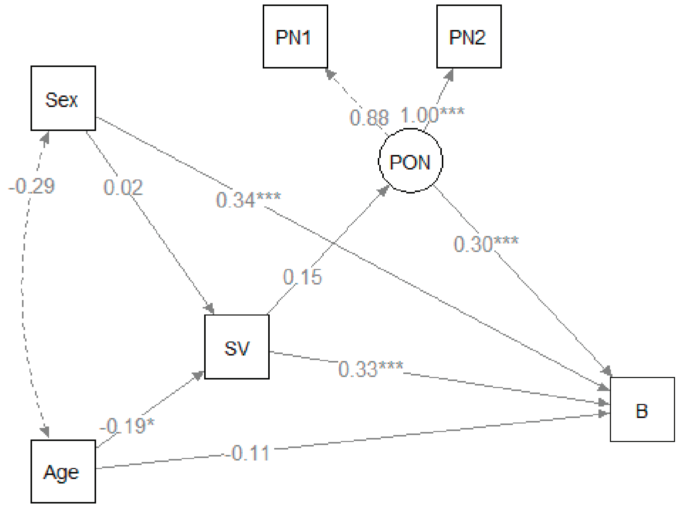

Figure 3. Path model illustrating regressions predicting B (Burnout) from PON (Perception of Occupational Noise) and SV (Stress Vulnerability). Standardized coefficients are depicted (n = 119). Men = 0; Women = 1. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Burnout was significantly and directly predicted by gender, Stress Vulnerability, and Perception of Occupational Noise. Being female (B = 0.91, SE = 0.21, $p < 0.001$) and having higher levels of both Stress Vulnerability (B = 1.01, SE = 0.23, $p < 0.001$) and Perception of Occupational Noise (B = 0.19, SE = 0.05, $p < 0.001$) were associated with higher Burnout scores. In addition, age significantly predicted Stress Vulnerability (B = −0.007, SE = 0.003, $p < 0.05$), with older workers showing lower levels on that scale.

4. Discussion

This exploratory study investigated the predicting role of the perception of occupational noise and stress vulnerability on burnout levels in a sample of Portuguese industrial workers. We have also investigated the moderating role of the variables age and gender. The results of the path analysis model revealed that being female, having higher levels of stress vulnerability, and greater levels of perceived occupational noise were significantly associated with increased burnout symptoms. The positive association between perceived occupational noise and burnout is consistent with previous research showing that noisy environments can impair concentration, disrupt communication, and lead to both physiological arousal and psychological strain [42]. These stress responses, if sustained over time, can contribute to emotional exhaustion and other components of burnout. While noise exposure has been more commonly studied in relation to auditory outcomes, our findings emphasize its broader psychosocial impact. The results align with studies in both educational [16] and industrial settings [43], where subjective noise perception was linked to irritation, fatigue, and stress-related outcomes. Stress vulnerability also emerged as a robust predictor of burnout, reinforcing the hypothesis that dispositional factors significantly influence how individuals respond to occupational stressors. As previously suggested [44], individuals with higher vulnerability may lack adequate coping strategies, making them more susceptible to emotional exhaustion and reduced psychological resilience in demanding work environments. This finding supports models of stress–burnout relationships that integrate both environmental and personal dimensions [22]. An interesting and theoretically grounded result concerns the inverse relationship between age and stress vulnerability. Older workers reported significantly lower vulnerability, which is consistent with the Strength and Vulnerability Integration (SAVI) model [45]. According to this framework, aging is associated with improved emotion regulation and more adaptive coping, which may buffer against the effects of chronic stressors in the workplace.

Gender differences in burnout were also observed, with women reporting significantly higher levels of burnout than men. This finding echoes the previous literature attributing higher burnout risk in women to increased emotional labor demands [46], work–family role conflict [47], and systemic gender-based inequities in the workplace [48]. It is also plausible that task assignment, support structures, and reporting patterns differ by gender, especially in male-dominated industrial contexts. Further studies should consider a more granular analysis of job roles, psychosocial hazards, and coping resources by gender. Taken together, these findings support a biopsychosocial model of occupational burnout, where both external stressors (e.g., noise exposure) and individual traits (e.g., stress vulnerability) interact to shape mental health outcomes. Importantly, this study highlights the relevance of subjective perception—how workers interpret and internalize environmental demands—as a key factor in understanding burnout.

5. Conclusions

To our knowledge, this is the first study on the role of noise perception and vulnerability to stress as predictors of burnout in an industrial environment. In these environments, occupational health and safety professionals are typically more focused on preventing professional hearing loss than on non-auditory effects, such as burnout. The assessment and prevention of non-auditory disorders, which can occur at exposure levels much lower than the recommended maximum levels for hearing loss prevention, represent a step forward in relation to the classic assessment of noise exposure at the workplace, typically focused on preventing hearing damage. The integration of occupational health psychologists in multidisciplinary teams could provide a valuable contribution to designing interventions against the detrimental psychological effects of noise exposure, namely, by focusing on coping mechanisms and stress management skills. While our exploratory study provides valuable insights that can guide future studies, it is essential to acknowledge some limitations. First, the cross-sectional design limits causal inferences. Future research should employ longitudinal designs to examine the temporal relations among these variables. Second, this study employed the self-report method, which is vulnerable to participants' reporting style, motivation, and social desirability. Third, our study focused on a specific population of industrial workers and a relatively small sample. Replicating these findings in other occupational settings would strengthen the generalizability of our results. Future studies on noise exposure (including objective measurements or eventually scales validated to quantify noise exposure) and other environmental factors, such as lightening, thermal environment, indoor air quality, and other variables, such as job demands, job control, and social support, could provide a more comprehensive understanding of burnout. In summary, this study highlights the importance of considering both environmental perceptions and psychological traits in understanding burnout among industrial workers. Perceived occupational noise and stress vulnerability emerged as significant predictors of burnout, reinforcing the need for integrated workplace interventions. These should include not only physical noise control measures, but also psychosocial support strategies tailored to individual profiles.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, authorized by the National Data Protection Commission (CNPD) (protocol no.7087/2028, 24 May 2018) and approved by the Ethics Committee for Health of National Institute of Health (CES-INSA) (18 June 2019).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding author.

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Conflicts of Interest: The authors declare no conflicts of interest.

Appendix A

English translation of the Stress Vulnerability Scale (23QVS).

1. I am a determined person when it comes to solving my problems
2. I have difficulty relating to unfamiliar people
3. When I have problems that bother me, I can count on one or more friends who serve as confidents
4. I usually have enough money to meet my personal needs
5. I worry easily about everyday setbacks
6. When I have a problem to solve, I usually find someone who can help me
7. I regularly give and receive affection
8. It is rare for me to be overwhelmed by unpleasant events that happen to me
9. When faced with daily difficulties, I tend to complain more than make an effort to solve them
10. I am the kind of person who gets easily upset
11. In most cases, the solutions to the important problems in my life do not depend on me
12. When I am criticized, I tend to feel guilty
13. People only pay attention to me when they need something for their own benefit
14. I spend more time responding to other people's demands than attending to my own needs
15. I prefer to stay quiet rather than contradict someone, even when they are wrong
16. I get nervous and annoyed when I do not perform as well as I expected
17. There are unpleasant aspects of myself that cause others to distance themselves
18. At the right moments, I find it difficult to express what I truly feel
19. I get nervous and upset if I don't get what I want immediately
20. I am the kind of person who, due to my sense of humor, can laugh about unpleasant events that happen to me
21. The money I have barely covers my essential expenses
22. When faced with life's problems, I am more likely to run away than to fight
23. I feel bad when I am not perfect in what I do

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Article

Worker Safety in High-Field NMR Spectroscopy Laboratories: Challenges and Risk Assessment

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Abstract: Magnetic Resonance (MR) technology is extensively used in academic and industrial research laboratories and represents one of the most significant methodologies in clinical radiology. Although MR does not use ionizing radiation, it cannot be considered risk-free due to the strong static magnetic fields and time-varying electromagnetic fields employed in the technology. To mitigate risks for MR operators, the European Community and ICNIRP have established safety limits based on the existing literature, primarily related to diagnostic MR. However, the literature on occupational exposure in non-clinical nuclear magnetic resonance (NMR) spectroscopy is limited. Due to their specificity, non-medical NMR environments present unique challenges from the point of view of operator exposure. NMR spectrometers are characterized by extremely high static magnetic fields, reaching up to 28 T in commercial systems; moreover, routine activities performed near the magnet, where field gradients are highest, increase operator exposure. Such environments are not typically perceived as hazardous and are frequented by various types of personnel, often without specific training. This study aims to highlight the critical issues in managing a preclinical MR laboratory equipped with a high-field NMR spectrometer, discussing operator safety challenges and presenting risk assessment data.

Keywords: nuclear magnetic resonance spectroscopy; NMR; occupational exposure; risk assessment

1. Introduction

Before its widespread adoption in medicine as a diagnostic technique, magnetic resonance (MR) was predominantly used in fundamental laboratory research, food quality assessment, and molecular studies through nuclear magnetic resonance (NMR) spectroscopy. NMR spectroscopy provides a comprehensive understanding of molecular structure, dynamics, reaction states, and chemical environments [1–3]. Concurrently, there has been a rapid proliferation of high-field magnetic resonance imaging (MRI) scanners in research settings (both academic and non-academic), particularly for preclinical studies involving animal models, especially rodents [4].

Diagnostic MRI and NMR spectrometers share the same operating principles, involving three phases: the polarization of nuclear spins in a static magnetic field (B0); the excitation of the sample with a radiofrequency (RF) magnetic field (B1) at the Larmor frequency; and the application of spatial magnetic field gradients for spin localization. NMR spectrometers generate extremely high magnetic fields (up to 28 T), which are typically well-confined near the instrument. Some risks associated with MR devices are documented in the literature and should not be underestimated, especially given the rapid development and dissemination of the technology [5,6].

In magnetic resonance environments, the primary exposure risks for workers stem from both static and spatially heterogeneous magnetic fields, as well as, in some cases, radiofrequency (RF) fields. Workers who move in close proximity to the magnet are additionally exposed to time-varying magnetic fields, which can induce electric currents within the body. If these currents reach sufficient strength, they may interact with the central nervous system (CNS), potentially leading to neurological effects, and can also stimulate peripheral nerves, causing sensations such as tingling or muscle contractions.

Recent research has documented various transient symptoms experienced by workers due to movement within these magnetic fields, including dizziness, nausea, visual disturbances, and a sensation of vertigo [7–12].

Recent studies have explored the neural impact of static magnetic fields and dynamic magnetic fields using animal models. Research on the influence of magnetic fields on cognitive functions such as learning and memory, as well as emotional behaviour, neuronal activity, and neurotransmitter dynamics, is steadily growing. However, due to variations in magnetic field parameters, experimental models, and study conditions, findings remain inconsistent [13,14].

As magnetic resonance technology advances and field strengths increase, further investigation into occupational safety measures and exposure limits is essential to mitigate potential health risks for personnel working in these environments.

To address these concerns, the European Union (EU) and the International Commission on Non-Ionizing Radiation Protection (ICNIRP) have established limits for the exposure of workers to the risks arising from physical agents (electromagnetic fields, EMF) [15–18]. Several studies evaluate health risks for workers in MR diagnostic environments [19–23]. Worker exposure to static magnetic fields and movements in fringe fields has been assessed and discussed for MRI scanners with field strengths from 0.25 T to 3.0 T [22,24–28].

However, there is limited research on occupational risk assessment for workers in NMR spectroscopy and, more broadly, in non-clinical magnetic resonance environments, such as preclinical or fundamental research laboratories. NMR spectrometers, operating at up to 28 T @ 1.2 GHz, are commonly found in universities and research centres. These instruments are also used by doctoral students and research fellows who are considered scientific users rather than workers. Although they may be proficient in the scientific applications of the technique, they often lack awareness of safety aspects and may mistakenly perceive NMR spectrometers as low-risk devices. In this context, it is crucial to educate workers on appropriate behaviour and movement control to prevent adverse events.

Given the nature of NMR equipment and considering that some operational tasks involve direct interaction with the devices, it is presumed that researchers working in spectrometry laboratories may experience daily exposure to relatively high levels of magnetic fields and/or EMF. However, these exposure levels and conditions have not yet been thoroughly analysed and require evaluation through targeted on-site measurements.

This study highlights the challenges of high-field NMR spectroscopy laboratories regarding magnetic field exposure and discusses risk assessment aspects for operators. Particular attention is given to workers at particular risk, such as operators with active implantable medical devices (AIMDs), a sensitive risk group requiring protection from electromagnetic field interference.

2. Materials and Methods

2.1. High-Field NMR Spectroscopy Laboratory

An NMR spectrometer (Bruker, Billerica, Massachusetts the manufacturer, city, and country) comprises a superconducting coil immersed in a liquid helium jacket surrounded by a liquid nitrogen jacket. At the centre of the spectrometer is an empty cylinder, known as the gantry, where the static magnetic field is generated. This bore accommodates the probe, a cylindrical container that holds the sample to be analysed. Depending on the experiment, different probes are used, which may be nucleus-specific or multinuclear, with variations in internal coil design determining specificity. Sample insertion operations are typically performed at the top of the equipment, accessible via ladders, or near the base of the magnet, requiring operators to crouch near the magnet.

A high-field NMR spectroscopy laboratory is a specialized environment housing the NMR spectrometer and essential components for its operation, including the cryogenic cooling system for the superconducting magnet with liquid helium and nitrogen tanks and the refilling system, the console and electronic components, and safety systems such as ventilation systems, quench piping, and oxygen sensors. Additional auxiliary systems (e.g., sample containers, ladders, and sample insertion/removal structures) and at least one workstation are typically present.

The NMR spectroscopy laboratories can house spectrometers of various generations. Older installations, with lower magnetic fields, often neglect manufacturer safety recommendations. For example, older NMR equipment typically lacks safety systems found in modern superconducting magnets used in medical imaging, such as quench piping to direct helium outside the laboratory, auxiliary safety devices (e.g., oxygen sensors), or ventilation systems to expel helium gas released within the laboratory during a quench event. Conversely, newer spectrometers, operating at higher fields and frequencies (up to 1200 MHz), necessitate advanced safety systems like cryogenic gas evacuation pipes and oxygen monitoring sensors. As a case in point, new-generation solid-state NMR spectrometers utilize ultra-high field pulses and decoupling power [29]. This may result in potential hazards relative to high-power RF fields, which may interfere with electronics and sensors within the NMR environment. It is imperative to ensure adequate RF shielding to prevent unintended exposure and to position sensitive equipment safely outside of high-field and high-RF zones. Manufacturers of modern equipment include detailed safety system guidelines in instruction manuals, outlining risk assessments and management strategies, which, if implemented, represent a significant safety improvement.

2.2. Potential Hazards and Specific Critical Points

In the context of NMR applications, it is hypothesized that workers may be exposed on a daily basis to relatively high levels of magnetic and/or RF fields. The primary source of exposure is the static magnetic field; as reported by Berlana and Ubeda [30], no detectable emissions of RF field were found in the surrounding environment, indicating that the electromagnetic radiation generated by the NMR remained confined within the devices. The potential hazards associated with magnetic fields can be classified as either direct or indirect. Direct risks manifest in the human body through biological effects, which can be sensory or health-related. Indirect risks are associated with magnetic fields, such as the projectile effect (attraction of ferromagnetic materials), a significant torque applied to objects, and potential interference with implanted medical devices.

In contrast to clinical MRI sites, the primary users of the NMR equipment consist of students, postgraduates, scholarship holders, and contract workers. These individuals do not qualify as employees but rather as scientific users, sometimes even occasional, often highly competent in the scientific application of technology but generally not very sensitive to safety aspects because they are unaware of the associated risks, having most often not been properly trained and made aware of these important aspects. Those with a greater familiarity with the operational situation may erroneously assume that the utilization of NMR spectrometers in the present context entails reduced exposure for operators. For example, the sample loading typically occurs over a significantly shorter time interval compared to other MRI applications. However, in the majority of cases, this process is carried out by approaching the instrument, either at the top or by crouching down with the arms positioned underneath the structure and the head placed very close to the instrument. Moreover, it should be noted that for NMR investigations, an additional level of exposure exists that is not present in other cases and is related to the tuning and matching procedure. This procedure must be performed for each type of sample introduced unless the analysis is repeated on the same types of samples. This underscores the significance of the dwell time at high levels of static magnetic field as a crucial factor in ensuring protection.

The NMR laboratory is typically a single room where the highest-risk exposure area (near the magnet) is easily accessible and not always marked with appropriate signage (such as the 5 Gauss line).

This also means that, in many NMR laboratories, the operators' workstation, the equipment controls area, and sometimes the chemical laboratory where the samples are prepared are situated within the same room as the NMR spectrometer or in close proximity. This configuration necessitates a comprehensive and detailed investigation into safety concerns.

2.3. Regulatory Framework and Current Challenges

Currently, there is a notable lack of a specific regulatory framework for NMR spectroscopy environments, resulting in limited awareness of safety requirements. In Europe, the primary regulatory reference is the Directive 2013/35/EU, which addresses worker exposure to electromagnetic fields, focusing on short-term effects while excluding long-term effects due to insufficient scientific evidence.

For general population protection, exposure limits are established by the European Recommendation 1999/519/EC, which sets a threshold of 40 mT for potential human risk (excluding indirect effects) [31].

According to current regulations, static magnetic fields are significant for operators when exposure exceeds 2 Tesla for sensory effects (transient sensory perception disturbances, nausea, vomiting, dizziness, and minor changes in brain functions) and 8 Tesla for health effects (thermal heating and/or the stimulation of nervous or muscular tissue).

It is important to note that these limits do not apply to individuals with specific contraindications to magnetic field exposure (e.g., wearers of active implantable devices), for whom the established threshold is significantly lower, at 0.5 mT (5 Gauss). With regard to passive implanted devices, current regulations do not set action values; therefore, an assessment must be conducted on a case-by-case basis. However, with regard to the projectile effect, European Recommendation 1999/519/EC establishes an action level of 3 mT (3 Gauss) [31].

In most NMR installations, the limits for direct effects—2 T for the body and 8 T for the limbs—remain confined within the equipment; consequently, workers are not directly exposed. Additionally, there are no exposures related to the radio frequencies emitted during the operation of the NMR. However, the 0.5 mT limit is probably exceeded in the vicinity of the NMR device. According to regulations, a colour-coded floor marking delineates the magnetic induction dispersion field, as outlined below:

Red/white line for 0.5 mT;
Yellow line for 0.4 mT;
Green line for 0.3 mT.

The 0.5 mT limit can only be exceeded by authorized personnel, who are trained, informed, and certified as fit for the specific task by the occupational physicians.

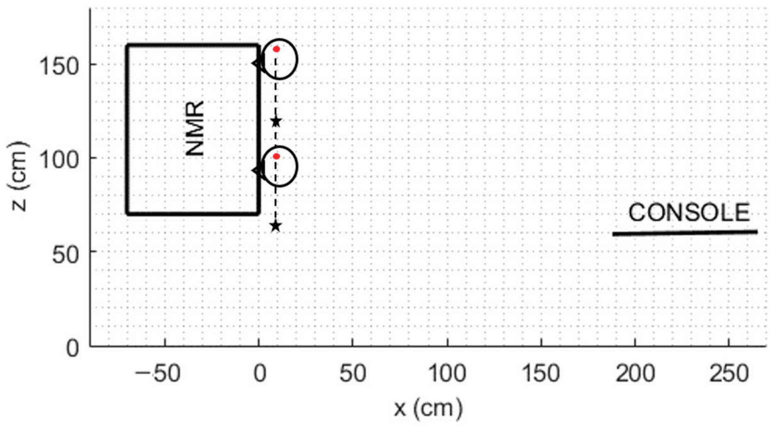
The ICNIRP guidelines published in 2014 provide recommendations for limiting exposure to static magnetic fields and time-varying magnetic fields below 1 Hz [18]. The primary objective of these guidelines is to prevent peripheral nerve stimulation (PNS) and reduce the likelihood of transient sensory effects caused by electric fields induced in the human body due to movements within spatially heterogeneous static magnetic fields. These effects can include sensations such as tingling, dizziness, or even muscle contractions, which may pose safety concerns in occupational and clinical settings. To ensure controlled exposure conditions, the ICNIRP has established specific safety thresholds. According to ICNIRP guidelines, a basic restriction is set at 1.1 V/m for peak-induced electric fields within the body. Additionally, a reference level of 2.7 T/s is defined for the time derivative of magnetic flux density (dB/dt), aiming to limit excessive exposure to rapidly changing magnetic fields that could exacerbate neuromuscular stimulation. These guidelines serve as an essential framework for safeguarding individuals working in or exposed to strong magnetic environments, such as those found in MRI facilities [18]. The basic restriction and reference levels for uncontrolled exposures (protection against magnetophosphenes and peripheral nerve stimulation) change as a function of 1/f (up to 0.66 Hz), where f is the frequency of motion-induced fields.

2.4. Risk Assessment Procedure

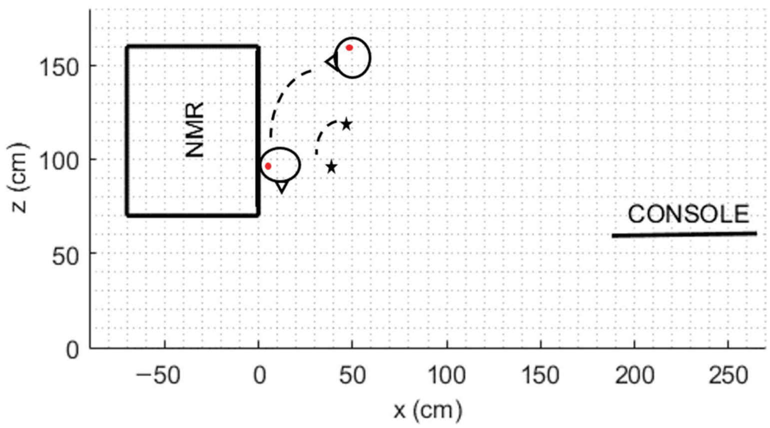
A correct risk assessment, linked to the presence of the static magnetic field in the NMR environment, must necessarily consider the construction characteristics of the equipment and the dispersion of the field around it in order to identify the areas of risk, the attention levels to be kept, and the operating procedures to be followed to minimize exposure and the possibility of the occurrence of risk scenarios. First of all, the 0.5 mT line should be identified to delineate the area restricted for unauthorized access, which is to be made accessible exclusively to authorized personnel (listed in a dedicated register). This is initiated by the precise measurement of the fringe field surrounding the NMR spectrometer.

Then, regarding the occupational exposure to time-varying magnetic fields, an estimation of the reference parameters should be conducted. In this evaluation, worker exposure is assessed as part of a comprehensive risk analysis, focusing on the induced electric field ($|E|$) and the time derivative of the magnetic flux density ($|dB/dt|$) to establish safe operating procedures. Special attention is devoted to individuals with active implantable medical devices (AIMDs), who represent a particularly vulnerable group requiring stringent protection from the risks associated with electromagnetic field interference [32].

We present here the risk assessment for a research NMR laboratory including a 7T (@300 MHz) spectrometer. First of all, the static magnetic field was mapped by positioning a three-axis Hall magnetometer (THM 1176, Metrolab Instruments SA, Plan-les-Ouates, Switzerland) at five different heights above the ground plane (z = 0 cm, 40 cm, 80 cm, 120 cm, and 160 cm). Measurements were taken along a predefined theoretical path extending from the console to the spectrometer and back, with a spatial resolution of 10 cm, as previously described in [27]. Based on these measurements, the fringe field distribution in the vertical (xz) plane was determined. Subsequently, the magnitude of the induced electric field $|E|$ was calculated for a trajectory representative of a worker's movement during routine sample processing operations. This calculation was performed using the analytical model outlined in the ICNIRP guidelines, allowing for an assessment of potential exposure risks associated with workplace activities in the presence of spatially varying magnetic fields [18]. By way of example, we considered the typical movement of an operator who, starting from a standing position, kneels down next to the NMR spectrometer (Figure 1a). The movement speed was set at 1 m/s along the entire movement [33]. Furthermore, a 90° torso flexion was also considered, with a maximum velocity of 4 rad/s (Figure 1b). For both of these movements, a point on the head (shown in Figure 1 as a red point) and a point on the torso corresponding to the heart (shown in Figure 1 as a black star), were designated as the reference points.



(**a**)



(**b**)

Figure 1. Schematization of the considered movements in the fringe field of a 7T NMR spectrometer: (**a**) linear movement along the z axis, (**b**) flexion movement of 90°. Red point: head reference point. Black star: torso reference point.

Finally, for both of the considered movements, we also calculated the maximum induced voltage (electromotive force, EMF) in an active device implanted in the torso (such as a pacemaker) by simplifying the Faraday–Neumann–Lenz law as reported in [32].

3. Results

Figure 2 shows the map of the fringe field on an xz plane $|B|_{xz}$ through the isocentre of the NMR spectrometer described previously, with the indication of the 0.5 mT line (dashed red line). Moreover, Figure 2 also shows the vector representation of the two-dimensional spatial gradient of the magnetic field $|B|_{xz}$ together with the contour plot of $|B|_{xz}$ around the NMR spectrometer.

For the considered xz plane, the maximum value of $|B|$ is 18.08 mT, the maximum value of $|dB/dx|$ is 58.8 mT/m, and the maximum value of $|dB/dz|$ is 19.35 mT/m.

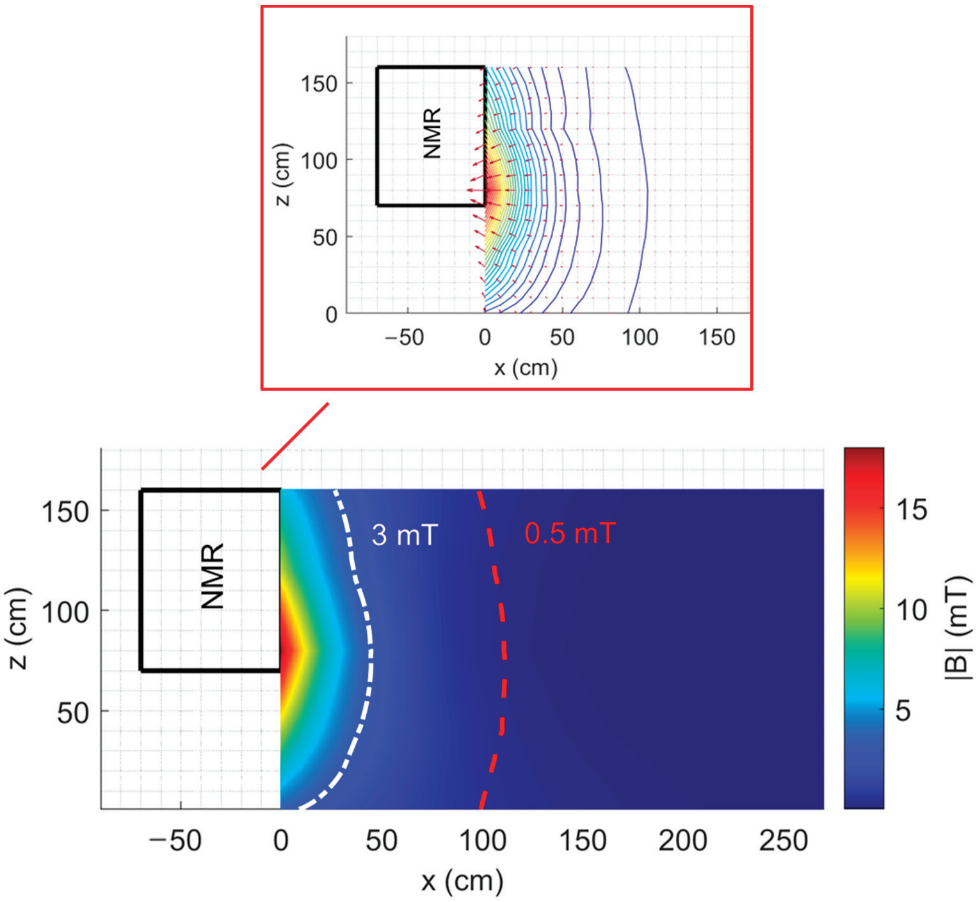


Figure 2. Map of the fringe field |B|xz with the indication of the 0.5 mT line and the representation of the two-dimensional spatial gradient around a 7 T NMR spectrometer.

Tables 1 and 2 present the peak values of the estimated parameters for the risk assessment relative to the linear movement along the z-axis and the flexion movement of 90°, considering the head and the thorax–heart reference points.

Table 1. Peak values of the estimated parameter for the risk assessment of a 7T NMR spectrometer: linear movement along the z-axis.

Linear Movement Along z Axis @v = 1 m/s	$\lvert B \rvert_{max}$ (mT)	$\lvert dB/dt \rvert_{max}$ (mT/s)	$\lvert E \rvert_{max}$ (mV/m)	EMF_{max} (mV)
Head	14.59	32.14	1.45	-
Thorax–Heart	18.00	32.93	5.27	0.74

Table 2. Estimated parameter for the risk assessment of a 7T NMR spectrometer: flexion movement of 90°.

Flexion Movement @90°, v = 4 rad/s	$\lvert B \rvert_{max}$ (mT)	$\lvert dB/dt \rvert_{max}$ (mT/s)	$\lvert E \rvert_{max}$ (mV/m)	EMF_{max} (mV)
Head	16.11	66.80	3.01	-
Thorax–Heart	7.48	17.88	2.86	0.40

4. Discussion

The occupational exposure literature in non-diagnostic NMR environments is currently sparse [30,34,35], particularly compared to the characterization of exposures for healthcare personnel working with MRI scanners [5,7,26,36–39]. However, well-established physical mechanisms describe interactions between electromagnetic fields and living tissues, responsible for acute and transient effects above exposure thresholds, leading to the establishment of exposure limits. For example, translational and rotational movements of operators within magnetic fields are the focus of numerous studies on occupational exposures in medical MRI environments, yielding insights into induced body currents and their effects on humans [7,40–43].

A classical NMR spectrometer generates a strong magnetic field that extends beyond the magnet itself, thereby creating a significant stray magnetic field around the instrument. This has the potential to interfere with nearby electronic devices and necessitates a dedicated, controlled environment to prevent unwanted interactions. The majority of new ultra-high field instruments (above 500 MHz) are ultra-shielded, with the design of these spectrometers being such that advanced shielding techniques are incorporated to minimize the stray magnetic field. In [30], the authors conducted a comparative analysis of the static magnetic field measurements obtained from both the classical and ultra-shielded NMR settings. It was established that all values were well below the exposure limits set by the European standard for workers' protection. However, the study revealed that ultra-shield technology can achieve a 20–65-fold reduction in the field strength received by the operator. This reduction in external magnetic field strength enables the instrument to be situated in a wider range of environments with fewer spatial constraints. However, this fact gives rise to another potential hazard, since the stray field strength is observed to increase in a direct and significant manner with decreasing distance from the magnet, both directly above and below it. This increase in the attractive forces exerted on magnetic items is a consequence of this phenomenon.

Up until today, little is known about the long-term effects of chronic occupational exposure to static magnetic fields, as the available epidemiological and experimental evidence remains limited and inconclusive [12,40,44]. This knowledge gap makes it difficult to establish definitive conclusions regarding potential health risks. Regarding the direct effects of magnetic fields, particularly for long-term exposures, the current body of literature does not provide enough evidence to draw definitive conclusions about the biological and health effects of exposure to weak static magnetic fields (SMF). A lack of consistency in the studied biological systems, the examined endpoints, and scientific rigour in many reviewed studies has weakened the credibility of reported findings. While direct effects of weak magnetic fields have been reliably reported, including effects on melatonin bio-synthesis, locomotor activity, blood pressure regulation, brain enzyme activities, or neurotransmitter levels [44], they remain insufficiently understood to be incorporated into existing safety standards. Despite the paucity of long-term risks and potential benefits observed in the majority of animal and human studies conducted to date [45], further research is required to comprehensively assess the exact long-term biological effects of various SMFs on different physiological and pathological conditions. A recent report by the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) updated the potential health effects of exposure to EMF with regard to frequencies between 1 Hz and 100 kHz [46]. The SCHEER report identified a lack of recent systematic reviews or meta-analyses on low-frequency EMF exposure to update the previous (2015) Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) [40] assessment and concluded that there is no convincing evidence of a causal relationship between ELF magnetic field exposure and self-reported symptoms.

Furthermore, standardized procedures for assessing occupational exposure in MR and NMR environments have yet to be developed. The lack of uniform assessment methods complicates efforts to evaluate and mitigate risks, particularly for highly specialized workers in industrial and research settings where exposure to extremely strong static magnetic fields—reaching up to 28 T in some NMR applications—is common. In view of the challenges identified, further studies are imperative to enhance our understanding of exposure conditions and establish safety guidelines that are tailored to workers in high-field environments. This is of crucial importance, as the basis for effective guidelines and best practices lies in a clear understanding of the physical parameters involved.

This is a significant consideration for risk assessment, as non-medical MR environments present unique challenges, including the presence of personnel often inadequately trained about occupational exposure, the high intensity of static magnetic fields and field gradients (active shielding), and the need to perform routine operations (such as tuning or cryogen refilling) in close proximity to the instrument, where magnetic field intensity is highest.

In this paper, we discuss a pathway for acquiring risk awareness for NMR laboratories. The pathway is based on a risk management model that is both concrete and applicable (Figure 3).

As an example, a case study is presented in which mathematical models and algorithms are used to explore and characterize occupational exposure levels to magnetic fields generated by a 300 MHz (7 T) NMR spectrometer. The findings of this study indicate that the maximum magnetic field levels ($|B|$) and associated exposure levels were observed in the proximity of the spectrometer. The measurements of $|B|$, spatial distribution, and gradient indicate high-risk areas corresponding to zones with steep magnetic field gradients, where operators should exercise caution and move slowly.

Despite the selection of elevated values for motion velocity and areas exhibiting greater values for magnetic field spatial gradient (worst case), none of the calculated exposure parameters surpassed the relevant limits stipulated by the applicable guidelines [18], meaning that the considered exposure conditions remained in compliance with the stipulated restrictions. Nevertheless, it is not possible to generalize this conclusion due to the high variability of movements, particularly in terms of speed. This variability is contingent on the operator's habits and body size, as well as the working conditions (whether routine or emergency). It is therefore important to have a simple yet reliable tool for risk assessment under different exposure conditions.

NMR environments can present significant risks for workers with certain implants, particularly AIMDs or other electronic medical equipment. Exposure to electromagnetic fields in these settings can interfere with the functionality of such devices, potentially leading to malfunctions, degraded performance, loss of functionality, or unintended physiological responses. Our findings indicate that workers may be exposed to magnetic fields exceeding 0.5 mT, especially during tasks that require close proximity to the equipment or at heights corresponding to the typical positioning of active medical implants, such as pacemakers and defibrillators. Additionally, movement within the fringe field can induce voltages in the leads of AIMDs, potentially triggering inappropriate device responses. These risks highlight the need for stringent safety measures and exposure assessments for workers with implanted medical devices in high-field NMR environments.

Mattei and colleagues [26] demonstrated that pacemaker (PM) performance degradation can occur during rotational movements at approximately 2 rad/s in an MRI environment. Similarly, for an implantable cardioverter-defibrillator (ICD), movements with a maximum speed of 6 rad/s may lead to a misclassification of ectopic beats as ventricular fibrillation. To the best of our knowledge, a comparable study has not yet been conducted in NMR laboratory settings.

Our simulation results indicate that the voltage induced by typical worker movements near an NMR spectrometer—at positions representative of those for individuals wearing a PM or an ICD—does not exceed the programmed sensitivity threshold of these devices (typically 2 mV) [47,48] in a unipolar configuration. However, in a bipolar configuration, the induced voltage can surpass the lower threshold of 0.3 mV. It is important to note that this threshold is defined for a standardized stimulus with higher frequency components than those of the low-frequency voltage signal induced by movement within the NMR magnetic field, which is approximately 1 Hz [24].

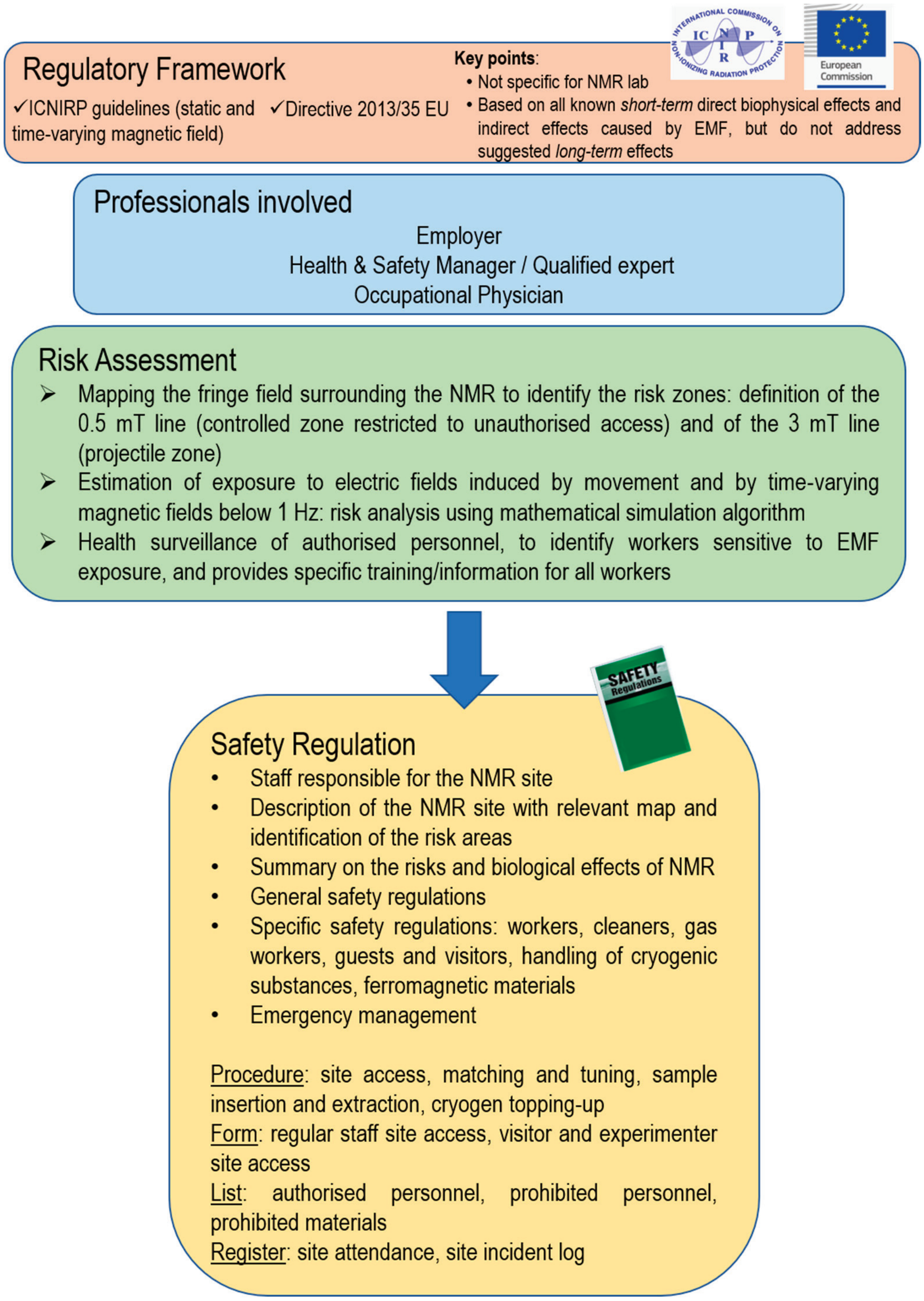


Figure 3. General overview of NMR laboratory safety management.

Additionally, comparing the computed maximum induced electric field (EMFmax) with the immunity levels required for PM/ICD compliance with international market-entry standards presents challenges. These immunity levels vary depending on frequency and generally do not account for signals below 16.6 Hz, making direct comparisons difficult.

5. Conclusions

The objective of this study was to enhance awareness of the necessity for safety measures in environments where they have yet to be implemented. The overarching aim is to ensure the safety of NMR environment workers and all other individuals involved. This work constitutes a rigorous attempt to provide original insights that address the critical gap in the extant literature regarding the safety of NMR laboratories. It also offers valuable implications for both research and practical applications.

In conclusion, it is essential to consider that technological advancements in NMR are pushing towards increasingly higher static magnetic field intensities and operating frequencies, significantly increasing the risk level for workers. The risk assessment process in NMR environments must involve all relevant stakeholders. Employers play a crucial role by ensuring that workers undergo medical examinations to certify their health suitability for tasks involving exposure to the spectrometer's magnetic fields. At the same time, workers must adhere to specific safety protocols and adopt appropriate behaviours, particularly when approaching the spectrometer, to minimize potential risks. Another critical aspect is the design and construction of NMR sites, which, in addition to incorporating necessary safety devices (e.g., quench pipes), must ensure adequate spaces for activities related to the spectrometer's use, minimizing occupational risks for workers.

With regard to the potential effects of chronic exposure, it is advisable to await further comprehensive knowledge and to adopt technical and operational strategies for exposure minimization. In the absence of substantial data regarding the potential consequences associated with long-term exposure to EMF, the adequacy of health risk assessments pertaining to MR workers remains questionable, particularly with respect to exposure levels that fall below the thresholds associated with acute effects [9]. Therefore, we strongly encourage further, more systematic research in this area. Future studies should specifically investigate the effects of SMF exposure on human biological functioning to determine whether SMF pose any significant health risks.

Finally, updating regulations to ensure safety is essential, particularly for laboratories with outdated equipment lacking advanced safety systems that may pose significant risks. Additionally, raising operator awareness of safety aspects, through specific training programs, for example, and systematically assessing risks using innovative tools and methods, is imperative.

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Article

Young Workers and Lifestyles in a Mediterranean Cultural Context: What Is the Contribution of Occupational Health Promotion?

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Abstract: Adherence to a healthy diet and an active lifestyle is now a key component of workplace health promotion (WHP) programs. The primary objective of the study is the assessment of the need for the implementation of corrective WHP interventions aimed at improving the lifestyle in students belonging to health-related degree programs. A prospective observational epidemiological study through the recruitment of a sample of 242 young adult-equated workers at the Vanvitelli University in Naples was conducted. Two questionnaires were administered, one related to Mediterranean diet adherence (PREDIMED) and one concerning daily physical activity (IPAQ). A total of 56.6% of the participants were in the intermediate level of adherence to the Mediterranean diet, 24.0% low and 19.4% in the high level, with highly significant differences in the distribution between the groups. The chi-square test revealed a statistically significant association between groups and physical activity level ($p = 0.0166$). A statistically significant association was also found between gender and physical activity level (men showing high levels of physical activity). The analysis showed significant differences in adherence to the Mediterranean diet between the different students' groups, with no gender-related differences. This study highlighted the need for a systematic and differentiated approach to WHP, differentiating the various groups.

Keywords: workplace health promotion (WHP); PREDIMED; Mediterranean diet; corrective interventions; epidemiological study

1. Introduction

The World Health Organization (WHO) has identified the workplace as an ideal setting for health promotion because it provides a prime environment for influencing people's health behaviors. Even in countries with high unemployment rates, most of the adult population is still employed, making the workplace a strategic platform for improving public health [1,2]. Since 2003, the National Institute for Occupational Safety and Health (NIOSH) has supported the integration of measures to protect occupational safety and health with interventions to promote the health and well-being of workers. Adherence to proper nutrition and active lifestyle is, to date, a key part of workplace health promotion

(WHP) programs. In Italy, the National Strategic Plan for Prevention drafted for the five-year period 2020–2025 calls for the need to adopt more effective intervention models for strengthening the overall health of workers, such as the WHO Healthy Workplace Model and the NIOSH Total Worker Health Model. The evolution of the WHP concept led, in 2011, to the creation of the Total Worker Health® (TWH) program. The Total Worker Health® approach is defined as a set of policies, programs and practices that integrate protection from occupational safety and health hazards with the promotion of injury and illness prevention initiatives to improve worker well-being. Worker well-being is an integrative concept that characterizes quality of life in relation to individual health and work-related environmental, organizational and psychosocial factors [3]. Poor nutrition is a modifiable and preventable risk factor that can lead to the onset or worsening of some chronic non-communicable diseases. As is well known, habitual consumption of unhealthy foods can result in weight gain and subsequent obesity [4], which in turn influence the development of chronic diseases, such as cardiovascular problems and diabetes [5,6]. Adherence to a proper diet is therefore, to date, a key part of workplace health promotion programs. The Mediterranean diet, recognized by UNESCO as an intangible heritage of humanity, represents a healthy eating pattern, rich in fruits, vegetables, legumes, whole grains, fish, olive oil and moderate consumption of wine. Adherence to the Mediterranean diet is associated with numerous health, socio-cultural, economic and environmental benefits [7] that make it one of the healthiest and most sustainable food models [8]. Adherence to the Mediterranean diet also results in lower mortality from cardiovascular and neoplastic diseases [9], and in addition to health effects, additional benefits include low environmental impact, biodiversity of products consumed, high socio-cultural value of foods and support for the local economy [10]. Sedentariness is a condition that can be fostered by the type of work performed, but it can also be a habit maintained in leisure time [11]. In Europe, it is estimated that more than 35 percent of people sit for more than 7 h a day [2]. In Italy, sedentary behavior, determined by long periods spent standing or sitting, throughout the day, is also widespread among the active adult population. According to the PASSI survey in the two-year period 2021–2022, among adults living in Italy, the "physically active" are 47% of the population, the "partially active" 24% and the "sedentary" 29% [12]. Existing scientific evidence shows that physical activity is a protective factor for health. The level of exercise is inversely related to mortality risk and thus associated with longer life expectancy [13]. Regular practice of adequate aerobic physical activity has been shown to act as a protective factor against high-incidence diseases in the general population, such as cardiovascular disease. For example, compared with inactive individuals, those who exercise for an average of 92 min per week or 15 min a day had a 14% reduced risk of all-cause mortality (0·86, 0·81–0·91) and had a 3-year longer life expectancy [14]. The primary purpose of this study is to assess the need for corrective health promotion interventions aimed at improving the lifestyle of young adults. Given that Italian university students engaged in internships are regarded as workers when exposed to health and safety risks, the occupational context represents an ideal setting for health promotion. Specifically, the study seeks to examine the dietary habits and metabolic health of young adults enrolled in health-related degree programs at Vanvitelli University in Naples, with a focus on adherence to the Mediterranean diet, the intensity of daily physical activity and body mass index (BMI).

2. Materials and Methods

A prospective observational epidemiological study was conducted to assess proper lifestyles in terms of adherence to the Mediterranean diet and performance of physical activity in a population of young adults enrolled in health-related degree programs. The study involved the administration of questionnaires during preventive visits carried out as part of the University's Health Surveillance Program as well as the direct detection of participants' weight and height. The study population is represented by students in the first year of the degree courses of the following health professions of the "Luigi Vanvitelli" University: Dentistry and Dental Prosthetics, Physiotherapy, Speech Therapy, Psychiatric Rehabilitation Technique, Neuropsychomotricity Therapy, Biomedical Laboratory Techniques, Orthotics, Medical Radiology Techniques, Dental Hygiene and Prevention Techniques in the Environment and Workplaces, and students attending the third year of the degree course in Medicine and Surgery.

Inclusion criteria were students equated with workers under Article 2 of Legislative Decree 81/2008 and belonging to the 18–34 age group. Exclusion criteria included the following: (1) the presence of known chronic diseases that affect metabolism or appetite; (2) the presence of pathologies or disabilities that prevent a proper active lifestyle; (3) pregnancy status; (4) taking medications that affect body weight or physical activity; and (5) failure to sign the informed consent. Indeed, the subjects involved in the study are students attending health study courses, subjected to preventive visits carried out as part of the University Health Surveillance Program, prior to the commencement of their internships and clinical placements. Therefore, recruitment was planned during the scheduled preventive visits. An information sheet on data processing for experimental purposes and an explanatory sheet on the contents and objectives of the study were distributed during the students' access to the University Health Surveillance Service. Informed consent was then collected using the forms prepared for data collection, processing and publication. Two questionnaires, one related to adherence to the Mediterranean diet (PREDIMED) and one to daily physical activity (IPAQ), were administered during the medical examination, and body weight and height measurements were taken with standardized instruments for calculating BMI.

2.1. PREDIMED and IPAQ Questionnaires

The PREDIMED (PREvención con DIeta MEDiterránea) questionnaire was designed to assess adherence to the Mediterranean diet. It is mainly used in the PREDIMED study, a major clinical trial that analyzed the effects of the Mediterranean diet on cardiovascular disease prevention [15]. The questionnaire contains 14 questions that address the consumption of specific foods (e.g., fruits, vegetables, legumes, fish, olive oil), indicating frequency, portions and eating habits (e.g., use of fat from seasoning). The result of the PREDIMED questionnaire is a score (varying between 1 and 14), the interpretation of which involves division into 3 classes: 1–5, poor adherence; 6–9 medium adherence; and greater than 10, good adherence.

The International Physical Activity Questionnaire (IPAQ) is designed to measure adults' physical activity in various settings and is used to quantify physical activity level to assess adherence to international physical activity recommendations and to correlate physical activity levels with various health conditions. For this study, the IPAQ-S (Short Form), a short questionnaire about physical activity performed in the past 7 days, was used. It consists of 7 questions and measures time spent in physical activities of different intensities (light, moderate and vigorous) and time spent sitting [16]. The result of the IPAQ questionnaire is reported in MET (Metabolic Equivalent of Task), which is the unit of measurement that estimates the amount of energy used by the human body during an activity compared to when at rest. Based on the frequency of activity during the past 7 days, a subject is described as inactive (<700 METs), sufficiently active (701–2519 METs) and active (>2520 METs).

2.2. Statistical Analysis

Each participant was assigned an anonymous ID to comply with the principles established by the GDPR. The collected data were organized into a structured database using Microsoft Excel (Office 365 version), where each row represented an individual participant and the columns contained the variables of interest. The database was exported for statistical analysis conducted with JASP software 0.19.3, while Julius AI, a specialized artificial intelligence system utilizing Python 3.11.6-based data science libraries (pandas for data manipulation, matplotlib and seaborn for visualization and scipy/statsmodels for statistical validation), was employed to generate graphical visualizations and validate the accuracy of statistical analyses. To ensure the integrity and quality of the data, periodic checks were conducted for completeness and accuracy, and any changes or corrections were documented.

3. Results

3.1. Descriptive Statistics and Sample Characteristics

The study involved a sample of 242 young adults equated within 11 health professions degree programs: Nursing (67, 27.7% of the total sample), Medicine and Surgery (36, 14.9%), Nursing and Midwifery Sciences (24, 9.9%), Speech Therapy (24, 9.9%), Medical Radiology Technicians (20, 8.2%) and the remaining percentage equally distributed at the lower levels represented by Biomedical Laboratory Technicians, Physiotherapy, Dental Hygiene, Environmental and Workplace Prevention Technicians, Orthoptics and Ophthalmic Care and Psychiatric Rehabilitation Technicians. The sample shows a prevalence of females (162, 66.9 percent) compared to males (80, 33.1 percent), with a heterogeneous distribution among the different degree programs. The mean age of participants is 22.5 years (SD $\pm$ 4.1) with a range of 18 to 34 years. Specifically, the highest mean age was found in Nursing and Midwifery (29.1 years) and Medicine and Surgery (26.0 years) courses, while the courses with the lowest mean age and least variability were Nursing (20.1 years) and Psychiatric Rehabilitation Techniques (20.0 years). Regarding BMI, the sample mean value of 23.7 kg/m^2 (SD $\pm$ 3.8) falls within the range considered as normal weight according to WHO (18.5–24.9 kg/m^2); however, it should be noted that 61.6% (149) of the participants fell into the category of normal weight, 8.3% (20) had a BMI above 30 kg/m^2, falling into the category of obesity; 23.1% (56) had a BMI above 25 kg/m^2, classifying as overweight; and 7.0% (17) had a BMI below 18.5 kg/m^2, a category of underweight. Inferential analysis was conducted to reveal whether there were differences in adherence to the Mediterranean diet, physical activity habit and BMI between study programs and genders. To optimize the statistical analysis, a reorganization of the sample was proposed, grouping participants according to their specialty. This division led to the creation of four main groups (Table 1):

Table 1. Distribution of students across the four groups of healthcare degree courses (N = 242).

Degree Course	Sample Size	Mean Age	% Male	Mean BMI
Group 1—Medicine	36 (14.9%)	26.0 $\pm$ 2.3	41,67	23.0 $\pm$ 3.9
Group 2—Nursing	67 (27.7%)	20.1 $\pm$ 2.8	26,87	24.2 $\pm$ 4.3
Group 3—Nursing and Midwifery	24 (9.9%)	29.1 $\pm$ 3.1	16,67	23.1 $\pm$ 3.2
Group 4—Other Health Professions	115 (47.5%)	21.5 $\pm$ 3.2	37,39	23.7 $\pm$ 3.6

Medicine (Group 1) and Nursing and Midwifery (Group 3) degrees were analyzed as distinct groups due to their significantly higher mean ages (26.0 $\pm$ 2.3 and 29.1 $\pm$ 3.1 years, respectively), as confirmed by one-way ANOVA with post hoc Tukey HSD tests ($F = 27.34$, $p < 0.001$). Nursing (Group 2) was maintained as a separate category given its substantial sample size (n = 67, 27.7%) and its unique professional training pathway. The grouping approach also accounted for differences in clinical exposure during internships and ensured adequate statistical power. Group 4 aggregated allied health professions that share comparable theoretical and practical training frameworks within the health sciences.

3.2. Analysis of Mediterranean Diet Adherence Based on PREDIMED Questionnaire Data

Analysis of adherence levels to the Mediterranean diet in the equated groups showed differences in the distribution of adherence categories (poor, average/sufficient, good). The results showed that 56.6 percent of participants were in the intermediate level of adherence, 24.0 percent in the low level and 19.4 percent in the high level. Analyzing the data broken down by the four main groups, as follows:

- Group 1—Medicine: Most participants (63.9%) reported sufficient adherence, followed by good adherence (19.4%) and poor adherence (16.7%).
- Group 2—Nursing: Reported the highest percentage of poor adherence (32.8%) and the lowest percentage of good adherence (3.0%), with 64.2% of participants falling into the sufficient adherence category.
- Group 3—Nurses and Midwives: The majority (75.0%) showed sufficient adherence, with a low percentage of poor adherence (8.3%) and good adherence of 16.7%.
- Group 4—Other Health Professionals: This group shows an intermediate distribution with 67.8% of participants showing adequate adherence, 24.3% poor adherence and 7.8% good adherence.

Inferential analysis revealed a statistically significant association between group membership and level of adherence to the Mediterranean diet ($\chi^2 = 14.54$; $p = 0.024$). Test for normality indicated that the data do not follow a normal distribution (Shapiro–Wilk test: $W = 0.975$, $p = 0.0004$); so, a Kruskal–Wallis test (Figure 1) was conducted on the total PREDIMED scores, showing highly significant differences between groups ($p = 0.00004$). To better understand these differences, a post hoc analysis was conducted using Dunn's test with Bonferroni correction, which revealed a significant difference between Group 1 and Group 2 ($p = 0.0031$); a significant difference between Group 1 and Group 4 ($p = 0.0258$); a significant difference between Group 2 and Group 3 ($p = 0.0008$); and a significant difference between Group 3 and Group 4 ($p = 0.0059$).

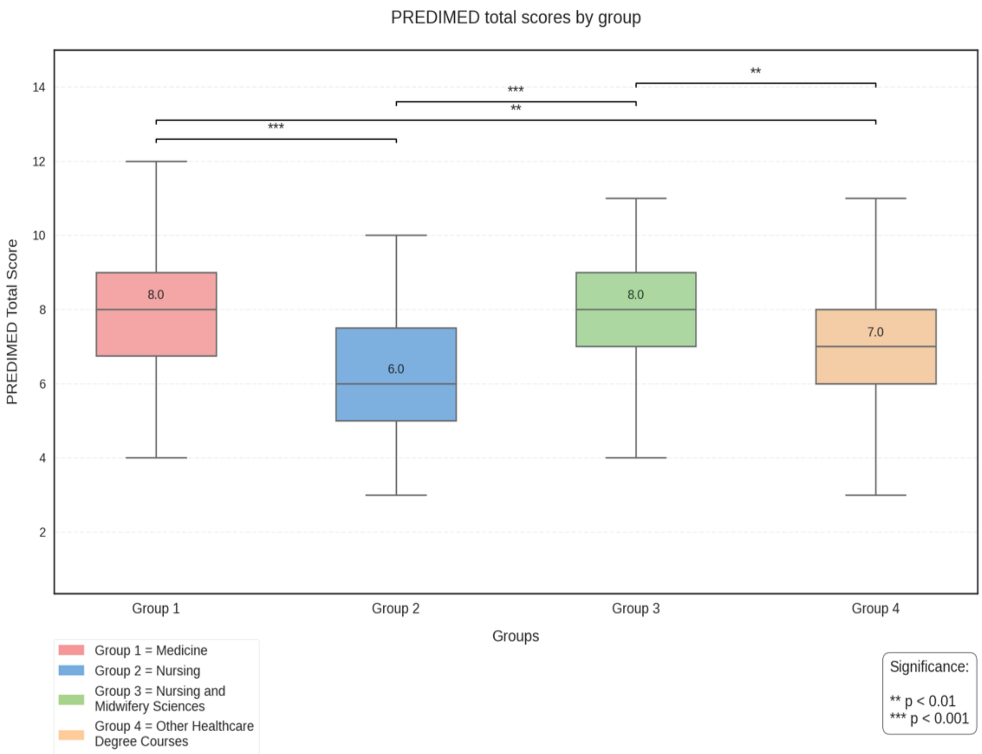

Figure 1. Results of the analysis of the total scores of the PREDIMED questionnaires administered.

Regarding the relationship between gender and adherence level, the chi-square test showed no statistically significant differences in the total population under study (χ^2 = 1.23; p = 0.54). Instead, statistical analysis showed a positive correlation between the level of adherence to the Mediterranean diet and BMI by the Kruskal–Wallis test (test = 12.415; p = 0.002), which was confirmed by post hoc analysis, with a significant difference especially between poor and good adherence (F = 5.9796; p = 0.015) (Figure 2).

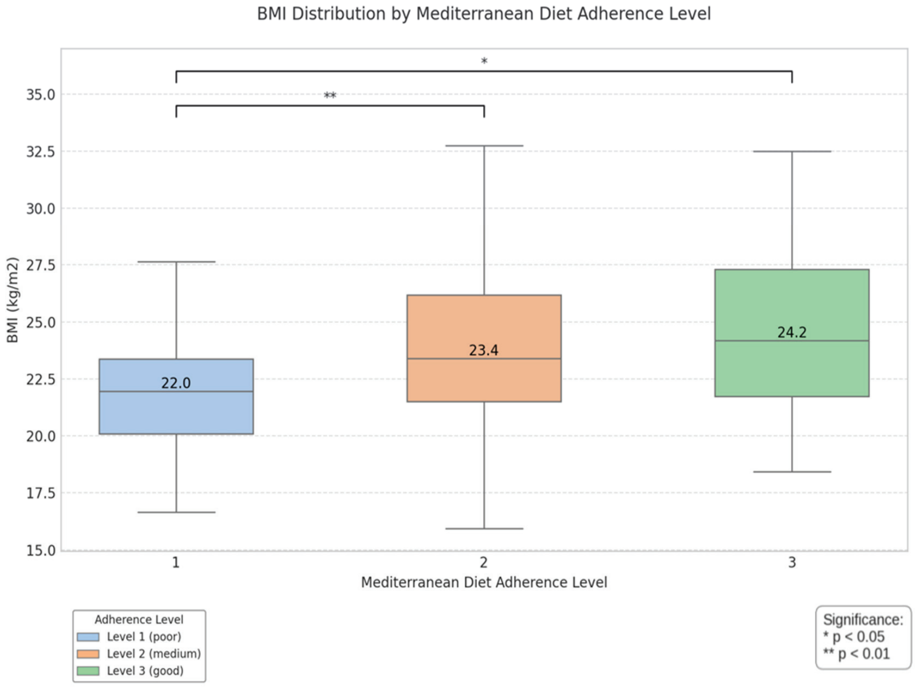

Figure 2. Box plots of BMI in relation to levels of adherence to the Mediterranean diet.

3.3. Analysis of Physical Activity Levels Based on IPAQ Questionnaire Data

The analysis of physical activity levels, based on the IPAQ questionnaire and classified into three categories (low, sufficient, good), showed that 43.4% was in the intermediate level, 33.5% in the high level and 23.1% in the low level. Significant differences emerged in the distribution of levels between the four groups:

- Group 1—Medicine: 44.4% of the participants reported a sufficient level of physical activity, while another 44.4% achieved a good level of physical activity. Only 11.2% of the participants fell into the poor physical activity category.
- Group 2—Nurses: The majority (55.2%) showed a sufficient level of physical activity, while 28.4% reported a poor level of physical activity and 16.4% a good level of physical activity.
- Group 3—Nurses and Midwives: This group shows a balanced distribution, with 41.7% of the participants falling into the categories of sufficient and good physical activity and 16.7% with poor physical activity.
- Group 4—Other Health Professions: 36.5% showed a sufficient level of physical activity, 38.3% good physical activity and 25.2% poor activity.

This performed analysis showed that men had a greater tendency towards high levels of physical activity, with almost 49% achieving a ‘good’ level compared to 26% of women. Moreover, the percentage of low physical activity is slightly higher in women (24.7%) than in men (20.0%).

Inferential analysis revealed a statistically significant association between peer group membership and physical activity level (χ^2 = 15.51; p = 0.0166). Figure 3 shows the box plot of the distribution of total MET scores by degree groups. Due to non-normal distribution, confirmed by the Shapiro–Wilk test (W = 0.97, $p = 0.001$), a non-parametric Kruskal–Wallis test was conducted, which demonstrated significant differences in total METs between groups ($p = 0.004$).

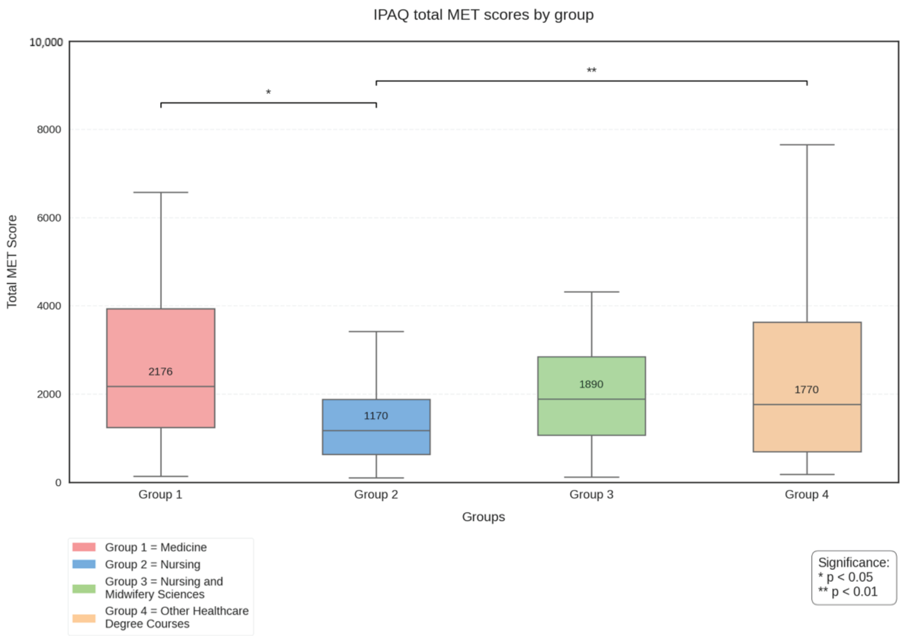

Figure 3. Results of the analysis of the IPAQ questionnaires broken down by total MET scores among the various groups.

A statistically significant association was also found between gender and physical activity level (Figure 4), confirmed by both the chi-square test ($\chi^2 = 12.90$; $p = 0.0016$) and T-test on total MET ($t = -2.26$; $p = 0.025$). The assessment of levels and quality of physical activity performed cannot be separated from the analysis of sedentary habits. The results obtained showed significantly different patterns among the equated groups, both during working days ($p < 0.001$) and, to a lesser extent, during rest days ($p = 0.005$) (Figure 5).

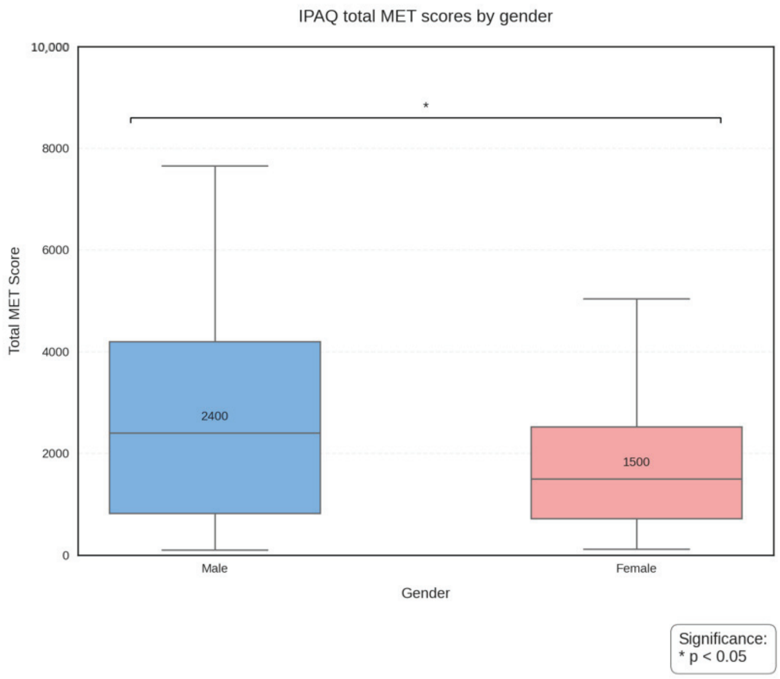

Figure 4. Results of the analysis of the participants' total MET scores in relation to their gender.

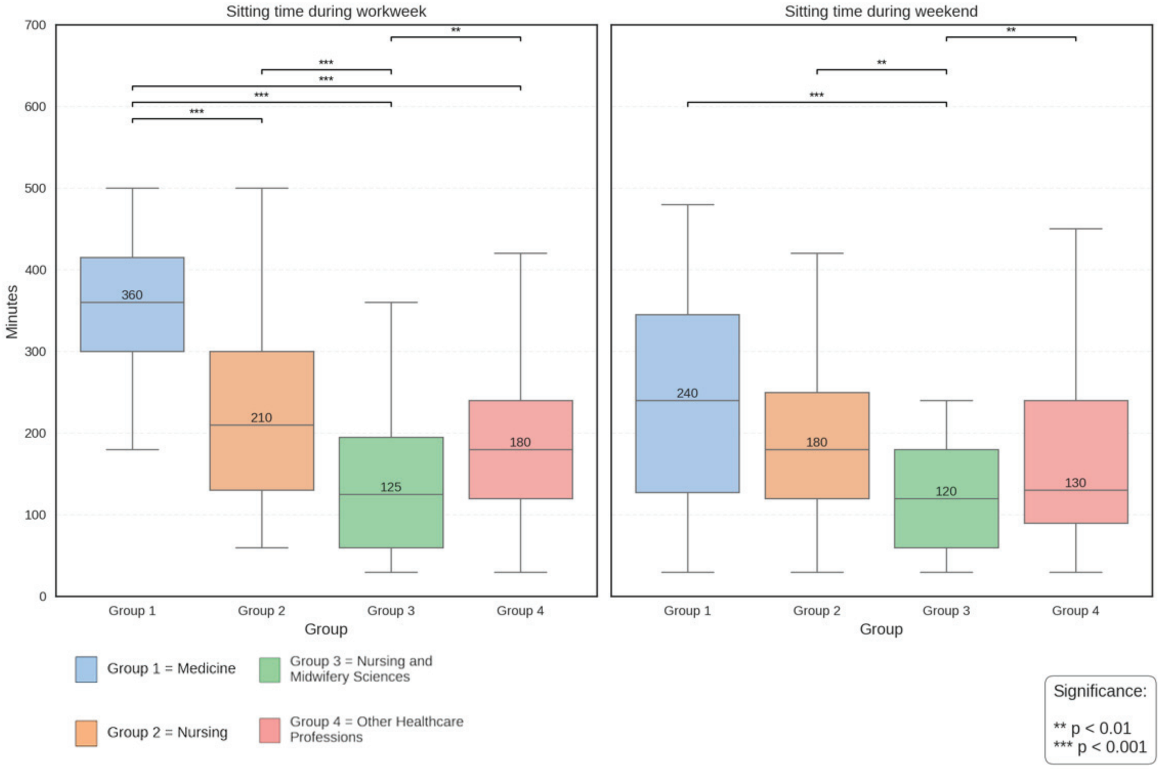

Figure 5. Results of the analysis of sedentariness on work days (left) and rest days (right) by groups.

4. Discussion

Italian Legislative regarding Health and Safety at Work has put trainees, interns and apprentices on the same footing as workers, recognizing their rights and protections in the workplace. This legislation is particularly important for a segment of the population that is going through a delicate phase of the life cycle, marked by fundamental choices such as the completion of studies, entry into the world of work and the development of social and territorial relations. Consequently, it is crucial to understand their state of well-being and monitor its evolution over time, as these challenges can profoundly affect not only their psychological health, but also their lifestyles, including diet and physical activity. In fact, as reported in the previous paragraph, while numerous studies demonstrate the positive impact of healthy eating habits on general health, research shows a progressive abandonment of the Mediterranean diet among young Italians, despite its documented benefits for the prevention of chronic diseases and for psychophysical well-being [17]. Young adults face intense life rhythms and social pressures that often lead them to prefer convenience and processed foods, which meet their needs for convenience but do not fully satisfy their nutritional needs [18]. In addition, there is a growing tendency towards physical inactivity, often sacrificed due to stress and study or workloads [19].

The analysis conducted in this work revealed significant differences in adherence to the Mediterranean diet between the different groups of healthcare workers, while no gender-related differences emerged. In particular, Group 2 (nurses) showed lower scores than the other groups, suggesting the need for possible targeted interventions for this group. The analysis of the individual responses to the questions of the PREDIMED questionnaire revealed interesting patterns in the distribution of positive responses among the participants (where 'positive' refers to the response indicating greater adherence to the Mediterranean diet). The questions with the highest rate of positive responses were those on the use of extra virgin olive oil (95.5%), less use of butter or margarine (90.5%) and low consumption of sugary drinks (81.4%). On the other hand, the questions with the lowest rate of positive answers were those on the consumption of wine (1.2%), fruit (10.3%) and fish (23.6%). Also interesting were the data on the consumption of vegetables (two or more portions per day for only 44.6%) and red meat and sausages (more than one portion per day for 41.3%). While virtuous behavior is observed in the use of healthy fats (extra virgin olive oil) and in limiting saturated fats (butter and margarine), significant criticism emerges in the low consumption of fundamental foods of the Mediterranean diet such as fruit, vegetables and fish, as well as in the excessive consumption of red meat and sausages for a good percentage of participants. It should be remembered that even the most recent WHO recommendations indicate the introduction in the diet of at least five portions of fruit and vegetables per day and two to three portions of fish per week and the reduction in red meat to once a week, while sausages should be avoided.

Concerning wine consumption, the latest scientific evidence is challenging the traditional paradigm of the benefits of moderate alcohol consumption. In particular, a meta-analysis published in 2023 [20] provided significant results that contradict previous beliefs on the subject, demonstrating the absence of a statistically significant correlation between moderate alcohol consumption and reduced mortality in general, thus disproving previously accepted assumptions about the supposed cardioprotective effects and other health benefits of alcohol taken in low doses. This new perspective finds further support in the official WHO position: there is no threshold of alcohol consumption that can be considered completely safe for an individual's health. These findings are particularly important in the context of the Mediterranean diet, whose moderate consumption of wine is historically considered one of its defining elements. Thus, the very low percentage of daily wine drinkers revealed in the study seems to be positive and not negative. The study shows that the surveyed population generally has a good propensity for moderate physical activity, especially when compared to regional data (17.3% partially active and 34.4% active). Taking the WHO guidelines for physical activity as a reference [11], to achieve substantial health benefits, adults should perform 150 to 300 min of moderate aerobic activity per week, 75 to 150 min of intense aerobic activity per week or an equivalent combination of both within the week. In general, the majority of students in all groups exceed the WHO minimum recommendations, with a relatively low percentage (between 8.3% and 12.5% depending on the graduating class group) not reaching the minimum recommended levels.

Examination of the four groups by degree course, however, revealed significant differences in the distribution of physical activity levels. Contingency table analysis showed a statistically significant association between occupational group and level of physical activity, while analysis of variance for total METs revealed significant differences between Group 2 (Nursing) compared to students in Medicine and other degree courses. The observed differences could be attributed to various factors, including workloads, schedules and the specific characteristics of each health profession, but it is clear that nursing students/workers are again a group worthy of attention for possible health promotion interventions. Similarly, the results regarding gender-related physical activity levels suggest that particular attention should be paid to the female gender when designing interventions to promote physical activity. Despite the sample being predominantly female (66.9%), 49% of men reached a level of physical activity, compared to 26% of women, indicating a greater male propensity for engaging in regular and high-intensity physical activity. On the other hand, the percentage of individuals with poor physical activity levels was higher among women (24.7%) compared to men (20.0%). Previous studies have demonstrated significant gender differences in physical activity levels among university students [21], with females generally engaging in less vigorous physical activity than their male counterparts. These differences may be influenced by multiple factors, including socio-cultural barriers, psychological aspects and environmental constraints. Eventual gender-specific barriers and motivators should be carefully considered when designing workplace health promotion programs.

The assessment of the level and quality of physical activity performed cannot be separated from the analysis of sedentary habits. This analysis is based on the separate examination of time spent sitting on working days and days off (questions from the IPAQ questionnaire). In particular, Group 1 (Medicine) shows the highest levels of sedentariness during the working day (365.0 ± 124.0 min), followed by Group 2 (Nursing) with 245.6 ± 170.3 min and Group 4 (Other Health Professions) with 224.1 ± 144.3 min. Group 3 (Nursing and Midwifery) presents the lowest levels of sedentary work. On rest days, a trend towards a reduction in sedentary time is observed in all groups, with Group 1 maintaining the highest values, while Group 3 confirms the lowest levels. Interestingly, the differences between the groups decrease on rest days, suggesting a homogenization of behavior outside the work environment. Since there is moderate evidence that correlates a sedentary lifestyle with increased mortality from all causes (cardiovascular diseases and cancer in particular), but there are no minimum levels at which sedentariness is not considered harmful, it is advisable to raise awareness among the population to remain as active as possible in their free time, since exceeding the recommended minimum levels of moderate-to-intense physical activity established by the WHO may reduce the negative effects associated with sedentariness. The positive correlation between the level of adherence to the Mediterranean diet and BMI on the Kruskal–Wallis test, with a significant difference especially between poor and good adherence, would seem to be counterintuitive to traditional expectations of the benefits of the Mediterranean diet; in reality, this suggests the presence of more complex dynamics in the relationship between dietary patterns and body composition. The surveyed population generally has a good propensity for moderate physical activity, especially when compared to regional data (17.3% partially active and 34.4% active), with significant differences in the distribution of physical activity levels.

Although the PREDIMED questionnaire is a validated tool for assessing adherence to the Mediterranean diet, it has inherent limitations. In particular, it does not consider the amounts of food actually consumed, but relies primarily on the frequency of food intake. This methodological feature could mask substantial differences in total caloric intake between individuals who instead show similar adherence scores. In addition, interpretation of the results must take into account an important confounding factor: overweight people very often tend to seek the advice of nutrition professionals and adopt healthier eating patterns, such as the Mediterranean diet. This could explain the seemingly counterintuitive correlation between higher BMI and greater dietary adherence. However, in the absence of information on the duration and timing of nutrition initiation, it is impossible to determine the causal direction of this relationship.

Regarding physical activity level, the Kruskal–Wallis test shows that there are no statistically significant differences in BMI values (p = 0.0698 > 0.05), although level 2 (Sufficient) shows slightly higher BMI values, but this difference is not statistically significant. Finally, it is interesting to note that there is a weak but significant positive correlation between the parameters of physical activity levels and adherence to the Mediterranean diet (r = 0.16; p = 0.01; χ^2 = 11.98; p = 0.017). This may suggest that there is a tendency, albeit modest, to associate higher levels of physical activity with greater adherence to the Mediterranean diet and vice versa, and that targeted health promotion interventions aimed at filling individual gaps in terms of information and education on these issues could be effective tools for improving lifestyles in general. Based on the analysis of the data collected, the discrepancy between some WHO recommendations and detected eating habits suggests the need to implement nutrition education programs for young health workers, focusing particularly on the nursing graduating class. It would be absolutely strategic to develop strategies to encourage general consumption of fruits, vegetables and fish and, at the same time, promote greater awareness of the importance of following international nutritional guidelines. The analysis of adherence to the Mediterranean diet showed different dietary patterns among the professional groups examined, with the nursing student group showing lower average adherence values than the other groups examined. In addition, the discrepancy observed between the eating habits of all participants and the WHO nutritional recommendations regarding the consumption of certain foods underscores the need for targeted educational interventions.

Regarding physical activity, the results showed a general propensity for moderate physical activity, with a relatively low percentage of individuals not reaching the minimum levels recommended by WHO. However, the significant differences found between occupational groups and between genders suggest the need for a differentiated approach in the design of physical activity promotion interventions. In particular, the nursing student group showed significantly lower levels of total physical activity, a finding that, combined with lower adherence to the Mediterranean diet, configures a risk profile that requires special attention. The assessment of sedentary behaviors also revealed significant differences between the groups, with the medical group showing the highest levels of sedentariness during the workday. This finding underscores the importance of implementing strategies to reduce time spent sitting, considering that it is an independent risk factor for many chronic diseases.

Finally, a weak but significant positive correlation was found between the parameters of physical activity levels and adherence to the Mediterranean diet, suggesting that there is a tendency, albeit modest, to associate higher levels of physical activity with greater adherence to the Mediterranean diet and vice versa, and that could target health promotion interventions. Another interesting finding from the study is the positive, albeit weak, correlation between adherence to the Mediterranean diet and body mass index (BMI). This seemingly counterintuitive result could be explained by several factors. The PREDIMED score, while validated for assessing Mediterranean diet adherence, may not fully capture the quantitative aspects of food consumption or other lifestyle factors that influence BMI. Additionally, it is possible that subjects with a higher BMI have already undertaken lifestyle modifications, including the adoption of healthier eating patterns, as a response to their condition. However, the cross-sectional nature of the study does not allow causal relationships to be established.

Strengths and Limitations

Our recruitment strategy through preventive health visits, while systematic, may have introduced selection bias: our sample of students belonging to health-related degree programs might represent a more health-conscious subset of the student population. Additionally, while participation was voluntary, those who chose to participate might have been more interested in health-related behaviors, potentially leading to self-selection bias. However, our achieved sample size (242) exceeded the minimum required sample size (174) calculated through G*Power analysis ($\alpha = 0.05$, power = 0.80, medium effect size = 0.25), suggesting adequate statistical power for our analyses.

The use of self-administered questionnaires to assess eating habits and physical activity may be subject to bias; the PREDIMED questionnaire, while a validated instrument, focuses on frequency of food consumption rather than actual quantities, limiting the ability to assess total caloric intake. Another limitation concerns the PREDIMED questionnaire's score regarding wine consumption, as future studies might benefit from modified scoring systems that better align with contemporary public health recommendations. Furthermore, although possible causal relationships between the variables are suggested, the cross-sectional design used does not allow for causal inferences to be drawn. Despite these limitations, the results provide important insights into health promotion for the University of Campania peer group. In particular, the following recommendations emerge: it would be necessary to implement specific nutrition education programs for different professional groups, with particular attention to nursing students. These programs should focus not only on the transmission of theoretical knowledge but also on the development of practical skills for the adoption of proper Mediterranean alimentation. In addition, physical activity promotion interventions should be differentiated according to gender and occupational group. Particular attention should be paid to reducing sedentary behavior during working hours.

5. Conclusions

The study highlighted the need for a systematic and differentiated approach to workplace health promotion, with special attention to the specifics of different occupational groups. It is desirable to implement a system of continuous monitoring radiation of eating habits and physical activity, possibly through the use of objective instruments and detailed food diaries. Integrating personalized dietary and physical activity assessment and counseling into routine occupational health surveillance would allow for early identification of individuals at risk and provide opportunities for personalized intervention. This could involve the use of validated questionnaires during periodic health checks and the provision of tailored advice. Targeted awareness campaigns should be developed to educate healthcare students about the benefits of regular physical activity, with particular attention to gender-specific barriers and motivators. In addition, for future research, longitudinal studies should be conducted to assess the temporal evolution of eating habits and physical activity. Furthermore, the relationship between Mediterranean diet adherence and BMI in young adult students may be influenced by factors not captured in our study, such as total caloric intake, portion sizes or the timing of meals—variables that should be considered in future investigations. It would also be necessary to expand the sample to include a more representative population of all equated workers and to adopt an integrated approach that considers not only individual behavioral aspects but also environmental and organizational factors that may influence workers' health choices. Even the understanding of the level of awareness regarding health risks associated with unhealthy lifestyles among healthcare students is crucial. Future studies should assess risk perception and health literacy concerning dietary habits and physical activity, as these factors may significantly influence behavior change and also influence the rate of participation in specific WHP initiatives.

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Impact of Environmental Pollutants on Otorhinolaryngological Emergencies in the COVID-19 Era

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Abstract: Air pollution (AP) is a critical environmental factor influencing public health, with well-documented associations with upper respiratory tract (URT) diseases. This study investigates the relationship between ENT emergency department (ENT-ED) visits at Azienda Ospedale Università di Padova (AOPD) and daily concentrations of environmental pollutants during the first year of the COVID-19 pandemic (March 2020–March 2021), compared to pre-pandemic data from 2017. The study focuses on patients diagnosed with URT inflammatory diseases, excluding those with COVID-19 infection, who sought care at the AOPD ENT-ED. Environmental data, including meteorological variables, air pollutants, and major aeroallergen levels, were collected from regional monitoring stations. A total of 4594 patients were admitted in 2020/2021, marking a 37% reduction from 2017, with URT inflammatory admissions decreasing by 52%. A significant decline in PM10, NO_2 and *Alternaria* levels was observed, whereas *Betullaceae* and *Corylaceae* concentrations significantly increased. Multivariate analyses revealed strong associations between aeroallergen exposure and ENT admissions, particularly for *Alternaria*, which had a notable impact on total admissions ($p < 0.001$) and was significantly linked to cases of otitis media and tonsillitis. PM10 concentrations on specific days preceding ED visits were associated with increased incidences of pharyngitis and rhinosinusitis ($p < 0.05$). These findings reinforce the connection between environmental pollutants and ENT emergency visits, highlighting the adverse effects of AP and climate variables on URT diseases, even during a pandemic when enhanced airway protection measures were in place. This study underscores the necessity of stringent air quality regulations and interdisciplinary strategies to mitigate environmental health risks and inform future public health policies.

Keywords: pollution; upper respiratory tract; emergency; pollens; particulate matter; COVID-19; air quality; environment

1. Introduction

The World Health Organization (WHO) officially declared COVID-19 a global pandemic on 11 March 2020 [1]. Governments around the world implemented massive travel restrictions (through the so called “lockdown”—partial or total) to mitigate the spread of this global infection [2]. These decisions brought sudden and immense changes to human activities: not only a reduction in traveling, but also a decrease in access to medical care for reasons unrelated to COVID-19 [3]. Healthcare providers reduced their routine activities, such as surgery or other medical services that were not considered "essential" or urgent, to provide treatment for COVID-19 cases [4]. Furthermore, people reduced their access to health institutions for fear of exposing themselves to the viral infection.

In the General Emergency Departments of the Veneto Region, Italy, an absolute decrease in hospitalizations was described during the lockdown periods, with some of them, such as those due to traumas, accidents at work and road accidents, declining due to lower risk exposure [5]. In other cases, a different perception of urgency in such a dramatic situation often caused patients to avoid seeking medical evaluation even when in need [6,7].

The forced reduction in human activity in cities resulted in a subsequent decrease in air pollution derived from vehicular traffic and industrial activity. In Italy, measurements and comparisons have been conducted on the concentration of environmental pollutants such as particulate matter (PM), carbon monoxide (CO), ozone (O_3) and nitrogen dioxide (NO_2), showing a significant decline in these pollutants during the restrictions [8,9]. Variations in air pollutants (AP), pollen concentration and climatic variations may have an impact on upper respiratory tract (URT) pathology, especially in pollen-allergic patients [10].

The impact of these variables on accesses to the Ear, Nose and Throat (ENT) Emergency Department (ED) admissions in the Azienda Ospedale Università di Padova (AOPD) has already been investigated in the pre-COVID era [11]. The correlation between air quality and human health is receiving increasing attention, yet its connection to ENT urgencies during the COVID-19 pandemic has remained relatively unexplored.

In this study, we aim to describe new data that may contribute to a deeper understanding of environmental impacts on otorhinolaryngological pathologies during the pandemic and provide useful insights for managing future health emergencies.

We examined the impact of the pandemic on ENT ED admissions in the AOPD (I), focusing on variations in the number and typology of admissions during restriction periods. We also conducted an analysis on the changes in environmental pollutants such as PM, chemicals and pollens in the same timeframe (II). Through a comparison with the pre-pandemic period, we aimed to identify trends and substantial changes in the patterns of ENT ED admission in our center (III), as well as to assess the potential role of environmental pollutants in this context (IV).

2. Materials and Methods

This is a retrospective study conducted at the ENT ED of the AOPD, Italy. The data analyzed were provided in reference to two timeframes: from 1 January 2017 to 31 December 2017 and from 9 March 2020 (beginning of Italian lockdown) to March 8th 2021. Both periods therefore cover the duration of one year and refer to two different circumstances: the first timeframe refers to a situation of normality, whereas the second refers to the first year of the COVID-19 pandemic.

The study was conducted in accordance with the ethical standards of the Helsinki Declaration. Data were examined in agreement with the Italian privacy and sensitive data laws and the internal regulations of the AOPD. Informed consent on personal data collection and use for research purpose was obtained from each subject.

2.1. Population Considered

The AOPD is a tertiary teaching hospital in the Italian region of Veneto that covers a population of roughly 350,000 people and records more than 85,000 referrals to the Emergency Department every year.

In this study, only patients admitted to the ED with a negative nasopharyngeal swab and then referred to the ENT emergency room during the aforementioned time frames were considered. All patients underwent high-sensitivity nasopharyngeal swab testing for SARS-CoV-2 upon ED admission, as soon as such tests became available. Those with signs or symptoms suggestive of COVID-19 followed a dedicated triage pathway. Only patients with confirmed negative results and no clinical suspicion of infection were eligible for ENT evaluation.

For each patient, we recorded the date of the ED admission, sex, date of birth, main diagnosis and comorbidities.

Patients with URT disorders (including pharyngitis, laryngitis, otitis, rhinosinusitis, tonsillitis and tracheitis) were included in the study group while those referred for facial trauma or foreign body inhalation formed the control group, as previously described by Ottaviano et al. [11].

2.2. Pollution and Meteorological Data

Daily AP concentration (NO_2, O_3 and PM10 expressed in $\mu g/m^3$), rainfall depth (mm), air temperature (°C), minimum and maximum relative humidity (%) and the concentration (g/m^3) of the most common aeroallergens in the Padua urban area were obtained from environmental monitoring stations operated by the Regional Agency for Environmental Protection and Prevention of the Veneto Region (ARPAV).

The aeroallergens considered were the following:

- *Alternaria*: A genus of fungi widely distributed in the environment, particularly in decaying vegetation and soil. It is a major source of outdoor mold allergens.
- *Betulaceae*: A family of trees including birch (*Betula* spp.), which are significant pollen producers in temperate regions, especially in the spring season.
- *Compositae* (*Asteraceae*): A large family of flowering plants including ragweed, mugwort, and others. These produce highly allergenic pollen particularly in late summer and autumn.
- *Corylaceae*: A botanical family that includes hazel (*Corylus* spp.) and hornbeam. Pollen from these trees is prevalent in early spring.
- *Gramineae* (*Poaceae*): The grass family, a major source of allergenic pollen worldwide. Grass pollens are typically abundant in late spring and early summer.

For O_3 and NO_2, the daily maximum value was considered, for humidity, the daily maximum and minimum values were considered and for all other variables, the average of 24-hourly measurements in the same day were used. To account for temporal trends and delayed effects, we also considered the moving average of mean values over four consecutive days [ma], as well as the lagged effects at one and two days [lag 1] and [lag 2].

2.3. Statistical Analysis

Descriptive statistics are represented by the median (interquartile range) for continuous variables and absolute values (percentage) for categorical variables. An exploratory analysis of environmental variables was carried out by studying the pairwise correlations (Pearson correlation coefficient).

The univariate analyses, which explored the relationships between response variables and risk factors, were carried out by generalized models with Poisson linkage, both in the linear (GLM—Generalized Linear Model) and additive (GAM—Generalized Additive Model) versions.

The model structure for generalized model is

$$g(\mu) = \alpha + \Sigma_j f_j\,(X_j)$$

where g is the link function (in the case of the Poisson model, the link function is the logarithmic function), α is the model intercept, μ is the mean of the response variable conditioned on the explanatory variables and X_j; f_j are the linear functions in the case of the GLM and non-parametric smoothing functions in the case of the GAM.

Multivariate analyses, considering the adjustment for potential confounders (climate variables: temperature, maximum and minimum humidity and rainfall), were carried out with the additive models to consider the possible presence of non-parametric effects. Interactions between timeframes and risk factors were examined with a non-parametric approach using GAMs. This approach was also used to assess the differences between temporal distribution of environmental variables and number of total admissions in the two timeframes.

It is important to note that the use of non-parametric methods, such as GAMs, helps reduce the influence of extreme values (outliers) on the analysis. These values were intentionally retained, as they may represent genuine extreme environmental events that are highly relevant to the objectives of this study.

p-Values were calculated, and 5% was considered the critical level of significance. All analyses were performed using R, a language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria) [12].

3. Results

3.1. Emergency Department Admissions

The total number of admissions in 2017 and 2020/2021 were 7278 and 4594, respectively.

Figure 1 shows the time series of total visits throughout the two years, with the interpolating curves fitted by the GAM.

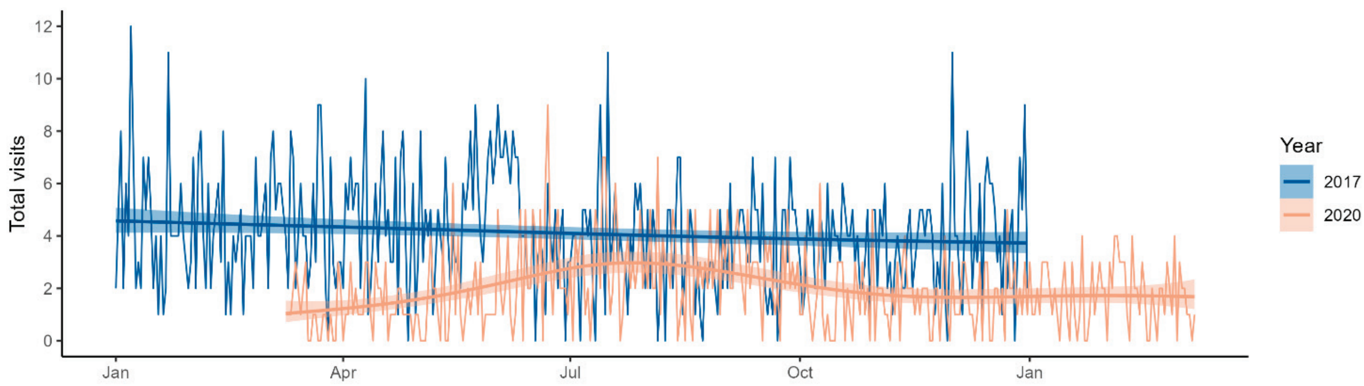

Figure 1. Number and temporal trends of emergency room admissions in 2017 and 2020/2021.

Table 1 displays the descriptive statistics of ENT emergency room admissions.

In 2020/2021, there was a reduction in total admissions of 37%. Focusing only on URT inflammatory disease admissions, there was a 52% reduction, decreasing from a total of 1502 admissions in 2017 to 726 in the 2020–2021 timeframe. In both cases, the reduction in admissions in the second timeframe was statistically significant (p-value < 0.001). When considering only admissions for URT inflammations, it was found that in 2017, the disease causing more admissions was otitis (29% of URT admissions), and this percentage decreased to 22% in 2020/2021, being surpassed by pharyngitis (37% of URT admissions).

Considering trauma and foreign bodies, in 2020/2021, there was a 35.6% reduction, decreasing from 4866 to 3137.

Table 1. Absolute distribution (percentage) by gender and main diagnosis of emergency room admission; median (IQR) by age.

	2017	2020/2021
Sex		
Female	3674 (50%)	2220 (48%)
Male	3604 (50%)	2374 (52%)
Age (years)	47 (29, 67)	52 (31, 71)
Diagnosis		
Pharyngitis	210 (3%)	272 (6%)
Laryngitis	273 (3.7%)	91 (2%)
Otitis	433 (6%)	158 (3.4%)
Rhinosinusitis	229 (3.1%)	84 (1.8%)
Tonsillitis	353 (4.8%)	112 (2.4%)
Tracheitis	4 (0.1%)	9 (0.2%)
Traumas	910 (12.5%)	731 (16%)
Others	4866 (66.8%)	3137 (68.2%)
Total admissions	7278 (100%)	4594 (100%)

Figure 2 highlights the percentage reduction in 2020/2021 compared to 2017 of URT admissions and traumas admissions, respectively.

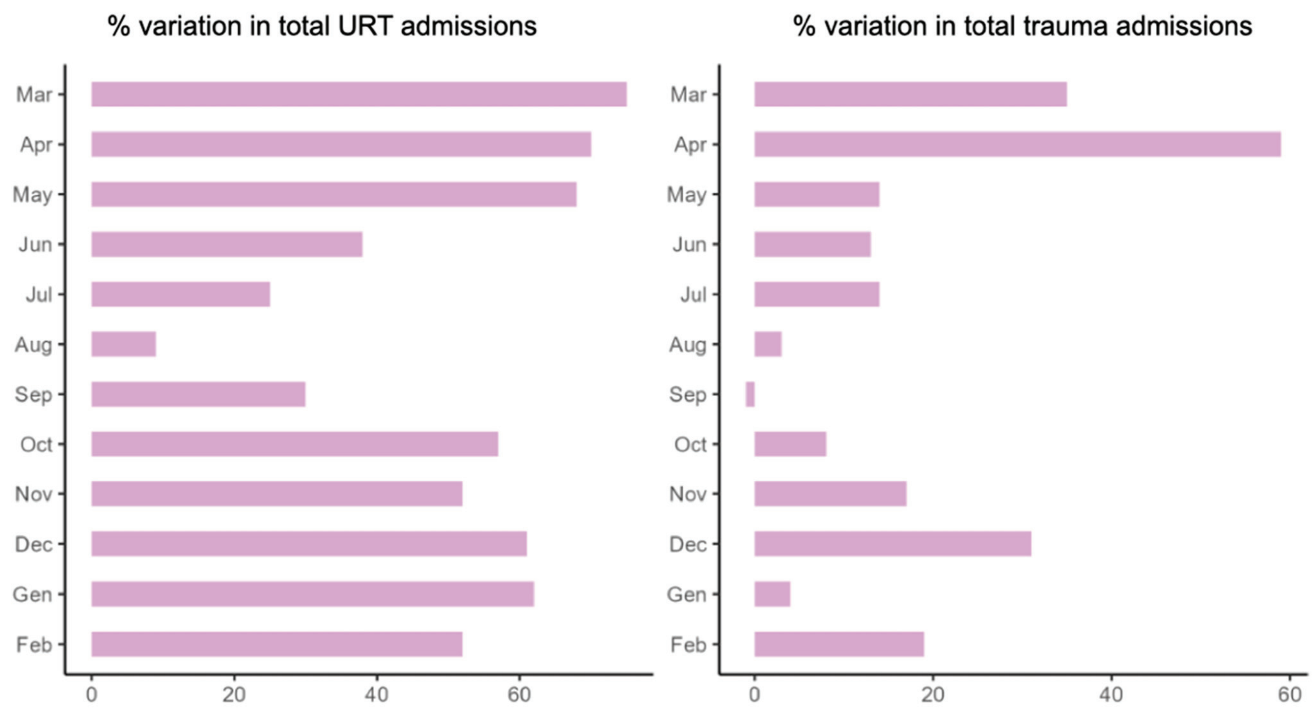

Figure 2. Percentage reduction in 2020/2021 compared to 2017 of total URT admissions and trauma admissions during 2020/2021.

3.2. Environmental Variables

The distributions of environmental variables have been depicted through box plots in Figure 3. For allergens and precipitation, the graph focuses on non-zero values for better interpretability. The significance of the difference in the distributions of the two timeframes was assessed based on the temporal trends, as follows.

Figures 4–6 compare the temporal trend of allergens, climatic variables and pollutants, respectively.

In 2020/2021, levels of *Alternaria* appeared significantly lower compared to 2017 (p-value < 0.001), especially during summer, when the concentration peaked. The release of *Betullaceae* and *Corylaceae* occurred later in the year, reaching higher peaks compared to those recorded in 2017 (p-value < 0.001). The concentrations of *Compositae* and *Gramineae* were essentially the same in both periods (p-value = 0.471 and p-value = 0.656, respectively).

No significant differences were detected in the two timeframes for temperature, minimum humidity and rainfall time trends. Maximum humidity was significantly higher in 2020/2021 compared to 2017 (p-value = 0.003). Regarding PM10 levels (Figure 6), the concentration was significantly lower in 2020/2021 compared to 2017 (p-value < 0.001), especially in the months between April and October. The same behavior was observed for NO_2, showing a significantly lower concentration in 2020/2021 (p-value < 0.001). O_3 levels remained substantially unchanged, similarly to the pattern observed for temperature (p-value = 0.284).

Figure 7 shows the scatter plots amongst the environmental variables with significant correlations in 2020/2021 (p-value < 0.05). PM10 results were negatively associated with temperature (correlation = −0.51), whilst they were positively correlated with NO_2 (correlation = 0.61). O_3 was positively associated with temperature and negatively with PM (correlation of 0.83 and −0.54, respectively). *Alternaria* concentration was positively correlated with temperature (correlation = 0.75), and *Betullaceae* concentration was positively associated with *Corylaceae* concentration (correlation = 0.82).

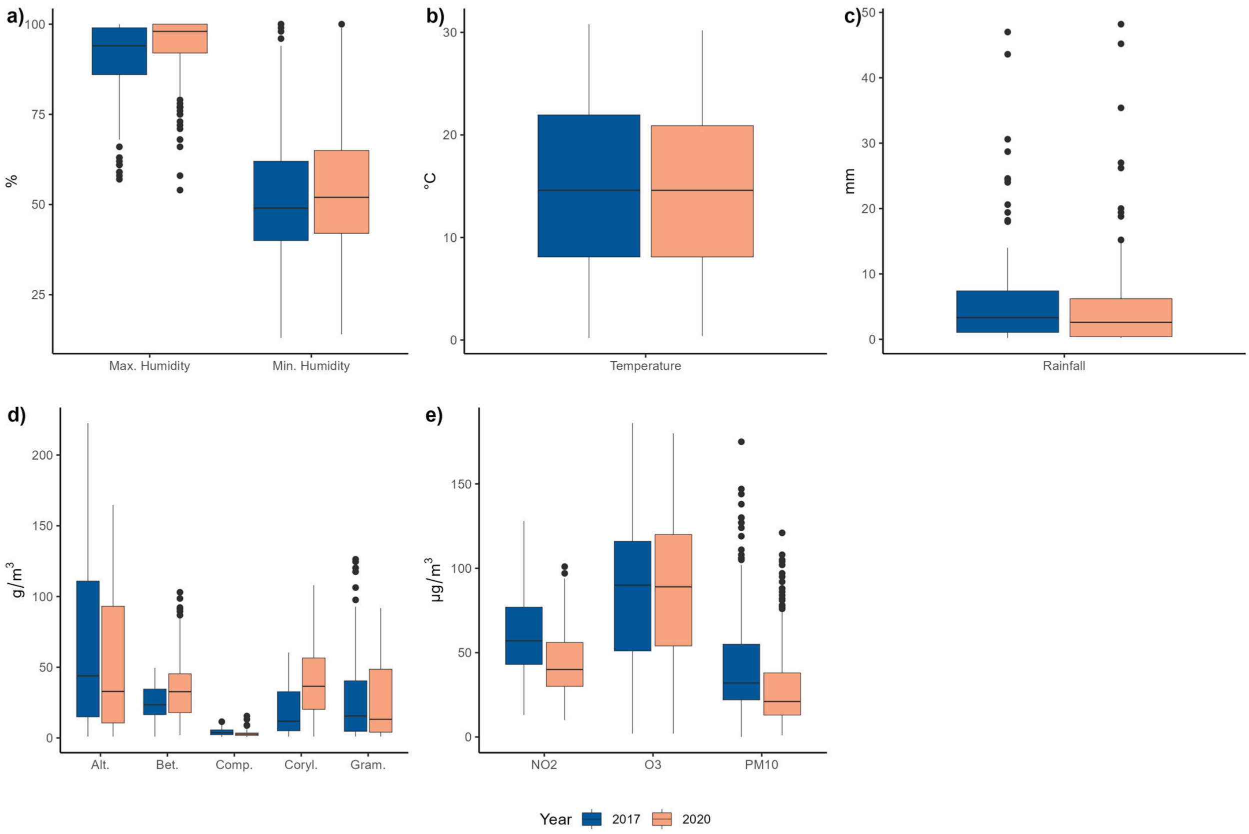

Figure 3. Distributions of environmental variables (**a**,**b**), precipitations (**c**), allergens (**d**) and AP (**e**) in 2017 and 2020/2021.

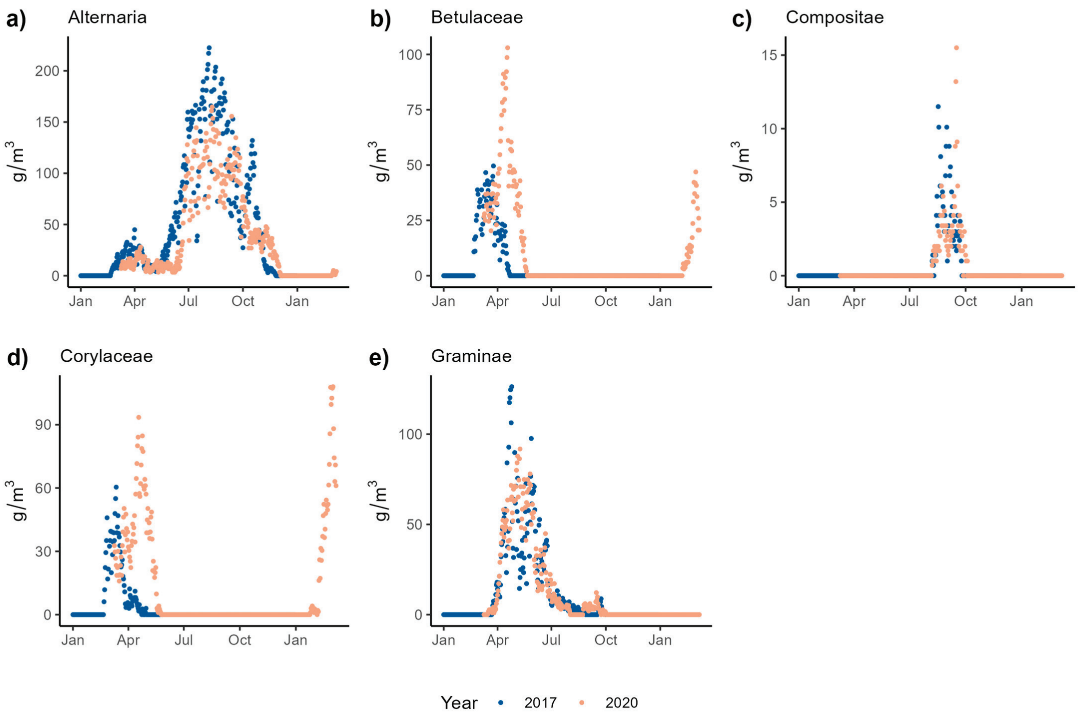

Figure 4. Temporal trends of allergens as measured by local environmental monitoring stations in 2017 and 2020/2021.

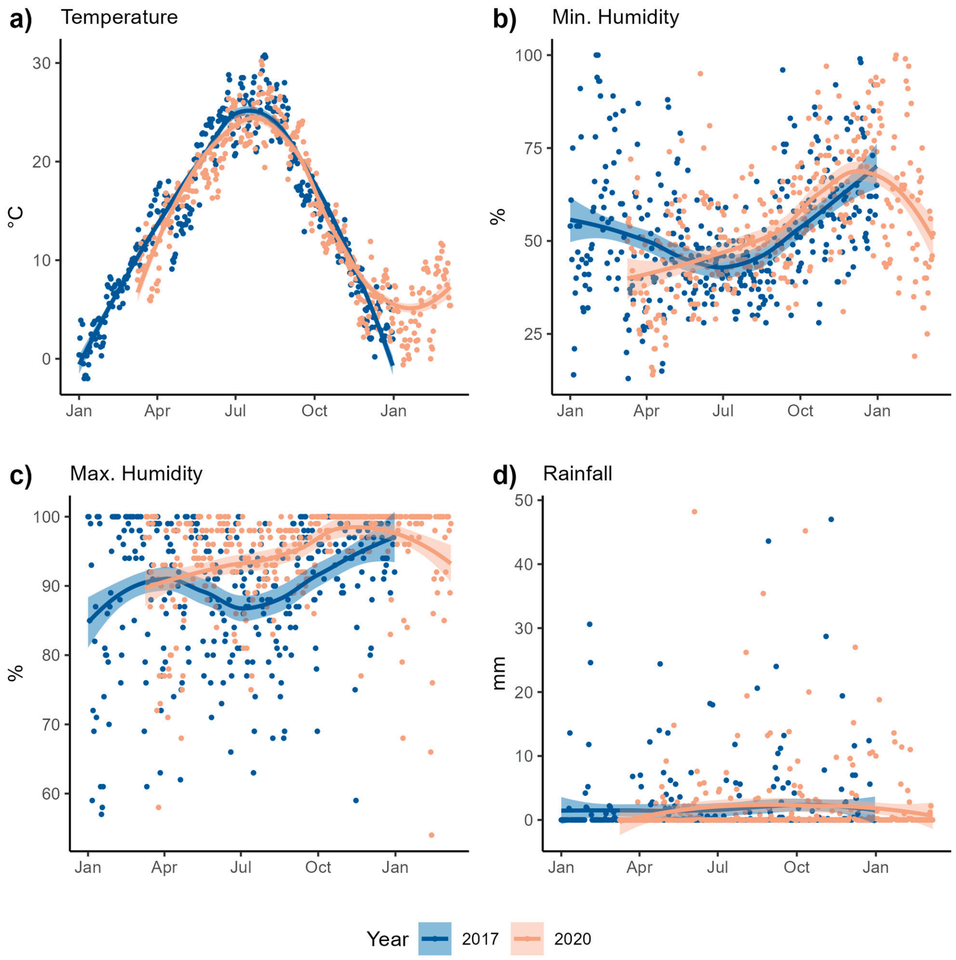

Figure 5. Temporal trends of climatic variables as measured by local environmental monitoring stations in 2017 and 2020/2021.

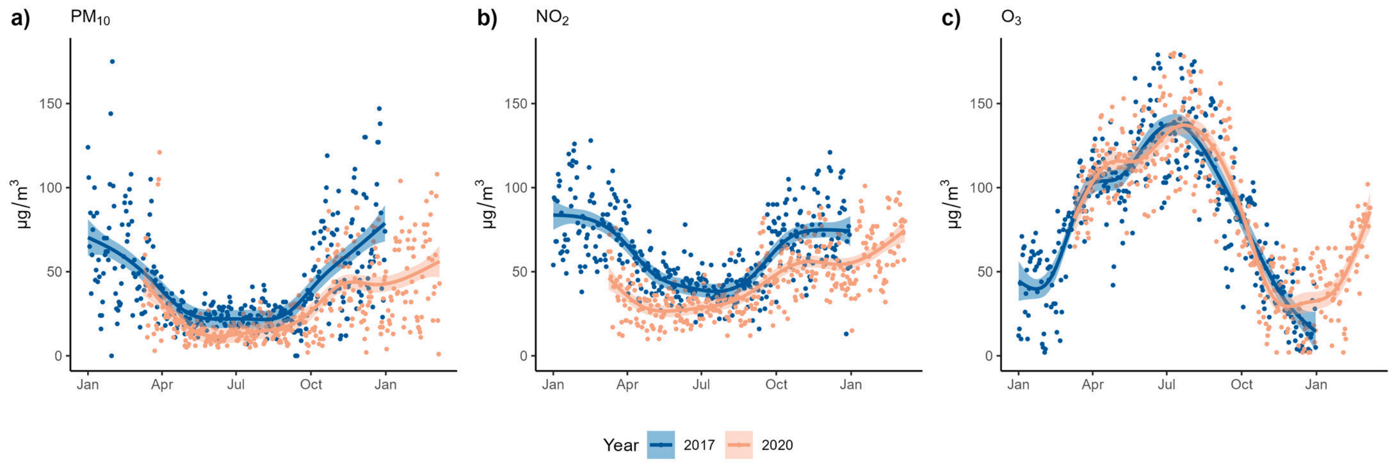

Figure 6. Temporal trends of AP in 2017 and 2020/2021.

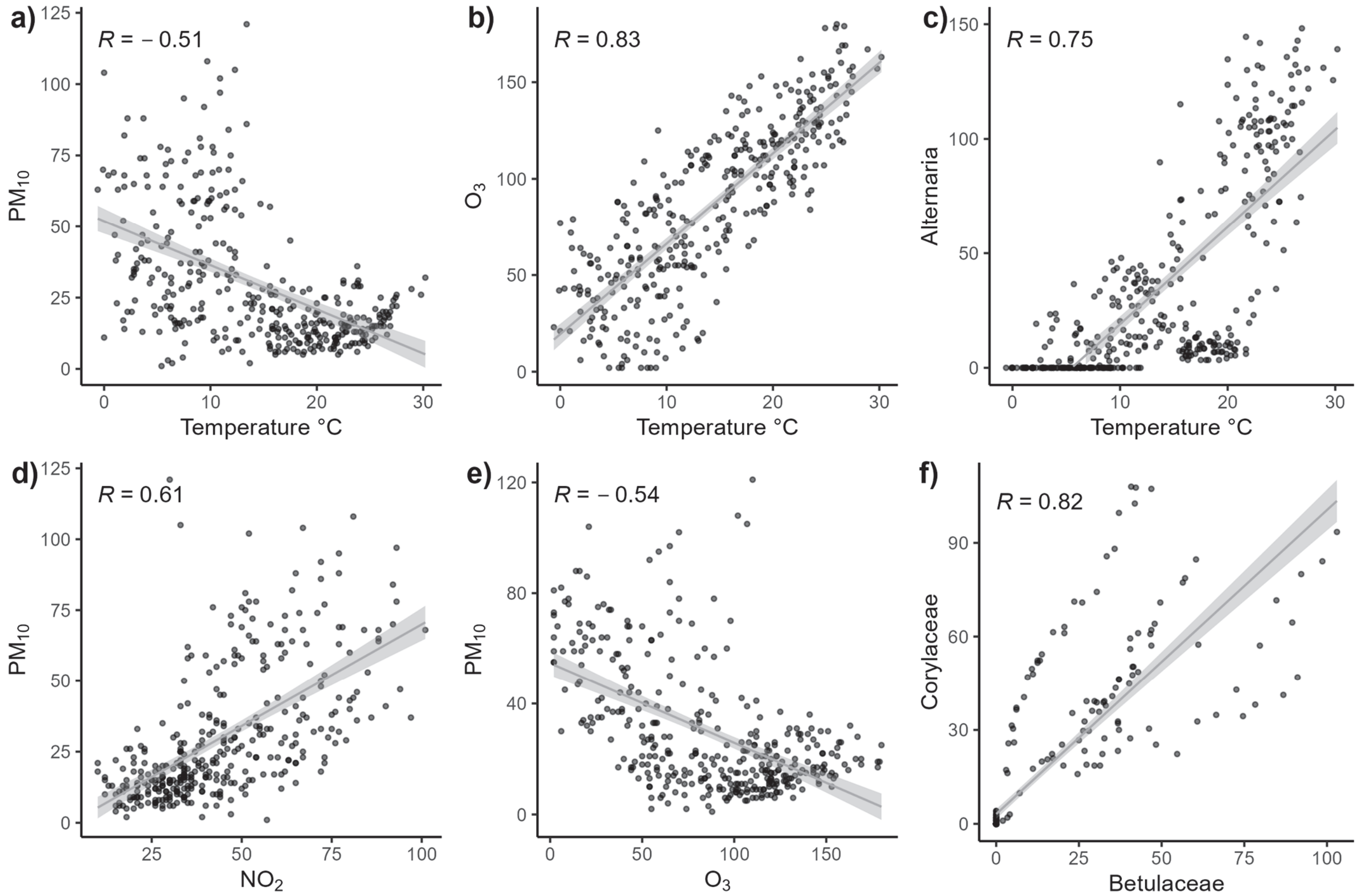

Figure 7. Scatter plots illustrating the relationships between the environmental variables with significant correlation in 2020/2021. Regression line with 95% confidence interval; *R* represents the Pearson correlation coefficient (all *p*-values < 0.001).

3.3. Environment and URT Admissions

The influence of environmental factors on the daily number of emergency room admissions in 2020/2021 was analyzed. To capture any non-linear effects, while maintaining good interpretability of the results, univariate Poisson-type GAMs were adapted. Table 2 shows the *p*-values associated with each non-parametric effect. For each model, graphs showing the significant effects are presented in Supplementary Materials Figure S1.1–S1.6.

Table 2. *p*-Values of the effects obtained from univariate GAMs.

	Total URT	Otitis	Rhino-Sinusitis	Pharyngitis	Laryngitis	Tonsillitis
Alternaria	**<0.001**	**<0.001**	0.108	**0.024**	**0.018**	**<0.001**
Betulaceae	**<0.001**	**0.001**	0.275	**<0.001**	0.314	**0.003**
Compositae	**0.002**	0.636	**0.004**	0.219	0.295	**0.003**
Corylaceae	**<0.001**	**0.042**	0.109	**0.002**	0.300	**0.003**
Gramineae	**0.001**	0.377	0.468	**<0.001**	0.840	**0.017**
PM10	**0.003**	0.407	0.155	**0.014**	0.992	0.354
O_3	**<0.001**	0.075	0.233	**0.004**	0.072	0.943
NO_2	**0.003**	0.083	0.960	0.055	0.184	0.265
Temperature	**<0.001**	**0.007**	**0.047**	**<0.001**	0.113	0.113
Max. Humidity	0.685	0.749	0.316	0.152	0.533	0.640
Min. Humidity	**0.046**	**0.034**	0.116	0.113	**0.004**	0.149
Rainfall	0.443	0.252	0.465	0.086	0.522	0.113

From the univariate analysis, it emerged that *Alternaria* had a positive and linear effect on admissions for middle ear infection, pharyngitis, laryngitis and URT diseases, while the effect of *Corylaceae* showed a decreasing and then increasing trend starting at approximately 60 g/m^3 (30 g/m^3 for middle ear infection). *Betullaceae* pollen had an increasing effect after about 40 g/m^3 on middle ear infection and respiratory system-related admissions; for the latter, *Gramineae* pollen started to have an increasing effect at around 50 g/m^3. *Compositae* pollen was a risk factor for sinusitis, tonsillitis and URT admissions up to approximately 5 g/m^3.

Regarding pollutants, there was a positive effect of O_3 on total admissions, URT-related admissions and pharyngitis, while NO_2 showed a nearly constant trend. Fine particulate matter had a negative effect on URT-related admissions and pharyngitis.

3.4. Multivariate Analysis

To investigate the effect of pollutants in greater detail, GAMs were fitted for each type of admission and separately for each pollutant, also considering delayed effects of the pollutant and adjustment for possible confounders (climate variables). In order to simplify the model, the non-parametric effects were converted to parametric if the effect was linear, and a stepwise backward selection procedure was adopted. The significant results are displayed in Table 3. For parametric effects, results are expressed as Incidence Rate Ratios (IRRs) with 95% confidence intervals (CIs), indicating the multiplicative change in the mean number of ED admissions per 10-unit increase in the exposure variable. When effects were non-parametric, they could not be summarized as IRRs and are instead graphically represented in the Supplementary Materials (Figure S2).

A significant effect of the cumulative mean value of PM10 was found for pharyngitis. The effect showed an increasing trend from around 30 μg/m^3. A positive, linear effect of the PM10 delayed at day 1 for rhinosinusitis was found, too (an increase of 10 μg/m^3 of PM10 delayed at day 1 is associated with an 35.4% [0.30–78.1] increase in the average number of rhinosinusitis admissions). A positive and linear effect of *Alternaria* was observed for tonsillitis and otitis admissions (increase of 15.1% [0.7–24.0] and 11.4% [0.5–18.5], respectively), confirming the results of the univariate analysis. Otitis was also positively influenced by the concentration of *Betulaceae* starting around 30 g/m^3, as were URT admissions. *Corylaceae* showed a positive effect on pharyngitis and URT admissions starting around 60 g/m^3.

Table 3. Significant effects obtained from multivariate GAMs are expressed as Incidence Rate Ratios, if parametric; (*p*) = non-parametric effect was turned into parametric; [ma] = mobile average, mean values in four consecutive days. Graphs showing the non-parametric effect are presented in Supplementary Materials Figure S2.

Risk Factor	Response	Incidence Rate Ratio [95% CI]	*p*-Value
O_3 lag 2 (*p*)	Pharyngitis	0.879 [0.776; 0.996]	0.042
O_3 lag 2 (*p*)	URT	0.959 [0.927; 0.991]	0.013
PM10 [ma]	Pharyngitis		0.017
PM10 lag 1 (*p*)	Rinosinusitis	1.354 [1.030; 1.781]	0.035
NO_2 [ma]	Pharyngitis		0.015
Alternaria (*p*)	Otitis	1.114 [1.046; 1.185]	<0.001
Alternaria (*p*)	Tonsillitis	1.151 [1.068; 1.240]	<0.001
Alternaria (*p*)	Pharyngitis	0.944 [0.904; 0.985]	0.008
Gramineae (*p*)	Otitis	0.894 [0.804; 0.994]	0.038
Gramineae (*p*)	Tonsillitis	0.804 [0.681; 0.948]	0.009
Gramineae	Pharyngitis		0.025
Betulaceae	URT		0.032
Betulaceae	Otitis		0.011
Corylaceae	URT		0.036
Corylaceae	Pharyngitis		0.008

3.5. Model Comparison Between 2017 and 2020/2021

A further comparison of the multivariate models investigating the effects of pollutants including the interaction between timeframe and risk factor was performed. The models were constructed by initially including lagged effects and confounders; they were then simplified by removing non-significant terms. The significant results are displayed in Table 4. The parametric effects are presented as IRRs. When effects were non-parametric, they could not be summarized as IRRs and are instead graphically represented in the Supplementary Materials Figure S3.

Table 4. Models that consider 2017 and 2020/2021 data by including the interaction between timeframe and risk factor. Significant effects obtained from multivariate GAM are expressed as Incidence Rate Ratioa, if parametric; (*p*) = non-parametric effect was turned into parametric; [ma] = mobile average, mean values in four consecutive days. Graphs showing the non-parametric effect are presented in Supplementary Materials Figure S3.

Risk Factor	Response	Incidence Rate Ratio 2017 [95% CI]	Incidence Rate Ratio 2020/2021 [95% CI]	*p*-Value 2017	*p*-Value 2020/2021
PM10 [ma]	URT			**0.037**	0.159
PM10 [ma] (*p*)	Otitis media	**1.047 [1.001; 1.094]**	0.939 [0.857; 1.030]	**0.046**	0.181
PM10 [ma]	Pharyngitis			0.347	**0.001**
PM10 [ma] (*p*)	Tonsillitis	**1.209 [1.054; 1.388]**	**1.234 [1.041; 1.463]**	**0.007**	**0.015**
NO_2 (*p*)	Otitis media	**1.067 [1.017; 1.120]**	0.923 [0.843; 1.009]	**0.009**	0.078
Alternaria (*p*)	URT	**0.971 [0.958; 0.983]**	**1.032 [1.013; 1.051]**	**<0.001**	**0.001**
Alternaria (*p*)	Otitis media	**0.958 [0.934; 0.983]**	**1.047 [1.008; 1.088]**	**0.001**	**0.018**
Alternaria (*p*)	Rinosinusitis	0.992 [0.959; 1.026]	**1.064 [1.009; 1.123]**	0.652	**0.023**
Alternaria (*p*)	Pharyngitis	**0.940 [0.910; 0.971]**	0.974 [0.940; 1.008]	**<0.001**	0.131
Alternaria (*p*)	Tonsillitis	0.987 [0.962; 1.013]	**1.079 [1.035; 1.125]**	0.314	**<0.001**
Betulacee	URT			**0.033**	**<0.001**
Betulacee	Otitis media			**0.001**	**<0.001**
Corylaceae	URT			**0.005**	**<0.001**

Table 4. *Cont.*

Risk Factor	Response	Incidence Rate Ratio 2017 [95% CI]	Incidence Rate Ratio 2020/2021 [95% CI]	*p*-Value 2017	*p*-Value 2020/2021
Corylaceae	Otitis media			**<0.001**	0.064
Corylaceae	Pharyngitis			0.978	**0.003**
Corylaceae	Tonsillitis			0.870	**0.007**

Regarding pollutants, the cumulative mean value of PM10 maintained its positive effect on tonsillitis in both time periods analyzed, while its effect on pharyngitis was detected only during the 2020/2021 period. The NO_2 effect on otitis media was not confirmed in the second timeframe, while it presented a positive linear effect in 2017.

Alternaria showed a significant positive linear effect in 2020/2021 on most URT-related admissions. *Betullaceae* concentration presented a risk effect for middle ear infection and URT-related admissions in 2020/2021 after about 50 g/m^3, while in 2017, the effect was almost linear. *Corylaceae* retained their effect on the total number of admissions in the two periods: in 2017, the effect was linear, whilst in 2020/2021, it showed a decreasing and then increasing trend starting around approximately 60 g/m^3.

4. Discussion

4.1. Reduction in ENT ED Accesses

Our research primarily examined how the Italian COVID-19 lockdown affected the number of admissions for ENT-related disorders at a tertiary emergency department in the Veneto Region. As expected, we found a consistent overall reduction in the number of patients admitted to our ED: the number of overall admissions was reduced by over a third while the number of specific admissions for inflammatory diseases of the URT was reduced by over half. This was in line with the previous findings in other tertiary referral centers in Italy that described a reduction in ENT-related ED admissions between 62.16 and 71.5% [13,14]. These studies, however, only focused on the earlier months of the pandemic. Similar trends have also been described in the pediatric population, with a significant decrease in patients' attendance to the pediatric ED, especially in cases caused by ENT-related disorders [15].

It was challenging to find a comprehensive explanation for the effect of the pandemic on ENT-emergencies. However, we had to consider that at the onset of the pandemic, the Veneto Region implemented healthcare policies aimed at discouraging non-urgent visits to hospital clinics and in-person visits to family practitioners. This might have resulted in several patients not seeking medical treatment for minor issues. The reduction could also be due to the fear of contracting the virus in hospitals or outpatient clinics. These elements, along with restricted access to consultations and the increased use of telemedicine [16], might have led to two outcomes: a reduction in the total number of ENT-ED admissions and the selection of only the most complex cases. Similar scenarios have already been described in previous investigations by Pontillo et al. [17] and Gallo et al. [18], emphasizing the increase in complex or late-diagnosed cases and emergency/urgent surgeries.

4.2. Environmental Pollutants and URT Manifestations

In parallel with the reduction in admissions to the ED, there was a significant reduction in AP, in particular PM and NO_2. Road traffic was the major anthropic component that showed a clear reduction relative to the lockdown period. The Italian national travelling reduction was approximately 80% compared to the pre-COVID-19 period for light vehicles and approximately 40% for heavy vehicles [19]. However, road traffic is only one source of particulate matter production. Other significant emissions, such as those from domestic heating systems, agricultural activities and animal farms were not affected by restrictions and were not as strongly regulated as road traffic [20].

Considering PM, which had lower concentrations in 2020/2021 than in 2017, it is reasonable to assume that lower PM10 levels probably resulted in milder manifestations of upper respiratory tract diseases. In fact, their incremental effect on total admissions and otitis media was not confirmed in 2020/2021. Nevertheless, the effect of increasing admissions for tonsillitis and pharyngitis remained, particularly when PM10 concentrations exceeded 40 $\mu g/m^3$. This was in line with a recent meta-analysis that confirmed how larger particles might trigger upper respiratory infections more than smaller ones [21]. On the other hand, O_3 concentrations were similar in the two years and the impact of this pollutant on URT diseases seemed limited. NO_2 levels were lower in 2020/2021 and their role in otitis media was not confirmed by the multivariate analysis in this timeframe.

4.3. Aeroallergens and URT Manifestations

Regarding aeroallergens, it is interesting to note that *Alternaria* levels appeared lower in 2020/2021. *Alternaria* is usually present in lower atmospheric concentrations compared to other allergenic airborne spores but is responsible for the highest rate of sensitization amongst atopic patients [22,23]. Exposure to *Alternaria* primarily occurs outdoors since fungal spores largely originate from agricultural lands. Seasonal variations are influenced by climate [24]. However, its presence as an indoor pollutant should not be overlooked, as it remains a dominant indoor fungus, alongside *Cladosporium* and *Penicillium* [25].

Urban areas typically have higher pollution levels and may also influence spore production and allergenicity. Increased levels of PM10 are linked to a rise in airborne fungi [26], and elevated CO_2 concentrations can triple the spore production of *Alternaria* species, doubling the number of allergenic proteins [27].

During the pandemic, reduced pollution in urban areas likely contributed to lower *Alternaria* levels in Padua. Despite this, it is worth noting that home confinement and mask usage only partly diminished *Alternaria*'s role in URT diseases. It emerged as a significant independent factor in conditions such as otitis media, tonsillitis and URT related diseases. Differently from *Alternaria*, *Gramineae* and *Compositae* levels did not have a significant change in the first year of the COVID-19 pandemic. Their pollens are a major cause of seasonal allergies in temperate climates, affecting up to 30% of the population in Western countries [28]. Although the levels of these allergens did not decrease as much as AP, the increased use of masks and indoor activities might be an explanation for the significant reduction in rhinitis/rhinosinusitis (over 60% in our series) and the reason for the decreasing trend of allergic rhinitis found during this period [29]. The protective effect of confinement, however, might have been mitigated in the case of *Betulaceae* and *Corylaceae* in view of the higher levels of pollen that were recorded. Their peculiar effect on total URT, tonsillitis and pharyngitis admissions could be partially explained by the trend in the spring and summer months: in fact, both had higher and later peaks in 2020/2021. In particular, the delayed peak in their pollen's concentrations observed in 2020/2021 compared to 2017 could plausibly be attributed to a slight delay in the seasonal rise in temperatures, which plays a key role in triggering pollen release for both families. The fact that they reached higher levels during a period of loosening of the restrictions, albeit with an almost constant use of masks even outdoors, may have contributed to the peculiar distributions of their effect, which appear to be decreasing up to a certain critical threshold and then reach significantly higher incremental trends when compared to 2017.

Social distancing and isolation, the use of masks and implemented hand hygiene measures were responsible for the significant decrease in new diagnoses of otitis media during the lockdown periods as recently demonstrated in a meta-analysis by Warner et al. [30]. In our cohort, we observed a reduction of almost two-thirds in the number of otitis admissions when compared to 2017. When looking at the effect of pollutants on otitis, it is interesting to highlight that only *Alternaria* and *Betullaceae* maintained their significant effect in the multivariate analysis in 2020/2021, whilst the other allergens and APs lost their level of significance, probably mitigated by the reduction in AP levels and the aforementioned behavioral measures.

The aim of the comparison between the two years was to determine whether different living conditions, in this case markedly changed due to the pandemic, lead to different associations between pollutants and admissions to emergency rooms. Although it was not easy to unambiguously determine what caused the differences that emerged, the present study supports the current literature and confirms the harmful effects of pollution on health. While climatic factors, such as temperature and humidity, are not directly controllable by human activity, it is possible to act on other elements that have an influence on public health. In addition to carefully choosing the trees that will be placed in the city to avoid harmful aeroallergens as much as possible, it is important to take measures to reduce air pollution and to raise awareness among the population for responsible behavior that may limit the anthropogenic impact on the environment, also in the interest of our own health.

The interplay between environmental changes, public health and clinical outcomes underscores the need for interdisciplinary collaboration. To better understand the environmental factors influencing public health, it is essential to foster cooperation among medical professionals, public health providers, environmental researchers and experts in animal health. Such an integrated approach would enable a more comprehensive analysis of how human activities and environmental modifications contribute to health outcomes, paving the way for evidence-based interventions and sustainable solutions.

Moreover, although this study focused on otorhinolaryngological pathologies, future research could expand the scope by applying the same statistical approach to other health domains, particularly cardiovascular diseases. There is increasing evidence that air pollutants (especially particulate matter) may contribute to cardiovascular morbidity [31,32]. Including these conditions in future analyses could provide a broader understanding of the impact of air pollution on human health and further strengthen the public health relevance of environmental monitoring.

The main limitations of the present study are its retrospective and monocentric design and the lack of comparison with data collected from other ENT emergency departments. Considering different time frames over several years and with different ENT centers could lead to more robust results.

5. Conclusions

The COVID-19 lockdown in the Veneto Region of Italy led to a significant decrease in the number of patients admitted to the emergency department (ED) for ENT-related disorders. This reduction was consistent with findings from other regions in Italy and was particularly notable for URT inflammatory diseases. The lockdown also resulted in decreased air pollution, particularly in PM and NO_2 levels. While certain allergens such as *Alternaria* showed lower levels during the lockdown, they continued to play a significant role in ENT disorders such as otitis media and tonsillitis. Other allergens, such as *Betulaceae* and *Corylaceae*, had higher peaks compared to 2017 and showed a significant and independent effect particularly regarding the total number of URT accesses, tonsillitis and pharyngitis. Social distancing, mask-wearing and enhanced hygiene practices likely contributed to a significant decrease in URT infections, especially in otitis media during the lockdown period.

These findings highlight the harmful effects of pollution on health even during global pandemic and underline the importance of reducing air pollution and promoting responsible behavior to minimize anthropogenic environmental impacts for better public-health outcomes.

Moreover, this study supported the value of integrating clinical data with environmental monitoring and advanced statistical modeling to elucidate complex cause–effect relationships in selected settings. This can contribute to the growing body of evidence supporting the inclusion of environmental health indicators in public health planning. In light of these findings, there is a rationale for deeply investigating the adoption of long-term strategies aimed at reducing pollutant emissions, regulating allergenic vegetation in urban planning and maintaining certain protective behaviors. Public health campaigns should also aim to raise awareness about the environmental determinants of ENT diseases.

While the study was limited by its retrospective, monocentric design and focused on a specific geographic area, its results lay the groundwork for broader investigations. Future research should aim to confirm these findings in other populations and expand the scope to other environmentally sensitive health conditions, such as cardiovascular and respiratory diseases or animal well-being. Multi-center, longitudinal studies with integrated environmental and clinical datasets would be instrumental in shaping evidence-based policy and reinforcing the environmental dimension of public health.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/environments12040115/s1, Figures S1.1–S1.6, S2 and S3.

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