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From Pandemics to Plasticizers: Environmental and Social Determinants of Health Across the Life Course

Insights from the COVID-19 Pandemic, Sustainable Nutrition, and
Pediatric Exposure to Environmental Chemicals in the Province of
Modena

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*To my best friend and safe haven,
to our incredibly curious son,
to our wonder-struck daughter,
to the Lord for these blessings.*

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1 PREFACE

Public health (PH) is an exciting discipline that allows you to combine critical observation of reality, the coolest and most complex epidemiological models, communication skills and research translation into policy. Though it seems a fun and sparkling path, the road to excellence in PH is lined with methodological rigor. The aim of researchers in this field is to provide the best available knowledge to inform health policy and behavioral changes. This is not a short task given that these changes may potentially have a vast impact and resonance on populations' health.

An esteemed colleague, Nino Cartabellotta, medical doctor and president of the GIMBE Foundation, is constantly underlining how given the very few resources our National Healthcare Service is left with, we should improve the value for money for healthcare spending. But to do so we need data. We need research to help guide the best allocation of the few resources we have, to improve health and reduce inequities, ensuring that evidence, not chance, drives our public health decisions.

This has been imperative during the COVID-19 pandemic, when the need for rapid, evidence-based action was essential. The pandemic exposed how environmental, social, and geographic determinants shape both exposure risk and health outcomes, emphasizing that preparedness must rest on the integration of data, context, and population needs. It also reaffirmed that research in public health is not a purely academic exercise but one that must be translated into policies capable of protecting the most vulnerable and preserving collective well-being even under resource constraints.

The main driver of my scientific work has been striving to ensure that every newborn might have the best possible future. Pediatric environmental epidemiology and public health therefore represent the natural intersection of my scientific and personal motivations: the former anchored in the methodological rigor of epidemiology, and the latter in the universal principle of safeguarding the most vulnerable. Children, by virtue of their developmental plasticity, represent both sentinels and promises, early warnings of environmental degradation, and living investments in a healthier, more equitable future.

Lucia Palandri

2 SUMMARY AND INTRODUCTION

This article-based dissertation is structured as the collection of the projects I had the honor to work on and contribute to significantly and examines how environmental, social, and policy determinants influence health across the life course, with a specific focus on the COVID-19 pandemic, sustainable nutrition, and exposure to environmental contaminants. By integrating approaches from public health, environmental epidemiology, and pediatric health, the dissertation aims to describe the interconnections between human and planetary health. It comprises eight peer-reviewed articles grouped into three thematic chapters: (1) Tackling the COVID-19 Pandemic; (2) Healthier Children for a Healthier Planet; and (3) Children and Phthalates, Are We Doing Enough?

Each chapter is presented with an introductory chapter describing the rationale of the chapter providing a summary with abstract and authors for each paper. In each summary I will also describe my scientific contribution, because even if I am a strong believer in teamwork and effort, the aim of a PhD dissertation is to show scientific maturity and independence.

Chapter 1 focuses on the general population investigating the multifactorial determinants of the COVID-19 pandemic in Italy. Through ecological and population-based analyses, the studies assessed how environmental, climatic, demographic, and socio-economic factors shaped infection rates, hospitalizations, and mortality. The research also evaluated the effectiveness of vaccination programs in preventing severe outcomes. The findings showed how the pandemic's spread and impact were not random but driven by spatial inequities, environmental vulnerabilities, and differences in the implementation of non-pharmaceutical interventions. Methodological contributions included the development of multivariable models and integrated analytical frameworks to assess complex public health risk domains. Together, these studies provided evidence supporting geographically and socially tailored pandemic responses.

Chapters 2 and 3 concentrated on the pediatric population, a population dear to the candidate, and aim to connect environmental epidemiology within child health promotion.

Chapter 2 examines dietary habits among Italian children aged 6 months to 14 years, evaluating their nutritional adequacy and environmental sustainability. The

studies demonstrated excessive consumption of animal-based and processed foods, resulting in diets misaligned with both healthy dietary recommendations and planetary sustainability targets. Additional analyses identified low parental awareness of the environmental implications of diet and limited engagement of pediatricians in promoting healthier, more sustainable eating patterns. By describing dietary epidemiology and societal factors, this chapter emphasizes that early-life interventions fostering sustainable diets can produce synergistic benefits for both child and planetary health.

Chapter 3 addresses children's exposure to phthalates, endocrine-disrupting chemicals present in a variety of consumer products. Drawing on empirical data and public health synthesis, it describes biomonitoring evidence of neurodevelopmental associations as well as evaluating current policy and regulatory measures against phthalates. Despite progress in restrictions, findings indicated that children remain exposed due to behavioral characteristics and physiological vulnerability. The chapter calls for enhanced regulation, surveillance, and integration of environmental toxicology into pediatric care and public health policy.

Overall, the dissertation provides a comprehensive understanding of how environmental and community indicators interact to affect health at both population and pediatric levels. It demonstrates the value of interdisciplinary, data-driven approaches in identifying modifiable determinants of disease and inequity. Conceptually, it advanced an overall framework that situates health within the broader context of planetary sustainability, underscoring that safeguarding human health requires addressing the environmental systems upon which it depends.

3 TACKLING THE COVID-19 PANDEMIC

3.0 INTRODUCTORY SUBCHAPTER

The COVID-19 pandemic revealed the spatial and social heterogeneity connected with population health. Despite its global spread, the pandemic's intensity and outcomes varied markedly across regions, even within single countries, with Northern Italy being one of the most heavily hit. Understanding why required a multidisciplinary approach that integrated geographic, environmental, socio-demographic, and policy dimensions. The first dissertation chapter, *Tackling the COVID-19 Pandemic*, brings together four published studies that collectively examined how place, environment and public health measures shaped the progression, severity, and mitigation of COVID-19 in Italy, particularly in the province of Modena and within the Alpine region of South Tyrol. The chapter advanced from broad conceptual mapping of literature (Vandelli et al., 2024) to a comprehensive multidomain modeling (Palandri et al., 2025) and finally to territory-specific empirical analyses (Lorenzon et al., 2024a, 2024b). This progression, from global synthesis to regional and local application, reflected the intention to link environmental epidemiology with actionable public health programs. In short, this chapter moves beyond “where did COVID hit hardest?” toward “why did COVID hit harder here than there?”.

In the following paragraphs you may find the full abstract and my contributions to each project. All the manuscript presented in this chapter were published in peer-reviewed journals.

3.0.1 Conditioning factors in the spreading of Covid-19 – Does geography matter?

Vittoria Vandelli, Lucia Palandri, Paola Coratza, Cristiana Rizzi, Alessandro Ghinoi, Elena Righi, Mauro Soldati

Journal: Heliyon

Doi: <https://doi.org/10.1016/j.heliyon.2024.e25810>

My contributions: As second author, contributed to drafting the original version, assisted in the specification of the classification/coding framework, and oversaw the curation and organization of the extracted metadata from the 112 studies.

Abstract

There is evidence in literature that the spread of COVID-19 can be influenced by various geographic factors, including territorial features, climate, population density, socioeconomic conditions, and mobility. The objective of the paper is to provide an updated literature review on geographical studies analyzing the factors which influenced COVID-19 spreading. This literature review took into account not only the geographical aspects but also the COVID-19-related outcomes (infections and deaths) allowing to discern the potential influencing role of the geographic factors per type of outcome. A total of 112 scientific articles were selected, reviewed and categorized according to subject area, aim, country/region of study, considered geographic and COVID-19 variables, spatial and temporal units of analysis, methodologies, and main findings. Our literature review showed that territorial features may have played a role in determining the uneven geography of COVID-19; for instance, a certain agreement was found regarding the direct relationship between urbanization degree and COVID-19 infections. For what concerns climatic factors, temperature was the variable that correlated the best with COVID-19 infections. Together with climatic factors, socio-demographic ones were extensively taken into account. Most of the analysed studies agreed that population density and human mobility had a significant and direct relationship with COVID-19 infections and deaths. The analysis of the different approaches used to investigate the role of geographic factors in the spreading of the COVID-19 pandemic revealed that the significance/representativeness of the outputs is influenced by the scale considered due to the great spatial variability of geographic aspects. In fact, a more robust and significant association between geographic factors and COVID-19 was found by studies conducted at subnational or local scale rather than at country scale.

3.0.2 Environmental, climatic, socio-economic factors and non-pharmacological interventions: A comprehensive four-domain risk assessment of COVID-19 hospitalization and death in Northern Italy

Lucia Palandri, Cristiana Rizzi, Vittoria Vandelli, Tommaso Filippini, Alessandro Ghinoi, Giuliano Carrozzi, Gianfranco De Girolamo, Isabella Morlini, Paola Coratza,

Enrico Giovannetti, Margherita Russo, Mauro Soldati, Elena Righi, on behalf of the DISCOV-19 study group

Journal: International Journal of Hygiene and Environmental Health

Doi: <https://doi.org/10.1016/j.ijheh.2024.114471>

My contributions: As first author, I led conceptualization, methodology selection, data curation, investigation, formal analysis, interpretation, visualization, and writing of both original draft and review versions.

Abstract

Introduction: Up to now, studies on environmental, climatic, socio-economic factors, and non-pharmacological interventions (NPI) show diverse associations, often contrasting, with COVID-19 spread or severity. Most studies used large-scale, aggregated data, with limited adjustment for individual factors, most of them focused on viral spread than severe outcomes. Moreover, evidence simultaneously evaluating variables belonging to different exposure domains is scarce, and none analyzing their collective impact on an individual level. **Methods:** Our population-based retrospective cohort study aimed to assess the comprehensive role played by exposure variables belonging to four different domains, environmental, climatic, socio-economic, and nonpharmacological interventions (NPI), on individual COVID-19-related risk of hospitalization and death, analyzing data from all patients (no. 68472) tested positive to a SARS-CoV-2 swab in Modena Province (Northern Italy) between February 2020 and August 2021. Using adjusted Cox proportional hazard models, we estimated the risk of severe COVID-19 outcomes, investigating dose-response relationships through restricted cubic spline modelling for hazard ratios. **Results:** Several significant associations emerged: long-term exposure to air pollutants (NO₂, PM₁₀, PM_{2.5}) was linked to hospitalization risk in a complex way and showed an increased risk for death; while humidity was inversely associated; temperature showed a U-shaped risk; wind speed showed a linear association with both outcomes. Precipitation increased hospitalization risk but decreased mortality. Socio-economic and NPI indices showed clear linear associations, respectively negative and positive, with both outcomes. **Conclusions:** Our findings offer insights for evidence-based policy decisions, improving precision healthcare

practices, and safeguarding public health in future pandemics. Refinement of pandemic response plans by healthcare authorities could benefit significantly.

3.0.3 Effectiveness of the SARS-CoV-2 Vaccination in Preventing Severe Disease-Related Outcomes: A Population-Based Study in the Italian Province of Bolzano (South Tyrol)

Antonio Lorenzon, Lucia Palandri, Francesco Uguzzoni, Catalina Doina Cristofor, Filippo Lozza, Riccardo Poluzzi, Cristiana Rizzi, Pierpaolo Bertoli, Florian Zerzer and Elena Righi

Journal: International Journal of Public Health

Doi: <https://www.ssph-journal.org/journals/international-journal-of-public-health/articles/10.3389/ijph.2024.1606792/full>

My contributions: As second and corresponding author, I co-led the methodology design, steered and performed data analysis and interpretation, and wrote the first draft of the manuscript. I led and contributed to all the phases of the project with the exception of data collection.

Abstract

Objective: To investigate the effectiveness of SARS-CoV2 vaccination in preventing ordinary or intensive care unit (ICU) admissions and deaths among cases registered during a variant transitional pandemic phase in the geographically and culturally unique territory of the Province of Bolzano (South Tyrol), an Italian region with low vaccination coverage. **Methods:** We collected data from 93,643 patients registered as positive for SARS-CoV2 by health authorities during the winter of 2021–22. The data were analyzed retrospectively using descriptive statistics and multiple logistic regression. **Results:** 925 patients were hospitalized (0.99%), 89 (0.10%) were in intensive care, and 194 (0.21%) died. Vaccinated patients had a significantly lower risk of being hospitalized: adjusted Odds Ratio (aOR): 0.39; 95% CI: 0.33–0.46, ICU admission: aOR: 0.16; 95% CI: 0.09–0.29 and death: aOR: 0.41; 95% CI: 0.29–0.58. Similar risk reductions were also observed in booster-vaccinated patients, independent of sex, age, and predominant variant. Furthermore, the median length of stay (LoS) in the ICU was significantly longer for unvaccinated individuals compared

to vaccinated subjects (9 vs. 6 days; $p < 0.003$). Conclusion: Primary series vaccination and ongoing campaign booster doses were effective in preventing all severe disease-related outcomes and in reducing ICU Length of Stay, even during a transitional pandemic phase and in a unique territorial context.

3.0.4 An Ecological Study Relating the SARS-CoV-2 Epidemiology with Health-Related, Socio-Demographic, and Geographical Characteristics in South Tyrol (Italy)

Antonio Lorenzon, Lucia Palandri, Francesco Uguzzoni, Catalina Doina Cristofor, Filippo Lozza, Cristiana Rizzi, Riccardo Poluzzi, Pierpaolo Bertoli, Florian Zerzer and Elena Righi

Journal: International Journal of Environmental Research and Public Health

doi: <https://doi.org/10.3390/ijerph21121604>

My contributions: As second and corresponding author I led and contributed to all the phases of the project with the exception of data collection. I guided methodology, executed data analyses, and drafted the initial manuscript. I contributed significantly to interpretive synthesis.

Abstract

The literature associating the spread of SARS-CoV-2 with the healthcare-related, geographical, and demographic characteristics of the territory is inconclusive and contrasting. We studied these relationships during winter 2021/2022 in South Tyrol, a multicultural Italian alpine province, performing an ecological study based on the 20 districts of the area. Data about incidence, hospitalization, and death between November 2021 and February 2022 were collected and associated to territorial variables via bivariate analyses and multivariate regressions. Both exposure variables and outcomes varied widely among districts. Incidence was found to be mainly predicted by vaccination coverage (negative correlation). Mortality and ICU admission rates partially followed this distribution, while the case fatality rate was inversely correlated to average salary, and hospital admission rates increased where hospitals capacity was higher, and from the southern to the northern border of the province. These findings, besides confirming the efficacy of vaccination in preventing both new

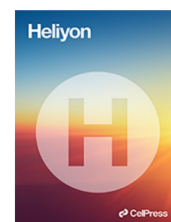
and severe SARS-CoV-2 cases, highlight that several geographical and socio-demographic variables can be related to disease epidemiology. Remote areas with wage gaps and lower access to care suffered most from the pandemic. Our findings, therefore, underly the existence of health inequity issues that need to be targeted by implementing specifically tailored public health interventions.

3.1 CONDITIONING FACTORS IN THE SPREADING OF COVID-19 – DOES GEOGRAPHY MATTER?

Vittoria Vandelli, Lucia Palandri, Paola Coratza, Cristiana Rizzi, Alessandro Ghinoi, Elena Righi, Mauro Soldati

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Review article

Conditioning factors in the spreading of Covid-19 – Does geography matter?

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ABSTRACT

There is evidence in literature that the spread of COVID-19 can be influenced by various geographic factors, including territorial features, climate, population density, socioeconomic conditions, and mobility. The objective of the paper is to provide an updated literature review on geographical studies analysing the factors which influenced COVID-19 spreading. This literature review took into account not only the geographical aspects but also the COVID-19-related outcomes (infections and deaths) allowing to discern the potential influencing role of the geographic factors per type of outcome.

A total of 112 scientific articles were selected, reviewed and categorized according to subject area, aim, country/region of study, considered geographic and COVID-19 variables, spatial and temporal units of analysis, methodologies, and main findings.

Our literature review showed that territorial features may have played a role in determining the uneven geography of COVID-19; for instance, a certain agreement was found regarding the direct relationship between urbanization degree and COVID-19 infections. For what concerns climatic factors, temperature was the variable that correlated the best with COVID-19 infections. Together with climatic factors, socio-demographic ones were extensively taken into account. Most of the analysed studies agreed that population density and human mobility had a significant and direct relationship with COVID-19 infections and deaths. The analysis of the different approaches used to investigate the role of geographic factors in the spreading of the COVID-19 pandemic revealed that the significance/representativeness of the outputs is influenced by the scale considered due to the great spatial variability of geographic aspects. In fact, a more robust and significant association between geographic factors and COVID-19 was found by studies conducted at subnational or local scale rather than at country scale.

1. Introduction

Admittedly, COVID-19 outbreak is linked to geographical factors and its diffusion across the globe reflects a geographic control, showing different impacts according to the scale considered (i.e., global, regional, national, sub-national).

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Geographical science through the use of cartographic techniques and analysis has demonstrated to be crucial in the study of the spatial dynamics of COVID-19 spread and transmission [1,2]. In the field of geography, a number of papers focus on the association between COVID-19 diffusion and geographic factors, including physical ones, as well as on the application of spatial tools/techniques for the study of the pandemic.

Already in the first months since the start of the pandemic a few reviews on the topic were published in international journals. One of the earliest was performed by Briz-Redón and Serrano-Aroca [3] who focused on studies investigating the relationships between meteorological variables and the global expansion of COVID-19 analysing both findings and statistical modelling techniques. This review highlighted contradictory results among the analysed literature in the definition of the relationship between climate variables and COVID-19 transmission. Similar conclusions were reached by Paraskevis et al. [4] who reviewed literature on the effects of weather and climate variables (also with reference to urban parameters and air pollution) on the impact of the COVID-19 pandemic. The inconsistency of results among studies investigating the association between weather variables and COVID-19 incidence was also highlighted in the review by McClymont and Hu [5] with the exception of temperature, for which a negative association with incidence was found by the majority of the examined studies. Briz-Redón and Serrano-Aroca [3] emphasized that detailed studies tend to provide more reliable data when climatic and non-climatic factors (e.g., population density, mobility) have to be associated.

One of the most recent reviews is by Wang et al. [6] who focused on the role of natural factors (e.g., climate, geographic location, air pollution) and human activity (e.g., mobility, health factor, economic conditions, demography) on global COVID-19 transmission. The authors found that spatial and temporal heterogeneity varied across countries and during different pandemic stages.

Geographical studies dealing with the COVID-19 pandemic benefitted from the use of mapping and spatial tools, including Geographic Information Systems (GIS). The mapping of territorial variables crossed with that of COVID-19 spread was found to be useful for the interpretation of COVID-19 geography [7]. Reviews on this topic were produced since 2020 [cf. 8,9].

In the early stages of the pandemic Franch-Pardo et al. [10] performed a review on the implementation of geographical and geospatial analyses for understanding distribution patterns of COVID-19. An update of this review [11] showed that the latest research improved in spatial resolution with a consequent decrease in studies conducted at global level. Additionally, the authors found an increase in the number of the studies considering socioeconomic variables which were found to have a greater influence on COVID-19 pandemic at more local level. Fatima et al. [12] produced a similar literature review with a specific focus on methodologies and associated outputs in relation to geospatial analysis applied to the study of COVID-19 showing that GIS was extensively used for analysing, visualizing and identifying COVID-19 patterns.

Another review on the use of GIS and geospatial tools for the study of COVID-19 pandemic was implemented by Ahasan et al. [13] who found an important lack in the literature related to spatial modelling aimed at identifying and predicting the location of potential future outbreak.

Since most of the reviews mentioned above were published during the first phases of the pandemic, we felt the need to provide an updated literature review on geographical studies analysing the factors which influenced COVID-19 spreading. The review presented here covers the period 2020–2022 and also comprises studies carried out after the pandemic peak benefiting from additional knowledge on COVID-19 outbreak and transmission.

The objectives of this review are to: i) understand the role of the geographic determinants in COVID-19 spreading (e.g., geographic location, climatic characteristics, altimetry, morphological features); ii) identify common approaches, materials and methods used in the study of the COVID-19 outbreak from a geographical perspective; iii) recognise possible research gaps to address future in-depth analyses.

2. Materials and methods

2.1. Bibliographic search

A literature search was performed in Scopus and Web of Science (WoS) on 23 January 2023 and updated in November 2023 by applying the following research query to “title”, “abstract” and “keywords”: (COVID-19 OR CORONAVIRUS OR SARS-Cov-2) AND Geography. The search was limited to peer-reviewed articles published since 2020 considering that the beginning of the COVID-19 outbreak was at the end of 2019.

Scopus and WoS databases were used for the search since they host the widest set of peer reviewed journal articles with reference to Natural Sciences and offer good quality of metadata.

An additional search was also performed in Google Scholar to confirm that no significant papers on the topic of interest were overlooked, having this database a more comprehensive coverage [14]. This literature search was performed by applying the above-mentioned query, looking for the combination of keywords within the entire text.

Articles were considered eligible for our review if they were (i) published in English language, (ii) peer-reviewed, and (iii) if they included statistical analysis, modelling or cartographic representations of one or more geographical factors/variables in relation to the outbreak of the COVID-19 pandemic. On the contrary, articles were excluded from the review if they were (i) not research articles (e.g., commentaries, reviews, editorials); (ii) not considering any geographic variable; (iii) exclusively focusing on COVID-19 medical aspects; (iv) focusing specifically on geography teaching and learning; (v) exclusively focusing on the secondary impacts of COVID-19 outbreak, such as on economy, mobility, and population life/working styles.

The review was performed according to the following steps (Fig. 1): (i) records were identified through Scopus, Web of Science and they were exported in bibtex and plaintext formats respectively; (ii) the retrieved records from both literature databases were merged using the RStudio tool bibliometrix [cf. 15] which also allowed us to remove duplicates; (iii) the identified records were screened and

selected according to the above-mentioned inclusion/exclusion criteria by title and abstract reading; (iv) selected records were included in or excluded from the final list after full text reading according to the eligibility criteria; (v) a check of the completeness of the literature search was done by consulting Google Scholar and by the list of references of the literature reviews mentioned above.

Records retrieved from Scopus and WoS were respectively 1730 and 768. The sum of the documents retrieved from both databases totalled 1940 excluding duplicates. Among these, 222 articles fulfilled the eligibility criteria based on their title and abstract. The subsequent analysis of the full texts led to the exclusion of 139 papers which did not satisfy all the eligibility criteria.

The search in Google Scholar returned 16,800 records ranked by pertinence by the default ranking algorithm, being the first 1000 results retrieved and analysed. This check revealed that the literature search carried out in Scopus and Web of Science was highly comprehensive; in fact, only four additional papers were found, making a total of 87 articles.

A further search was performed by checking the list of references of the most relevant papers selected. This allowed us to include 25 additional papers resulting in a total of 112 articles to be finally reviewed. The results from the publications' reference list search brought to our attention that many articles dealing with geographical aspects l.s. did not include "geography" in the papers' key fields (title, abstract, keywords). This was especially true for papers that analysed specific factors, such as air pollution.

2.2. Categorization criteria

The full texts of the articles fulfilling all the eligibility criteria were reviewed, and relevant data were extracted based on the following items.

- Subject macro-area
- Submission and publication date
- Region or country of study
- Aim of the study
- COVID-19 outcome data macro-area (infection, hospitalization, death) and detail (e.g., incidence, reproduction number, lethality, mortality)
- Geographic variables macro-area (e.g., territorial, climatic, socio-demographic) and detail (e.g., latitude, average temperature, population density)
- Data source
- Other variables (e.g., number per-capita of hospital beds, life expectancy)
- Investigated period
- Spatial and temporal resolution
- Statistical methodological approach
- Main findings.

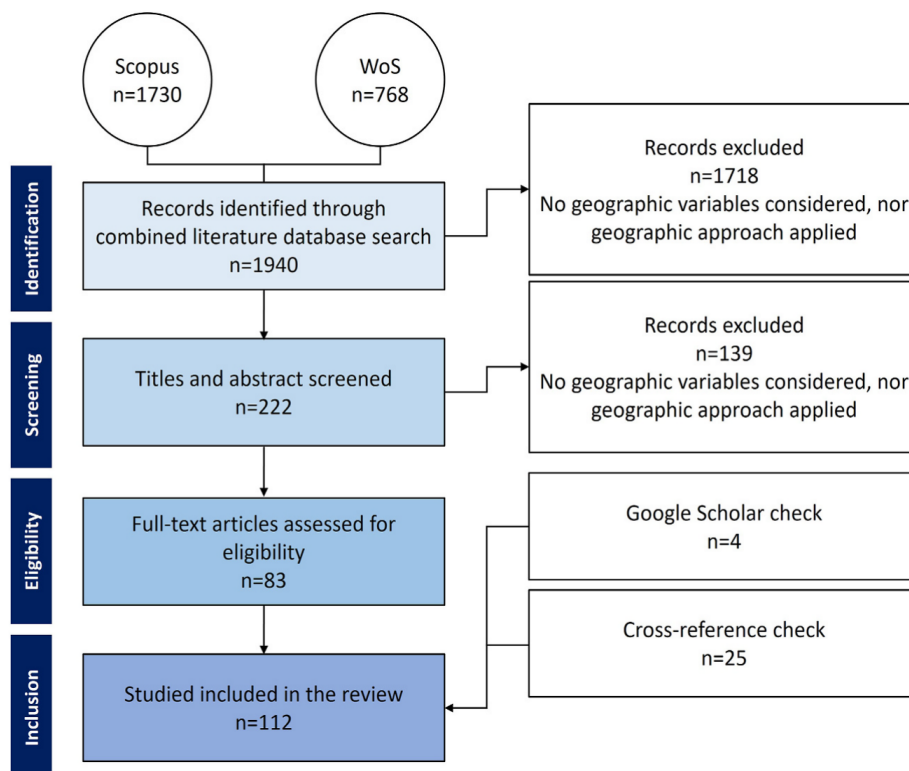


Fig. 1. Workflow of the literature search on the influence of geographic factors on COVID-19 pandemic.

The geographic variables are understood as parameters that provide information about the characteristics of an area (thus not only descriptive of the geographic location) [16].

The selected and analysed papers showed a high heterogeneity of methods, data, and outputs. A narrative description and synthesis of the main results achieved is presented in the following section.

3. Results and discussions

Among the 112 selected articles, 32 studies were conducted at a global scale (Fig. 2), considering single countries as the spatial unit of analysis. Studies conducted at national and subnational level were mainly focused on China, Italy and USA that were among the most affected countries in the earliest phases of the COVID-19 pandemic. With reference to the submission date, the selected literature is mainly clustered around mid-late 2020 on account of the initial/early worldwide interest of academia/science on COVID-19 during the very first period of the pandemic.

The selected papers took into account factors related to both physical and human geography. The factors related to physical geographical aspects comprise: (i) territorial variables, which are descriptive of the geographic location (latitude and longitude), and physical features of the area such as elevation and urbanization degree; and (ii) climatic variables including temperature, humidity, wind speed, precipitation and solar radiation. Air pollution was included among the climatic variables and proved to be an important environmental factor. As a matter of fact, a considerable number of reviewed studies examined the influence of both climatic/weather variables and air pollution on COVID-19 spread and health consequences, since those variables are closely linked one another [cf. 17, 18, 19 and references therein].

The latest studies on the COVID-19 pandemic [cf. 11,20] put a significant emphasis on human geographic aspects since they were found to have had a certain influence on the pandemic trends at a local level from both socio-demographic and socioeconomic aspects.

Based on the outputs of our review, the geographic variables were grouped into three macro-areas: (i) territorial variables, (ii) climatic/weather and environmental variables, (iii) socio-demographic and socioeconomic variables. The variables comprised in each macro-area are listed in Table 1.

Regarding health outcomes, COVID-19 data comprised a wide variety of items from which were grouped into three main categories: infections, hospitalisations and deaths. The infection category includes measures such as number of cases, incidence, prevalence, swab positivity, reproduction number (R_t), spread, transmission and related rates. The hospitalization category comprises measures such as hospitalization rates, hospital and ICU admissions (both COVID-19 positive or total inpatients). The death category relates to measures such as mortality and lethality (and related rates), fatality, absolute number of deaths, excess mortality. For a complete description of COVID-19 related outcomes found in reviewed articles please refer to Appendix A.

In the selected articles, we found that hospitalization variables were never studied independently/alone and had similar behaviour to infection and death in relation to geographic variables. Therefore, for the sake of clarity, we decided to present tabular data only on infections and deaths but detailed information on articles considering hospitalization and geographic variables can be found as supplementary data in Appendix A.

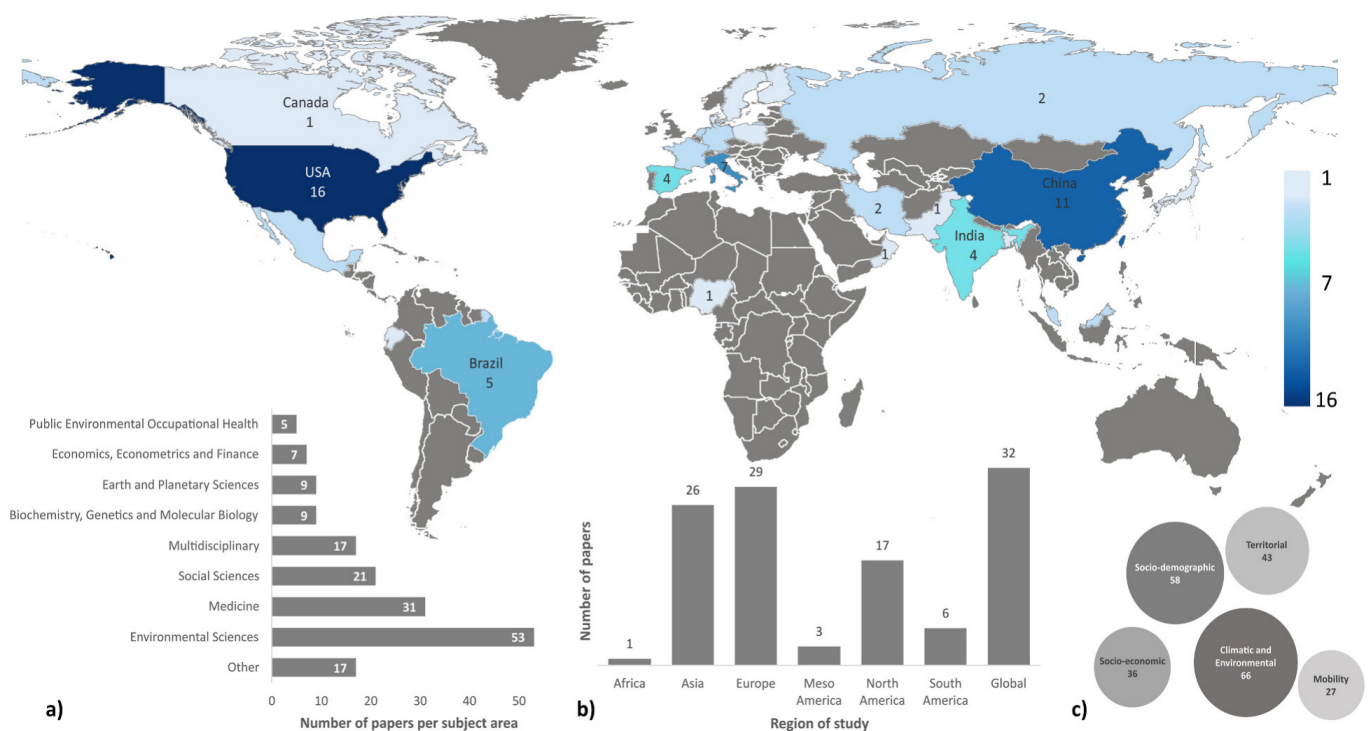


Fig. 2. Geographic distribution of the studied areas: (a) number of papers categorized by Scopus subject areas; (b) number of papers per region and global scale studies; (c) frequency of scientific articles per each group of variables considered.

Table 1
Geographic factors considered in the selected articles.

Geographic variable macro-area	Geographic variables
Territorial	Elevation
	Geographic location
	Land use
	Other territorial variables (e.g., distance from/density of human points of interest such as train stations, airports and other facilities)
Climatic/weather and environmental	Humidity
	Temperature
	Precipitation
	Wind speed
	Solar radiation
	Air pollution
	Other climatic/weather variables (e.g., hours of sunshine, evapotranspiration, permafrost coverage, Köppen classification group)
Socio-demographic and socioeconomic	Age and/or gender and/or ethnic group
	Total population and/or population density
	Mobility (e.g., human mobility trends, travel time, tourist flow)
	Economic stability (e.g., poverty, income, education, GDP, industrial production, trade intensity)
	Other socio-demographic variables (e.g., proportion of persons living in urban areas)
	Other socioeconomic variables (e.g., household occupancy/population, number of foreign citizens in residential building, households belonging to the lowest income category)

3.1. Territorial variables

Based on the analysis of the results presented in the reviewed articles, the influence of territorial variables on COVID-19 infections and deaths is discussed in the following sections and schematized in [Table 2](#).

3.1.1. Elevation

Many studies across the globe agree on the existence of a negative correlation between the severity of COVID-19 pandemic and the elevation, and show that infection rates are lower, and consequences less severe, in regions at high altitudes [52]. A medical review conducted by Millet et al. [53] speculated that this is related to the limited survival of the virus in such environments and to the biological mechanisms (e.g., high concentrations of erythropoietin, optimized cellular oxygenation and antioxidant systems, increased mitochondrial performance at the alveolar level) which may affect people living in those areas [see also 54 and references therein]. However, some authors highlighted that the association among lower case rate and mortality with increasing altitude may be confounded by factors such as population density, socioeconomic features, access to health care services etc. [55 and references therein].

Lower incidence and mortality of COVID-19 in high-altitude places has been outlined in several studies. This is the case of the work by Fernandes et al. [29] that investigated the effect of altitude on the incidence of COVID-19 in 154 Brazilian cities (with a population >200,000 inhabitants). The authors detected a negative correlation between altitude and incidence, being the latter lower in cities located at rather high altitudes (between 795 and 1135 m a.s.l.). Similarly, Gupta et al. [33] found that altitudinal variation had a negative relation with number of infections in India. Based on this finding, the authors suggested that regions located at low lying elevation in India are more prone to experience a higher COVID-19 transmission. The same correlation was found for China by Sun et al. [47] and Han et al. [34]. Han et al. [34] inferred that this negative correlation might be due to the interaction between the meteorological conditions and socioeconomic status which characterize the prefectures located at higher altitudes. Díaz Ramírez et al. [52] excluded elevation from the analysis of the patterns of excess mortality across regions in 36 countries around the globe because they found a multicollinearity between elevation and other variables, namely, share of youth, population density and air pollution (PM2.5).

3.1.2. Geographic location (latitude and longitude)

The relationship between geographic location and COVID-19 spreading appears quite controversial, having many authors found different evidence on its possible role.

Li et al. [38] conducted a study at global scale (154 countries) finding that the latitude has a negative correlation with COVID-19 cases and deaths. The authors inferred that this is mainly due to the latitude control on temperatures. On the contrary, they found that longitude has a positive correlation (i.e., direct correlation) with COVID-19 cases, deaths and case fatality rates. The authors did not provide any specific explanation of their finding. However, the fact that their statistical analysis revealed that longitude, as well as latitude, has a correlation with COVID-19 spread can be seen as further proof that there is a geographic signal in the evolution of the pandemic [cf. 56].

Conversely, Sarmadi et al. [43] recognised that latitude had a positive correlation between cases and deaths of COVID-19 at a global scale. The authors found evidence that at latitudes higher than 60° (referring to the northern hemisphere) there was a higher proportion of COVID-19 cases to population per 10⁵. According to their findings, this correlation may be due not only to the colder temperatures which favoured the survival of the virus (cf. section 3.2), but also to better socioeconomic conditions which imply, for

Table 2

Territorial variables considered in the selected literature: elevation (Elev), longitude (Long), latitude (Lat), urbanization (Urb) and their association (if any) with respective COVID-19 outcomes. The upturned arrow represents a positive association, the downturned stands for negative association and the horizontal bar is when no or non-statistically significant association was found.

Citation	Elev	Long	Lat	Urb	other	Country/Region of study	Territorial variable detail	COVID-19 outcomes
Amdaoud et al. [21]				X		Europe	Urban regions	Deaths ↑
Armillei et al. [22]				X		Italy	Peripheral areas	Deaths ↑
Ascani et al. [23]					X	Italy	Presence of an airport in the province	Infections ↑
Boterman [24]					X	Netherlands	Distance from train/motorway	Infections –
Chaves et al. [25]					X	Central America and Caribbean	Number of international territories/cities connected through the main airport	Death ↑
Chen et al. [26]					X	Hubei (China)	Distance by road from Wuhan	Infections ↓
Coker et al. [27]					X	Northern Italy	Distance in meters to the closest airport	Death ↑
Dixon et al. [28]				X		Indiana (USA)	Rural regions	Infections ↑
Fernandes et al. [29]	X					Brazil	Altitude	Infections ↓
Florida and Mellander [30]					X	Sweden	Presence of nursing homes	Infections ↑
Fortaleza et al. [31]				X	X	São Paulo State (Brazil)	Urban areas	Infections ↑
							Distance from the State capital	Infections ↓
							Proximity to main roadways/airports	Infections ↑
Grubestic et al. [32]					X	Wisconsin (USA)	Location of federal correctional facilities	Infections ↑
Gupta et al. [33]	X					India	Elevation	Infections ↓
Han et al. [34]	X					China	Elevation	Infections ↓
Hass and Jokar Arsanjani [35]					X	Europe	Number of amenities (e.g., cafes per cap., bars per cap.)	Infections ↑
He et al. [36]					X	Guangzhou (China)	Density of shopping malls, hotels, restaurants etc.	Infections ↑
Karim and Chen [37]				X		USA	Metropolitan areas	Infections ↑
Li et al. [38]		X	X			USA, World	Latitude	Infections and Deaths ↓
							Longitude	Infections and Deaths ↑
Murgante et al. [39]				X		Italy	Soil consumption	Infections and Deaths ↑
Nasiri et al. [40]				X		Tehran (Iran)	Commercial/residential land use	Infections ↑
Niu et al. [41]				X	X	Wuhan (China)	Building density, number of urban facilities	Infections ↑
							Distance from urban open space	Infections ↓
Ramírez and Lee [42]				X		Colorado (USA)	Urban regions	Infections ↑
Sarmadi et al. [43]			X			World	Latitude	Infections and Deaths ↑
Scarpone et al. [44]		X	X		X	Germany	Driving distance to train stations	Infections –
							Latitude	Infections ↓
							Longitude	Infections –
Sigler et al. [45]				X		World	Urbanisation rate	Infections ↑
							Urban density	Infections ↑
Sleszynski [46]				X		Poland	Degree of urbanization	Infections –
Sun et al. [47]	X		X			China	Altitude	Infections ↓
							Latitude	Infections ↓
Topîrceanu and Precup [48]					X	World	Inter- and intra-settlements travel distance	Infections ↑
Vaz [49]					X	Toronto (Canada)	Green spaces	Infections –
Wang et al. [50]				X	X	USA	Metropolitan areas	Infections ↑
							Proximity to nearest core airports	Infections ↑
Wheeler et al. [51]				X		SE Minnesota (USA)	Rural area	Infections ↑

example, a greater accessibility/availability of COVID-19 diagnostic kits.

Scarpone et al. [44] considered longitude and latitude in their models in order to identify spatial patterns for COVID-19 outbreak in the German counties. The results indicated no apparent correlation between longitude and incidence rates and a weak-to-moderate correlation with latitude. Sun et al. [47] found that the cumulative number of infected cases in China shows a linear negative relationship with latitude as well as infective spreading speed but, for the latter, this negative relationship is limited to the first phase of the pandemic (first 21 days). The same authors justified this negative relationship, in contrast with the findings of the other studies, by considering that it reflects a finer scale pattern, at provincial level, with uniform and strict lockdown policies.

3.1.3. Land use

Several studies, carried out at a country scale during the first wave of the pandemic, found a positive correlation with the increase in COVID-19 infections [31,37,42,50] and deaths [21] in urban and/or metropolitan settings with respect to rural ones. Schnake-Mahl and Bilal [57] confirmed this positive correlation after the first wave of the pandemic. Moreover, Sigler et al. [45] found evidence of contagion diffusion from urbanised to non-urbanised areas in a study conducted at a global scale. Furthermore, the authors found a

Table 3

Climatic variables considered in the selected literature: humidity (Hum), precipitation (Prec), solar radiation (SR), temperature (Temp), wind speed (WS) and their association (if any) with respective COVID-19 outcomes. The upturned arrow represents a positive association, the downturned stands for negative association and the horizontal bar is when no or not statistically significant association was found.

Citation	Hum	Prec	SR	Temp	WS	Country/Region of study	Climatic variable detail	COVID-19 outcomes
Ahmadi et al. [59]	X	X	X	X	X	Iran	Relative humidity Average precipitation Average solar radiation Average temperature Wind speed	Infections ↓ Infections – Infections ↓ Infections – Infections ↓
Azuma et al. [60]	X	X	X	X	X	Japan	Relative humidity Mean precipitation Sunshine hours Mean, maximum, minimum temperature Mean wind speed	Infections – Infections – Infections ↑ Infections ↑ Infections –
Baniasad et al. [61]	X			X		Global South (9 countries)	Relative humidity Daily average temperature	Infection and Death – Infection and Death –
Bilal et al. [62]	X	X		X		USA	Humidity Rainfall Average daily temperature	Infections ↑ Deaths ↓ Infections and Deaths ↓ Infection ↑
Cacho et al. [63]	X		X	X		Spain	Monthly average relative humidity Monthly average UVR Monthly average temperature	Deaths ↓ Infections and Deaths – Infections and Deaths ↑ Infections and Deaths ↓
Carleton et al. [64]	X		X	X		World (173 countries)	Daily average specific humidity Daily average UV radiation Daily average temperature	Infections – Infections ↓ Infections –
Chakraborti et al. [65]		X		X	X	World	Precipitation Minimum temperature Wind speed	Infections and Deaths – Infections and Deaths – Infections and Deaths ↓
Chen et al. [66]	X			X	X	World (15 countries)	Relative humidity Daily average temperature Daily average wind speed	Infections ↓ Infection ↑ Infections ↓
Cherrie et al. [67]			X			USA, England, Italy	Mean daily UVA	Deaths ↓
Coker et al. [27]				X		Northern Italy	Average temperature	Infections ↓
da Silva et al. [68]	X	X		X		Brazil	Daily air humidity Daily total precipitation Daily minimum, maximum temperature	Infections ↓↑ Infections ↓ Infections ↓↑
Díaz Ramírez et al. [52]				X		OECD and European countries	Average temperature	Deaths –
Fernandes et al. [29]	X					Brazil	Relative humidity	Infection ↑
Guo et al. [69]	X			X	X	World	Daily average relative humidity Daily average temperature Daily average wind speed	Infections ↓ Infections ↓ Infections –
Gupta et al. [33]	X	X	X	X	X	India	Specific humidity Annual rainfall Annual minimum, maximum, mean temperature Annual solar radiation Annual wind speed	Infections ↓ Infections ↓ Infections ↑ Infections ↑ Infections ↑
Han et al. [34]	X			X		China	Relative humidity, minimum relative humidity Daily minimum, maximum, mean temperature	Infections ↑ Infections ↑
Hass e Jokar Arsanjani [35]				X		Europe	Annual mean temperature	Infections –
Hofmeister et al. [70]			X			World	Global Horizontal Irradiance	Infections ↑
Iqbal et al. [71]	X			X		World	Relative humidity Average maximum, minimum temperature	Infections ↑ Infections ↑
Irfan et al. [72]				X		Pakistan	Daily mean temperature	Infections ↓

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Table 3 (continued)

Citation	Hum	Prec	SR	Temp	WS	Country/Region of study	Climatic variable detail	COVID-19 outcomes
Isaia et al. [73]	X		X	X		Italy	Relative humidity UV irradiance Monthly mean temperature	Infections and Deaths – Infections and Deaths ↓ Infections and Deaths ↓
Islam et al. [74]	X		X	X	X	World	Relative, absolute humidity UV index Daily maximum temperature Wind speed	Infections ↑ Infections – Infections ↑ Infections ↓
Jamshidi et al. [75]				X		USA, World	Equivalent temperature (combined effect of temperature and humidity)	Infections ↓
Kubota et al. [76]		X		X		World	Mean precipitation Mean temperature	Infections ↑ Infections ↓
Li et al. [77]				X		World	Daily temperature, temperature seasonality	Infections ↓
Li et al. [38]	X			X		USA, World	Relative humidity Medium, high, low temperature	Infections and Deaths ↓↑ Infections and Deaths ↓
Liu et al. [78]	X			X		World	Specific humidity Near surface temperature	Infections ↓ Infections and Deaths ↓
Ma et al. [79]	X			X		Wuhan (China)	Relative humidity Daily average temperature, diurnal temperature range	Deaths ↓ Deaths ↓
Mandal and Panwar [80]				X		World	Monthly average temperature	Infections ↓
Méndez-Arriaga [81]	X	X		X		Mexico	Specific humidity at 1000 hPa Monthly mean precipitation Highest, lowest and mean temperature	Infections ↑ Infections ↑ Infections ↓
Merow and Urban [82]	X		X	X		Australia, Canada, China, USA	Relative humidity, absolute humidity Total incoming UV radiation 14-days average temperature	Infections ↓ Infections ↓ Infections ↓
Meyer et al. [83]	X			X		World	Daily relative humidity Daily average temperature	Infections – Infections ↓
Moozhipurath et al. [84]	X	X	X	X		World (183 countries)	Daily ultraviolet index (UVI)	Deaths ↓
Paez et al. [85]	X			X		Spain	Relative humidity Mean temperature Daily hours of sunshine	Infections ↓ Infections ↓ Infections ↑
Pan et al. [86]	X		X	X	X	World (8 countries)	Relative humidity Daily erythemally weighted daily dose Daily mean temperature Wind speed	Infections – Infections – Infections – Infections –
Pramanik et al. [87]	X			X	X	Russia	Relative humidity Average temperature Wind speed	Infections ↑ Infections ↓ Infections ↑
Prata et al. [88]				X		Brazil	Annual average of temperatures compensation	Infections ↓
Rodríguez-Pose and Burlina [89]		X		X		Europe	Average precipitation 2019 Average temperature 2019	Deaths ↓ Deaths ↓
Sarkodie and Owusu [90]	X	X		X	X	World (20 countries)	Relative humidity Precipitation Maximum, minimum temperature Wind speed	Deaths ↓ Deaths ↓ Infections and Deaths ↓ Infections and Deaths ↑ Infections and Deaths ↓ Infections and Deaths ↑
Sarmadi et al. [43]				X		World	Average temperature	Infections and Deaths ↓
Sergeenko [91]			X				UV-index	Infections ↓
Shao et al. [92]				X	X	World (47 countries)	Mean temperature	Infections ↓
Sobral et al. [93]		X		X		World	Precipitation Maximum, minimum, average temperature	Infections and Deaths ↑ Infections ↓ Infections ↓
Su et al. [94]	X			X	X	World (277 countries)	Relative humidity Air temperature	Infections ↓ Infections ↑ Infections ↓

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Table 3 (continued)

Citation	Hum	Prec	SR	Temp	WS	Country/Region of study	Climatic variable detail	COVID-19 outcomes
Tang et al. [95] Tzampoglou and Loukidis [96]	X	X	X	X		USA World	Wind speed Daily sunlight UV radiation dose Monthly average relative humidity Cumulative precipitation Monthly average atmospheric temperature	Infections ↑ Infections ↓ Infections and Deaths – Infections and Deaths – Infections and Deaths ↓
Yang et al. [97]	X	X		X	X	China	Relative humidity Total precipitation Daily maximum, minimum, range, average temperature Average wind speed	Infections ↑ Infections – Infections ↑ Infections ↓↑
Yuan et al. [98]				X	X	World (127 countries)	Daily average temperature Average wind speed	Infections ↓ Infections ↓

positive correlation with infections and urbanisation rate/density, showing however that this correlation decreases with time. Dixon et al. [28] studied the spread of the pandemic among rural areas of the Indiana state (USA). They found that by autumn 2020 hospitalization and mortality rates in rural areas exceeded those of urban areas may be because of few ICU beds and lack of healthcare staff in rural regions. On the contrary, the investigation by Sleszynski [46] suggested that there is not a directly proportional correlation between the increase of COVID-19 infections in Poland and the degree of urbanization.

Based on the results of local spatial autocorrelation carried out at provincial scale in Italy, Murgante et al. [39] inferred a positive correlation between urbanization and particularly the lack of green spaces and the high number of positive cases and deaths of the earliest phases of COVID-19 pandemic in Lombardy [cf. 58]. Similarly, Vaz [49] considered the presence of green spaces as a variable which may have limited COVID-19 spreading within the districts of Toronto (Canada); however, the author did not find any significant correlation with COVID-19 density (number of cases per population considering the area of the respective administrative unit) and such variable. A spatial analysis enabled Nasiri et al. [40] to show that in Iran the number of COVID-19 hospitalised cases were higher in commercial and residential areas. By means of a clustering analysis, Niu et al. [41] inferred that floor area ratio and building density in China are positively correlated with COVID-19 middle-aged and elderly patients. The study by Wheeler et al. [51] analysed the spread of the pandemic among Minnesota (USA) rural counties which were found to host a significant number of COVID-19 hotspots. The presence of hotspots was attributed to socioeconomic disparities among Minnesota rural population.

3.2. Climatic variables

Based on the results of the reviewed articles, the influence of climatic/weather variables and air pollution on the spread of COVID-19 is discussed in the following sections and schematized in Tables 3 and 4 respectively.

3.2.1. Humidity

Among the climatic variables, humidity is considered one of the most relevant factors influencing COVID-19 spread and its consequences [cf. 56,59,62,96].

Most of the studies analysed in this review identified a negative association between humidity and COVID-19 infections and/or deaths at a global scale [69,71,78,79,82,83,90]. In particular, Iqbal et al. [71] inferred that this indirect association may be due to the fact that low relative humidity may prolong the survival of COVID-19 virus on surfaces, whilst Liu et al. [78] supposed that aerosol transmission, as one of the COVID-19 potential transmission routes, can be enhanced in low humidity environments. In fact, the predominant mode of viral particle transmission involves adherence to droplets. In humid areas, high humidity causes the droplets from an infected person to combine into larger drops that rapidly fall to the ground due to their increased weight [97,102–104]. Conversely, in arid regions, such as deserts, especially in summer, intense evaporation and high temperatures desiccate the virus, diminishing metabolic enzyme activity [105]. Worth mentioning are also the findings of Islam et al. [74] who identified a range among which the absolute humidity is positively associated with higher rates of COVID-19 cases, that is between 5 and 10 g/m³. Chen et al. [66] showed that the number of daily new cases was correlated with relative humidity with a 7-day lag from the exposure day, and that COVID-19 is easily spread under relative humidity between 70 % and 80 %.

A correlation between humidity and COVID-19 spread was found at a country scale in Brazil [29,68], China [34,97], India [33], Iran [59], Mexico [81], Russia [87], Spain [85] and the USA [62]. Among these studies, there is no agreement on the type of correlation between humidity and COVID-19 spread, e.g., Fernandes et al. [29], Han et al. [34] and Méndez-Arriaga [81] stated this correlation as positive, whilst Ahmadi et al. [59] and Paez et al. [85] as negative. Heterogeneity of results occurred also at a country level; for example, for six Brazilian capital cities humidity correlated negatively with COVID-19 infections whilst the opposite occurred for two others [68]. Similarly, Yang et al. [97] suggested that in China the type of correlation between relative humidity and COVID-19 transmission depends on the season (i.e., warm season or winter) and physiography of the region considered (i.e., coastal or arid inland). Worth mentioning is the study by Gupta et al. [33] from which it was observed that an absolute humidity range of 4–6 g/m³

Table 4

Air pollutants considered in the selected literature and their association (if any) with respective COVID-19 outcomes. The upturned arrow represents a positive association, the downturned stands for negative association and the horizontal bar is when no or not statistically significant association was found.

Reference	PM10	PM2.5	NO ₂	SO ₂	CO ₂	O ₃	Country/region of study	Environmental variable detail	COVID-19 outcome
Azuma et al. [60]		X	X					Five-day mean values	Infections –
Baniasad et al. [61]		X					Global South (9 countries)	Daily value for the period March–December 2020 (short term analysis); Average value for the period 1998–2017 (long-term analysis)	Deaths ↑
Bilal et al. [62]		X					USA	Daily value for the period 2 March - 17 September 2020	Infections, deaths ↑
Chakraborti et al. [65]		X	X		X		World	Mean annual exposure (period not specified)	Infections ↑
								Nitrous oxide emission (metric ton)	Deaths ↑
								Total CO ₂ emission; CO ₂ emission per capita	Deaths ↑
Coker et al. [27]		X					Northern Italy	Average of the annual mean for the period 2015–2019	Deaths ↑
Deguen and Kihal-Talantikite [99]			X				France	Average of the annual mean for the period 2014–2018	Deaths ↑
Díaz Ramírez et al. [52]		X					OECD and European countries	Mean value of 2019	Infections, deaths ↑
Han et al. [34]	X	X	X	X	X		China	PM10, PM2.5, NO ₂ , SO ₂ , CO ₂ - Daily values to which a lag of 1 and 9 days was applied	Infections ↑
Hass and Jokar Arsanjani [35]	X	X	X				Europe	PM10, PM2.5, NO ₂ - Average of the annual mean for the period 2019–2020	Infections ↑
Isaia et al. [73]	X						Italy	Average of the annual mean for the period 2015–2019	Infections, deaths –
Konstantinou et al. [100]		X	X				England (UK)	PM2.5, NO ₂ - Average of the annual mean for the period 2014–2018	Deaths ↑
Ma et al. [79]	X	X	X	X	X	X	Wuhan (China)	PM10, PM2.5, NO ₂ , SO ₂ , CO ₂ , O ₃ - Daily value for the period 20 January –29 February 2020	PM10 – Deaths ↓ PM2.5 – Deaths ↓ NO ₂ – Deaths ↑ SO ₂ – Deaths ↓ CO ₂ – Deaths – O ₃ – Deaths –
Middya and Roy [101]		X	X	X			India	PM2.5, NO ₂ , SO ₂ - Daily data averaged across the period 2016–2020	Deaths ↑
Murgante et al. [39]	X	X	X		X	X	Italy	PM10, PM2.5, NO ₂ , CO ₂ , O ₃ - Annual average values for the period 2019–2020	Infections, deaths ↑
Rodríguez-Pose and Burlina [89]		X			X		Europe	PM2.5 - Value of 2016 CO ₂ - Value of 2010	Deaths ↑
Vaz [49]		X	X			X	Toronto (Canada)	PM2.5, NO ₂ , O ₃ - Value of 2011	Deaths –

mainly influenced the spread of COVID-19 in India. This absolute humidity range is partially comparable with the one identified by Islam et al. [74] at a global scale. Furthermore, it has been proven that changes in air humidity can affect respiratory cells and impact mucosal clearance [103]. Therefore, alterations in air humidity can increase the risk of virus exposure for humans, and the severity of infections depends on specific climatic conditions in which changes in air humidity occur [79,97,87,63].

3.2.2. Temperature

The selected literature clearly showed the influence of temperature on COVID-19 spread, most of the authors being convinced that a negative correlation can be inferred. Some authors observed that COVID-19 is less stable at high temperatures [cf. 106]. At the same time, lower temperatures in winter enhance the survival time of viral particles in the atmosphere, facilitating transmission [97,81,63]. However, rising temperatures may be associated with behaviours that increase human exposure to the virus, e.g., increased human mobility and gathering of people for recreational purposes [60,92,107–109]. From a medical point of view, Irfan et al. [72] noted that exposure to colder temperatures adversely affects the immune function of the respiratory tract (see also [63,79,87,97]). In cold weather, the ability of certain lung cells to engulf and remove harmful particles significantly decreases, weakening the body's defence system [110,111].

In the investigated literature, only few authors found a positive association between global COVID-19 spread and deaths and temperature [82,74,65]. Chakraborti et al. [65] collected data on COVID-19 cases and deaths in 180 countries across the globe, finding a positive correlation between minimum temperatures and COVID-19 deaths, whilst Islam et al. [74] found a positive association with 14-day-lagged temperature and COVID-19 confirmed cases. In their study, which considers data from 31 countries all around the world and 428 Chinese cities and districts, Chen et al. [66] found that (i) a temperature range from 5 to 15 °C favours the spread of COVID-19 and (ii) the association between the number of newly confirmed cases correlated best with air temperature with a lag of 3–7 days. Jamshidi et al. [75] found that global highest infections were within the range of –10–0 °C and the lowest in the 20–30 °C range. Li et al. [38] inferred that medium temperatures were a positive predictor of COVID-19 deaths, whilst low temperatures were a negative predictor.

Similarly, several authors found a negative association with the number of COVID-19 cases at a global scale [69,92,76,80,93,98] and deaths [43,96,71,90]. The negative association was generally explained as the warmer temperatures diminish the survival and transmission of the virus [cf. 90], and by the fact that the immune system efficiency decreases at lower temperatures [43]. Li et al. [77] suggested that colder seasons discourage outdoor activities, increasing the probability of being infected indoors. Rodríguez-Pose and Burlina [89] performed a study across European countries with reference to the first wave of COVID-19 discovering a negative correlation with average temperature and excess mortality.

As for single countries, Bilal et al. [62] statistically determined that average daily temperatures in the USA had a positive association with daily new cases and a negative association with daily new COVID-19 deaths. Méndez-Arriaga [81] in Mexico found that temperature negatively associated with the local confirmed COVID-19 cases. Cacho et al. [63] and Paez et al. [85] found a negative association in Spain. In Italy, a negative association between temperatures and COVID-19 deaths was found by Coker et al. [27] and Isaia et al. [73]. An earlier study by Prata et al. [88], focusing on the 27 Brazilian capital cities, showed a negative correlation between temperature and COVID-19 cases below 25.8 °C. More recently da Silva et al. [68], considering the same case studies, found that the statistical significance and the type of correlation between the number of COVID-19 cases and temperature varied depending on the region where the capital cities were located. Gupta et al. [33] discovered a positive relationship with temperature and number of infections in their analysis on all the Indian states. Irfan et al. [72] found that temperature was inversely correlated with COVID-19 cases in Pakistan. As for China, the same type of correlation with COVID-19 deaths was found by Ma et al. [79], while the findings by Han et al. [34] suggested that the number of COVID-19 cases tended to increase with extreme temperatures. Moreover, according to Yang et al. [97], who studied the relationship between meteorological factors and COVID-19 transmission in seven Chinese cities, the influence of temperature (as well as of other meteorological factors) depends on the geographic location. In particular, they stated that, in the arid inland region, the warm season limited COVID-19 transmission and minimum temperatures accelerated COVID-19 transmission. Finally, Pramanik et al. [87] found that temperature had a varied role in influencing the number of COVID-19 cases across Russia. For example, in the humid continental region, the number of cases was mainly linked to temperature seasonality, whilst mean temperature diurnal range was found to be the main influencing factor in the sub-arctic region. In both cases the correlation with temperature is however positive.

3.2.3. Wind speed

The role of wind speed in influencing the geography of COVID-19 is twofold. Chakraborti et al. [65] performed a study at global scale (180 countries) during the first half of 2020 and found that for Europe wind speed was one of the variables which showed the highest relative negative influence on COVID-19 cases. Guo et al. [69] performed a study considering COVID-19 confirmed cases and deaths from 190 countries during the earlier pandemic phases (January–April 2020) investigating the role of meteorological factors on COVID-19 incidence, and they found a weak negative correlation with wind speed.

A 7-day-lagged and 14-day-lagged global analysis revealed that for the latter there is a significant negative correlation between wind speed and COVID-19 cases [74]. A negative association between wind speed and daily new cases was also discovered by Yuan et al. [98]. In 20 countries across the globe, the association with daily recoveries was found as negative whilst the one with confirmed cases and deaths was found as positive [90]. Su et al. [94] also suggested a positive relationship between wind speed and number of confirmed cases.

At a country scale, Chen et al. [66] found that the number of confirmed new cases in the city of Wuhan (China) correlated well with wind speed on the exposure day (no temporal lag) and that a peak of cases was recorded when wind speed was 1.88 m/s. Moreover, the

authors suggested that COVID-19 spread easier under wind speed ranging between 1.5 and 4.5 m/s. In China, Yang et al. [97] found that the influence of wind speed on infections varied according to geographic locations. For example, a significant positive influence was found in Beijing, but not in other cities. The authors tried to explain the nature of this relation by stating that wind speed turbulence increases the spread distance and the virus diffusion rate in the atmosphere. As wind speed is positively related with the speed and distance of virus transmission in the atmosphere, and the virus is also adsorbed on suspended particles that accumulate near the ground, an increase in wind speed is likely to accelerate the spread of COVID-19 [90,97,63]. As for other countries, wind speed showed a significant and inverse relationship with COVID-19 infections in Iran [59], whilst the same correlation was found to be positive in India [33].

3.2.4. Precipitation

In the analysed literature, precipitation is rarely taken into account and this is accompanied by the lack of a common agreement on its role in influencing COVID-19 spread and deaths. Kubota et al. [76] suggested that precipitation is relevant to habitat suitability for the virus.

Globally, the conclusion of studies which investigated the impact of precipitation on COVID-19 pandemic are varied depending on the outcome variable and the study period considered. Kubota et al. [76] and Sobral et al. [93] identified a positive correlation of the number of COVID-19 cases with precipitation, in the earlier phases of the pandemic; on the contrary, Sarkodie and Owusu [90] discovered a negative association with both infections and deaths. Instead, neither significant nor weak correlation has been identified with COVID-19 deaths [96,93].

At a national level, precipitation showed varied relationships with COVID-19 depending on the region considered as well as on the considered health outcomes. Gupta et al. [33] found a negative association with COVID-19 number of infections in India. The analysis conducted by Bilal et al. [62] suggested that precipitation was among the most significant factors influencing COVID-19 pandemic in the 10 greatly affected states of the USA. The study also showed that daily new cases and deaths had a negative association with this weather variable. A negative correlation was found also for some capital cities in Brazil [68] and Europe [89]. On the contrary, a study focused on 31 states and the capital of Mexico outlined that daily local COVID-19 confirmed cases and local transmission ratio had a positive association with precipitation [81]. No significant correlation was found by Ahmadi et al. [59] in Iran and by Yang et al. [97] in China.

3.2.5. Solar radiation

Studies carried out at both global and national levels suggested that Solar UV radiation may have an impact on the development of COVID-19 through the positive effect of vitamin D on the immune system. In fact, UV rays play a crucial role in converting provitamin D3 into the active form vital for immune defence mechanisms [63,112–114]. Moreover, increased solar radiation, particularly in the UV-B region, may serve as a disinfectant for non-porous materials, potentially reducing the spread of the virus.

In this context, at a global level, a negative association of COVID-19 cases [82,64] and deaths [84] was found. This negative correlation was confirmed also at a national level [33,59,73,91]. In contrast, Hofmeister et al. [70] suggested that the increases in COVID-19 cases in spring and summer may be linked to high solar irradiance, causing ultraviolet immune suppression as one means of amplification. Only a few studies discovered no correlation between solar radiation and COVID-19 at global [74,86] and country scales [63].

3.2.6. Air pollution

Literature on the topic suggests that air pollution could act as a carrier of the viral particles and a factor which aggravates COVID-19 severity [115–121]. In particular, it has been considered as a potential explanatory variable for COVID-19 geography in 15 studies. The main air pollutants considered were PM10, PM2.5 (fine particle matter with a diameter smaller than 10 and 2.5 μm respectively), nitrogen dioxide (NO_2), sulphur dioxide (SO_2), carbon dioxide (CO_2) and ozone (O_3). The possible correlations between air pollutants and COVID-19 outcomes are reported in Table 4. According to the literature review by Copat et al. [116] regarding the influence of air pollution on COVID-19 infectivity and lethality, PM2.5 and NO_2 are the most influent pollutants, and to a lesser extent PM10. Worth mentioning is that Deguen and Kihal-Talantikite [99] found NO_2 to be a good indicator for traffic-related air pollution since it correlates well with other traffic-related air pollutants, (i.e. particulate matter), and chose it for their analysis due to its higher spatial variability.

At a global scale, Chakraborti et al. [65] found that environmental pollution had a strong causal impact on COVID-19 cases in Asian countries. In particular, NO_2 and PM2.5 concentration was significantly correlated with total cases and deaths. The same study showed that CO_2 emissions had a certain influence in American countries whilst in African countries, considering COVID-19 deaths as the response factor in the modelling, only PM2.5 and CO_2 emission proved to be statistically significant. It was also discovered that NO_2 was positively correlated with deaths in Oceania.

Baniasad et al. [61] investigated the long-term effect of air pollution on COVID-19 health outcomes for eight countries of the Global South considering PM2.5 data over the period 1998–2017. The authors did not find any significant correlation between the air quality and a possibly higher risk of COVID-19. They suggested that it is necessary to consider a greater scale, e.g., at a subnational level, in order to better investigate this association.

At a country scale, the statistical analysis of Bilal et al. [62] highlighted a negative association of PM2.5 with daily new cases as well as COVID-19 daily fatalities in the USA. On the contrary, the analysis by Coker et al. [27] suggested a positive association of ambient PM2.5 concentration and excess mortality in northern Italy. In France, the analysis carried out by Deguen and Kihal-Talantikite [99] revealed a significant correlation between long-term exposure to NO_2 and COVID-19 incidence and hospitalised cases. As for China, the

analysis by Han et al. [34] revealed a positive correlation of PM2.5 with infected cases. Hass and Jokar Arsanjani [35] found that PM10 is one of the variables with higher significance in the northern European countries. In England (UK), COVID-19 mortality risk positively correlated with long-term exposure to NO₂ and PM2.5 [100]. A strong positive correlation was found mainly in the western part of India between PM2.5 and COVID-19 deaths, whereas in the other parts of the country such a relationship was not observed [101]. Finally, Rodríguez-Pose and Burlina [89] found a positive correlation of COVID-19 deaths with PM2.5 in their study at a European level.

3.3. Socio-demographic and socioeconomic variables

As far as human geography factors are concerned, the reviewed articles showed a significant influence of demographic and socioeconomic features on COVID-19 infections and deaths, which is discussed in the following sections.

3.3.1. Age

The age structure of a population may help in explaining differences in the severity of COVID-19 consequences, e.g., in terms of hospitalization and fatality rates throughout regions and on how transmission took place [21]. It is clear that age is an important parameter to be considered in studying a pandemic. In fact, it has been estimated that 95 % of COVID-19 deaths in Europe were among people aged over 60 years old being more than 50 % $\geq$ 80 years old [21,30].

Only a few studies considered age structure in their analysis at a global scale. Chakraborti et al. [65] found that for 180 countries COVID-19 infection risk was high with age >80 . Li et al. [38] found that a high percentage of the population less than 10 years old was a negative predictor of the number of COVID-19 cases in 154 countries. Su et al. [94] reported that the percentage of people aged over 65 can explain approximately 50 % of variation in transmission rate across the 277 regions. Finally, Tzampoglou and Loukidis [96] found a strong correlation between both the total cases and the total deaths per million of inhabitants with the increasing median age of the population.

At a national level, Middya and Roy [101] observed that the total number of persons aged 50 years or more positively correlated with COVID-19 mortality in India. On the contrary, Paez et al. [85] stated that the percentage of older people was negatively associated with incidence in Spain. The authors inferred that this finding might have been due to the fact that older adults may tend to have a lower level of social contacts/higher level of social distancing than younger people. This evidence is also confirmed by Rahman et al. [122] who found that the infection rate was the highest among those aged 21–50 years. The authors also underlined that this did not contradict the evidence that older adults are more vulnerable, since older people mortality rates are the highest among all age groups. This finding actually indicates that older people's presence within a community tends to lower virus transmission.

As for studies conducted at a more local scale, Lopez-Gay et al. [123] found that in Barcelona higher rates of infection characterized geographical units that had more residents aged 70 years, and that the percentage of people older than 70 years was positively correlated with COVID-19 infection rates. Similarly, Coker et al. [27] showed that COVID-19 infection risk was high with age >80 in northern Italy. In New York (USA), percentages of people aged 18–44 and 45–64 were negatively associated with COVID-19 death rate [124].

3.3.2. Population size and density

Since the earlier phases of the pandemic, population size and density were considered to play a central role in explaining the geography of COVID-19. The pandemic has in fact hit harder the highly connected global cities [cf. 30] which are characterized by high frequency of social interaction that can surely be a driver of rapid contagion [23,125]. A total of 50 studies examined data relative to population size or population density to analyse possible relationships with COVID-19 infections and deaths. Twenty-three of these studies considered population density whilst the other 27 took into account the total population of the spatial unit of analysis (e.g., state, county, region). Actually, the above-mentioned positive correlation was confirmed by many of the studies analysed in our literature review, both at global and national/subnational levels.

At a global level, it was found that population size was directly associated with case-fatality rate [126] and number of infections [45,75,76]. The factors that may have determined this direct correlation are: i) the higher strain on the healthcare system, ii) the higher risk of transmission, and/or iii) scant population health conditions in highly populated countries. On the contrary, the correlation of population density with COVID-19 infections and deaths is not univocal. For example, some authors found no significant correlation between population density and transmission and fatalities [38,126], whilst Díaz Ramírez et al. [52] found a strong association with mortality excess in their study focused on OECD and European countries. The discordant results are perhaps due to the fact that the population density was calculated by dividing population size by the country extent, being in many countries the population not homogeneously distributed (see also [96]).

At a country scale, it was confirmed the positive correlation between population size and/or density. For example, in Iran Ahmadi et al. [59] and, specifically for the city of Tehran, Nasiri et al. [40] found a significant and direct relationship between the number of infected people and population density. In São Paulo State (Brazil), Fortaleza et al. [31] discovered a higher influence of demographic density on COVID-19 spread during the earlier phases. Similarly, population density showed a positive correlation with COVID-19 spread in Malaysia [127,128]. The same correlation was found for China [34], Nigeria [129] and India [33,101,130]. Holmager et al. [131] reported that high population density in Denmark as well as large households, seemed to increase the risk of COVID-19 spread. A positive association between COVID-19 deaths and population density [42,50] and county population [37] were found in the USA.

On the contrary, no or unclear correlation between population and the geographic variation of COVID-19 was found in Italy [23,

27], The Netherlands [24] and Sweden [30].

It is worth mentioning that not in all the studies analysed population was used as a conditioning factor for COVID-19 geography; in fact, in some of them, population data were used to normalize infections and deaths [cf. 75] or to assign weights to the investigated spatial unit of analysis [22,132]. In some other studies, population was also considered as a confounding factor [83,133].

3.3.3. Economic stability (e.g., poverty, income, education, GDP, industrial production, trade intensity)

Admittedly, welfare and income dimensions had a major role in driving the pattern of COVID-19 cases and deaths around the world.

The Gross Domestic Product (GDP) well represents the country wealth and GDP per capita was taken into account as an explanatory variable in many of the analysed studies. In fact, at least during the first phase of the pandemic, the importance of GDP for the geography of COVID-19 could be inferred by observing that the regions hardest affected by the pandemic were characterized by relatively higher GDP. This was the case of northern Italy, where the provinces most affected by the pandemic were those characterised by a GDP above the national average [23]. Statistical analysis conducted at the national level for Chinese prefectures confirmed the positive correlation between the GDP [34] and, more broadly, economic development [134], with the number of confirmed COVID-19 cases. Paez et al. [85] estimated that higher incidence was associated with higher GDP per capita in Spain. At a global level, almost all the investigated studies agree on the existence of a positive correlation between country GDP per capita and COVID-19 infections [76, 126] and deaths [43,65]. This is probably due to the fact that high GDP implies more intense international economic exchanges and consequently higher levels of global interconnection among individuals increasing the possibilities of virus transmission [135]. This is supported also by some studies which conclude that trade intensity showed a positive correlation with COVID-19 infections and deaths [25,136].

The role of income in affecting the distribution of COVID-19 was investigated mainly at sub-national level. Studies conducted in Sweden and in Finland [cf. 30,137] found that COVID-19 cases were more concentrated in the less advantaged areas. The impact of unemployment rate on COVID-19 at country level is twofold. A negative correlation was found in Italy and the USA regarding the number of infections and deaths, respectively [37,23] whilst a positive correlation was found with infections in Germany. The unemployment status implies no human interactions within the working environment as well as reduced necessity to commute e.g., by using crowded public transport, thus less chance for virus transmission; on the contrary, a lower unemployment rate implies poor economic conditions which are often accompanied by scant access to medicine and health assistance.

3.3.4. Human mobility

Owing to the high transmissibility of COVID-19, many studies in literature analysed the effects of human mobility on infections and/or death rates. Topîrceanu and Precup [48] modelled epidemic diffusion integrating population characteristics with human mobility, finding that the number of infections was more sensitive to the increase in travel distance between settlements (positive

Table 5

Main methods and tools applied in the 112 reviewed studies. Classification of methodology macro-area and area is based on the work by Franch-Pardo et al. [11]. In the second column, the figures in the brackets represent the numbers of papers which have applied a methodology included in the respective area.

Methodology macro-area	Methodology area (number of articles)	Specific methods and/or tools
Mapping	Choropleth mapping (56)	Mapping spatial distribution of COVID-19 data (e.g., number of infections/deaths per administrative unit) and geographic factors (e.g., temperature, rainfalls, population density)
	Hotspot and cluster mapping (19)	Mapping spatial autocorrelation based on hotspots and cluster analysis (e.g., LISA maps)
	Dot distribution mapping (11)	Mapping locations of COVID-19 cases or points of interest
	Spatial heat mapping (11)	Mapping geographic factors (e.g., temperature, precipitation) and COVID-19 spread (e.g., density of infections, COVID-19 risk) through interpolated surfaces
	Flow mapping (4)	Mapping mobility and urban networks
Statistical analysis/modelling	Aspatial models (49)	Pearson Correlation; Poisson regression; Kendall and Spearman test; Negative binomial model; Analysis of variance (ANOVA); Exponential regression; Zero-inflated negative binomial (ZINB) regression; Quantile regression model; Generalized additive model (GAM)
Spatial statistics	Machine learning (10)	Random Forest algorithm; LASSO regression; Gradient Boosting Decision Tree
	Hotspots and clustering (22)	Spatial autocorrelation (Global Moran Index, Local Indicator of Spatial Association, LISA); Getis-Ord Gi; Kernel density estimation; Spatial and Space-Time Scan Statistics
	Spatial regression (13)	Geographical weighted regression (GWR); Ordinary Least Square (OLS) model; Spatial error model (SEM); Spatial lag model (SLM); Conditional autoregressive (CAR) model; Spatial Seemingly Unrelated Regressions (SPSUR); Autoregressive Integrated Moving Average (ARIMA)
	Interpolation and geostatistics (3)	Inverse Distance Weighting
Multicriteria analysis	Other spatial models (5)	Global geographical gravity models
	Multicriteria analysis (12)	Analytical hierarchical process; Hierarchical cluster analysis; Bayesian hierarchical Poisson log-linear models; Bayesian hierarchical space-time SEIR model; Geo-hierarchical population mobility model; Time-geography model based on space-time discs and control points; Grey relational analysis model (GRA)

association), rather than to the travel frequency.

Generally speaking, it was observed that government-imposed mobility restrictions were successful in mitigating COVID-19 transmission [61,138]. At a global level, a positive correlation was found between human mobility and COVID-19 infections [45, 92,75,76,139]. At a national scale, several studies found that mobility reduction generally implies a restraint on infections [59,140, 141]. A positive correlation between mobility and excess mortality was also found in Italy [23] and Ecuador [142].

Established that mobility is a very important variable in explaining the geography of COVID-19, retrieving mobility data is often challenging [143]. Considering this, it is worthy to mention that for the studies conducted at a global scale, mobility data were mainly retrieved from Google's or Apple's COVID-19 Community Mobility Reports [52,92,65,138]. At a national level, where a granular scale was required, human mobility data were often provided by mobile phone datasets [e.g., 124,142]. Additionally, Ascani et al. [23] studying the effect of mobility on the spread of COVID-19 pandemic between Labour Market Areas (LMAs) used Facebook Disease Prevention Maps data based on tracking Facebook users' movements.

In other studies, conducted at both global and country scales, mobility was measured by passenger traffic in airports [30,65,89, 144], finding a positive correlation with COVID-19 outcomes.

3.4. Spatial and temporal resolution, and statistical methodological approach

Among the revised studies, 71 were conducted at sub-national level considering varied spatial units of analysis (e.g., counties, provinces, districts, municipalities, cities) almost exclusively based on administrative boundaries. This was due to the fact that COVID-19 data, climatic/weather and environmental data, as well as the socio-demographic and socioeconomic ones, were mostly provided for administrative units (e.g., regions, provinces, municipalities). In this context, the variations that can significantly affect such data within a certain administrative unit are often disregarded [145]. This may prevent the understanding of the significant uneven patterns of COVID-19 pandemic which in fact overcame administrative boundaries.

Only a few studies considered spatial units not based on administrative boundaries. For example, Ascani et al. [23] studied the geography of COVID-19 at a local level in Italy by considering labour market areas based on commuting data as spatial units of analysis. Similarly, Carballada and Balsa-Barreiro [2] based their analysis on mobility areas in Spain. Only a few studies were performed at a neighbour level [cf. 44,123,140] counting on granular data on COVID-19 and socio-demographic/socioeconomic features.

With reference to the temporal resolution, most of the studies were relevant to the first phases of the pandemic, during the year 2020, and mainly focused on a relatively short time frame, varying from 30 to 180 days, whilst only few studies exceeded one year of data collection and analysis [50,65,133]. If, on the one hand, the level of spatial granularity of the studies was modest, on the other hand, we encounter that the analyses were based on a high temporal resolution mainly including daily or weekly data. This reflects the wide availability of daily or weekly open data concerning both COVID-19-related outcomes (e.g., available at Our World in Data or John Hopkins University Coronavirus Research Centre websites), and geographic factors (e.g., available at Copernicus Climate Change Service and NASA Climate Data Service repositories).

The literature review carried out showed that integrating both space and time in the analysis of COVID-19 spread is a challenging issue. In most of the studies, the time dimension is considered by comparing the results of the analysis at discrete individual time points. Only few studies integrated both temporal and spatial dimensions in their analysis and/or models [e.g., 66,68,76,146].

Different approaches in trying to decipher the role of geographical and environmental factors in the spreading of the COVID-19 pandemic were applied including both spatial and aspatial techniques. The spatial distribution of COVID-19 data (e.g., infection and excess mortality rates) and geographic factors (e.g., temperatures, precipitation, population density) have been represented primarily through choropleth maps. Regression models were used to analyse the correlation with many kinds of variables. Among others, the Pearson correlation was used to investigate the correlation of COVID-19 related outcomes with climate/weather variables [33,59,97], elevation and geographic location [29,47]. The Poisson regression was instead applied to study the correlation between the independent socioeconomic and demographic variables with COVID-19 related outcomes [e.g., 123,142,147] but this method is also suitable for investigating the relation with meteorological factors [e.g., 148].

The geography of COVID-19 was also investigated by applying the hotspots and clustering analysis through the Global Moran Index, which measures the spatial correlation based on spatial distribution of the values of a variable. This tool evaluates if the variable values are spatially clustered, dispersed or random [149]. Since the Moran index is a global statistical index and provides only one value for the entire spatial pattern (and no information on the location of the clusters), the Local Indicators of Spatial Association (LISA) tool was frequently applied to achieve more significant outputs. The hotspot and clustering analysis were generally accompanied by the related maps (e.g., LISA maps).

The limit of the spatial techniques used in the analysed studies is that they are generally based on the Tobler's law according to which "everything is related to everything else, but near things are more related than distant things" [150] but many studies revealed that this cannot always be applied in describing COVID-19 spatial dynamics. This was particularly true in the first phases of the pandemic during which transmission could occur over a long distance through train and highway networks and airplane routes. On the contrary, aspatial techniques did not consider the potential spatial correlation of both COVID-19-related outcomes (e.g., infections, hospitalization and deaths) and geographic variables.

Other methods and tools, which are not mentioned above, were applied in the analysed investigations (see Table 5).

4. Conclusions and perspectives

The literature review confirmed that there is a geographic signal in COVID-19 spreading since both physical and human

geographical factors have proved to be significant in explaining the spatial distribution of the contagion and its consequences. The novelty of our review with respect to the previous ones resides in: (i) the use of an interdisciplinary approach to analyse the selected papers, including expertise in epidemiology and physical geography; (ii) the emphasis on the spatial and temporal resolution of the analysed papers; (iii) the wider range of variables influencing COVID-19 outbreak and transmission considered; and (iv) the overview of the varied health outcomes considered by the reviewed studies, which are aspects often neglected by existing literature reviews in the field.

Among the territorial variables, latitude and elevation, due to their control on temperatures and environmental features, showed a negative association with COVID-19 related outcomes. For what concerns elevation, its negative association with infections and deaths must be taken with caution since other factors, such as population density, socioeconomic characteristics, availability of health care services, may act as confounders. Urbanization was one of the most investigated variables in the analysed literature which in general showed a certain agreement in stating that there is a positive correlation between urbanization degree and COVID-19 infections. However, some studies highlighted that often COVID-19 had more severe consequences in rural settings due to the lower availability/accessibility of health care services.

For what concerns climatic variables, temperature is the one that best correlates with COVID-19 infections and this correlation was found to be negative in most of the analysed studies. From the analysis of the literature under investigation, it has also been revealed that correlations between humidity and COVID-19 must be considered. However, the role played by humidity can vary depending on factors such as scale and seasonality.

The influence of wind speed on the geographical spread of COVID-19 is twofold. According to literature, wind speed is positively correlated with the speed and distance of virus transmission in the atmosphere, and an increase in wind speed will expedite the spread of COVID-19. Solar UV radiation was identified as impacting the development of COVID-19 through the positive influence of vitamin D on the immune system or virus inactivation.

Admittedly, owing to the high transmissibility of COVID-19, human interactions must have played a major role in virus diffusion, in fact, the pandemic hit the highly populated and connected cities harder. This is in accordance with most of the analysed studies which showed that population density and human mobility have a significant and direct relationship with COVID-19 infections and deaths.

The analysis of the different approaches used to decipher the role of geographic and environmental factors in the spreading of the COVID-19 pandemic revealed that it is advisable to look at the geographic aspects, considering their great variability, at a high level of granularity (e.g., subnational or local scales) in order to ensure the representativeness of the data with respect to the spatial unit of analysis. This is particularly true for the climatic/weather and environmental variables.

From a public health perspective, the significant heterogeneity of the epidemiological outcomes measured in the analysed works makes it challenging to compare and interpret the actual contribution of each geographic parameter on COVID-19 outcomes.

Given the transdisciplinary character of investigations linking geographical factors and COVID-19 spread, it would be desirable to involve public health experts in such kind of research, in addition to the necessary expert knowledge in physical geography, economy, sociology etc. This would avoid inappropriate usage of epidemiological terms (i.e., using the term “mortality” when considering the absolute number of COVID-19 related deaths), or not accounting for outcome indicators limits. In fact, the number of COVID-19 hospitalised patients can be overestimated during periods of intense virus circulation, when all the patients are tested for SARS-CoV-2 infection independently from the reason of hospitalization (“incidental COVID-19 hospitalizations”). In this context, it would be advisable to align with the indications provided by the World Health Organization (WHO) in the specific interim guidance published in March 2023 [151]. The latter proposes a series of COVID-19 indicators capable of providing epidemiological assessment methods which consider, as key areas, COVID-19 transmissibility, impact on comorbidity and mortality, and impact on the health system.

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Data availability statement

Data regarding the detailed information on the 112 papers analysed and commented in this review are included in the supplementary material (cf. [Appendix A](#)).

CRediT authorship contribution statement

Vittoria Vandelli: Writing – original draft, Investigation, Data curation. **Lucia Palandri:** Writing – original draft, Methodology, Data curation. **Paola Coratza:** Writing – review & editing. **Cristiana Rizzi:** Investigation, Data curation. **Alessandro Ghinai:** Investigation. **Elena Righi:** Writing – review & editing, Funding acquisition, Conceptualization. **Mauro Soldati:** Writing – review & editing, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.heliyon.2024.e25810>.

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3.2 ENVIRONMENTAL, CLIMATIC, SOCIO-ECONOMIC FACTORS AND NON-PHARMACOLOGICAL INTERVENTIONS: A COMPREHENSIVE FOUR-DOMAIN RISK ASSESSMENT OF COVID-19 HOSPITALIZATION AND DEATH IN NORTHERN ITALY

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Environmental, climatic, socio-economic factors and non-pharmacological interventions: A comprehensive four-domain risk assessment of COVID-19 hospitalization and death in Northern Italy

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ABSTRACT

Introduction: Up to now, studies on environmental, climatic, socio-economic factors, and non-pharmacological interventions (NPI) show diverse associations, often contrasting, with COVID-19 spread or severity. Most studies used large-scale, aggregated data, with limited adjustment for individual factors, most of them focused on viral spread than severe outcomes. Moreover, evidence simultaneously evaluating variables belonging to different exposure domains is scarce, and none analysing their collective impact on an individual level.

Methods: Our population-based retrospective cohort study aimed to assess the comprehensive role played by exposure variables belonging to four different domains, environmental, climatic, socio-economic, and non-pharmacological interventions (NPI), on individual COVID-19-related risk of hospitalization and death, analysing data from all patients (no. 68472) tested positive to a SARS-CoV-2 swab in Modena Province (Northern Italy) between February 2020 and August 2021.

Using adjusted Cox proportional hazard models, we estimated the risk of severe COVID-19 outcomes, investigating dose-response relationships through restricted cubic spline modelling for hazard ratios.

Results: Several significant associations emerged: long-term exposure to air pollutants (NO₂, PM₁₀, PM_{2.5}) was linked to hospitalization risk in a complex way and showed an increased risk for death; while humidity was inversely associated; temperature showed a U-shaped risk; wind speed showed a linear association with both outcomes. Precipitation increased hospitalization risk but decreased mortality. Socio-economic and NPI indices showed clear linear associations, respectively negative and positive, with both outcomes.

Conclusions: Our findings offer insights for evidence-based policy decisions, improving precision healthcare practices, and safeguarding public health in future pandemics. Refinement of pandemic response plans by healthcare authorities could benefit significantly.

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1. Introduction

Over the past four years, we have witnessed the spread of SARS-CoV-2 and the resulting pandemic, characterized as one of the most serious global socio-health emergencies since the last century, with profound socio-economic and public health consequences (Bambra et al., 2020; Fonseca and Azevedo, 2020; Miyah et al., 2022; Naseer et al., 2023).

Scientists and researchers worldwide have often questioned the various factors influencing the spread of the virus, conducting large-scale investigations into meteorological, socio-economic, and demographic factors and their effects on COVID-19 related outcomes such as hospitalizations and deaths (Barceló and Saez, 2021; Vandelli et al., 2024; Wachtler et al., 2020; Weaver et al., 2022). Recent studies have identified many factors among which temperature, humidity, air pollution, and UV radiation were the most influential. However, they failed to clearly define the size and contribution of these factors (Ford et al., 2022; Hao et al., 2024). Many inconsistencies in results can be observed across different studies (Balboni et al., 2023; Jerrett et al., 2023). These discrepancies may be determined by actual differences in the effect played by the same factor in different local contexts or could depend on the scale considered and the seasonality, however, they may be as well the result of different methodological weaknesses, such as the absence of control for other influencing or confounding factors or the use of aggregated data (Barceló and Saez, 2021; Nottmeyer et al., 2022).

Considering socio-economic factors, various studies have analyzed worldwide the influence of individual factors, as well as factors related to the socio-economic context showing that COVID-19 had a higher toll on socially disadvantaged populations (Duhon et al., 2021; Lippi et al., 2020). On the other hand, non-pharmacological interventions (NPI) that governments have implemented at the national and local levels have shown to play an important role in containing the spread of the virus. The adoption of these measures, however, has had a varying impact, still under study, due to the implementation of a wide range of interventions differing greatly in timing and strength (Gianino et al., 2021; Mateo-Urdiales et al., 2021).

Further, most studies are often large-scale investigations, frequently based on aggregated data with partial or absent adjustment by sex and age (Bartolomeo et al., 2022; Filippini et al., 2021) and, therefore, many reviews claim the need to investigate exposure at individual level to implement precision based public health interventions. Moreover available studies typically refer prevalently to the first pandemic phase (spring 2020) when testing and data flow were not yet standardized and explore mainly SARS-CoV-2 spread rather than disease severity (Gianino et al., 2021; Vandelli et al., 2024). Finally, literature investigating simultaneously variables related to different exposure domains (such as environmental and climatic factors, individual and socio-economic characteristics, and NPIs) is scarce and to the best of our knowledge no studies investigated the overall concurrent impact of all these factors at an individual level.

Since the very beginning, Italy has been one of the most affected European countries, recording its first case on February 21, 2020, and with a toll of over 26 million infections and 196 thousand related deaths to date (Ministry of Health, 2024). The Province of Modena (Emilia-Romagna, Northern Italy) was one of the most heavily hit by the first pandemic waves, counting over 320,000 cases over approximately 700,000 inhabitants up to March 2024 (Protezione Civile, 2024). Several authors have investigated this or nearby areas, yet in most cases, studies were carried out on specific subpopulations (Djuric et al., 2022; Mangone et al., 2023; Paduano et al., 2021, Paduano et al., 2023b; Serafini et al., 2023; Sileo et al., 2023; Ugolini et al., 2023), or, using aggregated data (Caranci et al., 2021; Gandolfi et al., 2021; Vinceti et al., 2021a, 2021b) or focusing on a specific factor or domain (Ferroni et al., 2020; Giorgi Rossi, 2020).

The purpose of this study was to investigate the overall and comprehensive effect of several exposure variables belonging to different exposure domains (environmental, climatic, socio-economic

factors, and non-pharmacological interventions) on the individual risk of COVID-19 related hospitalization and death, during the first three waves in the specific context of the Province of Modena.

2. Methods

2.1. Study design

This is a population-based, retrospective cohort study. The cohort included all subjects (no. 68472) living in the province of Modena who tested positive to a SARS-CoV-2 real-time polymerase chain reaction rhino-pharyngeal swab performed between February 21, 2020 (first local diagnosed case) and August 30, 2021. The investigated period included the first three pandemic waves occurred in Italy according to data from National Institute of Health (Stafoggia et al., 2023). The study was approved by the Ethics Committee of the Area Vasta Emilia Nord (study protocol no. AOU 0028505/21 approved on September 23, 2021) and was carried out in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardian/s/next of kin in accordance with the national legislation and institutional requirements.

2.2. Study population

Data on subjects were provided by the Local Health Authority (LHA) of Modena (Emilia-Romagna, Northern Italy). During the pandemic the Public Health Service of the LHA, through the Active Surveillance and Isolation program (SAI), collected on a daily based data on suspected and confirmed cases as well as their contacts, encompassing the handling of isolation measures, quarantine, diagnostic and follow-up testing, and the ongoing surveillance of individual cases.

For each individual the following anonymized information was extracted: age (in years), sex and residence census area (using as reference the 2011 Population National Census data, (ISTAT - Italian Institute of Statistics, 2024)), time (week) and length of positivity, symptoms and outcome (hospitalization/death). We queried vaccination status as well and found only 3184 members of our cohort were vaccinated prior to the positive swab; thus about 95% of the cohort was unvaccinated during the study period (Paduano et al., 2023a).

2.3. Setting

The Province of Modena is situated in the Emilia-Romagna region, Northern Italy, and spans over 2500 km², with a population exceeding 700,000 individuals (average population density of 261 inhabitants/km²). Modena itself is a mid-sized city, while the province comprises a combination of urban centers and rural areas. In terms of demographic composition, the province exhibits significant variations based on factors such as age, sex, ethnicity, educational attainment, and employment. Geographically, the area can be described as a diverse territory extending from the Apennine mountains, reaching an altitude of up to 2165 m above sea level, to the Po Valley (8 m) (Province of Modena, 2021).

2.4. Outcomes

The primary outcomes were COVID-19 related hospitalizations (yes/no) and COVID-19 related deaths (yes/no). Time-to-event for each outcome was available and was calculated from positivity to outcome or swab negativization. Events occurring until October 24, 2021, were included. Due to data protection issues, time-to-event was calculated referring to the week in which the event occurred.

2.5. Exposure domains and variables

Information on different exposure variables were extracted from different data sources, specifically processed and integrated, and then linked to the cohort dataset.

2.5.1. Environmental long-term exposure domain

Data pertaining to long-term air pollution was retrieved from the Regional Agency for Prevention, Environment, and Energy of the Emilia-Romagna Region (ARPAE - Regional Agency for Prevention, Environment, and Energy of the Emilia-Romagna Region, 2023). Extracted data includes particulate matter with aerodynamic diameter <10 and <2.5 μm (PM_{10} and $\text{PM}_{2.5}$ respectively) (expressed in $\mu\text{g}/\text{m}^3$); nitrogen dioxide NO_2 measured as annual mean concentrations at ground level (expressed in $\mu\text{g}/\text{m}^3$), and ozone (O_3) as expressed as the yearly number of days exceeding the threshold value of $120 \mu\text{g}/\text{m}^3$. Air pollution data was available in ASCII raster format as a grid with a resolution of $3 \text{ km} \times 3 \text{ km}$ for the years 2016, 2017, 2018, and 2019. Data was processed and averaged to obtain an estimate of long-term exposure for the years 2016–2019 for each subject's census tract and then linked to our cohort dataset. The average over the previous four years was chosen according to availability of data unaffected by the pandemic (e.g. prior lockdown and limitation of people movements) and previous literature on the topic (Ranzi et al., 2023; Stafoggia et al., 2020, 2023). More details on environmental variables may be found in Supplementary Material.

2.5.2. Climatic short-term exposure domain

Concerning climatic data, we retrieved hourly average temperature at 2 m (Celsius degrees), hourly cumulated precipitations (mm), average wind speed (m/s) and direction (degrees) at 10 m, relative humidity (percentages), hourly potential evapotranspiration (mm) according to Penman-Monteith (Monteith, 1965; Penman, 1948), hourly average global radiation flux at 2 m (W/m^2) for the period January 2020–August 2021. This data was obtained from the daily high-resolution ERG5 gridded meteorological dataset, developed by the Hydro-Meteorological-Climate Structure of Regional Agency for Prevention, Environment, and Energy (ARPAE-SIMC) of the Emilia-Romagna Region. ERG5 data has been provided since 2001 by interpolating hourly measurements from weather stations for the main meteorological variables onto a $5 \text{ km} \times 5 \text{ km}$ grid that covers the Emilia-Romagna Region (Antolini et al., 2016). Data was then processed to obtain weekly averages for each subject's census tract and then linked to the cohort dataset. More details on climatic variables may be found in Supplementary Material.

2.5.3. Socio-economic exposure domain

To assess the socio-economic context, we used the Italian Deprivation Index (DI) at the census section level, calculated on 2011 census data (the most recent available) and commonly used in the assessment of deprivation in Italy (Bartolomeo et al., 2022; Rosano et al., 2020; Fortunato et al., 2023; Mateo-Urdiales et al., 2021).

The Italian DI is mainly used as a proxy of social disadvantage, especially when such data at the individual level are difficult to access or unavailable, and the higher the score, the higher is the social disadvantage (Bartolomeo et al., 2022).

The values of the Italian Deprivation Index (DI) per census area were extracted from the Emilia-Romagna Region website and then linked to the cohort dataset. More details on Italian DI may be found in Supplementary Material.

2.5.4. Non-pharmacological interventions (NPI) exposure domain

Italy, and the Province of Modena, as many other countries, have responded by implementing non pharmaceutical interventions (NPI) which include school and workplace closures, cancellation of public events and gatherings, stay-at-home orders, and international and domestic travel restriction (Duhon et al., 2021).

Restrictive measures were analyzed calculating the Stringency Index (SI) and Containment and Health Index (CHI), as proposed by the Oxford COVID-19 Government Response Tracker (Hale et al., 2021). The SI is a composite index based on eight social measures: school closure, workplace closure, cancellation of public events, restrictions on gatherings, public transport closure, stay at home requirement, restrictions on internal movements, international travel controls. The CHI is a composite index based on the same eight social measures and six other public health interventions. The six public health interventions are: public information campaigns, testing policies, contact tracing, facial coverings, vaccination policies, protection of elderly people.

The index on any given day is calculated as the mean score of the specific metrics, each taking a value between 0 and 1. A higher score indicates a stricter response (i.e. 1 = strictest response)

To calculate the values of both Indexes in the Province of Modena, we analyzed 135 regulations issued at both the national and local level, resulting in 62 distinct scores over the course of period under consideration. Single daily CHI and SI values were then averaged to obtain weekly values, that were then merged with the dataset with individual data. More details on non-pharmacological interventions may be found in Supplementary Material.

2.6. Spatial frames and time lag

For addressing the spatial frame, we were able to collect data with a minimal spatial resolution up to the census tract of subjects' home for environmental, climatic, and socio-economic variables. NPI variables were homogeneous across the province of Modena, changing only according to time.

Considering the timeframe, due to data-protection constrictions we were able to obtain for each subject the weeks referring to first positivity and health outcomes. Time to event for survival analysis as well as lag time were therefore calculated using weeks as temporal unit. In order to estimate the correct exposure at time of infection, as suggested by existing literature, we defined different specific lag time between each variable exposure and week of swab positivity. For short-term climatic exposure, we considered a lag time of 2 weeks based on a 7-day incubation period (Wu et al., 2022) and the mean delay between onset of symptoms and swab outcome, estimated to be 5 and 3 days, respectively, in the first and second pandemic wave (ISS - Italian National Institute of Health, 2020). For NPI's lag time, we considered a lag time of 3 weeks, based on the average time required for restrictions to have an impact on SARS-CoV-2 incidence in Italy during the first waves (Guzzetta et al., 2021).

2.7. Statistical methods

Quantitative variables were summarized in the main manuscript using median and interquartile range. For full descriptive statistics, please refer to Supplementary Material. Qualitative variables were summarized by absolute and relative frequencies.

To investigate the role played by factors and exposure variables belonging to different domains on the risk of hospitalization or death for COVID-19 we used a Cox proportional hazard model with adjustment of potential confounders.

The Cox model estimated the instantaneous hazard of a health outcome (hospitalization or death) during the follow-up as:

$$h_{ij}(t) = h_0(t)^{(X_{ij} + E_{ij} + C_{ij} + S_{ij} + N_{ij})} \quad \text{Equation 1}$$

where.

$h_{ij}(t)$ = hazard function for the i th subject in the j th census tract neighborhood;

$h_0(t)$ = baseline hazard;

X_{ij} = individual risk factors (sex and age) for individual i ;

Table 1

Main socio-demographic characteristics and exposure levels of infected subjects Data is reported for the overall cohort and for subjects stratified by outcome (hospitalization or death). Continuous data are shown as median (interquartile range), categorical data as number (percentage) (Province of Modena, Italy, 2020–2021). Pollutants are expressed in $\mu\text{g}/\text{m}^3$, precipitation in mm, temperature in Celsius degrees, wind speed in m/s, relative humidity in percent, solar radiation in W/m^2 , Italian Deprivation Index (DI) in quintiles and Containment and Health Index (CHI) and Stringency Index (SI) in relative frequencies (1 equal to the highest level of restriction).

Characteristics	Overall	Hospitalized		Died	
	N = 68472	no, N = 62119	yes, N = 6353	no, N = 66740	yes, N = 1732
Sex					
M	34348 (50.2%)	30659 (49.4%)	3691 (58.1%)	33377 (50.0%)	971 (56.1%)
F	34124 (49.8%)	31460 (50.6%)	2662 (41.9%)	33363 (50.0%)	761 (43.9%)
Age (y)	43.00 (24.00, 57.00)	40.00 (23.00, 54.00)	71.00 (57.00, 81.00)	42.00 (24.00, 56.00)	84.00 (77.00, 90.00)
Unknown	1	1	0	0	1
A – Environmental domain					
NO ₂	24.30 (19.65, 28.00)	24.30 (19.65, 28.00)	24.18 (18.71, 27.82)	24.30 (19.65, 28.00)	23.71 (17.69, 28.00)
Unknown	3358	3224	134	3309	49
PM _{2.5}	20.06 (18.75, 20.62)	20.06 (18.75, 20.62)	20.04 (18.74, 20.62)	20.06 (18.75, 20.62)	20.06 (18.23, 20.68)
Unknown	3358	3224	134	3309	49
PM ₁₀	29.75 (28.55, 31.14)	29.76 (28.55, 31.14)	29.71 (28.41, 31.14)	29.75 (28.55, 31.14)	29.77 (28.20, 31.26)
Unknown	3358	3224	134	3309	49
B – Climatic Domain					
Minimum Temperature	3.92 (1.18, 8.34)	3.96 (1.17, 8.39)	3.53 (1.21, 7.07)	3.93 (1.17, 8.36)	3.71 (1.61, 6.93)
Unknown	3358	3224	134	3309	49
Total Precipitation	0.37 (0.03, 2.00)	0.37 (0.03, 2.00)	0.33 (0.03, 1.96)	0.37 (0.03, 2.00)	0.41 (0.50, 2.05)
Unknown	3358	3224	134	3309	49
Wind speed	1.47 (1.13, 1.75)	1.46 (1.13, 1.74)	1.52 (1.20, 1.87)	1.47 (1.13, 1.75)	1.51 (1.18, 1.94)
Unknown	3358	3224	134	3309	49
Relative humidity	77.65 (66.16, 86.50)	77.80 (66.28, 86.62)	76.15 (65.36, 85.72)	77.64 (66.14, 86.50)	77.85 (66.64, 86.05)
Unknown	3358	3224	134	3309	49
Radiation	106.97 (61.86, 158.24)	106.54 (61.84, 158.32)	111.03 (68.49, 157.89)	106.91 (61.86, 158.39)	109.25 (61.09, 152.10)
Unknown	3358	3224	134	3309	49
C – Socio-economic domain					
Italian Deprivation Index (DI)	3.00 (2.00, 4.00)	3.00 (2.00, 4.00)	3.00 (2.00, 4.00)	3.00 (2.00, 4.00)	3.00 (2.00, 4.00)
Unknown	3910	3710	200	3805	105
D – Non-pharmacological domain					
Stringency Index (SI)	0.66 (0.58, 0.74)	0.66 (0.58, 0.74)	0.67 (0.58, 0.74)	0.66 (0.58, 0.74)	0.67 (0.58, 0.74)
Containment and Health Index (CHI)	0.74 (0.63, 0.80)	0.74 (0.63, 0.80)	0.74 (0.64, 0.80)	0.74 (0.63, 0.80)	0.69 (0.64, 0.75)
C1 - School closure	0.50 (0.17, 0.71)	0.50 (0.17, 0.71)	0.50 (0.21, 0.83)	0.50 (0.17, 0.71)	0.50 (0.21, 0.93)
C2 - Workplace closure	0.50 (0.50, 0.67)	0.50 (0.50, 0.67)	0.50 (0.50, 0.67)	0.50 (0.50, 0.67)	0.50 (0.50, 0.67)
C3 - Cancellation public events	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
C4 - Restrictions on gatherings	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (0.88, 1.00)
C5 - Public transport closure	0.50 (0.50, 0.50)	0.50 (0.50, 0.50)	0.50 (0.36, 0.50)	0.50 (0.50, 0.50)	0.50 (0.00, 0.50)
C6 - Stay at home requirements	0.50 (0.00, 0.50)	0.50 (0.00, 0.50)	0.50 (0.21, 0.50)	0.50 (0.00, 0.50)	0.50 (0.00, 0.50)
C7 - Restrictions on internal movement	0.32 (0.00, 0.75)	0.32 (0.00, 0.75)	0.32 (0.25, 0.75)	0.32 (0.00, 0.75)	0.32 (0.00, 0.75)
C8 - International travel controls	0.88 (0.88, 0.88)	0.88 (0.88, 0.88)	0.88 (0.88, 0.88)	0.88 (0.88, 0.88)	0.88 (0.88, 0.88)
H1 - Public information campaigns	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
H2 - Testing policy	0.67 (0.67, 1.00)	0.67 (0.67, 1.00)	0.67 (0.67, 1.00)	0.67 (0.67, 1.00)	0.67 (0.67, 1.00)
H3 - Contact tracing	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
H6 - Facial coverings	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (0.93, 1.00)	1.00 (1.00, 1.00)	1.00 (0.25, 1.00)
H7 - Vaccination policy	0.60 (0.00, 0.60)	0.60 (0.00, 0.60)	0.00 (0.00, 0.60)	0.60 (0.00, 0.60)	0.00 (0.00, 0.60)
H8 - Protection of elderly people	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)

E_{ij} = long-term environmental exposure core variables for the individual i in census tract j ;

C_{itj} = climatic exposure core variables for the individual i in census tract j at the time of infection t ;

S_{ij} = socio-economic exposure core variable for the individual i in census tract j ;

N_{itj} = non-pharmacological intervention core variable for the individual i in census tract j at the time of infection t .

Equation (1) represents the general form of the model. To assess the role played by different exposure variables and different exposure domains we built different models. Firstly, for each exposure variable we ran separate unadjusted models and models adjusted only for individual risk factors (age and sex). Then, we set up four independent models, one for each exposure domain (environmental, climatic, socio-economic, NPI). To adjust each domain model for the potential confounding effect of variables belonging to the other exposure domains, we selected core variables for each exposure domain according to the following steps. For socio-economic and NPI domains, we used respectively Italian

DI and CHI as these indexes represent a composite measure for their domains. For identifying the composite measure for the environmental or climate domain, we performed a principal component analysis (PCA) of standardized variables in each domain and we selected the minimum number of components explaining at least a percentage of variability equal to 0.95p, where p is the number of variables in each domain (Kleinbaum and Klein, 2012; *Principal Component Analysis*, 2002).

Each of the four independent models was run for each variable of an exposure domain, adjusting it, as shown in eq. (1), for the individual risk factor and the exposure core variables of the other exposure domains. The model frames were as follows:

Model A.x (environmental domain assessing of environmental variable x) was adjusted for age, sex, PCA climate factor scores, deprivation index and CHI index.

Model B.y (climatic domain assessing climatic variable y) was adjusted for age, sex, PCA climate factor scores, deprivation index and CHI index.

Model C.z (socio-economic domain assessing socio-economic variable z) was adjusted for age, sex, PCA environmental factor scores, PCA

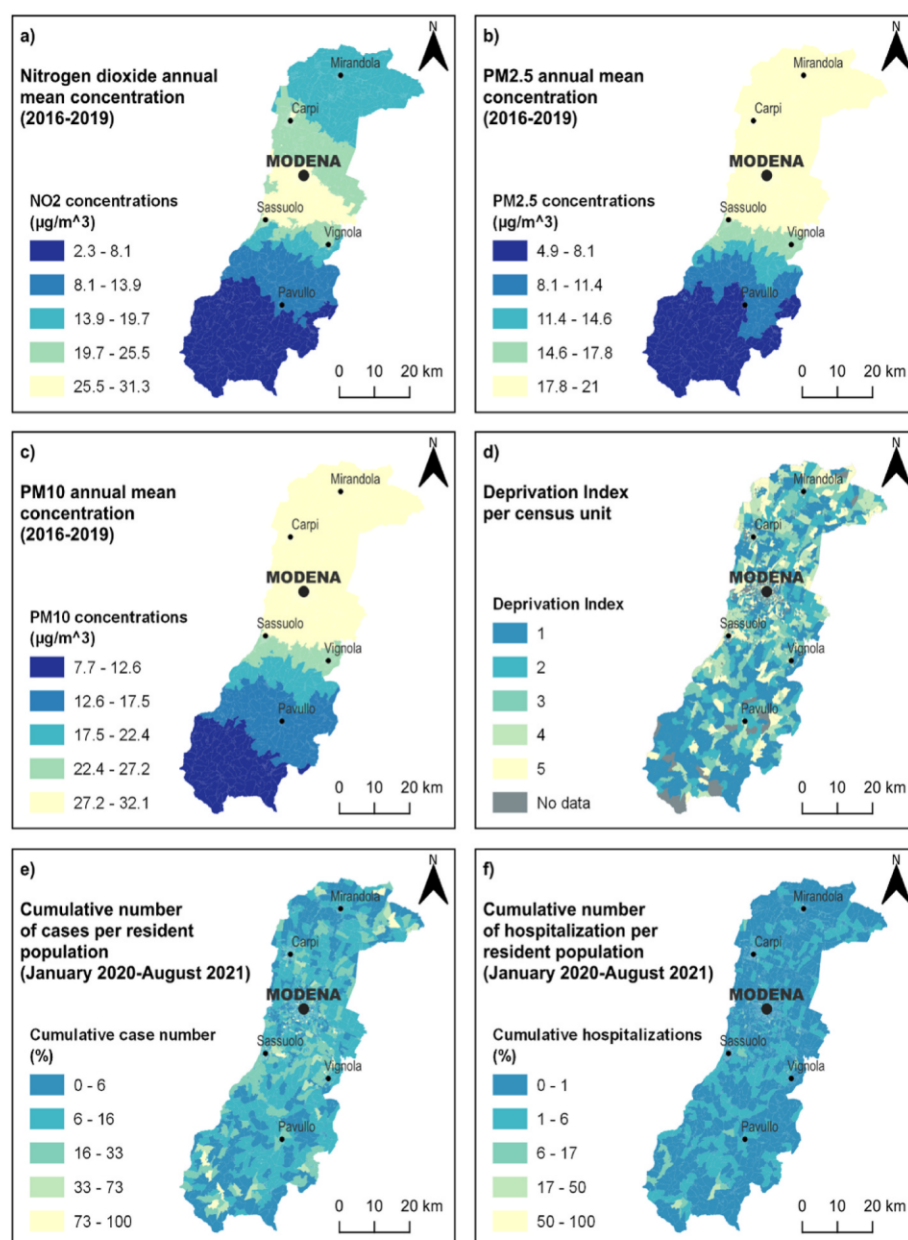


Fig. 1. Spatial distribution time-invariant factors considered for the Province of Modena: a) NO_2 annual mean concentration averaged over 2016–2019 ($\mu\text{g}/\text{m}^3$); b) $\text{PM}_{2.5}$ annual mean concentration averaged over 2016–2019 ($\mu\text{g}/\text{m}^3$); c) PM_{10} annual mean concentration averaging over the period 2016–2019 ($\mu\text{g}/\text{m}^3$); d) Italian Deprivation Index (Rosano et al., 2020) per census unit; e) cumulative number of COVID-19 cases per resident population per census unit for the investigated period (January 2020–August 2021); f) cumulative number of COVID-19 cases per resident population per census unit (for the investigated period (January 2020–August 2021)).

Data clustering in maps a), b) and c) is based on equal interval mode, while in maps e) and f), classification follows Jenks natural breaks method.

climate factor scores and CHI index.

Model D.w (NPI domain assessing NPI variable w) was adjusted for age, sex, PCA environmental factor scores, PCA climate factor scores and deprivation index.

Finally, we explored the dose-response functions for each exposure variable by producing restricted cubic splines. Restricted cubic splines were calculated using 4 knots (5th, 35th, 65th, 95th percentile) and using the median as reference for each exposure variable. To assess the impact of outliers on our curves, we ran a sensitivity analysis eliminating data below the 2.5 and above 97.5 percentile.

The most relevant findings are shown in the main text while the results of all statistical analyses carried out may be found in Supplementary Material.

We used Excel (Microsoft, Redmond, WA, USA) and R (R Core Team version 4.3.1 (2023), Vienna, Austria (R Project, 2023)) for descriptive statistics, plotting and advanced statistical analysis, with packages

including tidyverse, survival functions and using the rcs function of the rms and plotHR to create spline curves.

This study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Vandenbroucke et al., 2007).

3. Results

Table 1 and corresponding Table A in Supplementary Material, displays the main features and the individual exposure distribution of the cohort of the 68472 patients (median age: 43 years; 50.2% males), who were infected by SARS-CoV-2 from the beginning of the pandemic (February 20, 2020) to August 31, 2021, of whom 6353 (9%) were hospitalized and 1732 (3%) died.

Fig. 1 shows the spatial distribution for long-term exposure variables and cumulative number of cases and hospitalizations per residents in the

Table 2

Results of adjusted Cox proportional hazard model for COVID-19 related hospitalization and death (Province of Modena, Italy, 2020–2021). aHR: adjusted Hazard Ratios. aHR calculated for each increment of 1 unit.

Pollutants are expressed in $\mu\text{g}/\text{m}^3$, precipitation in mm, temperature in Celsius degrees, wind speed in m/s, relative humidity in percent, solar radiation in W/m^2 , Italian Deprivation Index (DI) in quintiles and Containment and Health Index (CHI) and Stringency Index (SI) in relative frequencies (1 equal to the highest level of restriction).

	Hospitalization	Death
	aHR (95%CI)	aHR (95%CI)
A - Environmental domain ^a		
NO ₂	1.0047 (1.0006–1.0087)	1.0020 (0.9947–1.0093)
PM ₁₀	1.0058 (1.0004–1.0113)	1.0071 (0.9972–1.0170)
PM _{2.5}	1.0059 (0.9989–1.0130)	1.0088 (0.9960–1.0219)
B - Climatic domain ^b		
Minimum temperature	0.9747 (0.9678–0.9816)	0.9653 (0.9530–0.9778)
Total precipitation	0.9823 (0.9724–0.9922)	0.9948 (0.9773–1.0125)
Wind speed	1.3898 (1.3251–1.4577)	1.4098 (1.2950–1.5348)
Relative humidity	0.9835 (0.9814–0.9856)	0.9874 (0.9834–0.9914)
Radiation	1.0024 (1.0020–1.0027)	1.0013 (1.0005–1.0021)
C - Socio-economic domain ^c		
Italian Deprivation Index (DI)	1.0413 (1.0223–1.0606)	1.0650 (1.0292–1.1020)
D - Non-pharmacological domain ^d		
Stringency Index (SI)	0.3833 (0.2887–0.5089)	0.2066 (0.1290–0.3310)
Containment and Health Index (CHI)	0.1712 (0.1265–0.2317)	0.0554 (0.0359–0.0857)
C1 - School closure	1.1970 (1.0909–1.3135)	1.8778 (1.5821–2.2289)
C2 - Workplace closure	0.6697 (0.5750–0.7801)	0.5326 (0.4120–0.6884)
C3 - Cancellation public events	0.7025 (0.5971–0.8266)	0.5889 (0.4337–0.7997)
C4 - Restrictions on gatherings	0.8646 (0.7305–1.0232)	0.5830 (0.4253–0.7993)
C5 - Public transport closure	0.2970 (0.2530–0.3487)	0.1144 (0.0871–0.1503)
C6 - Stay at home requirements	0.8322 (0.7159–0.9673)	0.4692 (0.3609–0.6098)
C7 - Restrictions on internal movement	0.8625 (0.7792–0.9546)	0.7533 (0.6237–0.9046)
C8 - International travel controls	0.8575 (0.5279–1.3927)	0.7751 (0.3131–1.9187)
H1 - Public information campaigns	0.1974 (0.1610–0.2421)	0.1591 (0.1180–0.2145)
H2 - Testing policy	0.4738 (0.3910–0.5742)	0.1344 (0.0968–0.1866)
H3 - Contact tracing	0.2343 (0.1593–0.3446)	0.3958 (0.1878–0.8338)
H6 - Facial coverings	0.4093 (0.3662–0.4575)	0.2204 (0.1834–0.2648)
H7 - Vaccination policy	0.7197 (0.6492–0.7979)	0.3354 (0.2747–0.4095)
H8 - Protection of elderly people	0.2343 (0.1593–0.3446)	0.3958 (0.1878–0.8338)

^a Model adjusted for age, sex, PCA climate factor scores, deprivation index and CHI index.

^b Model adjusted for age, sex, PCA environmental factor scores, deprivation index and CHI index.

^c Model adjusted for age, sex, PCA environmental factor scores, PCA climate factor scores and CHI index.

^d Model adjusted for age, sex, PCA environmental factor scores, PCA climate factor scores and deprivation index.

Province of Modena. Significant geographical differences in air pollution exposure levels can be observed across the investigated area as well as in Italian DI and in the outcomes of interest.

The results of adjusted Cox proportional hazard models are shown in Table 2 and corresponding Table B in Supplementary Material. After adjusting for many confounders, several variables show a significant effect on COVID-19 hospitalization. More specifically an increasing risk is highlighted for all air pollutants, while a negative trend can be observed for all the climatic variables except for wind speed and UV radiation. Increasing socio-economic deprivation appears significantly associated with a higher risk of hospitalization while all non-pharmacological interventions, excluding school closure, reduce the risk of hospitalization. Among them, public health interventions seem to have a higher impact on risk reduction than social measures. Similar associations can be observed for COVID-19 related deaths. Tables with all investigated variables as well as unadjusted models may be found in Supplementary Material.

Figs. 2 and 3 show dose-response curves modelled excluding outliers (curves with outliers, as well as curves of other investigated variables not reported in the main text, may be found in Supplementary Material). Where not otherwise specified, hospitalization and death curves appear consistent across exposure variables, as well as with curves with outliers.

Different shapes and relationships can be observed for the investigated variables. Long-term environmental domain variables show complex trends with the risk of hospitalization. All three pollutants present elevated risks at relatively low concentrations, though with significant uncertainty; lower risks at moderate concentrations, followed by higher risks at elevated levels, and then decreasing risks at

extremely high concentrations. As for death they show a quasi-linear relationship with the risk increasing with higher exposure levels.

Considering the climatic domain, wind speed shows a positive quasi-linear response curve. Relative humidity shows a steep indirect risk response in the central part of the curve characterized by a particularly narrow confidence interval. Minimum temperature shows an N-shaped curve showing an increased risk at extreme temperatures and this trend remains consistent when analyzing average and maximum temperatures (Supplementary Material). UV radiation shows an inverse U-shaped curve. Precipitation exhibits a direct quasi-linear risk curve that reverses when considering fatalities and outliers.

The Deprivation Index and the Containment and Health Index demonstrate a clear linear association, respectively positive and negative, with the risk of COVID-19-related hospitalizations and deaths. Notably, among NPI, only school closure (Supplementary Material) shows an inverse trend with hospitalization risk showing lower risks at lower levels of restrictions and higher risks of hospitalization with greater restrictions. This trend, however, is not confirmed when the risk of death is evaluated as the curve shows a direct linear trend.

4. Discussion

To the best of our knowledge this is the first study to investigate individual-level risk of severe COVID-19 outcomes comprehensively and simultaneously across four exposure domains (environmental, climatic, socio-economic, and non-pharmacological interventions). By employing time-to-event analysis, we were able to explore the risks of hospitalization and mortality using survival analysis techniques, enabling the

estimation of Hazard Ratios for COVID-19-related outcomes with a spatial resolution extending down to the census tract level of the patients' neighborhoods. We focus on the period starting from the local first case occurred in February 2020 and leading up to September 2021 in the Province of Modena, where significant challenges arose due to the COVID-19 pandemic (Serafini et al., 2023; Ugolini et al., 2023). Vaccination coverage was still scarce and therefore our results provide valuable insights on the impact of the several exposures on a highly contagious respiratory virus before implementation of vaccination strategies. After adjusting for several confounding factors, we were able to observe a plethora of factors still able to modify, often with complex relationships, the risk for severe COVID-19 outcomes.

4.1. Main results and literature comparison

4.1.1. Environmental domain

In our study, we observed significant positive associations, although extremely complex, between COVID-19 hospitalization risk and long-term exposure to different air pollutants (NO_2 , O_3 , PM_{10} , and $\text{PM}_{2.5}$). Similar associations were observed for COVID-19-related deaths, with a weaker link for NO_2 . Our results are in accordance with previous studies carried out at national level. The extremely high air pollution levels typically recorded in Northern Italy, including the Province of Modena, were identified as an additional co-factor for the region's high lethality (Filippini et al., 2020, 2021). Upper airways defenses can be weakened by chronic exposure to pollutants and this has been hypothesized to facilitate virus penetration in lower airways, especially in colder climate that reduce cilia mobility (Conticini et al., 2020). International evidence also highlighted connections between air pollution and COVID-19 related outcomes (Vandelli et al., 2024). Several studies indicate a positive association between average air pollution levels and mortality from COVID-19, some focusing on individual pollutants, such as $\text{PM}_{2.5}$ (Travaglio et al., 2021; Wu et al., 2020), NO_2 (Filippini et al., 2020, 2021; Ogen, 2020), and others identifying a cumulative effect (Jerrett et al., 2023).

4.1.2. Climatic domain

Different climatic factors appeared significantly related to the risk of COVID-19 hospitalization or death in our study, some results were in accordance and others in contrast with previous evidence (Balboni et al., 2023; Isaia et al., 2021; Li et al., 2022).

Humidity showed a steep reduction of risk the higher the percentage, an increased risk was observed both at very low and at very high temperatures, while wind speed showed a positive linear response with COVID-19 related outcomes.

Both humidity and temperature can affect the defense mechanisms of the nasal mucosa promoting therefore a deeper reach of the virus into the airways, which can lead to more severe infections and contribute to a poor prognosis (Kifer et al., 2021; Pramanik et al., 2022; Sera et al., 2021; Weaver et al., 2022; Yang et al., 2021). Temperature and humidity can interfere as well with the size of droplets and their persistence in the air, but the extent to which this would affect severity is not known (Bourdrel et al., 2021).

Wind speed may increase the risk of severe COVID-19 outcomes in different ways. For instance, it can favor immobility of the cilia of the respiratory system if associated with low temperatures and, further, it may modify the distance of virus transmission via droplets, and, as the virus can also be adsorbed on suspended particles that accumulate near the ground, an increase in wind speed is likely to accelerate as well the airborne transmission spread of COVID-19 (Barceló and Saez, 2021; Yang et al., 2021).

Temperature extremes (both hot and cold) may increase the risk of severe COVID-19 outcomes also through complex interactions with social behavior leading the population to prefer enclosed spaces, limiting non artificial air circulation, as it has been observed by some authors (Damette et al., 2021; Nottmeyer et al., 2022).

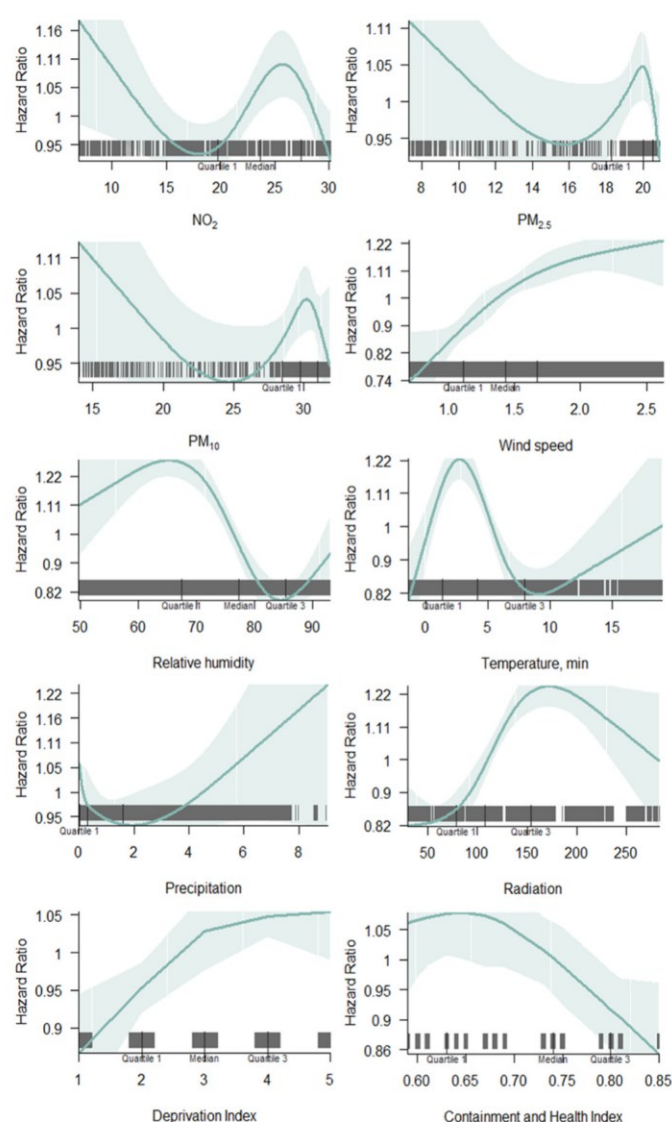


Fig. 2. Dose-response splines for hospitalized patients, excluding outliers. Adjusted Hazard Ratios calculated for each increment of 1 unit. Pollutants are expressed in $\mu\text{g}/\text{m}^3$, precipitation in mm, temperature in Celsius degrees, wind speed in m/s, relative humidity in percent, solar radiation in W/m^2 , Italian DI in quintiles and CHI in relative frequencies (1 equal to the highest level of restriction).

Similar curves have been observed in another COVID-19 survival study (Jerrett et al., 2023). This study, akin to our own work, employs Cox proportional hazards models to assess whether prolonged exposure to air pollution and meteorological conditions at the time of diagnosis influenced the mortality risk in patients with a COVID-19-related disease. Authors observed that temperature exhibited a U-shaped relationship, with higher risks apparent at lower temperatures. Conversely, for most pollutants, linear trends were observed, provided sufficient data was available to support spline derivation. However, other evidence suggests the existence of a correlation between humidity and COVID-19 but shows a role played by humidity changing according to the scale considered and seasonality (Vandelli et al., 2024). Regarding wind speed, some studies found a negative association with COVID-19 cases, but others have reached different conclusions (Vandelli et al., 2024; Yang et al., 2021).

Further, in our study also solar radiation emerged as a factor influencing the risk of hospitalization and death. Once again, previous evidence shows contradictory results, even though several studies suggest that solar radiation may have a protective effect against the development and severity of COVID-19. Our study, on the contrary, highlights

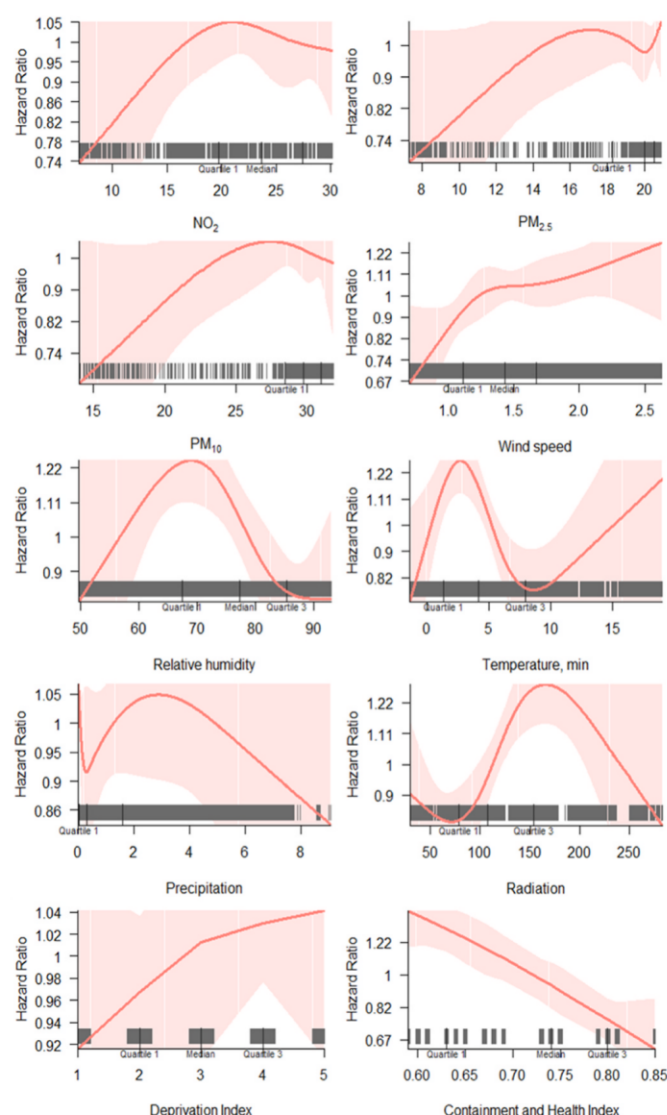


Fig. 3. Dose-response splines for deceased patients, excluding outliers. Adjusted Hazard Ratios calculated for each increment of 1 unit. Pollutants are expressed in $\mu\text{g}/\text{m}^3$, precipitation in mm, temperature in Celsius degrees, wind speed in m/s, relative humidity in percent, solar radiation in W/m^2 , Italian DI (median of quintiles) and CHI in relative frequencies (1 equal to the highest level of restriction).

seemingly conflicting results, indicating a potential increased risk of hospitalization associated with higher levels UV rays and a decreased risk of hospitalization only in the presence of the highest level of radiation. While UV radiation seems crucial for viral instability in sun-exposed areas, most of the SARS-CoV-2 transmission occurs indoors, where sunlight's impact on transmission may be limited (Isaia et al., 2021; Qian et al., 2021). To interpret these contradictory findings, it is essential to consider the geographical context, other environmental factors, and human mobility (Moriyama et al., 2020; Vinceti et al., 2022).

Finally, in our study, we observed opposite relationships between precipitation and COVID-19-related hospitalization (indicating an increased risk) and mortality (suggesting a decreased risk). Our hypothesis posits that precipitation may influence social behaviors, potentially leading individuals to favor enclosed spaces. On the other hand, segments of the population, particularly the elderly, who are more susceptible to severe outcomes, might exhibit a tendency to stay at home, thereby reducing their exposure to the virus.

4.1.3. Socio-economic domain

Our results on COVID-19 severity and mortality confirmed higher risks for disadvantaged groups as demonstrated by many other authors (Di Girolamo et al., 2020; Wu et al., 2020). However, literature shows once again inconsistent findings (Wachtler et al., 2020) as UK and US ecological studies found a positive link between deprivation and SARS-CoV-2 outcomes, while other authors found no such association or identified wealthier groups facing higher COVID-19 impact (Mateo-Urdiales et al., 2021).

Considering specific socio-economic features, numerous studies connect both lower education and belonging to a lower social status to more severe outcomes in SARS-CoV-2 infection (Vandelli et al., 2024). We can also hypothesize that higher education may lead to quicker healthcare-seeking behavior, reducing complications and the impact of unrecognized chronic diseases on the infectious clinical picture.

Considering education, employment disparities arise, particularly for low-educated individuals involved in manual jobs for which remote work is impractical, and maintaining safety distances is challenging (Nayak et al., 2020). Further, these jobs often involve exposure to environmental and chemical risks, contributing to increased risks of respiratory diseases, cancers, hypertension and stress, that is chronic conditions known to increase the risk of hospitalization and mortality in COVID-19 infection (Mateo-Urdiales et al., 2021). Inequalities in working conditions therefore likely contribute to the uneven distribution of the COVID-19 disease burden (Gianino et al., 2021). In the Province of Modena, construction companies, metalworking and food industries are prevalent, exposing individuals to extreme temperatures and unfavorable working conditions, increasing vulnerability to respiratory infections.

4.1.4. Non-pharmacological interventions

Evidence on NPI yield conflicting results. Some studies show a relative impact, weaker than climatic and socio-demographic factors (Duhon et al., 2021), while others fail to replicate these conclusions (Wagner et al., 2020). Literature generally agrees on the greater effectiveness of a combination of interventions, changing across time adapting to the evolving epidemiological situation, over a single drastic measure like the long-term lockdown set up in Wuhan (China), and these observations are contradicted only by studies carried out immediately after the first wave, even in Italy (Haug et al., 2020; Meunier, 2020).

Our results align with these findings highlighting how the composite of distinct restrictive social and public health measures exhibits a discernible protective effect concerning both Stringency Index (SI) and Community Health Index (CHI).

Individual measures implemented within the realm of public health appear to have the highest impact on risk reduction, manifesting a protective trend that intensifies with the increasing stringency of implementation. On the other hand, certain measures, particularly those of a social nature, display a more intricate pattern, with an interpretation that is not immediately clear, prompting nuanced reflections.

One possible explanation could link to the prolonged adherence to stringent restrictions that may lead to opposing behaviors, especially in domestic and private settings, thereby potentially diminishing their effectiveness. Additionally, it is essential to acknowledge that these restrictions in Italy entail a complex bureaucratic process for implementation, resulting in a time lag between the observed outcome variations and the execution of subsequent restrictive interventions. Furthermore, Genovese et al. (2022) showed that the Italian population behavior had a general low levels of risk perception and low perception of self-efficacy, especially in the first phase of the pandemic (Genovese et al., 2022).

In particular, in our study, school restrictions show conflicting results, as we observed that lighter forms of restrictions seem effective in reducing COVID-19 outcomes, while stricter restrictions (which in Italy involved complete closure of infant and children's schools) result in an increased risk of hospitalization and death. This increased risk could be

explained by the fact that the total closure of schools, which is not paralleled by the cessation of remote work and the lack of support measures for working parents, already burdened the effects of the pandemic (Ferrari et al., 2022; Righi et al., 2024), results in the possibility of relying on grandparents for the daily management of children, especially in those age groups that are not yet self-sufficient. This results in an increased exposure of the most vulnerable segments of the population.

Literature as well shows conflicting evidence on the role played by school activities restrictions. Some studies find school closures more effective than other measures like gathering bans or business closures, considered to have a moderate effect (Brauner et al., 2021) while other authors highlight that in deprived public and private spaces (schools, workplaces, houses) with inadequate ventilation, the risk of infection may be higher (Bartolomeo et al., 2022). Anyhow, most literature studies focus on incidence impact, with fewer addressing hospitalizations and deaths.

Of all the preventive measures, only the vaccination strategy is aimed not only against the infection but also against the severity of the disease. In the province of Modena, vaccination has been available since January 2021 for healthcare workers and extremely fragile subjects, such as immunosuppressed patients and patients residing in healthcare facilities. Starting from the following months, the group of recipients has been gradually expanded based on criteria relating to age, the presence of chronic pathologies and the type of work performed. Despite a very low vaccination rate in these early periods of the pandemic, this measure has indeed shown significant protective effects as it is aimed at subjects at high risk of developing serious infections, in accordance with previous literature (Homan et al., 2022; Lorenzon et al., 2024).

4.2. Limitations and strengths

Our study must be read considering its limitations and strengths. Due to privacy reasons, we were not able to obtain the exact date of positivity and outcomes, thus we could only consider the week in which the event occurred. For the same reasons, we were not able to retrieve data on patients' comorbidities or health statuses, other than sex and age. Furthermore, the socio-economic features of the area were estimated based on the last available Italian deprivation index data which dates to 2011. Finally, the data focus on a relatively confined geographic area. Although this may appear to limit the generalizability of the findings, adapting models to encompass diverse and relevant exposures that impact COVID-19 related outcomes, enhances their applicability across various contexts, thereby enabling the adaptation of our findings to different regions. Another issue to consider is the evolution over time of the available therapeutic strategies and its potential impact on the risk of hospitalization and death, given that the clinical picture of COVID-19 was a novel situation, with its pathogenetic understanding having varied over time. In the very early stages, with the pathogenetic mechanism not yet clear, the therapy for severely ill patients primarily included the use of antibiotics, steroids, low molecular weight heparin, and ventilatory support. For patients with a less severe clinical situation, a watchful waiting strategy was employed, along with the use of paracetamol and symptomatic drugs for respiratory issues, gradually transitioning to the use of low molecular weight heparin in patients with a higher thromboembolic risk at home. Starting from May 2020, the use of oral corticosteroids was also implemented for non-hospitalized patients. Between late spring 2020 and autumn 2020, there was a discontinuation of the use of paracetamol, replaced using NSAIDs. However, only in the later stages, of the pandemic, starting from autumn 2021, therapeutic strategies based on more specific drugs such as monoclonal antibodies and antiviral drugs were implemented extensively, and this timeframe is not included in the period under study in our research. Finally, results for some climate and environmental factors were characterized by high variability and imprecision of the estimates, suggesting some caution in their interpretation.

This study has indeed numerous strengths as well. Firstly, our results are grounded in a large sample size (about 68500 who tested positive to a SARS-CoV-2 real-time polymerase chain reaction rhino-pharyngeal swab performed between February 21, 2020, and August 30, 2021), a valuable asset given the challenges associated with data collection during the early stages of the pandemic. Secondly, we investigated for the first time the individual-level risk of severe COVID-19 outcomes comprehensively and simultaneously across four exposure domains (environmental, climatic, socio-economic, and non-pharmacological interventions). Moreover, the presence of a free, public healthcare system in Italy implies minimal deficiencies depending on socio-economic status in testing and admissions. Finally, the consistency of our results both internal and with the existing literature underscores the reliability of the collected data and the validity of the employed methodologies.

5. Conclusions

In conclusion, the findings of this study hold significant implications from a public health perspective, offering valuable insights for policy-makers in managing future pandemics. Firstly, our results may help guide the adaptation of local preventive healthcare policies by enabling targeted interventions and more efficient allocation of healthcare resources. Furthermore, understanding behavioral characteristics and health consequences related to geographic exposures (both environmental and climatic) and non-pharmacological interventions allows the development of personalized preventive interventions, fostering effective precision public health strategies. Our study also underscores the importance of recognizing socio-economic determinants in assessing the impact of pandemics, aiding in the identification of vulnerable groups, and reducing healthcare disparities and inequities. Moreover, the comprehension of risk factors associated with severe outcomes, such as hospitalization and mortality, is pivotal for planning responses to similar health emergencies in the future. The application and sharing of our model with communities grappling with COVID-19 challenges or pathogens with similar behavior could foster national and international collaboration in pandemic mitigation efforts and preparedness for future events. Ultimately, our findings may serve as a resource for guiding policy decisions, improving healthcare practices, and safeguarding public health in future pandemics, with significant benefits for the refinement and updating of pandemic response plans by healthcare authorities.

Competing interests

The authors have no relevant financial or non-financial interests to disclose that are relevant to the content of this article.

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Ethics approval

The study was approved by the Ethics Committee of the Area Vasta Emilia Nord (protocol no. AOU 0028505/21 approved on September 23, 2021) and was carried out in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

CRediT authorship contribution statement

Lucia Palandri: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Cristiana Rizzi:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation. **Vittoria Vandelli:** Writing – review & editing, Methodology, Data curation. **Tommaso Filippini:** Writing – review & editing, Writing – original draft, Validation, Supervision, Data curation. **Alessandro Ghinai:** Writing – review & editing, Investigation, Data curation. **Giuliano Carrozzi:** Writing – review & editing, Investigation, Data curation. **Gianfranco De Girolamo:** Writing – review & editing, Investigation, Data curation. **Isabella Morlini:** Writing – review & editing, Supervision, Methodology. **Paola Coratza:** Writing – review & editing, Methodology, Data curation. **Enrico Giovannetti:** Writing – review & editing, Methodology, Data curation. **Margherita Russo:** Writing – review & editing, Supervision, Funding acquisition. **Mauro Soldati:** Writing – review & editing, Supervision, Funding acquisition. **Elena Righi:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **DISCOV-19 study group:** Data curation.

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Appendix A. Supplementary data

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3.3 EFFECTIVENESS OF THE SARS-CoV-2 VACCINATION IN PREVENTING SEVERE DISEASE-RELATED OUTCOMES: A POPULATION-BASED STUDY IN THE ITALIAN PROVINCE OF BOLZANO (SOUTH TYROL)

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Effectiveness of the SARS-CoV-2 Vaccination in Preventing Severe Disease-Related Outcomes: A Population-Based Study in the Italian Province of Bolzano (South Tyrol)

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Objective: To investigate the effectiveness of SARS-CoV2 vaccination in preventing ordinary or intensive care unit (ICU) admissions and deaths among cases registered during a variant transitional pandemic phase in the geographically and culturally unique territory of the Province of Bolzano (South Tyrol), an Italian region with low vaccination coverage.

Methods: We collected data from 93,643 patients registered as positive for SARS-CoV-2 by health authorities during the winter of 2021–22. The data were analyzed retrospectively using descriptive statistics and multiple logistic regression.

Results: 925 patients were hospitalized (0.99%), 89 (0.10%) were in intensive care, and 194 (0.21%) died. Vaccinated patients had a significantly lower risk of being hospitalized: adjusted Odds Ratio (aOR): 0.39; 95% CI: 0.33–0.46, ICU admission: aOR: 0.16; 95% CI: 0.09–0.29 and death: aOR: 0.41; 95% CI: 0.29–0.58. Similar risk reductions were also observed in booster-vaccinated patients, independent of sex, age, and predominant variant. Furthermore, the median length of stay (LoS) in the ICU was significantly longer for unvaccinated individuals compared to vaccinated subjects (9 vs. 6 days; $p < 0.003$).

Conclusion: Primary series vaccination and ongoing campaign booster doses were effective in preventing all severe disease-related outcomes and in reducing ICU Length of Stay, even during a transitional pandemic phase and in a unique territorial context.

Keywords: SARS-CoV-2 vaccination, vaccine effectiveness, COVID-19, hospitalisation, intensive care, severe disease, death, length of stay

INTRODUCTION

The autonomous province of Bolzano, also known as South Tyrol, is the northernmost administrative region in Italy and is completely immersed in the Alps. Its mountainous landscape and proximity to the Austrian border make it a very complex territory, both geographically and socially. The population is mainly composed of Tyroleans, a traditionally

German-speaking ethnic group, with two other consistent minorities featuring Ladins, an ancient population living in a few high alpine valleys, and Italians, who have recently settled in the region and especially in the cities. The territorial conformation is represented by small rural mountain valleys with a highly developed tourist economy, that converge into larger ones, where important trade routes connect Italy to Central Europe, and where the main settlements are located with relevant institutional centers and health facilities [1].

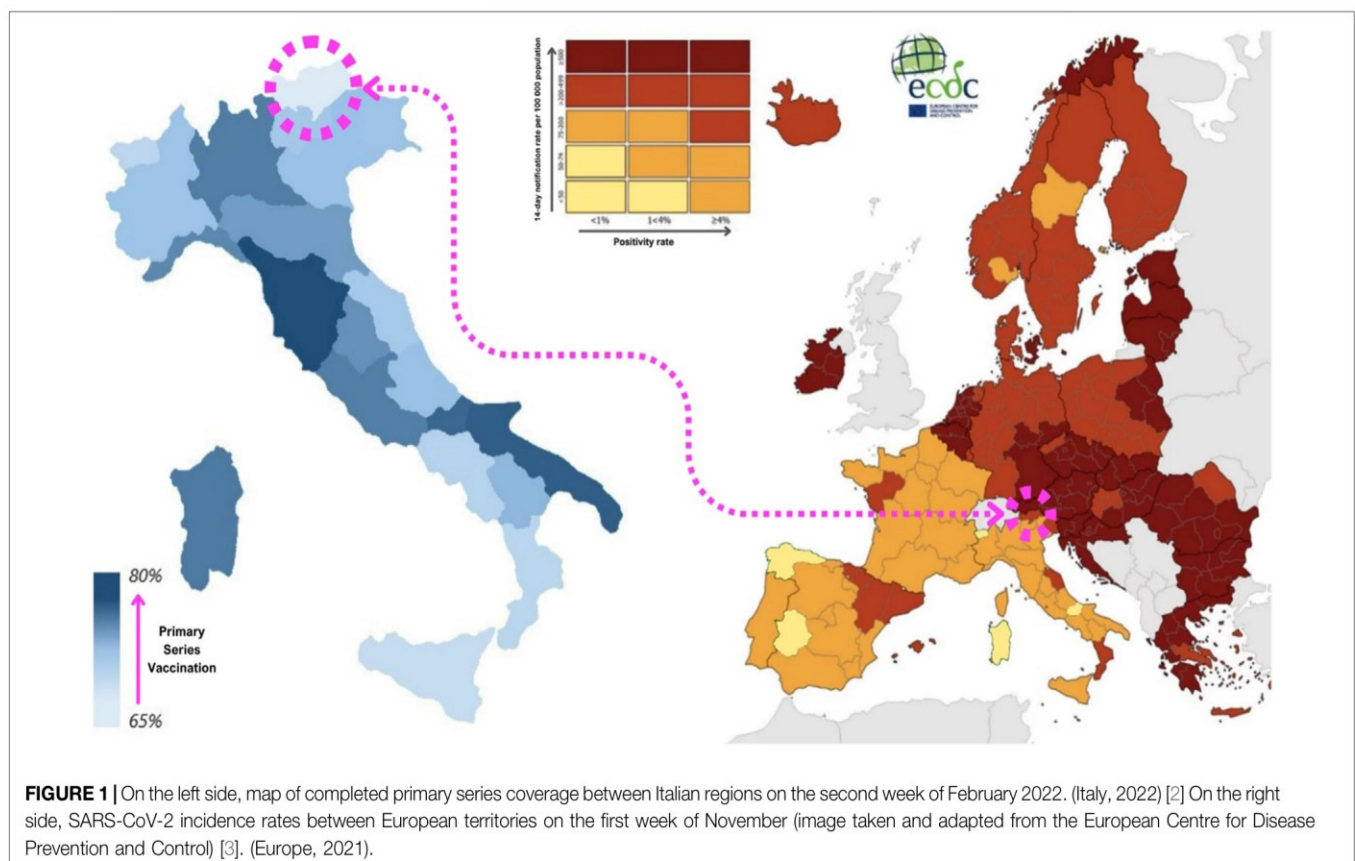
The specificity of this territory has been maintained in the dynamics of the SARS-CoV-2 pandemic. As a matter of fact, South Tyrol showed indicator trends that were often unique and not in line with the rest of Italy or with the bordering countries beyond the Alps, such as Germany and Austria, with which it has high cultural and commercial exchange. For example, during the fall of 2021, the Delta SARS-CoV-2 variant affected Central Europe with a particularly violent wave, while Mediterranean countries were impacted with less intensity. However, South Tyrol had a much higher incidence than the Italian average, with nearly 200 cases per 100,000 people in early November 2021, compared with 62 cases per 100,000 in Italy (**Figure 1**). The even more infectious Omicron variant, on the other hand, hit the area during the following Christmas holidays with a timing and intensity similar to the national one [3, 4].

Although the incidence of SARS-CoV-2 reached its highest levels at that time, the winter of 2021–2022 was the first period without social restrictions in Italy, except for the use of personal protective equipment (PPE) and the requirement to be tested or vaccinated to take part in social activities [2]. Indeed, the SARS-CoV-2 vaccine played a key role in the resumption of activities

during the pandemic, and even in this case the province of Bolzano showed unique characteristics, being simultaneously one of the regions with the most advanced booster vaccination campaign and the one with the lowest primary series coverage (**Figure 1**) [5].

At the beginning of February 2022, the Italian primary series vaccination coverage was 80%, compared with the South Tyrolean average of 66%, despite the great heterogeneity within the region, which again is proof of its complexity [5]. The booster dose vaccination campaign was initially reserved for the most fragile and high-risk individuals, and then gradually made available to everyone free of charge. From the beginning of November 2021 to 10 February 2022, while the primary series coverage of the South Tyrolean population increased by 8%, the booster dose coverage rose from 3% to 46%, although with strong variability according to age. In the 65+ age group, for example, coverage grew from 8% to 73%. This is much higher than the 52% booster dose coverage achieved by the 30–65 age group, which experienced steady growth, and even higher than that of the under-30s, who only started being administered boosters around Christmas time and reached 19% [6, 7].

Despite the consolidated evidence on the effectiveness of SARS-CoV-2 vaccines in preventing severe disease, literature on real-world data collected during specific pandemic periods, such as those characterized by the spread of the new variants or the onset of a booster campaign, is scarce. In addition, evidence is lacking on the actual effectiveness of vaccination campaigns in areas characterized by specific epidemiological, cultural, or geographical characteristics, making the province of Bolzano an ideal study setting. As suggested by the literature, analysis



of data from the region should confirm a reduced risk of encountering a worse outcome, such as hospitalization, ICU admission, or death, in patients with higher vaccination status [8–10].

Therefore, our study started with some research questions: Was the risk of severe disease-related outcomes significantly reduced by vaccination, even in such a unique context? Could positive effects of the booster dose on outcomes already be observed, while the booster administration campaign was still ongoing?

The aim of the study is to describe the effectiveness of vaccination against COVID-19 (primary series or booster dose) in preventing severe disease-related outcomes in a specific territory and during a transitional phase of the pandemic.

METHODS

A population-based epidemiologic study was conducted retrospectively using health data extracted from the surveillance system database covering the entire territory of South Tyrol and referring to the winter season 2021–22.

The information used for the study came from the Bolzano Epidemiological Surveillance Unit of the Local Health Authority (Südtiroler Sanitätsbetrieb—Azienda Sanitaria dell' Alto Adige) and was collected to track SARS-CoV-2 cases in the territory. One of the tasks of the unit was to collect pandemic data from the entire area and process both aggregated and individual data streams, addressed to the press and the Ministry of Health, thus constituting the official data source of the local health authority.

For our study, we extracted data on new diagnoses of the resident population that occurred between 1 November 2021 and 12 February 2022 and were reported to the Ministry of Health, as part of the COVID-19 pandemic health surveillance. Information on hospitalization and death collected up to 21 days (by 4 March) after diagnosis was added to these cases.

The study protocol was approved by the Ethics Committee of the Hospital of Bolzano on 16 March 2022 (Prot. 0259655-BZ).

Inclusion and Exclusion Criteria

The inclusion criterion for SARS-CoV-2 cases was that they had been reported as a new case of SARS-CoV-2 to the Ministry of Health by the Health Authority of the Province of Bolzano between 1 November 2021 and 12 February 2022. This category includes all patients who took a diagnostic swab with a positive result at an authorized center without a recorded positive result in the previous 90 days [11].

Only cases residing in South Tyrol were included in the study because vaccination information for the non-resident population might be missing from the database.

For each subject included in the study, we collected main demographic information (age, sex, district of residence); vaccination status (vaccine type, dose, date of vaccination), and characteristics of the infection course, including the date of the first positive swab, hospitalization (date of admission and discharge, general or intensive care ward) and death (yes/no and

date) that occurred in the 21 days following the date of the first positive swab (until 4 March 2022) or after a previous hospitalization during the infection.

Only deaths caused by SARS-CoV-2 were recorded, while hospitalizations were excluded if they occurred in ordinary wards under either of these two conditions:

- Patients admitted in a ward not designed for COVID-19 hospitalization and no symptomatic COVID-19 diagnosis code reported: ICD10 043.1, 043.2, and all 480 subcategories [12].
- Patients in wards designated for COVID-19, for which some diagnosis codes were reported, but none indicating the symptomatic infection.

Information on the prevalent variant, obtained from the weekly reports of the Public Health Laboratory and the Health Authority, was collected to investigate its role as a covariate. All vaccinations whose validity was not recognized by Italian Law at the time of the study were excluded [13].

Measurements

Vaccination against SARS-CoV-2 was considered the primary exposure. Vaccination status was summarized in a single categorical variable (*vaccination status*) with three immunization groups (no vaccination/primary series/booster dose). In accordance with national guidelines and scientific evidence, a previous infection that occurred at least 90 days prior to the current one was considered a new positive and was ranked within the immunization groups as equivalent to a single dose of vaccination. Therefore, the presence of a previous infection along with one or two doses of vaccine constitutes the completion of the primary series or booster vaccination [14–16].

More specifically

- “Unvaccinated” included all subjects who did not complete or even start the first vaccination cycle, regardless of the number of previous infections.
- The primary series included all patients who, at the time of diagnosis, had correctly completed the primary series of a vaccine recognized by the Italian Ministry of Health, but not a booster or additional dose. This included:
Two doses of Comirnaty (Pfizer/BioNTech) or Moderna, given between 15 and 42 days apart; or two doses of Vaxzevria/AstraZeneca, given between 70 and 84 days apart. All three vaccines had to be given at least 15 days before diagnosis [17].
Other vaccines approved by the EU [13].
One dose of Johnson & Johnson (manufactured by Janssen) at least 15 days before diagnosis [18].
One dose of vaccine and a documented infection between 14 and 180 days after vaccination; or a prior infection and a vaccine dose taken from 3 to 12 months later [19, 20].
- Booster patients are defined as those with an additional or booster dose of any of the licensed vaccines, or an infection that occurred at least 5 months after the primary series and 4 months after the last infection [19, 21].

Furthermore, the variable named *Days since the last dose*, available only for vaccinated patients, was created by reporting the number of days elapsed since the last dose (booster or primary series) on the day of diagnosis.

Variables related to sex, age (at diagnosis), and predominant viral variant during the week of the positive swab were considered covariates, as they are known to be associated with COVID-19-related outcomes [10, 22].

Some of these variables were grouped into categories:

- Age was categorized as 0–29, 30–65, and over 65 years according to the United States Department of Health and Human Services guidelines, which indicate a 97-fold higher risk of death for category 3 compared to category 1 [23, 24].
- Weekly data on viral variant prevalence, extracted from viral RNA samples obtained from nasopharyngeal swabs and extracted by PCR methodology by the Public Health Laboratory of Microbiology and Virology, were grouped into three categories based on the percentages detected in each week's total sampling. *Delta week* if this variant was present in more than 90% of the samples, *Omicron week* if this variant was present in more than 90% of the samples, and *Transition week* in all other cases. This categorization resulted in three different time ranges in which the other events took place. The first one corresponded to the *Delta period* and ran from the beginning of the study until 17 December. This was followed by the *Transition Period*, which lasted 4 weeks, until 14 January, and gave way to the *Omicron period*, which lasted until the end of the study [25].

The severity of the infection course, specifically hospitalization (general or intensive care) and death were considered as primary outcomes:

- Hospitalization: refers to the stay (yes/no) of a positive swab subject in one of the hospitals equipped to treat COVID-19 patients. These were located in Merano, Bolzano, Bressanone, Brunico, Silandro, Vipiteno, and San Candido. The wards equipped to receive these patients, in addition to the dedicated ward set up in the hospital of Bolzano, were intensive/sub-intensive care and ordinary wards, such as pediatrics (and neonatology), geriatrics, internal medicine, and emergency (casualty ward).
- Admission to an intensive care unit (ICU): refers to the stay (yes/no) of a positive case in one of the four intensive and sub-intensive care units in the province of Bolzano, located in the hospitals of Bressanone, Brunico, Merano, and Bolzano.
- Death: refers to the death (yes/no) of positive swab patients reported as symptomatic for COVID-19 infection.

Additionally, the length of stay (LoS), both overall and in the ICU, was determined by calculating the time (in days) elapsed between admission and discharge or death. In the same way, the days elapsed between diagnosis and hospital admission were estimated.

Full information on the variables and potential risks of bias can be found in the **Supplementary Material**.

Statistical Analysis

Categorical variables were summarized using absolute and relative frequencies. The median and interquartile range (IQR) were used to summarize continuous variables due to their non-normal distribution. Pearson's chi-squared test was used to compare categorical variables. The Mann–Whitney U-test was used to analyze numerical variables according to their distribution. Multiple logistic regression models were constructed to examine the association of vaccination status with hospitalization, ICU admission, or death due to COVID-19. The summary variable *Vaccination status* was used as the primary exposure variable in the model. To control for potential confounders and evaluate their role, covariates were also included in the model. Associations are reported as adjusted Odds Ratios (aOR) and 95% confidence intervals (95% CI).

A second logistic regression model including days since last dose was run only for vaccinated patients was used to assess the time-effectiveness of vaccines.

Finally, vaccine effectiveness was calculated using the formula: $VE = (1 - odds\ ratio) * 100$

SPSS Statistics, version 27, and Excel, version 16.0, were used to perform the analyses [26].

This study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [27].

RESULTS

We collected data on 93,642 patients who tested positive for SARS-CoV-2; the main characteristics of the entire sample, overall and stratified by vaccination status, are described in **Table 1**. In total, slightly more cases occurred in women (52%), in the 30–65 age group (48%) and during the Omicron period (67%). Slightly more than half of the cases were unvaccinated (53%), one-third were vaccinated with a primary series (33%), and one-sixth (15%) with a booster dose.

Within the positive swab population of the study, differences in age and sex prevalence were observed between vaccination groups, as well as in the frequency of vaccination status across variant periods.

A total of 925 subjects (0.99% of the sample) were hospitalized, 89 (0.10%) were admitted to an ICU ward and 194 (0.21%) died. Differences in severity of the disease between unvaccinated, vaccinated, and booster subjects were significant mainly for ICU admission, which showed a frequency equal to 0.13%, 0.04%, and 0.07% for subjects unvaccinated, with the primary series completed and with a booster dose, respectively (p -value < 0.001).

Considering the median length of stay in the intensive care unit of the overall population, unvaccinated patients stayed in the ICU 5 days longer than those vaccinated with the primary series, and 2 days longer than those with the booster, while the overall length of hospitalization was similar in the three categories (1 day difference). The distribution by age and variant is shown in **Supplementary Table S1**.

TABLE 1 | Main characteristics and outcomes of the total sample according to vaccination status (South Tyrol, Italy, 2021–2022).

Sample	Characteristics	Total	Vaccination status			p-value
			Unvaccinated	Primary series	Booster dose	
Overall		93,642	49,176 (52.51%)	30,581 (32.66%)	13,885 (14.83%)	
Sex	Male subjects	44,996 (48.05%)	24,119 (49.05%)	14,622 (47.81%)	6,255 (45.05%)	<0.001
	Female subjects	48,646 (51.95%)	25,057 (50.95%)	15,959 (52.19%)	7,630 (54.95%)	
Age	Under 29	41,899 (44.74%)	27,821 (56.57%)	11,857 (38.77%)	2,221 (16%)	<0.001
	Adults 30–65	44,989 (48.04%)	19,416 (39.48%)	16,377 (53.55%)	9,196 (66.23%)	
	Over 65	6,754 (7.21%)	1,939 (3.94%)	2,347 (7.67%)	2,468 (17.77%)	
	Years	33 (16–50)	23 (9–45)	36 (22–50)	47 (36–60)	
Variant	Delta	16,905 (18.05%)	10,799 (21.96%)	5,625 (18.39%)	481 (3.46%)	<0.001
	Transition Period	13,831 (14.77%)	6,925 (14.08%)	5,468 (17.88%)	1,438 (10.36%)	
	Omicron	62,906 (67.18%)	31,452 (63.96%)	19,488 (63.73%)	11,966 (86.18%)	
Hospitalization	No	92,717 (99.01%)	48,670 (98.97%)	30,317 (99.14%)	13,730 (98.89%)	0.018
	Yes	925 (0.99%)	506 (1.03%)	264 (0.86%)	155 (1.11%)	
ICU ^a admission	No	93,553 (99.90%)	49,111 (99.87%)	30,567 (99.96%)	13,875 (99.93%)	<0.001
	Yes	89 (0.10%)	65 (0.13%)	14 (0.04%)	10 (0.07%)	
Death	No	93,448 (99.79%)	49,077 (99.80%)	30,515 (99.78%)	13,856 (99.79%)	0.907
	Yes	194 (0.21%)	99 (0.20%)	66 (0.22%)	29 (0.21%)	
LoS	Days in the ICU ^a	7 (4–12)	9 (5–19)	4 (2–7)	7 (5–14)	0.022
	Length of hospitalization (days)	7 (4–13)	7 (4–14)	8 (4–13)	7 (4–12)	0.793
Other time ranges	Days between Diagnosis and Hospitalization	1 (0–5)	2 (0–7)	0 (0–3)	0 (0–1)	<0.001
	Days since last vaccination Dose	112 (48–166)	—	147 (103–181)	42 (18–59)	<0.001

Numbers are presented as n (%) or median (IQR).

^aIntensive Care Unit.

TABLE 2 | Severity of infection in the entire sample among covariates and time since the last vaccine dose (South Tyrol, Italy, 2021–2022).

Exposition	Outcome	Hospitalization			ICU ^a admission			Death		
		No	Yes	p-value	No	Yes	p-value	No	Yes	p-value
Sex	M	44,471 (98.83%)	525 (1.17%)	<0.001	44,943 (99.88%)	53 (0.12%)	0.03	44,887 (99.76%)	109 (0.24%)	0.023
	F	48,246 (99.18%)	400 (0.82%)		48,610 (99.93%)	36 (0.07%)		48,561 (99.83%)	85 (0.18%)	
Age	Median	33 (16–49)	75 (60–84)	<0.001	33 (16–50)	66 (56–78)	<0.001	33 (16–50)	85 (78–90)	<0.001
	under 30	41,848 (99.88%)	51 (0.12%)		41,897 (99.96%)	2 (0.01%)		41,899 (100%)	0 (0%)	
	30–65	44,741 (99.45%)	248 (0.55%)		44,950 (99.91%)	39 (0.09%)		44,980 (99.98%)	9 (0.02%)	
	over 65	6,128 (90.73%)	626 (9.27%)		6,706 (99.29%)	48 (0.71%)		6,569 (97.26%)	185 (2.74%)	
Variant	Delta	16,487 (97.53%)	418 (2.47%)	<0.001	16,846 (99.65%)	59 (0.35%)	<0.001	16,801 (99.39%)	104 (0.62%)	<0.001
	Transition Period	13,684 (98.94%)	147 (1.06%)		13,814 (99.88%)	17 (0.12%)		13,805 (99.81%)	26 (0.19%)	
	Omicron	62,546 (99.43%)	360 (0.57%)		62,893 (99.98%)	13 (0.02%)		62,842 (99.90%)	64 (0.10%)	
Days from last vaccination dose ^b	Median	111 (47–166)	140 (66–223)	<0.001	112 (48–166)	124 (70–257)	<0.001	111 (47–166)	210 (95–261)	<0.001

^aNumbers are presented as n (%) or median (IQR) as appropriate.

^bIntensive Care Unit.

^cRelating only to the 44,466 patients who received the COVID-19 vaccination.

The median number of days elapsed between diagnosis and hospitalization was 2 for the unvaccinated and 0 for both vaccinated categories (p -value < 0.001). The primary Series and Booster dose groups differed in the number of days elapsed between the last dose administered and the day of diagnosis: 147 (103–181) for the primary series, and 42 (18–59) for the booster (p -value < 0.001).

Table 2 describes the COVID-19-related outcomes in relation to vaccination status, sex, age, and variant prevalence.

Disease severity showed significant differences in relation to covariates. Outcomes were significantly higher in male patients than in female patients, occurred more frequently during the Delta period, increased with age, and, if vaccinated, also increased with the

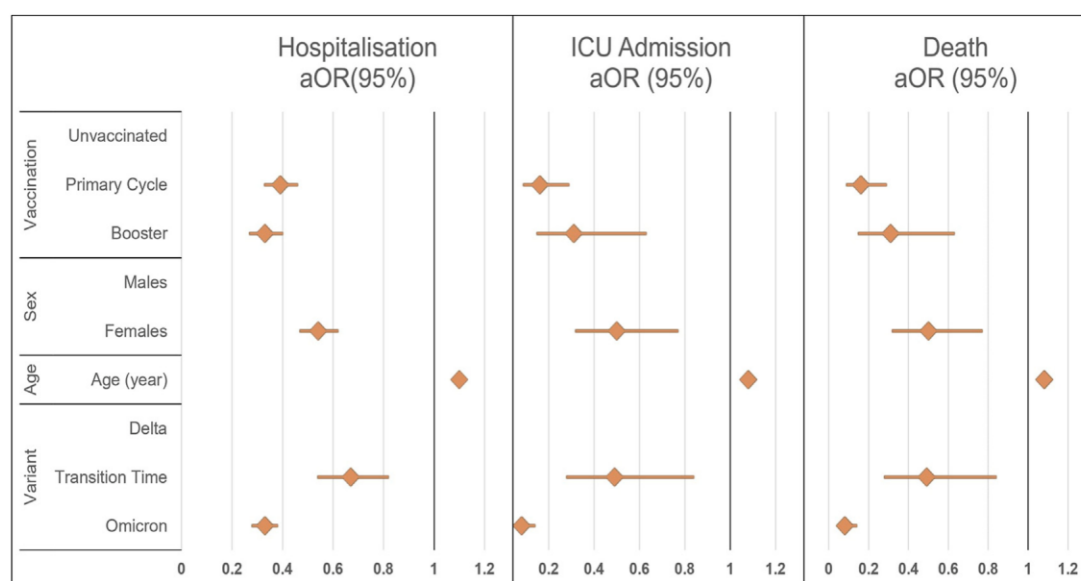


FIGURE 2 | Results of the multiple logistic regression model for the three different outcomes of disease severity, overall hospitalization, Intensive Care Unit admission, or death. ICU, intensive care unit; aOR (95%), adjusted odds ratio with 95% confidence intervals (South Tyrol, Italy. 2021–22).

number of days since the last dose. Outcomes also varied by age and variant stratified together, as shown in **Supplementary Table S2**.

Figure 2 shows the results (aOR and 95% CI) of the multiple logistic models analyzing the 3 main COVID-19 outcomes evaluated in the study in relation to vaccination status, age, sex, and prevalent variant.

Both primary series and booster-vaccinated subjects had a reduced probability of hospitalization, ICU admission, or death compared with unvaccinated patients. Reduced odds for all outcomes were also observed in female patients, in those of younger age, and during the Transitional and Omicron periods. Adjusted Odds Ratios are shown in **Supplementary Table S3**.

According to the results of multiple logistic regression, the vaccine effectiveness (VE) for preventing hospitalization was found to be 61% (67%–54%) for the primary series and 67% (60%–73%) for the booster dose; for preventing ICU admission 84% (71%–91%) for the primary series and 69% (37%–85%) for the booster dose, and for preventing death, 59% (42%–71%) for the primary series and 79% (67%–86%) for the booster dose.

The results of the second logistic model showed that the probability of the three primary outcomes also increased with time since vaccination; by 0.3% for hospitalization, 0.2% for ICU admission, and 0.5% for death for each additional day since the last dose, as shown in **Supplementary Table S4**.

DISCUSSION

Key Results

This study analyzed real-world data from the winter of 2021–22 in the Italian province of Bolzano, also known as South Tyrol, with the main aim of evaluating the effectiveness of vaccination against severe COVID-19 disease during a transitional pandemic phase.

Consistent with worldwide data, our findings showed significant differences in the probability of hospitalization, admission to intensive care, or death according to sex, age, and circulating variant [28–30]. The odds of experiencing these outcomes increased by approximately 50% in male patients, decreased from Delta variant to Omicron (by approximately 70% for death and hospitalization, more than 90% for ICU admissions), and increased by approximately 10% for each additional year of age (18% for death).

Despite the significantly lower vaccination coverage compared to the rest of Italy, the protective effect of the vaccines was significant [5]. In this study, among subjects who completed the primary vaccination cycle, the probability of being hospitalized or dying was nearly one-third when compared to that of unvaccinated subjects, and more than one-fifth when considering ICU admissions. Even the booster dose, although the campaign was ongoing and started by targeting the most vulnerable individuals, was shown to reduce the probability of COVID-19-related outcomes compared to the unvaccinated.

Unlike other similar studies, we had the opportunity to evaluate the length of hospital stay both in regular wards and the ICU. Overall, the average LoS in regular wards showed only small differences. However, LoS in the ICU was significantly longer for unvaccinated patients (median LoS: 9 days) in comparison to primary series (4 days) and booster (7 days) vaccinated patients. Notably, the probability of experiencing the primary outcomes increased by shifting temporally away from vaccination.

Furthermore, the median number of days elapsed between the last dose of vaccine and the detection of SARS-CoV-2 was interestingly long: 147 days after completion of the primary series and 42 days for those who also received a booster dose. The coincidence of vaccination with a period of high viral circulation suggests that some factors may have reduced the risk of contagion in the weeks immediately after dose

administration, such as the vaccination itself, as suggested by previous studies [31, 32].

Interpretation and External Validity

In conclusion, the findings of our study support vaccination against SARS-CoV-2, in line with other population studies and systematic reviews [33–35].

The results of this study confirmed the ability of vaccines to prevent severe COVID-19 disease, even in such a unique context. Vaccine effectiveness ranged, depending on the outcome considered, from 59% to 84% for the primary series and 67%–79% for the booster dose. These are slightly lower than those reported in other national and international studies. Data coming from the Apulia region, for example, showed vaccine effectiveness of more than 90% in preventing hospitalization and death during the Alpha to Delta period, while a study carried out in the UK during the Delta period only estimated it at 71%–84% [36, 37]. Probably, the lower protection observed in our results—referring to the Delta to Omicron period—is due precisely to the variants considered. In fact, a study conducted in the UK during the Omicron period found an even lower effectiveness against symptomatic disease, ranging from 75.1% 2–4 weeks after vaccination to 14.9% at 2 years [38]. In this context, the time elapsed since vaccination also seems to have determined a progressive loss of effectiveness, as widely described in the literature and confirmed by our data [36, 38].

However, the potentially diminished protective effect of the vaccine against new variants was also suggested by a reduction, shifting from the Delta to the Omicron period, in the difference in outcome frequency between vaccinated and unvaccinated. Together with the loss of vaccine protection over time, this underlines the necessity to maintain immunity with updated booster doses of new variants [10]. The limited diagnoses in the first weeks after booster inoculation observed in our study, also support this administration policy in order to reduce the virus circulation [31, 32].

Furthermore, our results evidenced a shorter LoS for vaccinated patients compared to unvaccinated patients, suggesting a more rapid attenuation of severe symptoms, and providing insight for future research on an aspect that is still understudied and the subject of scientific debate [39, 40]. Overall, this study contributes valuable information to the existing literature.

Limitations and Strengths

The results of the present study must be read in light of their limitations. First, a possible underdiagnosis could have occurred, especially in the vaccinated group, since during the study period unvaccinated subjects had to routinely test negative to obtain a green pass to work or participate in most social activities. This theory is supported by the difference, between vaccinated and unvaccinated, in the days between diagnosis and hospitalization: those who were vaccinated were on average tested positive on the same day of hospital admission, while those who were unvaccinated tested positive 2 days before. Consequently, this underdiagnosis could also lead to an overestimation of the hospitalization and mortality rates in the vaccinated groups and therefore to an underestimation of vaccine effectiveness. In contrast, the number of COVID-19-positive hospitalizations

and deaths is not affected by this limitation because all hospitalized and deceased subjects were tested [2].

Another limitation of the study is the lack of information on the symptomatology and comorbidities of the patients, which makes it difficult to ascertain the quantitative contribution of COVID-19 to the outcome itself. Moreover, the study has the inherent limitation of not being able to capture the overall development of the pandemic as it covers a brief period compared with the entire course of the pandemic and the vaccination campaign. For the same reason, since the most vulnerable individuals, and therefore those most at risk of negative outcomes, were enrolled first during the vaccination campaigns, the booster group is not perfectly comparable with those who were vaccinated with the primary series, whose vaccination campaign was more advanced, nor with the pediatric unvaccinated, who had just had their first access to vaccination. Finally, the days elapsed since the last dose were only available for the vaccinated [6, 7].

However, this study also has many strengths. First, our results rely on a large sample size which is valuable considering all the difficulties in data collection during the first period of the pandemic. Furthermore, the Italian healthcare system is predominantly public and there should be no lack of admissions. Finally, the results were consistent with each other and with the existing literature, a sign of the reliability of the data collected and the correctness of the methods used.

Conclusion

The implications of the study are multifaceted. First, it confirms the effectiveness of SARS-CoV-2 vaccines in a large sample, and with a high proportion of unvaccinated patients, especially in preventing severe outcomes in the elderly. It also suggests an effect on reducing the duration of hospitalization and preventing contagion. The study also confirms the decreasing risk of severe disease passing from the Delta to the Omicron variant, although the absolute frequencies of outcomes were similar due to the larger number of cases.

By proving the effectiveness of both the primary series and the booster dose in a region characterized by low vaccination coverage and high hesitancy, our research suggests an estimate of the health benefits, and cost savings due to the reduction in the number and duration of hospitalizations that can be obtained and achieved through the vaccine and booster campaigns. This supports the policy of administering booster doses, whose effectiveness is also proven compared to primary series vaccination, whose protection tends to decline over time.

Future studies should focus on larger samples of hospitalized patients to further investigate the length of hospital stay (LoS), as this study provides promising evidence of a shorter duration for vaccinated individuals. In addition, data on comorbidities and symptomatology should be recorded as these would allow for the building of more robust and informative models. Finally, further research could focus on a deeper analysis of this unique territory, also using different methodological approaches, to better understand both the epidemiology of the disease and vaccination adherence.

Overall, this study contributes to the growing body of evidence supporting the importance of vaccination in mitigating the impact of COVID-19, providing solid and consistent results on the one hand, and insights for future research on the other.

ETHICS STATEMENT

The studies involving humans were approved by Comitato Etico dell'Azienda Sanitaria dell'Alto Adige. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

AUTHOR CONTRIBUTIONS

AL contributed to all the phases of the present work accompanied by LP; AL, RP, FL, CC, and FZ actively participated in the collection of the data; CR participated in the literature search together with FU, AL, LP, and FU performed data analysis as well as writing the first draft of the manuscript; Critical analysis of results was performed by CC, FZ, and PB. All phases of the study took place under the critical supervision of ER. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

The authors declare that they do not have any conflicts of interest.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.ssph-journal.org/articles/10.3389/ijph.2024.1606792/full#supplementary-material>

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3.5 AN ECOLOGICAL STUDY RELATING THE SARS-CoV-2 EPIDEMIOLOGY WITH HEALTH-RELATED, SOCIO-DEMOGRAPHIC, AND GEOGRAPHICAL CHARACTERISTICS IN SOUTH TYROL (ITALY)

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Article

An Ecological Study Relating the SARS-CoV-2 Epidemiology with Health-Related, Socio-Demographic, and Geographical Characteristics in South Tyrol (Italy)

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Abstract: The literature associating the spread of SARS-CoV-2 with the healthcare-related, geographical, and demographic characteristics of the territory is inconclusive and contrasting. We studied these relationships during winter 2021/2022 in South Tyrol, a multicultural Italian alpine province, performing an ecological study based on the 20 districts of the area. Data about incidence, hospitalization, and death between November 2021 and February 2022 were collected and associated to territorial variables via bivariate analyses and multivariate regressions. Both exposure variables and outcomes varied widely among districts. Incidence was found to be mainly predicted by vaccination coverage (negative correlation). Mortality and ICU admission rates partially followed this distribution, while the case fatality rate was inversely correlated to average salary, and hospital admission rates increased where hospitals capacity was higher, and from the southern to the northern border of the province. These findings, besides confirming the efficacy of vaccination in preventing both new and severe SARS-CoV-2 cases, highlight that several geographical and socio-demographic variables can be related to disease epidemiology. Remote areas with wage gaps and lower access to care suffered most from the pandemic. Our findings, therefore, underly the existence of health inequity issues that need to be targeted by implementing specifically tailored public health interventions.

Keywords: SARS-CoV-2; herd immunity; health inequities



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1. Introduction

The SARS-CoV-2 pandemic has dramatically affected our planet in its entirety, with the total amount of registered cases reaching about 250 million by November 2021, just a year and a half after the pandemic began [1]. Due to the arrival of new variants, this figure even tripled by the end of the same winter [2]. The impact on people's health was immense, with 5 million detected deaths rising to almost 7 during the same period [1]. Although the virus reached every continent, its spreading varied significantly in different geographical habitats, seasons, and communities [3–5], and factors related to this phenomenon are still under study worldwide [6,7].

In Italy, for example, in the northernmost province of Bolzano, also called South Tyrol, the SARS-CoV-2 pandemic showed epidemiological characteristics differing greatly both from the neighboring territories and across its territory, notably during winter 2021/2022, such as a higher incidence and lower vaccination adherence [8,9]. This area has also peculiar and heterogeneous geo-morphological and socio-cultural characteristics. Its natural

environment resembles that of further northern countries, although the peaks of the southern Alpine slope protect it from the cold polar currents, giving it a sunny Mediterranean climate, especially in its southern part bordering other Italian regions [10]. Further, its multifaceted historic background is reflected in the great socio-cultural heterogeneity of its 534,912 inhabitants, with 65% of the population being German-speaking and evenly distributed across the territory; 30% Italian-speaking and concentrated in the low-altitude cities; and 5% Ladin, a local ancient population of the higher mountains, although there is considerable mixing between groups [11].

South Tyrol is administered as an ‘autonomous statute region’ and divided into 20 health districts grouped into four sections built up around the four largest municipalities in the area (Bolzano, Merano, Bressanone, and Brunico), where the main health services are located [11,12], as represented in Figure 1. The section of Bolzano, the densely populated capital city with 107,467 inhabitants, includes both the southern, low-lying districts, with a strong Italian cultural influence, and those higher up, more anchored in the German or Ladin tradition. Around Merano, the districts are mostly composed of isolated rural sunny valleys devoted to agriculture and farms. The Bressanone section is a predominantly mountain area, where low tourism is balanced by high trade, thanks to the presence of the main link between Italy and Austria. Finally, the Brunico section is characterized by isolated and highly touristic valleys, which are important links with Austria and the other Italian Dolomite regions [12].

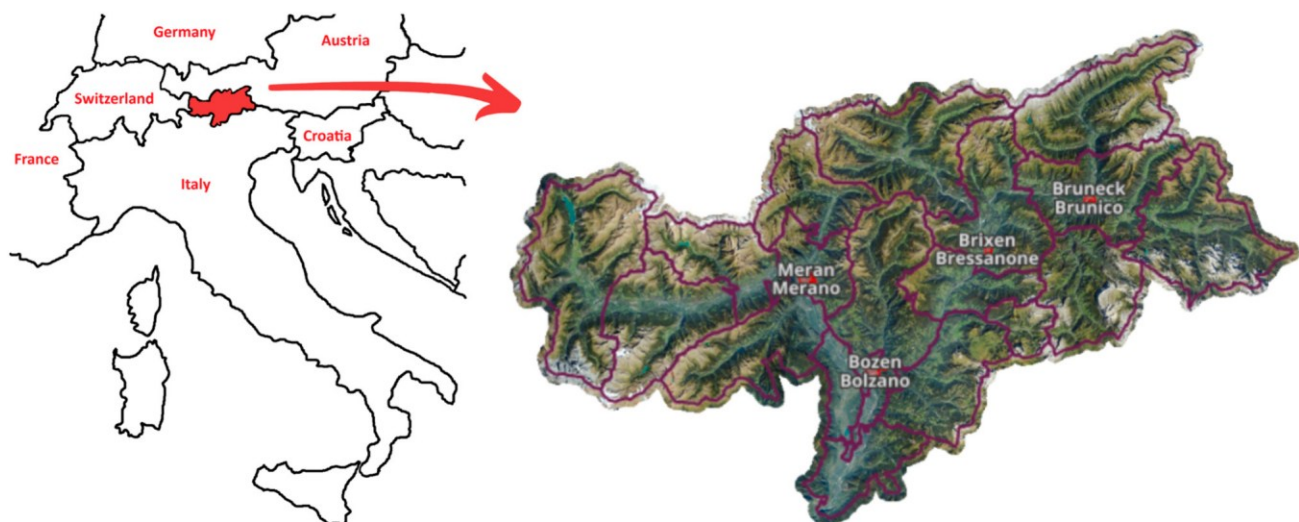


Figure 1. Geographical representation of South Tyrol’s position in relation to Italy and neighboring countries (**left**) and physical map of the province divided into the 20 health districts with the four main section centers (**right**). Image adapted from the online public geographic data tool of the Autonomous Province of Bolzano [13].

The literature investigating the epidemiological variability of the disease related to health services provision and vaccination coverage (herd immunity) and to the geographical or cultural characteristics that mark this territory, such as altitude, tourism, and population dynamics, is scarce, and evidence is conflicting [9,14–18]. Therefore, the aim of this study is to investigate whether the deep geographical heterogeneity of socio-cultural, morphologic, and health-related features characterizing the South Tyrol territory (northern Italy) can be related to the differing spread of SARS-CoV-2 observed across the region in the first winter of the pandemic characterized by the absence of social restrictions and the availability of effective preventive measures, including vaccination.

2. Materials and Methods

We carried out an ecological study based on the 20 districts composing the Province of Bolzano (South Tyrol), Italy. Aggregated data on geo-morphological, socio-cultural, and health service-related features and SARS-CoV-2 cases and deaths were collected from the Local Health Authority (SABES) [19] or the Provincial Institute of Statistics (ASTAT) [20].

Geographical, socio-demographic, and health service-related variables of the area were the exposure variables of interest, while SARS-CoV-2 epidemiological measures of occurrence (incidence, hospitalization, or death) were the outcomes evaluated.

The study protocol was approved by the Bolzano Hospital Ethics Committee on 16 March 2022 (Prot. 0259655-BZ).

2.1. Exposure Variables

Geo-morphological, socio-cultural, and health service-related data were taken from the public ASTAT database (accessed in April 2024), referring to the most recent period available for each variable [20]. Information on vaccination coverage was provided by the Local Health Authority [19].

The following data were available.

Demographics:

- Inhabitants, represented by the resident population amount (2021);
- Population density (people living in every square km, 2021).

Social dynamics variables:

- Average yearly salary, for employees in the private sector (2019, before the pandemic);
- Winter tourism, expressed as the number of tourists from outside the province who overnighted at least once in any type of local accommodation (November–April 2019).

Geographic variables:

- Presence of main cities;
- Average altitude, or vertical distance above the reference sea level (meters, current);
- Bordering other Italian regions through winter-opened mountain passes or ordinary roads (current);
- Bordering other countries (Austria and Switzerland) through the same roads (current).

Health Services-related variables:

- Number of pharmacies every square km (2010);
- Presence of small (without an intensive care unit—ICU) or big-sized (with ICU) hospitals (current) [19];
- Primary series vaccination coverage, updated as of 12 February 2022 and expressed as the number of subjects who received primary vaccination reported for the total resident population (%). In this variable, we included subjects with one dose of viral vector vaccine, two of the mRNA vaccine, or one of any with a previous infection, in the timeframe and with the vaccines authorized by the Italian Health Ministry [21,22];
- Booster/additional dose coverage, a variable including the number of subjects who received a booster (or additional) dose of vaccine with the serums defined by the Italian Health Ministry, reported for the total resident population, updated as of 12 February 2022, and expressed as a percentage [23]. The booster vaccination campaign in South Tyrol began in November 2021 and was initially reserved for the most vulnerable. The vaccination was available at general practitioners and major public health facilities of the province.

2.2. Outcome Variables

Health data on SARS-CoV-2 cases referring to winter season 2021/2022 were provided by the Epidemiological Surveillance Unit of Bolzano that oversaw tracking SARS-CoV-2 cases in the entire territory of South Tyrol [11].

The following information was available.

- SARS-CoV-2 cases: the total number of all new cases occurring in the resident population between 1 November 2021 and 12 February 2022. To this category belong all patients who had taken a diagnostic swab with a positive result in any authorized center of the province without a recorded positive result in the previous 90 days [24].
- Hospitalizations: total number of hospitalizations related to the SARS-CoV-2 cases occurring up to 21 days (lastly up to 4 March 2022) after diagnosis [25]. Total hospitalizations for SARS-CoV-2 and ICU admissions were considered. Admissions were excluded if referring to patients who were positive but asymptomatic for COVID and suffered from diseases unrelated to the infection.
- Deaths: total number of deaths caused or contributed to by SARS-CoV-2, linked to the cases included in the study (lastly up to 4 March 2022) after diagnosis.

2.3. Data Processing

ASTAT data were displayed by municipality, so an aggregation of data at the district level was performed to make them comparable with district-related outcome data, following the belongings of each municipality to the 20 districts, as depicted in Supplementary Table S1.

A sum was made for the numeric variables, such as winter tourists, inhabitants, and surface. A weighted average for the number of inhabitants was performed to assess districts' average salary. Average altitude, pharmacies density, and population density were weighted for the surface size, while the highest municipality value for hospital presence and size, borders information, and main cities was used for the district.

Outcome amounts were clustered for each district and divided into epidemiological measures.

- Incidence of SARS-CoV-2 during the whole winter 2021/2022 was calculated for each district, relating the cases amount to the number of inhabitants and expressed per 100,000 inhabitants.
- Hospitalization Rates were assessed in the same way, relating both ordinary and ICU admissions to the inhabitant amount of each district and reported for every 100,000 inhabitants.
- Hospitalization proportion corresponded with the number of both ordinary and ICU admissions related to the number of cases in the same district and expressed per 10,000 cases.
- Mortality and case fatality rate (CFR) were assessed relating the district's death amount per 100,000 inhabitants and per 10,000 cases, respectively.

2.4. Statistical Analyses

The variables were first summarized by descriptive analyses, and then correlations and bivariate non-parametric statistical analyses were performed (Spearman's correlation, Kruskal–Wallis, and Mann–Whitney U tests) to assess the relationships between the variables.

The variables associated with each outcome (p -value < 0.1) were then analyzed together by multiple linear regression, performing the model for the outcomes with at least three non-collinear variables associated with it. An easier interpretable scale for the exposure variable was used in the model: population density was considered for inhabitants per hectare (10,000 m²), winter tourist amount expressed by 100,000 units, and altitude expressed in kilometers. Variables with VIF (Variance Inflation Factor) > 5 were considered collinear and not included in the linear regression. The distribution of residuals and Nagelkerke's adjusted R square were evaluated to ensure a good fit of the model to the data.

Statistical analyses were performed using Jamovi software (version 2.5.5) [26].

3. Results

3.1. Main Features of the Area

The 20 districts in the province of Bolzano differ greatly in geo-morphological and socio-cultural characteristics and health-care facilities distributions, as shown in Figure 2 and Supplementary Tables S2 and S3.

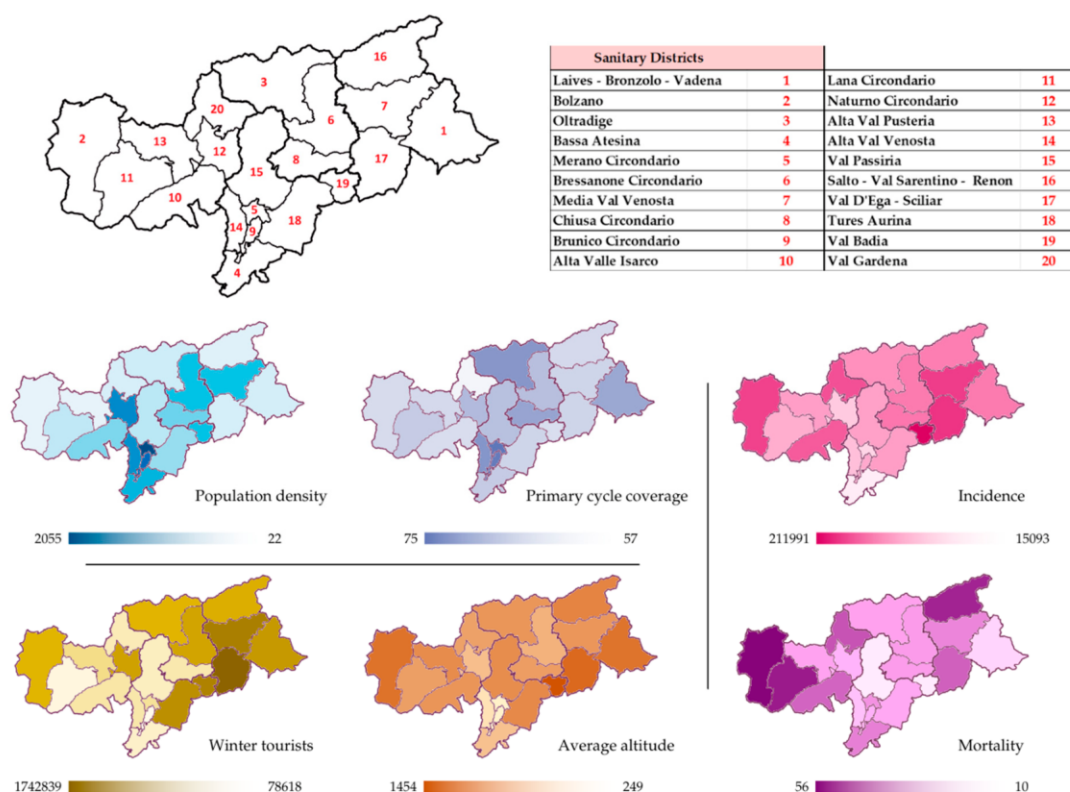


Figure 2. Demographic (population density—inhabitants/km²), healthcare (primary series vaccination coverage), social dynamics (number of winter tourists), and geographical (average altitude (m)) characteristics of the 20 districts of South Tyrol. Distributions of SARS-CoV-2 incidence and mortality are also represented and expressed as cases or deaths per 100,000 inhabitants.

Four districts are directly connected with Austria, six with other Italian regions. Laives-Bronzolo-Vadena (LBV) has the lowest altitude (249 m to the sea level), Val Gardena the highest (1454 m), and the median of the province is 961 m (IQR of 338).

The number of inhabitants (district median: 20,259; IQR: 11,536) ranges from less than 10,000 in Val Passiria to over 100,000 in Bolzano, that of winter tourists (median: 491,182; IQR: 701,423) from 78,618 in LBV to 1.7 million in Val Badia. The lowest wage in the private sector is in Val Passiria (25,591 euros/year), the highest in Brunico (29,132 euros/year).

Big hospitals are located in the four main cities (Bolzano, Merano, Bressanone, Brunico) and small ones in Media Val Venosta, Alta Val Pusteria, and Alta Valle Isarco. Pharmacies for each district are a median of 1 per every 100 square km. At winter 2021/2022 end, primary series vaccination coverage varied extremely, with an IQR between 68% and 72% (median: 70%); booster dose coverage was 43–46% (median 45%). The lowest values are in Val Passiria (57% primary series, 31% booster), the highest in Bolzano (75% and 51%).

The geographical distribution of the SARS-CoV-2 pandemic is shown in Figure 2 and Supplementary Table S4. Outcomes varied greatly across districts. The SARS-CoV-2 incidence was lowest in Bolzano and highest in Val Gardena, with an overall district median of 18,090 cases per 100,000 inhabitants (IQR: 2356). The hospitalization rate (per 100,000 inhabitants) ranged from 90 in Bassa Atesina to 256 in Brunico (district median: 162; IQR: 48). The ICU admissions rate median was 15 per 100,000 inhabitants (IQR: 4–23). The district median of CFR was 19 per 10,000 cases (IQR: 4), ranging between 5 in Val Gardena and 31 in Media Venosta.

3.2. Territorial Characteristics and SARS-CoV-2 Epidemiology

According to bivariate analyses (Tables 1 and 2), the SARS-CoV-2 incidence at the district level appeared significantly correlated to several district factors and features, in-

cluding the total number of inhabitants and of winter tourists, the average altitude, and both primary and booster dose coverage. On the contrary, the distribution of healthcare facilities such as pharmacies or hospitals was not associated with any significant variation in this parameter.

Table 1. SARS-CoV-2 incidence, hospitalization, and mortality correlation (Spearman's Rho, *p*-value) with quantitative district characteristics of the 20 districts in South Tyrol, Italy, during winter 2021/2022.

District Characteristics		Incidence *	Hospitalization Rate *	ICU ^a Admission Rate *	Mortality *	Hospitalization on Cases **	ICU ^a Admission on Cases **	Case Fatality Rate **
Demographics	Inhabitants	−0.54 (0.015)	0.19 (0.416)	−0.27 (0.253)	−0.17 (0.478)	0.4 (0.077)	−0.23 (0.332)	−0.09 (0.696)
	Population Density	−0.44 (0.050)	−0.18 (0.435)	−0.54 (0.014)	−0.4 (0.077)	0.03 (0.905)	−0.52 (0.020)	−0.36 (0.120)
Social Dynamics	Average Salary	0.269 (0.250)	−0.114 (0.630)	0.093 (0.697)	−0.289 (0.216)	−0.205 (0.385)	0.091 (0.704)	−0.462 (0.040)
	Winter Tourism	0.54 (0.015)	0.22 (0.359)	0.29 (0.208)	−0.11 (0.645)	0.12 (0.627)	0.29 (0.218)	−0.2 (0.405)
Health Services	Primary Series	−0.62 (0.004)	0.01 (0.970)	−0.4 (0.081)	−0.43 (0.061)	0.25 (0.298)	−0.4 (0.080)	−0.36 (0.123)
	Booster Dose	−0.68 (0.001)	0.11 (0.65)	−0.38 (0.095)	−0.34 (0.139)	0.39 (0.091)	−0.37 (0.11)	−0.23 (0.326)
Geography	Pharmacies (/km ²)	−0.326 (0.161)	−0.095 (0.690)	−0.436 (0.055)	0.109 (0.647)	−0.424 (0.062)	−0.401 (0.080)	−0.363 (0.116)
	Average Altitude	0.67 (0.001)	−0.11 (0.631)	0.23 (0.339)	0.04 (0.865)	−0.34 (0.141)	0.19 (0.420)	−0.05 (0.830)

To facilitate interpretation, cells with a *p*-value < 0.10 are colored in light grey, dark grey if *p*-value < 0.05. * Every 100,000 inhabitants. ** Every 10,000 cases. ^a Intensive Care Unit.

Table 2. SARS-CoV-2 incidence, hospitalization, and mortality (median, IQR, *p*-value) according to qualitative characteristics of the 20 districts in South Tyrol, Italy, during winter 2021/2022.

District Characteristics		Incidence *	Hospitalization Rate *	ICU ^a Admission Rate *	Mortality *	Hospitalization on Cases **	ICU ^a Admission on Cases **	Case Fatality Rate **
Health Services	Big hospitals	17,298 (16,035–18,910)	199 (177–230)	20 (14–29)	36 (34–37)	116 (111–121)	12 (8–16)	19 (19–20)
	Small hospitals	17,825 (16,969–18,479)	160 (159–237)	5.3 (4.8–24.7)	33.9 (18.5–53)	94 (87–133)	3.1 (2.7–13.4)	19 (10–31.2)
	No hospitals	18,354 (17,365–19,661)	139 (123–168)	12.5 (0–23.1)	34.6 (31.7–43.5)	76 (68–97)	6.2 (0–12.4)	19.3 (18.5–23)
	<i>p</i> -value	0.707	0.054	0.739	0.993	0.01	0.683	0.987
Geography	Main Cities	17,298 (15,958–19,336)	199 (176–239)	19.9 (10.6–35.3)	35.5 (32.9–37.1)	116 (111–123)	11.7 (5.9–18.9)	19.1 (18.8–21.1)
	Rural/Towns	18,090 (17,240–19,510)	159 (128–173)	8.9 (1.9–23.9)	34.3 (28.9–44.4)	86 (70–97)	4.7 (1.3–12.9)	19.2 (17.2–24.4)
	<i>p</i> -value	0.617	0.029	0.554	0.963	0.005	0.437	0.963
	Bordering abroad	19,263 (18,152–20,118)	221 (183–247)	18.6 (8.7–36.4)	36 (26.2–47)	115 (95–130)	9.8 (4.5–18.6)	18.9 (14.4–23.5)
	Not bordering	17,419 (16,708–18,974)	159 (128–176)	11.3 (1.9–22.8)	34.7 (31.4–43.2)	88 (70–98)	5.8 (1.2–13.2)	19.3 (18.6–23)
	<i>p</i> -value	0.178	0.022	0.335	0.82	0.05	0.437	0.82
	Bordering Italian regions	18,479 (16,446–20,475)	132 (93–160)	4.7 (0–19.5)	33 (18.5–42.8)	75 (59–84)	2.7 (0–10.1)	18.9 (10–22.1)
	Not bordering	17,825 (17,115–18,589)	177 (160–206)	17.4 (4.8–33.7)	34.8 (33.7–45.2)	98 (94–112)	9.4 (2.7–19.3)	19.3 (18.8–23)
	<i>p</i> -value	0.643	0.006	0.275	0.351	0.003	0.211	0.351

To facilitate interpretation, cells with a *p*-value < 0.10 are colored in light grey, dark grey if *p*-value < 0.05. * Every 100,000 inhabitants. ** Every 100,00 cases. ^a Intensive Care Unit.

Both the hospitalization rate and the proportion of hospitalization cases resulted in being significantly higher in districts with main hospitals and cities and in districts bordering other countries or not bordering other Italian regions. District ICU hospitalization, the proportion of ICU cases, mortality, and CFR resulted in being less related to the ecological

4. Discussion

During winter 2021/2022, SARS-CoV-2 was diagnosed in almost one out of every six people in Bolzano province (South Tyrol). However, the incidence was unevenly distributed across the territory, reflecting its complexity. According to our ecological study, the variable most related with its distribution across districts was the vaccination coverage [9]. In addition, different geographical and socio-demographic features of the territory appeared to play a role in the spread of the disease. Namely, the incidence was higher in districts where population density was greater, in traditional mountain areas, and in those with higher tourist flows.

ICU admissions and mortality due to SARS-CoV-2 partially tracked the incidence, being higher at higher altitudes and in districts with less vaccination coverage, while higher rates of overall hospitalization were observed in the districts bordering other countries in the north, and lower rates in those bordering the Italian regions to the south. Moreover, hospitalization was highest where the capacity of healthcare facilities was the greatest, i.e., in major cities, where major hospitals are located, and the lowest in districts where hospitals are absent. Case fatality rate (CFR), on the other hand, was found to be negatively correlated with the average district salary.

The results of this study can be evaluated in the light of the existing literature, even though comparisons can be difficult due to the scarce studies analyzing similar variables often reporting contrasting results [7,27]. The role played by altitude, for example, is still unclear, as it has been found in previous studies to be both negatively and positively associated with the spread of the disease [14], and this relationship is only partially supported by pathophysiological hypotheses [28]. Population density and number of inhabitants, on the other hand, resulted in being almost always positively associated with incidence, since a larger and more concentrated population increases human contact and consequently also the likelihood of contagion. In our study, we found similar correlations; nevertheless, the strength of these relationships fades when performing multivariate analyses.

Indeed, vaccination coverage was confirmed to be the most relevant predictor of the geographical distribution of SARS-CoV-2 incidence, being also associated with intensive care admissions and deaths. Although this is one of the first studies suggesting the presence of a herd immunity effect at the ecological level, a lower prevalence of the disease had already been predicted at a higher vaccination coverage [18], and the effectiveness of vaccination at the individual level has been well established in preventing severe SARS-CoV-2 disease [29,30], but also the contagion, both through increased protection against infection [31] and less contagiousness [32]. The lower vaccination coverage could be therefore the underlying reason of the increased incidence of the disease in the less inhabited and higher districts, geographically and culturally distant from the health governance authorities, which have very little trust placed both in them and their promoted public health interventions, such as vaccines.

Finally, we analyzed the role played by winter tourism, which is an important part of the local economy and was considered responsible for a significant spread of the virus in the first pandemic wave [17]. However, our study highlights how during the first winter without lockdowns, tourism contributed to a very limited extent to the spread of the disease in the resident population, even not followed by an increase in the severe form. This is probably due to an effective implementation of the social and community preventive measures, such as isolation of positive people, social distancing, personal protection equipment (PPE), made mandatory during that winter. Effective public health training and communication might prove to be crucial for managing outbreaks [33,34]. Clear communication on prevention and vaccination might help build trust and compliance with public health measures.

Geographical and socio-demographic features of this territory seem to have a greater influence on the hospital admissions, which did not follow exactly the distribution of incidence, ICU admissions, and mortality, and which resulted in being linked also to other variables, such as geographical location (higher rates were observed on the northern

border with other countries, lower in the south close to the other Italian regions) and the accommodation capacity of health facilities. If, for the former association, we can assume a protective role of the milder and sunnier climate in the southern districts of the province [35], as already shown by other reliable studies [4,5], the second association strongly suggests that living in a district with highly responsive healthcare structures facilitates access to it, underlying the potential of health inequalities. The possible presence of health disparities is further highlighted by the negative correlation between the CFR of infection and the average income of the district.

Finally, a regional infectious disease surveillance system is vital for monitoring and controlling disease spread. It allows for the timely collection and analysis of data, helping to identify outbreaks early and implement targeted interventions [36,37]. In Bolzano province, localized surveillance revealed how factors like vaccination coverage and population density influenced SARS-CoV-2 incidence. This enables efficient resource allocation and tailored public health measures, reducing disease burden.

This article has considerable strengths, such as the possibility of including all SARS-CoV-2 cases detected during the period of interest by the surveillance system implemented by the Local Health Authority and of analyzing a very wide and varied range of geographical, socio-cultural, and health-related variables in the area studied. Nevertheless, there are also some important limitations, first of all that of analyzing only a specific period of the pandemic (winter 2021/2022), without therefore considering the previous waves, the deaths that had already occurred, and their distribution, although the total number of cases recorded in the province up to that time we considered was less than a third of that at the end of the period studied [38].

Furthermore, a possible under-diagnosis could have occurred, especially in the more vaccinated district, since during the period under study, only non-vaccinated subjects had to routinely test negative to obtain a green pass to work or participate in most social activities [39]. Consequently, this could have led to the detection of a higher number of asymptomatic cases in districts with less vaccination coverage, explaining the higher incidence. However, the ICU admissions rate and mortality distribution showed similar correlations patterns of incidence rate, and similar associations patterns were observed when considering cases or inhabitants as rate denominators; all these findings suggest a uniform detection of cases across the territory. Furthermore, the number of SARS-CoV-2-positive hospitalizations and deaths data should be really accurate, since all hospitalized and deceased subjects were tested, and no private hospitals for acute diseases are found in South Tyrol.

Finally, ecological bias cannot be ruled out, as the variability of SARS-CoV-2 epidemics in South Tyrol is driven also by several underlying individual-level conditions. Further studies based on individuals are therefore needed to investigate deeper the main findings emerging from this study.

5. Conclusions

This study, by analyzing the distribution of SARS-CoV-2 and its outcomes during a high-incidence period in the multifaceted territory of South Tyrol, shows that, besides the effective protective effect played by vaccination coverage, several geographical and socio-cultural variables can be associated with the disease incidence, hospitalization, and mortality. Overall, more remote and higher-altitude areas with less availability of health facilities suffered the most, confirming the need of targeting specific subgroups and geographical areas by implementing specific territorial-tailored public health interventions to address more efficiently potential health inequities and reduce social and economic health-related costs both to individuals and society.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/ijerph21121604/s1>, Table S1: The 118 municipalities in South Tyrol grouped in the 20 districts and 4 health sections to which they belong; Table S2: Quantitative variables representing the geo-morphological and social characteristics of each district, health section, and the

whole province; Table S3: Qualitative variables representing the geo-morphological and health-service related characteristics of each district, health section, and the whole province; Table S4: Distribution of outcomes in each district, health section, and in the whole province; Table S5: Collinearity diagnoses between variables analyzed in the two linear regressions.

Author Contributions: A.L. contributed to all the phases of the present work, accompanied by L.P.; A.L., R.P., F.L., C.D.C., and F.Z. actively participated in the collection of the data; C.R. participated in the literature search, together with F.U.; A.L., L.P., and F.U. performed data analysis as well as writing the first draft of the manuscript; Critical analysis of results was performed by C.D.C., F.Z., and P.B. All phases of the study took place under the critical supervision of E.R. All authors contributed to the article and approved the submitted version. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of the South Tyrolean Healthcare Agency on 16 February 2022 with protocol code 0259655.

Informed Consent Statement: Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Data Availability Statement: The data presented in this study are available on request from the corresponding author due to privacy reasons.

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4 HEALTHIER CHILDREN FOR A HEALTHIER PLANET

4.0 INTRODUCTORY SUBCHAPTER

In this chapter, the focus was turned toward the connection between child nutrition, sustainability, and planetary health. Through the two published manuscripts presented in this chapter, we explored how children and planetary health are deeply connected (Palandri et al., 2024a; Rocca et al., 2025). Early childhood diets drive pressures on environment and climate, yet climate and environment may harm (and is already harming) children. These papers explored both what children eat (and the environmental footprint thereof) and how social systems (parents, schools, pediatricians) influence transitions toward sustainable, health-protective diets.

By situating child nutrition in a planetary health frame, these works extended my dissertation's trajectory from spatial and environmental epidemiology (Chapter 1) into exposure via diet, processed through social systems, with implications for both child health and ecological burden. In what follows, I present my author's contributions and the full abstract of the manuscripts, the full text of which you may find in the following chapters. All the manuscript presented in this chapter were published in peer-reviewed journals. As the second manuscript (Rocca et al., 2025) was published in Italian, with the intent of reaching and informing the local community and healthcare professionals, the original version is presented here together with a summary of its principal results.

4.0.1 Investigating Eating Habits of Children Aged between 6 Months and 3 Years in the Provinces of Modena and Reggio Emilia: Is Our Kids' Diet Sustainable for Their and the Planet's Health?

Lucia Palandri, Laura Rocca, Maria Rosaria Scasserra, Giacomo Pietro Vigezzi, Anna Odone, Lorenzo Iughetti, Laura Lucaccioni and Elena Righi

Journal: Healthcare

Doi: <https://doi.org/10.3390/healthcare12040453>

My contributions: Being the first and corresponding author I contributed to the conceptualization and design of the study, coordinated and supervised data

collection, wrote the initial manuscript as performed analysis and critical interpretation of results.

Abstract

A healthy and balanced diet is crucial for children's well-being and aids in preventing diet-related illnesses. Furthermore, unhealthy dietary habits indirectly impact children's health, as the food industry stands as one of the primary drivers of climate change. Evidence shows the Mediterranean diet is sustainable for both children's and the planet's health. The aim of this cross-sectional study was to evaluate the eating habits of children aged between 6 months and 3 years, in the province of Modena and Reggio Emilia, in Italy, along with their adherence to the guidelines for a healthy diet and examine the role of pediatricians in promoting knowledge about nutrition and sustainability. In our sample (218 children), most children exceeded the recommended meat and cheese intake, while consuming insufficient amounts of vegetables, fruit, and legumes. Vegetable and fruit consumption declined with the increase in age category while eating sweets, soft drinks, and processed food increased. Incorporating school meals' data into this analysis, we observed a modification in dietary compliance, characterized by an increase in meat and cheese consumption, alongside improvements in the intake of vegetables, fruits, fish, eggs, and legumes. This study suggests that supporting an integrated approach that combines social and educational initiatives is crucial. Future research should prioritize fostering sustainable eating habits within communities to facilitate dietary habits' transformation and encourage healthier lifestyles.

4.0.2 What Italian children usually eat: how to harm ourselves and the environment

[Cosa mangiano i nostri bambini: come far male a se stessi e anche all'ambiente. Consapevolezza dei genitori, ruolo del sistema scolastico e del pediatra nella transizione verso diete sane e sostenibili]

Laura Rocca, Laura Lucaccioni, Francesco Leo, Daniela Azzalini, Barbara Predieri, Viola Trevisani, Elena Righi, Lorenzo Iughetti, Lucia Palandri

Journal: Medico e Bambino

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My contributions: Being the last author I contributed to the conceptualization and design of the study, coordinated and supervised data collection, performed analyses and supervised critical interpretation of results. I supervised the writing of the initial draft and revised the final version.

Abstract

Background. The growth of the human population and expanding consumption patterns are among the primary causes of climate change and its health effects. The food system significantly contributes to climate change, as it is responsible for 26% of CO₂ emissions, uses 50% of habitable land and 70% of water resources and causes biodiversity loss. Animal-based and processed foods have a greater environmental impact, and the widespread adoption of a western diet is unsustainable for both the planet and human health. Materials and methods. This study examined the dietary habits of a pediatric sample (aged: 6 months-14 years) to assess adherence to guidelines by focusing on the consumption of high-impact foods. It also analysed whether school canteens promote a sustainable and healthy diet and assessed parents' awareness of these issues and the role of pediatricians in disseminating this information, as well. Results. The results showed an excessive consumption of meat (68%) and dairy products (49%), making the diet unsustainable for both human and planetary health. The school system, while promoting overall healthy eating, increases the consumption of high-impact foods already excessively consumed at home. There is a lack of parental awareness about what a healthy diet and its environmental impact are, topics that are also under-addressed by pediatricians. The paper highlights the need for better training for pediatricians to promote healthy and sustainable diets.

4.1 INVESTIGATING EATING HABITS OF CHILDREN AGED BETWEEN 6 MONTHS AND 3 YEARS IN THE PROVINCES OF MODENA AND REGGIO EMILIA: IS OUR KIDS' DIET SUSTAINABLE FOR THEIR AND THE PLANET'S HEALTH?

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Article

Investigating Eating Habits of Children Aged between 6 Months and 3 Years in the Provinces of Modena and Reggio Emilia: Is Our Kids' Diet Sustainable for Their and the Planet's Health?

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Abstract: A healthy and balanced diet is crucial for children's well-being and aids in preventing diet-related illnesses. Furthermore, unhealthy dietary habits indirectly impact children's health, as the food industry stands as one of the primary drivers of climate change. Evidence shows the Mediterranean diet is sustainable for both children's and the planet's health. The aim of this cross-sectional study was to evaluate the eating habits of children aged between 6 months and 3 years, in the province of Modena and Reggio Emilia, in Italy, along with their adherence to the guidelines for a healthy diet, and examine the role of pediatricians in promoting knowledge about nutrition and sustainability. In our sample (218 children), most children exceeded the recommended meat and cheese intake, while consuming insufficient amounts of vegetables, fruit, and legumes. Vegetable and fruit consumption declined with the increase in age category while eating sweets, soft drinks, and processed food increased. Incorporating school meals' data into this analysis, we observed a modification in dietary compliance, characterized by an increase in meat and cheese consumption, alongside improvements in the intake of vegetables, fruits, fish, eggs, and legumes. This study suggests that supporting an integrated approach that combines social and educational initiatives is crucial. Future research should prioritize fostering sustainable eating habits within communities to facilitate dietary habits' transformation and encourage healthier lifestyles.

Keywords: infant nutrition; dietary habits; sustainability; health promotion; greenhouse gas emissions; obesity prevention; public health; school meals

1. Introduction

The first three years of life are crucial for establishing healthy and balanced dietary habits to ensure that infants receive all the necessary nutrients for proper physical and cognitive development. This is vital in preventing nutrition-related problems, particularly obesity [1].

Early in life, it is recommended to adopt a balanced diet with appropriate fat and protein intake and ensuring proper consumption of fruit and vegetables. Inadequate food

items consumption, imbalances in macronutrients, as well as genetic and socio-economic factors, can contribute to an obesogenic environment. Pediatric obesity has seen a significant increase in prevalence over the last few decades, especially in high-income nations [2].

Indeed, the period of life between 6 and 36 months is characterized by a rapid transition from a milk-based diet to the introduction of various food categories daily. From the outset, parents should be able to choose healthy foods for the complementary feeding period. It is important to highlight that unbalanced pediatric nutrition and unhealthy dietary habits present two significant criticalities.

On one hand, pediatric nutrition stands as a pivotal life-course health determinant, notably influencing diseases like obesity, diabetes, and cardiovascular ailments [3]. These conditions incur substantial healthcare costs and societal burdens while impacting individual life expectancy and quality [4,5]. Already in 2015, Gorski and Roberto suggested how unhealthy dietary patterns, such as low fruit consumption and high levels of sodium intake, were responsible for up to 10% of global disability-adjusted life years [6]. Overweight and obesity, which represent important risk factors for diseases such as type 2 diabetes, heart disease, and high blood pressure, contribute significantly to mortality and disabilities in Europe, accounting for over 1.2 million deaths annually, approximately 13% of the region's total mortality. Childhood obesity not only affects immediate health and education but also predicts adult obesity and elevates the risk of non-communicable diseases. Italy's 'Okkio alla Salute' national survey (2019) [7] revealed concerning rates: 20.4% overweight and 9.4% obese children aged 8–9, with slightly higher obesity rates in males. Geographically, southern regions show a higher prevalence. Socioeconomic disparities and shorter breast-feeding durations correlate with increased obesity rates [8]. Numerous studies observe a global obesity trend linked to an increasing preference for Western diets, abandoning traditional ones. The initial decline in Mediterranean diet adherence, circa the 1960s, coincided with economic growth and food market industrialization, promoting processed foods and the greater availability of red meats and sugars, reducing vegetables and cereals consumption. Presently, Westernized diets, especially among young generations, contribute to lifestyle imbalances impacting energy intake and expenditure [3,9,10].

On the other hand, unhealthy dietary habits also indirectly impact children's health. The food industry stands as one of the primary drivers of climate change. With current diets and production practices, feeding 8 billion people is degrading terrestrial and aquatic ecosystems, depleting water resources, and contributing to greenhouse gas emissions [11]. The food system impacts the environment in three primary ways: CO₂ emissions, water consumption, and land use, further affecting biodiversity changes and water eutrophication [12].

Nutrition significantly influences disease prevention, impacting human health in morbidity and mortality. Additionally, as observed earlier, the food system notably impacts climate change, affecting agricultural productivity and generating adverse health outcomes. The Lancet Commission in 2019 categorized global epidemics of malnutrition, obesity, and climate change as components of a global syndemic, coexisting and interacting to produce intricate consequences [13]. Among all food categories, meat (especially red meat), dairy products, sweet beverages, and ultra-processed food represent the principal drivers of this global syndemic.

A healthy and balanced diet is crucial for the physical and mental well-being of children and aids in preventing diet-related illnesses. Evidence shows the Mediterranean diet as beneficial for both mental and physical health in adults and children [14]. This diet comprises a high consumption of vegetables, fruit, nuts, whole grains, and olive oil, moderate intake of fish and poultry, and low consumption of sweets, red meat, and dairy [15].

The aim of this study is to evaluate the eating habits of children aged 6 months to 3 years living in the province of Modena and Reggio Emilia, in Italy. The goal is to assess food items' consumption frequency and compare intake to pediatric dietary guidelines, accounting for school meals offerings as well, as there is a lack of information about eating

habits in this specific age range. The secondary aim of this study is also to assess parents' knowledge regarding the role of family pediatricians in disseminating knowledge about a healthy diet and the environmental impact of nutrition.

2. Materials and Methods

2.1. Study Design

This cross-sectional study was conducted through the development of a questionnaire targeting the parents of children aged between 6 months and 3 years. Adherence to nutritional guidelines was assessed using age-appropriate proportions from the 2018 CREA-Healthy Eating Guidelines [16]. We investigated items, portion, and frequencies and aggregated into 14 groups according to the CREA guidelines: *Total Cereals*: pasta, bread, rice, other cereals (barley, spelt, corn, quinoa, buckwheat, oat, kamut), bread substitutes (crackers, breadsticks), breakfast cereals. *Total Meat*: red meat (beef, veal, pork, sheep, goat, game meat, red meat in the pasta sauce), white meat (chicken, turkey, rabbit, white meat in the pasta sauce). *Processed Meat*: cured meat, dried meat, cooked ham, salami, bresaola, sausage, industrial burgers. *Fish*: fresh fish, frozen fish, clams, crustaceans. *Legumes*: beans, peas, chickpeas, lentils, grass peas. *Total Cheese*: light cheese, with less than 25% fat (mozzarella, stracchino, crescenza, ricotta, provola); fatty cheese, with more than 25% fat (robioia, caciotta cheese, aged cheese). *Vegetables*: fresh vegetables, leafy salads (excluding potatoes). *Sweets*: ice cream, pudding, candies, Nutella, chocolate, bakery products (cake, tarts, croissants, biscuits). *Sweet Soft Drinks*: fruit juice, orange soda, sweet tea, coke soda. *Processed Food*: sweet snacks, savory snacks, potato chips, ready-to-eat and pre-cooked food, fish sticks, fast food, fruit in syrup. To help parents to correctly assess portions, age-specific food portion images drawn from the photographic atlas of food portions for the pediatric age—Bassani Scotti Institute [17]—were shown in the questionnaire.

The questionnaire was designed to be easily accessible and anonymously fillable. The study did not gather specific personal data or identifiable information (e.g., names). We drew insights and utilized materials from the scientific literature related to studies on adherence to the Mediterranean diet in both adults and children [18,19].

The questionnaire was designed using Google Forms to facilitate its prompt online distribution and to ensure compatibility with smartphones, allowing completion within approximately ten minutes. It was distributed from 7 February to 11 May 2023, through various channels, including social media platforms targeting parents, instant messaging, and QR codes on flyers distributed to parents in Modena Hospital's pediatric clinics or displayed on posters in pediatricians' waiting areas.

The questionnaire was subdivided into three sections: *General socio-economic data*, aimed at characterizing the study population by collecting personal information from parents, detailing their child's and family's status; *Eating Habits*, designed to investigate the dietary habits of our pediatric population, estimating the quantities of food items consumed on a daily or weekly basis: parents were asked to respond only regarding meals that the child consumed at home; *Role of the Pediatrician*, which aimed to explore how frequently pediatricians provide recommendations on proper nutrition and the environmental sustainability of food production (details of variable categories in Tables 1 and 2).

2.2. Processing of the Results

Working groups were defined according to the European socioeconomic groups (ESeG) [20] classification composed of 3 classes of 9 categories: upper class (managers, professionals), middle class (technicians and associated professionals employees, small entrepreneur), working class (clerks and skilled service employees, skilled industrial employees, lower-status employees), and not working.

For dietary assessment, after collecting responses for single food items, we aggregated the categories 'Total cereals', 'Total meat', and 'Total cheese', derived from the overall consumption frequencies of their respective subclasses. Furthermore, to provide a more accurate assessment, the sample was divided into those who ate lunch at school and those who did

not. In the first scenario, we supplemented parent-provided food with item frequencies from school meals. To ensure anonymity, we could not ascertain the child's school nor their exact food consumption, we examined school menus from several towns in the province of Modena and Reggio Emilia to determine the average frequency of offerings for different food categories, with the assumption that the child consumed all provided items. In these provinces, school meals are strictly regulated by the two local health authorities and are similar across different educational facilities.

We then categorized responses about food consumption frequency, labeling them as "According to Guidelines", "Below Guidelines", or "Above Guidelines". Yet, for certain foods (cereals, fresh fruit, and vegetables), excess consumption did not indicate non-compliance with guidelines. In these cases, a higher intake was marked "According to Guidelines". To gauge overall adherence, we assigned scores: 1 for "According to Guidelines" and 0 for "Below or Above Guidelines". This scoring system allowed us to tally scores across food categories, generating a range from 0 to 14, indicating adherence levels to Italian dietary guidelines. For instance, a higher score suggests closer alignment with recommended consumption frequencies outlined in dietary guidelines. This method facilitated an overview of our population's adherence to dietary recommendations, emphasizing variations in adherence levels to these guidelines among the studied group. The study aimed to assess our sample's adherence to the Italian dietary guidelines rather than the Mediterranean diet. Consequently, previously validated Mediterranean diet indices were not utilized. Additionally, the most commonly used scores in the pediatric population, such as the relative Mediterranean diet score (rMED) [21,22] or the KIDMED score [19,23,24], have been validated from 2 years of age, which does not encompass our specific population.

Finally, to assess if there were patterns in dietary adherence, we recategorized adherence responses as yes (According to Guidelines) and no (Below or Above Guidelines), and we performed an adherence clustering analysis.

2.3. Statistical Analysis

Categorical variables were summarized by absolute and relative frequencies. The mean and standard deviation (SD) or median and interquartile range (IQR) were used to summarize continuous variables according to their distribution. Pearson's chi-square test or Fisher's exact test was used to compare categorical variables.

For the analysis of adherence clustering, we used the Jaccard similarity coefficient (values between 0 and 1, where the higher the number, the higher the co-occurrence of adherence to a specific food category) and presented as a hierarchically ordered heatmap. Clustering was obtained using the complete linkage agglomerative hierarchical clustering method. Estimation of the optimal number of clusters was performed using the silhouette method (Supplementary Figures S1 and S2) [25]. Missing data were dealt with in complete-case data analysis. We used Excel (Microsoft, Redmond, WA, USA) and R (R Core Team version 4.1.1 (2021), Vienna, Austria [26]) for descriptive statistics, plotting and advanced statistical analysis, with packages including tidyverse, ggplot2, ggrepel, dendextend, gplots, and UpSetR.

2.4. Ethical Considerations, Patient Information, and Written Informed Consent

This study did not require the approval of an ethics committee because the questionnaire data were anonymous, making it impossible to identify and harm any respondent. Moreover, neither drugs nor medical devices were prescribed or administered. As a result, the responses were collectively examined while taking into account Italian and European regulations governing the management of personal data [27–29].

In more detail, anonymity was granted by not requesting the name, surname, and date of birth. In order to retrieve information about the geographical area of participants while still preserving anonymity, the province in which the participants lived was asked instead of their address. To further protect identities, it was possible to choose not to specify a gender.

The cover letter of the questionnaire informed the participants that the data would be used only for scientific purposes, that the raw data would be archived for a maximum of five years, and they would be accessible only by researchers at the University of Modena and Reggio Emilia. Google Forms was used only to spread the questionnaire and to collect data. All the collected data were then downloaded and stored on a professional computer and protected by a password.

It was possible to complete the questionnaire only after the participants declared that they understood the methods and purposes of the study by clicking on the “I give the consent” option in reference to the processing of personal data. Participants who disagreed were redirected to a thank you message.

3. Results

Tables 1 and 2 describe the overall characteristics of caregivers and children of our study involving 218 families living in the provinces of Modena (70%—153 families) and Reggio Emilia (30%—65 families), in the Emilia-Romagna region, with children aged from 6 months to 3 years.

Table 1. Demographic and socio-economic characteristics of caregivers and families, overall and stratified by age categories.

Variables		Total (%)	6 m–1 y	2–3 y	p-Value
Provinces					<0.001
	Modena	153 (70%)	58 (88%)	95 (63%)	
	Reggio Emilia	65 (30%)	8 (12%)	57 (38%)	
Median Age—Mother		34 (32–37)	33 (31–36)	35 (32–38)	0.035
Median Age—Father		36 (33–40)	36 (32–40)	36 (33–40)	0.3
	Unknown	1	0	1	
Nationality—Mother					0.4
	Italian	212 (97%)	63 (95%)	149 (98%)	
	Not Italian	6 (3%)	3 (5%)	3 (2%)	
Nationality—Father					0.4
	Italian	210 (96%)	65 (98%)	145 (95%)	
	Not Italian	8 (4%)	1 (2%)	7 (2%)	
Educational Level—Mother					0.2
	Up to high school	71 (33%)	24 (36%)	47 (31%)	
	University	146 (67%)	42 (64%)	104 (69%)	
	Unknown	1	0	1	
Educational Level—Father					0.7
	Up to high school	114 (56%)	35 (53%)	79 (57%)	
	University	91 (44%)	31 (47%)	60 (43%)	
	Unknown	13	0	13	
Occupational Category—Mother					0.7
	Upper class	66 (30%)	23 (35%)	43 (28%)	
	Middle class	42 (19%)	11 (17%)	31 (20%)	
	Working class	100 (46%)	30 (45%)	70 (46%)	
	Not working	1 (1%)	2 (3%)	8 (5%)	
Occupational Category—Father					0.5
	Upper class	64 (31%)	24 (37%)	40 (29%)	
	Middle class	52 (25%)	17 (26%)	35 (25%)	
	Working class	88 (43%)	24 (37%)	64 (46%)	
	Not working	1 (1%)	0 (0%)	1 (1%)	
	Unknown	13	1	12	
Marital Status					0.9
	Married	106 (49%)	31 (47%)	75 (49%)	
	Living with partner	105 (48%)	33 (50%)	72 (47%)	
	Single/Separated	7 (3%)	2 (3%)	5 (3%)	
	Widowed				

Table 1. Cont.

Variables		Total (%)	6 m–1 y	2–3 y	p-Value
Family Income					0.4
	EUR > 2500	110 (50%)	32 (48%)	78 (51%)	
	EUR 1500–2499	52 (24%)	13 (20%)	39 (26%)	
	EUR < 1499	11 (5%)	3 (5%)	8 (5%)	
	Unknown	45 (21%)	18 (27%)	27 (18%)	
Number of Children					<0.001
	1 child	157 (72%)	61 (94%)	96 (63%)	
	2 children	57 (26%)	4 (6%)	53 (35%)	
	3 or more children	3 (1%)	0 (0%)	3 (2%)	
	Unknown	1	1	0	
Grandparents' Aid					0.3
	Yes	159 (73%)	51 (77%)	108 (71%)	
	No	59 (27%)	15 (23%)	44 (29%)	
Other Aids					<0.9
	Babysitter	20 (9%)	6 (9%)	14 (9%)	
	Domestic worker	44 (20%)	12 (18%)	32 (21%)	
	Both aids	5 (2%)	1 (2%)	4 (3%)	
	None	149 (68%)	47 (71%)	102 (67%)	

Table 2. Characteristics of children in our sample, overall and stratified by age categories.

		Tot = 218	6 m–1 y	2–3 y	p-Value
Overall			66 (30%)	152 (70%)	
Sex					0.7
	Male	108 (50%)	32 (48%)	78 (51%)	
	Female	110 (50%)	34 (52%)	74 (49%)	
Chronic Condition					0.015
	Yes	4 (2%)	0 (0%)	4 (3%)	
	No	213 (98%)	65 (100%)	148 (97%)	
	Unknown	1	1	0	
Nursing					0.2
	Breastfeeding	138 (63%)	40 (61%)	98 (64%)	
	Combination	51 (23%)	20 (30%)	31 (20%)	
	Formula	29 (14%)	6 (9%)	23 (15%)	
	Breastfeeding duration mean	12 (9–18) months	12 (10–12) months	13 (8–18) months	
Weaning					0.030
	Conventional	77 (35%)	15 (23%)	62 (41%)	
	Supplementary feeding	115 (53%)	43 (65%)	72 (47%)	
	Baby-led	26 (12%)	8 (12%)	18 (12%)	
	Unknown	1	0	1	
	Weaning start mean	6 (5.5–6) months	6 (5.5–6) months	6 (5.5–6) months	
Baby food					0.9
	Daily	70 (32%)	20 (30%)	50 (33%)	
	1–2 times per week	47 (22%)	15 (23%)	62 (41%)	
	1–2 times per month	32 (15%)	11 (17%)	21 (14%)	
	Not used	69 (31%)	20 (30%)	49 (32%)	
Meals					<0.001
	At home	50 (23%)	40 (61%)	10 (6.6%)	
	At home and school	168 (77%)	26 (39%)	142 (93%)	

The questionnaire was filled out by 208 mothers and 10 fathers. The median age for the mothers was 34 years old (interquartile range 32–37 years), and the median age for the fathers was 36 years old (interquartile range 33–40 years). Most of the parents were Italian. For marital status, 49% of the parents were married, 48% were living with a partner,

and the remaining parents were either single, separated, or widowed (respectively, 2%, 1%, and 1%).

In terms of educational levels, 67% of the mothers held a master's degree or a bachelor's degree, and 33% had a secondary school diploma or a professional school diploma. Among the fathers, 44% held a master's or a bachelor's degree, 56% had a secondary school diploma, and 13 did not respond.

Regarding occupational categories, mothers were distributed as follows: 30% upper class, 19% middle class, 46% working class, and 5% not working. Conversely, fathers are distributed as 31% upper class, 25% middle class, 43% working class, 1% not working, and for 13 no answer was given. The families in our sample had a monthly family income as follows: 5% less than EUR 1499, 24% between EUR 1500 and 2499, and 50% above EUR 2500. The remaining 21% preferred not to respond.

Out of the families in our sample, 72% had one child, 26% had two children, and the remaining 3 had three or more children. One participant did not respond to the question. In 73% of cases, our families could rely on the assistance of their grandparents, while 27% did not. Additionally, or in lieu of being helped by grandparents, 9% of families relied on a babysitter for childcare, 20% on a domestic worker for household duties, 2% had both types of assistance, and the remaining 68% did not rely on any form of assistance [30].

In our sample, 92% of families had no members following a personalized diet, while in the remaining, 8% were vegetarian, had celiac disease, were lactose intolerant, pescatarian, vegan, or flexitarian, and 4 did not provide a response (Table 1).

3.1. Children's Characteristics

Regarding the children of our sample, we had 50% females and 50% males, respectively, 110 and 108. In total, 66 children (30%) were aged between 6 months and 1 year (6 to 23 months), and 152 children (70%) were aged between 2 and 3 years (24 to 47 months). They were mostly healthy and had no food allergies or intolerances.

Regarding the nursing characteristics of the children in our sample, 63% of the children were breastfed exclusively, 23% of the children were nursed in combination, and 14% were fed formula solely. The interquartile range for the length of breastfeeding was 9 to 18 months, with a median of 12 months. Weaning usually started at 6 months of age (median), with an interquartile range of 5 to 6 months. In terms of weaning approaches, 35% of parents opted for conventional weaning, 53% chose supplementary feeding, and 12% opted for baby-led weaning. During the weaning process, baby food was used daily in 32% of cases, not utilized in 31% of cases, used 1–2 times per week in 25% of cases, and used at least 1–2 times per month in 15% of cases (Table 2).

3.2. Eating Habits

The frequency of the main food groups intake for the entire sample and adherence to CREA guidelines [16], stratified by age category, is presented in Tables 3 and 4, respectively. For the food frequencies of all the food items (e.g., red meat, white meat, etc.) please refer to Supplementary Table S1.

Regarding cereals consumption, it is observed that 67% of our pediatric population consumed one portion of cereals multiple times a day, predominantly pasta and bread.

Concerning total meat consumption, 17% of the sample adhered to the CREA Guidelines (GL), consuming meat three times a week, while 63% consumed meat more frequently, ranging from four times a week to several times a day. In 38% of cases, red meat consumption exceeded the once per week recommendation. For fish, 49% of the sample ate it two to three times a week, and 40% ate it at least once. As for legumes, 50% of the children consumed two to three servings a week, aligning with the GL and adhering to recommendations for both the age group of 6 months to 1 year (46%) and 2–3 years (53%).

Table 3. Children’s food frequency consumption for the main food categories in the overall sample and divided by age categories.

		Tot = 218	6 m–1 y = 66	2–3 yrs = 152	p-Value
Total Cereals					0.004
	2–3 per day	147 (67%)	53 (80%)	94 (62%)	
	1 per day	29 (13%)	10 (15%)	19 (13%)	
	Almost daily	35 (16%)	3 (4.5%)	32 (21%)	
	3–5 per week	5 (2%)	0 (0%)	5 (3%)	
	2 per week	2 (1%)	0 (0%)	2 (1%)	
Total Meat					0.2
	1–2 per day	28 (13%)	12 (18%)	16 (11%)	
	Almost daily	31 (14%)	10 (15%)	21 (14%)	
	4 per week	79 (36%)	23 (35%)	56 (37%)	
	3 per week	37 (17%)	10 (15%)	27 (18%)	
	2 per week	30 (14%)	6 (9%)	24 (16%)	
	1 per week	7 (3%)	1 (2%)	6 (4%)	
	Rarely/never	28 (13%)	12 (18%)	16 (11%)	
Fish					0.5
	4–5 per week	8 (4%)	3 (5%)	5 (3%)	
	2–3 per week	107 (49%)	37 (56%)	70 (46%)	
	1 per week	88 (40%)	22 (33%)	66 (43%)	
	Rarely/never	15 (7%)	4 (6%)	11 (7%)	
Cheese					0.12
	1 per day	77 (35%)	32 (48%)	45 (30%)	
	Almost daily	34 (16%)	9 (14%)	25 (16%)	
	4–5 per week	13 (6%)	2 (3%)	11 (7%)	
	3–4 per week	42 (19%)	8 (12%)	34 (22%)	
	2–3 per week	27 (12%)	7 (11%)	20 (13%)	
	1–2 per week	25 (11%)	8 (12%)	17 (11%)	
Legumes					0.001
	Almost daily	11 (5%)	6 (9%)	5 (3%)	
	4–5 per week	25 (11%)	15 (23%)	10 (7%)	
	2–3 per week	108 (50%)	28 (42%)	80 (53%)	
	1 per week	58 (27%)	11 (17%)	47 (31%)	
	Rarely/never	16 (7%)	6 (9%)	10 (7%)	
Vegetables					<0.001
	1–2 per day	108 (50%)	48 (73%)	60 (39%)	
	1 per day	39 (18%)	5 (8%)	34 (22%)	
	4–6 per week	42 (19%)	10 (15%)	32 (21%)	
	2–3 per week	20 (9%)	2 (3%)	18 (12%)	
	1 per week	5 (2%)	0 (0%)	5 (3%)	
	Rarely/never	4 (2%)	1 (2%)	3 (2%)	
Fruit					0.001
	1–2 per day	121 (56%)	44 (67%)	77 (51%)	
	1 per day	49 (22%)	9 (14%)	40 (26%)	
	4–6 per week	29 (13%)	8 (12%)	21 (14%)	
	2–3 per week	10 (5%)	2 (3%)	8 (5%)	
	1 per week	4 (2%)	0 (0%)	4 (3%)	
	Rarely/never	5 (2%)	3 (5%)	2 (1%)	
Sweets					<0.001
	1–2 per day	3 (1%)	0 (0%)	3 (2%)	
	Almost daily	21 (10%)	1 (2%)	20 (13%)	
	3–5 per week	33 (15%)	6 (9%)	27 (18%)	
	1–2 per week	71 (33%)	6 (9%)	65 (43%)	
	Rarely/never	90 (41%)	53 (80%)	37 (24%)	
Processed Foods					<0.001
	1–2 per day	3 (1%)	0 (0%)	3 (2%)	
	3–5 per week	18 (9%)	1 (2%)	17 (12%)	
	1–2 per week	55 (26%)	7 (11%)	48 (33%)	
	Rarely/never	136 (64%)	58 (88%)	78 (53%)	
	Unknown	6	0	6	

Table 4. Adherence to food consumption recommended by the Italian guidelines for healthy eating (CREA 2018) [16] for the main food categories calculated only on home-consumed meals, overall and stratified by age categories. * Expressed as the median (IQR).

	Tot = 218 (%)	6 m–1 y = 66	2–3 yrs = 152	p-Value
Overall Adherence score *	7.00 (5.00, 8.00)	7.00 (6.00, 8.00)	6.00 (5.00, 7.25)	0.015
Cereals Adherence				0.10
Less than GL	7 (3%)	0 (0%)	7 (5%)	
According to GL	211 (97%)	66 (100%)	145 (95%)	
Meat Adherence				0.6
Less than GL	43 (20%)	11 (17%)	32 (21%)	
According to GL	37 (17%)	10 (15%)	27 (18%)	
More than GL	138 (63%)	45 (68%)	93 (61%)	
Fish Adherence				0.3
Less than GL	103 (47%)	26 (39%)	77 (51%)	
According to GL	107 (49%)	37 (56%)	70 (46%)	
More than GL	8 (4%)	3 (5%)	5 (3%)	
Legumes Adherence				<0.001
Less than GL	74 (34%)	17 (26%)	57 (38%)	
According to GL	108 (50%)	28 (42%)	80 (53%)	
More than GL	36 (17%)	21 (32%)	15 (10%)	
Cheeses Adherence				0.2
Less than GL	25 (11%)	8 (12%)	17 (11%)	
According to GL	69 (32%)	15 (23%)	54 (36%)	
More than GL	124 (57%)	43 (65%)	81 (53%)	
Vegetables Adherence				<0.001
Less than GL	110 (50%)	18 (27%)	92 (61%)	
According to GL	108 (50%)	48 (73%)	60 (39%)	
Fresh Fruit Adherence				0.029
Less than GL	97 (44%)	22 (33%)	76 (49%)	
According to GL	121 (56%)	44 (67%)	77 (51%)	
Dried Fruit Adherence				0.095
Less than GL	136 (62%)	48 (73%)	88 (58%)	
According to GL	22 (10%)	6 (9%)	16 (11%)	
More than GL	60 (28%)	12 (18%)	48 (32%)	
Milk Adherence				<0.001
Less than GL	136 (62%)	57 (86%)	79 (52%)	
According to GL	72 (33%)	9 (14%)	63 (41%)	
More than GL	10 (5%)	0 (0%)	10 (7%)	
Yogurt Adherence				0.001
Less than GL	158 (72%)	57 (86%)	101 (66%)	
According to GL	37 (17%)	9 (14%)	28 (18%)	
More than GL	23 (11%)	0 (0%)	23 (15%)	
Eggs Adherence				0.3
Less than GL	165 (76%)	54 (82%)	111 (73%)	
According to GL	50 (23%)	11 (17%)	39 (26%)	
More than GL	3 (1%)	1 (2%)	2 (1%)	
Sweets Adherence				<0.001
According to GL	161 (74%)	59 (89%)	102 (67%)	
More than GL	57 (26%)	7 (11%)	50 (33%)	
Soft Drinks Adherence				<0.001
According to GL	166 (76%)	61 (92%)	105 (69%)	
More than GL	52 (24%)	5 (8%)	47 (31%)	
Processed Food Adherence				<0.001
According to GL	136 (62%)	58 (88%)	78 (51%)	
More than GL	82 (38%)	8 (12%)	74 (49%)	

Fifty-seven percent of children consumed more cheese than advised by the GL, with a higher prevalence in children aged 6 months to 1 year than 2–3 years old (65% and 53%, respectively).

Regarding vegetable consumption, up to 50% of children adhered to the GL, consuming them more than once a day, with the percentage decreasing from 73% in the age group 6 months–1 year and to 39% from 2 to 3 years.

Approximately 13% of children consumed vegetables less than four times a week. Regarding fruit, 56% of children adhered to the GL, consuming more portions per day, with a higher percentage in the 6 months–1 year age group, reaching 67%. Concerning eggs, 76% consumed less than the GL.

As for adherence to the optimal consumption of sweets, soft drinks, and processed food, we observed an age-dependent declining trend with children having an extremely high adherence, over 88% in early infancy, decreasing up to 51% in children aged 2–3 years old.

Overall adherence to the GL was higher in children aged 6 months (7.00) to 1 year than 2–3 years old (6.00).

To evaluate the impact of schools on adherence to dietary guidelines (GL), we incorporated the food consumption data of a typical school weekly meal for the 77% of children who consumed lunch at school.

Figure 1 shows how having lunch at school increased the overall number of food categories to which the child adhered. That being said, eating a school lunch demonstrated varying effects on GL adherence, improving it in certain categories while worsening it in others.

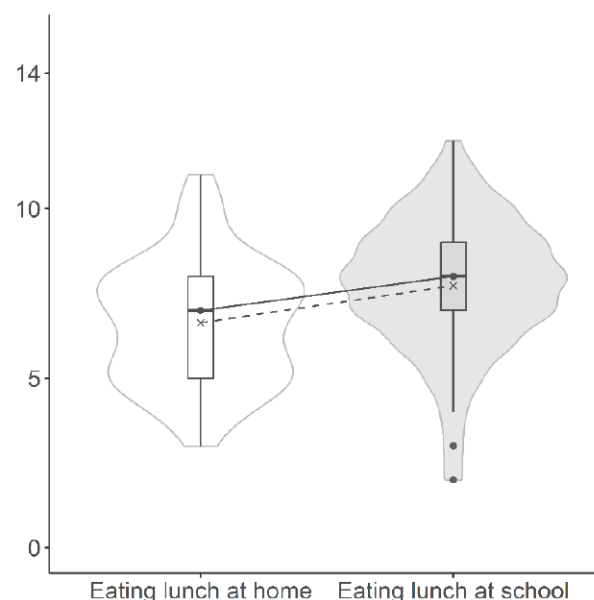


Figure 1. Adherence score to food consumption recommended by the Italian guidelines for healthy eating (CREA 2018) [15] differentiated by school meal consumption. Black continuous lines connect median values (black dot), while black dashed lines connect means (x).

Figure 2 (refer to Supplementary Table S2 for frequencies) depicts the variations in food categories when accounting for school meals among children having lunch at school. The inclusion of school meals notably increased meat and cheese consumption. Overall, on one hand, meat and cheese consumption exceeded the GL in 89% and 83% of children, respectively. On the other hand, counting school meals increased the adherence to vegetables, fruit, fish, eggs, and legumes recommendations, resulting in a general higher adherence score in children who had meals at school (median of 8.00 vs. 7.00).

Table 5 shows the difference in GL adherence among children who ate at home and at school.

Table 5. Adherence to food consumption recommended by the Italian guidelines for healthy eating (CREA 2018) [16] for the main food categories calculated including standard school meals for those children who had lunch at school, overall and stratified by consuming lunch at home or at school.
* Expressed as the median (IQR).

	Tot = 218 (%)	Eating Lunch at School (168)	Eating Lunch at Home (50)	p-Value
Overall Adherence Score *	8.00 (6.00–9.00)	8.00 (7.00, 9.00)	7.00 (5.00, 8.00)	<0.001
Cereals Adherence				0.052
Less than GL	2 (1%)	0 (0%)	2 (4%)	
According to GL	216 (99%)	168 (100%)	48 (96%)	
Meat Adherence				<0.001
Less than GL	11 (5%)	2 (1%)	9 (18%)	
According to GL	14 (6%)	6 (9%)	8 (16%)	
More than GL	193 (89%)	160 (95%)	33 (66%)	
Fish Adherence				0.5
Less than GL	103 (47%)	78 (46%)	25 (50%)	
According to GL	107 (49%)	85 (51%)	22 (44%)	
More than GL	8 (4%)	5 (3%)	3 (6%)	
Legumes Adherence				<0.001
Less than GL	25 (11%)	11 (7%)	14 (28%)	
According to GL	157 (72%)	140 (83%)	17 (34%)	
More than GL	36 (17%)	17 (10%)	19 (38%)	
Cheeses Adherence				<0.001
Less than GL	7 (3%)	0 (0%)	7 (14%)	
According to GL	30 (14%)	18 (11%)	12 (24%)	
More than GL	181 (83%)	150 (89%)	31 (62%)	
Vegetables Adherence				0.002
Less than GL	45 (21%)	27 (16%)	18 (36%)	
According to GL	173 (79%)	141 (84%)	32 (64%)	
Fresh Fruit Adherence				<0.001
Less than GL	35 (16%)	16 (10%)	19 (38%)	
According to GL	183 (84%)	152 (90%)	31 (62%)	
Dried Fruit Adherence				0.8
Less than GL	136 (62%)	103 (61%)	33 (66%)	
According to GL	22 (10%)	18 (11%)	4 (8%)	
More than GL	60 (28%)	47 (28%)	13 (26%)	
Milk Adherence				0.001
Less than GL	136 (62%)	94 (56%)	42 (84%)	
According to GL	72 (33%)	65 (39%)	7 (14%)	
More than GL	10 (5%)	9 (5)	1 (2%)	
Yogurt Adherence				0.3
Less than GL	158 (72%)	118 (70%)	40 (80%)	
According to GL	37 (17%)	30 (18%)	7 (14%)	
More than GL	23 (11%)	20 (12%)	3 (6%)	
Eggs Adherence				<0.001
Less than GL	73 (33%)	29 (17%)	44 (88%)	
According to GL	97 (44%)	92 (55%)	5 (10%)	
More than GL	48 (22%)	47 (28%)	1 (2%)	
Sweets Adherence				0.026
According to GL	161 (74%)	59 (89%)	102 (67%)	
More than GL	57 (26%)	7 (11%)	50 (33%)	
Soft Drinks Adherence				0.063
According to GL	166 (76%)	123 (73%)	43 (86%)	
More than GL	52 (24%)	45 (27%)	7 (14%)	
Processed Food Adherence				0.003
Less than GL	82 (38%)	72 (43%)	10 (20%)	
More than GL	136 (62%)	96 (57%)	40 (80%)	

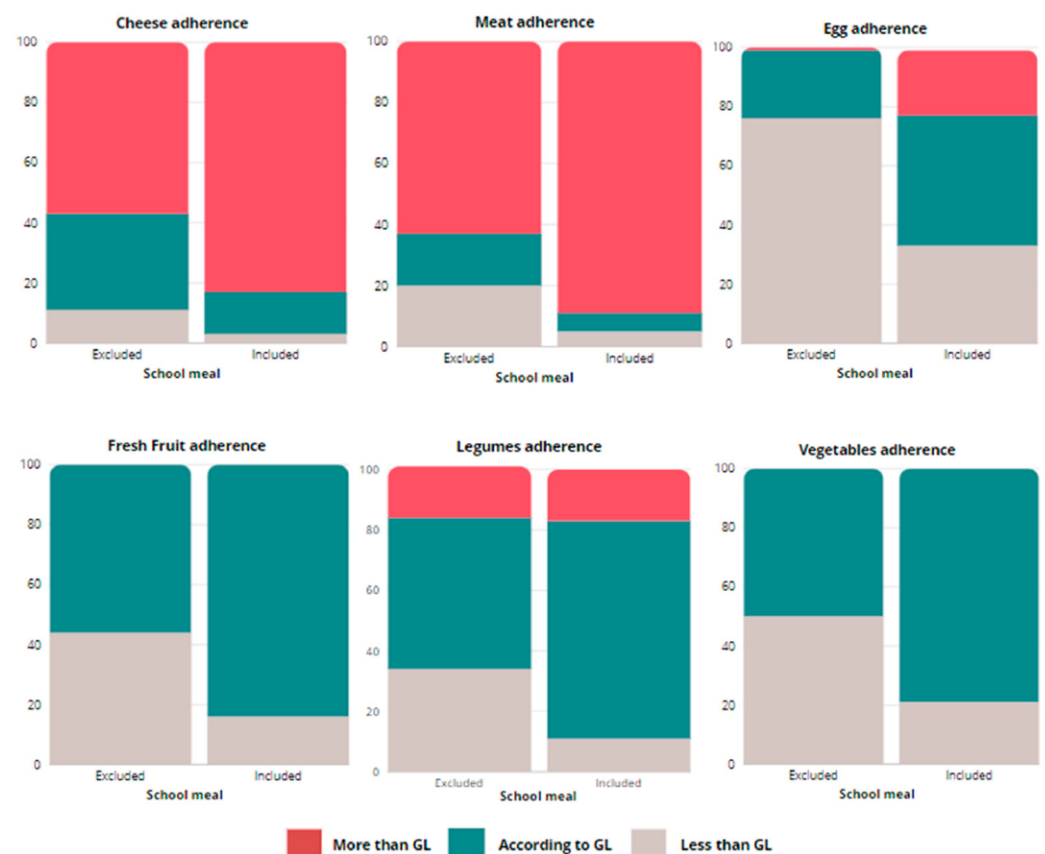


Figure 2. Differences for adherence in food categories comparing food categories excluding and including standard school meals for the children who had lunch at school.

The results of the clustering analysis of food categories adherence showed two distinct clusters of adherence phenotypes (Figure 3). Food categories that more frequently clustered were adherence to the GL on industrial products, sweets, soft drinks, and cereals (forming a sub-cluster) and legumes, fish, vegetables, and fruit (forming a second sub-cluster) with a Jaccard similarity index (which defines the co-occurrence of a pair of food categories) varying from 0.62 to 0.76 for the first sub-cluster and from 0.35 to 0.54 for the second sub-cluster. This cluster was followed by a second cluster formed by the remaining food categories showing a Jaccard similarity index ranging from 0.17 to 0.34 and forming a much looser association. When accounting for school meals, three clusters seemed to appear, with one resembling the first cluster. A second cluster formed by adequate adherence to eggs, fish, cow's milk, and dried fruit that branches from the same cluster of the first one and an independent loose cluster of meat, yogurt, and cheese (please refer to Supplementary Tables S3 and S4 for Jaccard index matrices).

Finally, we asked parents if and how often their pediatricians spoke to them about a healthy diet and environmental sustainability. Most parents reported that their pediatricians discussed healthy eating at each visit (41%), followed by often (36%), sporadically (19%), and never (4%). Interestingly, families whose pediatricians talked about a healthy diet often or at each visit had a higher adherence score (median of 6 vs. 7). However, the majority of pediatricians never addressed topics related to environmental sustainability (78%), with only 7% performing this often or at each visit.

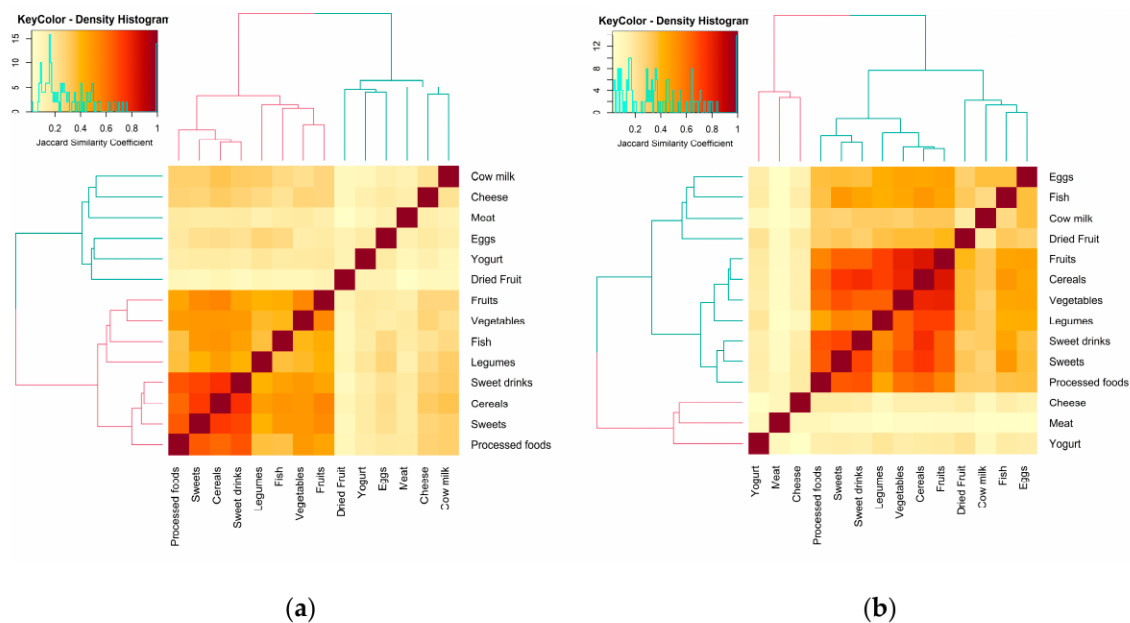


Figure 3. Dendrogram and heatmap describing adherence clustering for main food categories and representing food categories adherence co-occurrence. Co-occurrence was calculated using the Jaccard similarity index, where 0 (light yellow) represents when two food categories adherence never occur together and 1 (dark red) if they always appear together. Clustering was obtained using the complete linkage agglomerative hierarchical clustering method: (a) without accounting for school meals, (b) accounting for school meals.

4. Discussion

The study encompassed 218 families with children aged 6 months to 3 years in the Modena and Reggio Emilia provinces. The findings revealed parents' higher education levels and diverse occupational statuses. Breastfeeding was prevalent (63%), and varied weaning practices were observed.

In our population, we have observed some unhealthy dietary patterns; in particular, most children exceeded the recommended meat and cheese intake while insufficiently consuming vegetables, fruit, and legumes. Furthermore, consumption of vegetables and fruits declined with increasing age categories. Conversely, eating sweets, soft drinks, and processed food increased with age. School meals notably impacted dietary compliance, elevating meat and cheese intake above the recommended GL while improving vegetable, fruit, fish, eggs, and legume intake.

In our population, we have identified noteworthy unhealthy dietary patterns. Specifically, a significant proportion of children exhibited elevated consumption levels of meat and cheese, exceeding the recommended GL, coupled with a suboptimal intake of essential food groups such as vegetables, fruits, and legumes. Notably, the consumption of vegetables and fruits exhibited a declining trend as age categories advanced. Conversely, there was an observed increase in the consumption of sweets, soft drinks, and processed foods as age advanced.

The influence of school meals on dietary habits was evident, resulting in heightened adherence to meat and cheese consumption, albeit exceeding recommended thresholds, and concurrently enhancing the intake of vegetables, fruits, fish, eggs, and legumes. Through clustering analysis, distinct dietary patterns emerged, underscoring both prevalent adherence to unhealthy food groups and commendable compliance with healthier dietary choices.

Our findings align with those reported by Steenbergen et al. in 2021 [31], who conducted a study on the dietary habits of Dutch children aged 1 to 3 years. The outcomes of our study parallel theirs, revealing similar dietary patterns. Notably, the intake of animal proteins in the Dutch population was generally within acceptable limits, with

only 5% above the recommended guidelines. However, vegetable consumption fell below recommended levels in over 50% of toddlers, despite each child consuming at least one serving of vegetables daily.

Focusing on vegetable consumption in our population, up to 50% of children adhered to the recommended GL, with adherence rates decreasing from 73% in the age group of 6 months to 1 year, and further declining to 39% in the 2 to 3 years age bracket. Additionally, in the Dutch study it was found that the consumption of bread, cereals, and soft drinks exceeded the recommended guidelines. In contrast to this, our population exhibited an exceptionally high adherence rate in early infancy, exceeding 88%, which gradually decreased to 51% in children aged 2 to 3 years.

In 2014, Tognon et al. conducted a study focusing on adherence to the Mediterranean diet in European children aged 2 to 9 years [32]. The analysis considered the daily intake of vegetables and legumes, fresh and dried fruits, cereals and potatoes, fish, meat, and dairy, using data from SACINA. It is important to note that, unlike our study, this covered a different age range with older children, and the socio-economic heterogeneity across various European countries must also be considered.

In this study, Swedish children were found to have below-standard consumption levels for both meat and dairy. Both Swedish and Estonian children exhibited higher intakes of cereals and potatoes compared to established guidelines. Optimal fish consumption was observed in Spanish children. Similar to our analyses, this study also assessed how the introduction of school meals influences adherence to the Mediterranean diet guidelines. In Swedish preschoolers (aged 2 to 5 years), the addition of school meals resulted in decreased adherence, while the opposite trend was observed in school-aged children (aged 6 to 9 years), leading to improved adherence. Improved adherence with the addition of school meals (both in preschool and school age) was also noted in Hungarian and Spanish children. In our population, having lunch at school demonstrated varying effects on GL adherence, improving it in certain categories (vegetables, fruit, fish, eggs, and legumes) while worsening it in others (meat and cheese).

Through an examination of international scientific literature, it becomes evident that most studies exploring the dietary habits of young children tend to concentrate on these habits and their implications for the child's growth. They also investigate the potential consequences of an unbalanced dietary choice. However, these studies often overlook the crucial connection between a healthy diet and environmental sustainability. Our study aims to fill this gap by emphasizing the importance of addressing both aspects, shedding light on their interconnected nature. Notably, pediatricians in the Italian healthcare system often discussed healthy eating topics but rarely addressed issues related to environmental sustainability.

This study emphasizes the need for targeted interventions to improve children's dietary habits, especially in light of the inconsistent changes observed in the adherence to healthy diets, as well as infants' well-being during and beyond pandemic times [33,34]. Greater attention should be given to proper nutrition in the early years of life, extending through the preschool-age period.

According to Temme et al., adopting a healthy diet would also help to reduce the environmental impact by lowering greenhouse gas emissions and minimizing the extent of cultivated land for animal fodder, in order to promote both sustainability and the reduction in environmental damage [35].

In addressing the issue of children eating more meat and dairy products than recommended, it is crucial to consider the potential health and sustainability implications of such dietary patterns. Research has shown that reducing the intake of animal proteins during infancy may also decrease the risk of experiencing an early resurgence of obesity [1,36].

In pursuit of this goal, the EAT-Lancet dietary GL recommend decreasing the intake of animal proteins, particularly those derived from red meat, milk, and dairy products, transitioning towards increased consumption of plant-based foods [37]. Limiting the intake of animal protein, with particular reference to animal-origin proteins, GL suggests higher

quantities of poultry meat over beef and pork. Likewise, there is a need to enhance the consumption of legumes, nuts, and vegetables, and in addition, refined grains should be replaced with whole grains whenever feasible [11].

The many sustainable diets, such as the Mediterranean diet and the EAT-Lancet diet, could yield benefits in terms of both health outcomes and reduction in greenhouse gas emissions and land use. It has the potential to contribute to climate change mitigation, align with other planetary health goals, and to help to lower the incidence of diet-related diseases [11]. This is due to greenhouse gas emissions being reduced by up to 31% and arable land use decreasing by up to 42% [37]. While the EAT-Lancet diet may meet the recommended intake for most nutrients, it is important to note that its nutritional adequacy has not been extensively studied yet, and reliable and objective data are needed, as assessed by an index [38]. This is significant for understanding the potential impact of transitioning to a more sustainable food consumption pattern on nutrient intakes, especially in the early stages of life, since in toddlers, even a minor modification in dietary habits can significantly influence dietary benefits and prove to be a successful approach, but it can also lead to nutritional inadequacies.

This study underlines the importance of the school system in helping our children achieve the proper intake for important food categories, such as fruit and vegetables, whose consumption significantly improves, reaching recommended levels, with the addition of the school meal. Regarding the role of school meals in increasing meat and cheese consumption, the authors emphasize the importance of not altering the school menu but, instead, raising parental awareness and suggesting a reduction in the number of home meals involving these products. For many children, school meals constitute their sole access to animal protein, highlighting the significance of this food category in their diet. Schools could instill a strong foundation of knowledge about healthy food choices and sustainable eating practices, thereby empowering children and their families to make informed decisions about their diets, creating a holistic approach to promote not only individual health but also contributing to the well-being of the planet we all share.

Our study also highlights that an unhealthy lifestyle pattern can manifest from the early years of a child's life, and this emphasizes how crucial it is to begin early intervention programs to promote a healthy lifestyle and guarantee lasting benefits for the children's health in the future. Furthermore, the environmental impact of very early life nutrition, infant formula, baby food consumption, and the kind of weaning has spiked the interest of researchers in recent years. Several studies acknowledge the environmental footprint of baby food in particular formula feeding, indicating breastfeeding as pivotal in sustainable diets [39–41]. Townsend and Pitchford observed how baby-led weaning promoted toddlers' liking for healthy and sustainable foods such as carbohydrates [42].

The goal is to establish a diet that is both health-promoting and environmentally sustainable. To this end, pediatricians play a central role in conveying the correct messages to parents about the importance of proper and balanced nutrition for the development and growth of the child while also keeping an eye on environmental sustainability and the environmental impact of nutrition. Undoubtedly, given the insufficient free time of pediatricians during regular visits, public health officials might play a relevant role in addressing these topics. Promoting healthy eating habits also requires adopting caregivers' perspectives and implementing nutritional education in households and school food programs, and it should encompass both the physical and psychological factors of healthy and appropriate eating and nutrition [43]. Furthermore, studies have reported a connection between children's eating habits and mothers' dissatisfaction with their toddlers' body size, highlighting the significance of parental influence on their nutritional needs [44].

The results of this study must be read considering its limitations. First, the questionnaire was written and distributed in Italian, which implied a high prevalence of Italian respondents. Most respondents come from high-income families with a high educational status. Furthermore, to preserve anonymity, the lack of sensitive data did not allow us to dig deep into the sociocultural and health-related aspects linked to correct nutrition

or sensibility to environmental sustainability. Additionally, to maintain questionnaire anonymity and brevity, we were unable to determine the precise school meal consumption of children, even when accounting for school meal offerings. This presents a significant limitation only in evaluating the nutritional aspects of a child's healthy meal. The results of our study suggested that the issue must be thoroughly studied, enriching the sample to cover a higher percentage of respondents and performing a more accurate assessment of children's dietary habits, including school meal consumption.

This being said, our data shed light on the impact of children's nutrition not only on their own health but also on our planet's health. Furthermore, the data account for the role played by educational institutions in correcting children's nutrition. Comprehending the complex connection between the dietary choices of children and the wider environmental consequences is essential for shaping sustainable eating habits.

Creating new public health policies aimed at safeguarding children's health requires a comprehensive nutritional assessment of infants and toddlers, extending its scope to encompass the family, school, and community. We could achieve improvement by raising awareness among families about balancing the proper intake of food categories, as for the GL. Supporting an integrated approach that combines social and educational initiatives is crucial and future research should prioritize fostering sustainable eating habits within communities to facilitate the transformation of dietary habits and encourage healthier lifestyles.

5. Conclusions

Our study underscores the crucial role of children's dietary habits in their own and the environment's sustainability, emphasizing the need to achieve recommended levels of essential food categories like fruits and vegetables, while reducing meat and dairy consumption. It highlights the importance of school meals' offering in achieving adherence, while underlining the necessity of raising parental awareness about integrating said meals with meals offered at home. Furthermore, our findings show early signs of unhealthy lifestyle patterns in children, underscoring the urgency of early intervention programs for lifelong health commitment. The study advocates for a diet promoting both individual health and environmental sustainability. In conclusion, a comprehensive approach is essential to instill healthy eating habits early, addressing individual well-being and the broader environmental impact. This necessitates collaborative efforts from healthcare professionals, educators, and policymakers to encourage positive changes in children's dietary behaviors and contribute to sustainable lifestyles in communities.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/healthcare12040453/s1>, Figures S1 and S2: Estimation of the optimal number of clusters using the silhouette method for describing adherence clustering for main food categories with and without accounting for school meals. Table S1: Children's food frequency consumption for all the food categories in the overall sample and divided by age categories. Table S2: Adherence to food consumption recommended by the Italian guidelines for healthy eating (CREA 2018) for the main food categories calculated including standard school meals to those children who had lunch at school, overall and stratified by age categories. Tables S3 and S4: Jaccard index matrix for adherence clustering for main food categories without accounting for school meals and representing food categories adherence co-occurrence.

Author Contributions: L.R., L.L. and L.P., conceptualized and designed the study, coordinated and supervised data collection, L.P., L.R. and M.R.S. drafted the initial manuscript, L.R. and L.L. reviewed and revised the manuscript. L.R. and L.P. collected data. L.P., L.L. and M.R.S. critically analyzed and interpreted data. G.P.V., A.O., L.I. and E.R. critically reviewed the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. All authors contributed to the article and approved the submitted version. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki. This study did not require the approval of an ethical committee because the questionnaire data were anonymous, making it impossible to identify and harm any respondent. Moreover, neither drugs nor medical devices were prescribed/administered. As a result, the responses were collectively examined while taking into account Italian and European regulations governing the management of personal data [27–29]. In more detail, anonymity was granted by not asking the name, surname, and date of birth. To retrieve information about the geographical area of participants while still preserving anonymity, the province in which the participants lived was asked instead of their address. To further protect identities, it was possible to choose to not specify a gender. The cover letter of the questionnaire informed the participants that the data would be used only for scientific purposes, that the raw data they would be archived for a maximum of five years, and they would be accessible only by researchers at the University of Modena and Reggio Emilia. Google Forms was used only to spread the questionnaire and to collect data. All the collected data were then downloaded and stored on a professional computer and protected by a password. It was possible to complete the questionnaire only after the participants declared that they understood the methods and purpose of the study by clicking on “I give the consent” option in reference to the processing of personal data. Participants who disagreed were redirected to a thank you message.

Informed Consent Statement: Informed consent to collect and process anonymized data was asked to all survey participants prior to survey completion.

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4.2 WHAT ITALIAN CHILDREN USUALLY EAT: HOW TO HARM OURSELVES AND THE ENVIRONMENT

[Cosa mangiano i nostri bambini: come far male a se stessi e anche all'ambiente. Consapevolezza dei genitori, ruolo del sistema scolastico e del pediatra nella transizione verso diete sane e sostenibili]

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4.2.1 English summary

Background

The article examines the environmental and health implications of Italian children's diets, focusing on the connections between nutrition, sustainability, and pediatric well-being. It highlights that the global spread of Western-style diets, rich in animal-based and processed foods, has rendered both human and planetary health unsustainable. The food industry alone contributes about 26% of total CO₂ emissions, consumes 50% of habitable land, and utilizes 70% of freshwater resources.

The study aimed to:

1. Assess dietary habits of children aged 6 months to 14 years.
2. Evaluate adherence to the Italian CREA 2018 Dietary Guidelines.
3. Describe environmental sustainability of children's diets, investigate parental awareness of sustainable nutrition and explore the role of pediatricians and schools in promoting sustainable diets.

Methods

A cross-sectional, questionnaire-based survey was conducted among 1,069 families in Modena and Reggio Emilia. Parents provided information on children's eating habits, demographics, and sustainability awareness. Responses were compared with national dietary guidelines, yielding adherence scores from 0 (poor) to 14 (optimal).

Results

Adherence to dietary guidelines was low: only 16% of children consumed recommended meat portions, while 68% exceeded them. Similar excesses were observed for dairy products (49%), whereas consumption of fruits, vegetables, and legumes was below recommended levels (39%, 48%, and 40%, respectively). School meals improved intake of plant-based foods but increased consumption of meat and cheese, maintaining a Westernized dietary profile. Parents demonstrated limited understanding of environmental impacts, overestimating packaging and transport while underestimating production. 42% of parents discussed nutrition with pediatricians at every visit, and 76% had never discussed sustainability during visits.

Discussion

The findings show that Italian children's diets deviate substantially from the Mediterranean model and align with the Western dietary pattern. This shift, high in animal protein and saturated fats, contributes to obesity and environmental degradation. While parents value healthy and organic food, their actual consumption patterns do not align with these beliefs. Moreover, healthcare professionals often lack sufficient training in nutrition and sustainability, underscoring the need for enhanced pediatric education.

Conclusions

Ensuring sustainable diets for the pediatric population is a critical challenge. The Mediterranean diet remains the optimal model for combining nutritional adequacy and environmental sustainability. Pediatricians, as trusted health educators, must integrate sustainability into clinical counseling. The concept of planetary health should underpin pediatric and public health practice, recognizing that children's health is inseparable from environmental health.

Key Messages

- Food production, rather than packaging or transport, is the main driver of environmental impact.
- Overconsumption of meat and dairy renders current diets unsustainable for the child's and for the planet's health.
- Parental understanding of healthy and sustainable eating remains limited.

- Pediatricians have a crucial educational role which requires specific training and engagement.

Cosa mangiano i nostri bambini: come far male a se stessi e anche all'ambiente

Consapevolezza dei genitori, ruolo del sistema scolastico e del pediatra nella transizione verso diete sane e sostenibili

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L'industria alimentare ha un importante impatto sul cambiamento climatico. Questo studio va ad analizzare il ruolo dell'alimentazione pediatrica, dei pediatri e del sistema scolastico sulla salute dei nostri bambini e dell'ambiente.

Il termine "cambiamento climatico" include i cambiamenti fisici, chimici ed ecologici planetari dovuti all'aumento delle temperature globali causato principalmente dalle emissioni di gas serra di origine antropica che hanno diverse fonti, *in primis* il settore energetico (con i combustibili fossili), ma anche quello che deriva dai processi industriali, quello alimentare, i cambiamenti nell'uso del suolo e nella gestione dei rifiuti. Gli effetti del cambiamento climatico impattano negativamente sulla salute umana e specialmente sui bambini, aumentando patologie legate al caldo, infezioni, danni fisici e psicologici da eventi meteorologici estremi e compromettendo la sicurezza alimentare nei paesi vulnerabili^{1,2}.

L'industria alimentare contribuisce significativamente al cambiamento climatico, essendo responsabile del 26% delle emissioni globali di CO₂, utilizzando il 50% della terra abitabile e il 70% delle risorse idriche³.

WHAT ITALIAN CHILDREN USUALLY EAT: HOW TO HARM OURSELVES AND THE ENVIRONMENT

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Key words

Infant nutrition, Environmental sustainability, Sustainable diets, Climate change, School meals impact

Summary

Background. The growth of the human population and expanding consumption patterns are among the primary causes of climate change and its health effects. The food system significantly contributes to the climate change, as it is responsible for 26% of CO₂ emissions, uses 50% of habitable land and 70% of water resources and causes biodiversity loss. Animal-based and processed foods have a greater environmental impact and the widespread adoption of a western diet is unsustainable for both the planet and human health.

Materials and methods. This study examined the dietary habits of a paediatric sample (aged: 6 months-14 years) to assess adherence to guidelines by focusing on the consumption of high-impact foods. It also analysed whether school canteens promote a sustainable and healthy diet and assessed parents' awareness of these issues and the role of paediatricians in disseminating this information, as well.

Results. The results showed an excessive consumption of meat (68%) and dairy products (49%), making the diet unsustainable for both human and planetary health. The school system, while promoting overall healthy eating, increases the consumption of high-impact foods already excessively consumed at home. There is a lack of parental awareness about what a healthy diet and its environmental impact are, topics that are also under-addressed by paediatricians. The paper highlights the need for a better training for paediatricians to promote healthy and sustainable diets.

L'impatto ambientale di un alimento è principalmente dovuto alla sua fase produttiva, mentre imballaggio e trasporto hanno un impatto minore³.

Mangiare "locale" non sempre riduce l'impatto ambientale se non si consumano alimenti di stagione, poiché la produzione in serra è più impattante dell'importazione^{4,5}.

La produzione di alimenti ha impatti ambientali variabili: carne e prodotti animali hanno un impatto molto maggiore rispetto agli alimenti vegetali. La carne, in particolare bovina e ovina, è l'alimento meno sostenibile: per la produzione di 1 kg di carne bovina vengono emessi 60 kg di CO₂, contro 1 kg di CO₂ emessa per 1 kg di piselli. La diffusione globale di una dieta occidentale, ricca di prodotti processati (con la cottura, congelazione, conservazione, aggiunta di ingredienti) e animali, insieme alla crescita della popolazione, aggrava l'insostenibilità del sistema alimentare. La transizione verso diete sostenibili è quindi imperativa³.

La FAO definisce le diete sostenibili come "diete a basso impatto ambientale che contribuiscono alla sicurezza alimentare e nutrizionale e alla vita sana per le generazioni presenti e future". Ridurre o eliminare i prodotti animali dalla dieta rende i modelli dietetici più sostenibili: una dieta vegetariana è meno impattante di una onnivora, e una vegana lo è ancora di più⁶.

Secondo l'*American Dietetic Association*, una dieta ben pianificata prevalentemente a base di alimenti vegetali è nutrizionalmente adeguata in tutte le fasi della vita, comprese prima e seconda infanzia e adolescenza, promuovendo abitudini alimentari salutari nell'età adulta⁷.

Dobbiamo ricordare che la prima e più importante missione di un pediatra è quella di proporre una dieta che sia innanzitutto sana ed equilibrata, adatta a un organismo in costante crescita come quello del bambino nelle diverse fasi della vita.

La dieta mediterranea è associata a una miglior salute sia mentale che fisica negli adulti e nei bambini e rappresenta, a oggi, il *gold standard* dietetico⁸. È caratterizzata, infatti, da un

elevato consumo di verdura, frutta, noci, cereali, cereali integrali e olio d'oliva, nonché da un consumo moderato di pesce e pollame e da un basso consumo di dolci, carne rossa e latticini⁹. È anche il regime alimentare a più basso impatto ambientale¹⁰, soprattutto rispetto alla dieta occidentale, a base di prodotti processati e di origine animale¹¹. È corretto, dunque, che le principali linee guida alimentari per l'età pediatrica, tra cui le Linee Guida CREA¹² prese come riferimento in questo studio, si basino sulla dieta mediterranea.

I bassi livelli di aderenza alla dieta mediterranea che caratterizzano la società contemporanea contribuiscono all'epidemia di obesità e all'aumento delle malattie croniche non trasmissibili in Europa meridionale, dove prevale una dieta di tipo occidentale con scarsa qualità (con elevato consumo di grassi saturi e zuccheri raffinati e scarsa di fibre - frutta e verdura -) e alto apporto calorico, dovuto principalmente all'alto introito di grassi saturi (carni e latticini) e carboidrati raffinati (con farina non integrale). Tale scarsa aderenza è diventata un problema per la salute pubblica e anche per la sostenibilità ambientale.

OBIETTIVI DELLO STUDIO

Il nostro studio ha lo scopo di descrivere le abitudini alimentari di bambini dai 6 mesi ai 14 anni di età al fine di valutarne l'aderenza alle linee guida (LG) per una sana alimentazione¹² ed evidenziare per quali categorie alimentari se ne discostino maggiormente; abbiamo poi valutato se il consumo del pasto a scuola abbia un impatto sul raggiungimento di una buona aderenza alle LG.

Siamo passati poi a esaminare quanto l'alimentazione della nostra popolazione sia sostenibile dal punto di vista ambientale.

Infine, abbiamo rilevato la conoscenza e la consapevolezza dei genitori sull'impatto che l'alimentazione ha sull'ambiente e il ruolo del pediatra di famiglia (PdF) nella diffusione di queste tematiche.

MATERIALI E METODI

Abbiamo condotto uno studio trasversale basato sulla raccolta di un questionario rivolto a genitori di bambini di età compresa tra i 6 mesi e i 14 anni. Il questionario è stato rielaborato usando strumenti validati in letteratura, in particolare su studi di aderenza alla dieta mediterranea in età adulta e pediatrica¹²⁻¹⁴.

Il questionario è stato distribuito tramite l'applicazione *Google Moduli* e strutturato in modo da raccogliere informazioni anonime in merito alle caratteristiche sociodemografiche delle famiglie, alle loro abitudini alimentari dei pasti consumati a casa, oltre a porre domande volte a indagare la consapevolezza dei genitori sulle tematiche di sostenibilità ambientale.

La diffusione del questionario è avvenuta attraverso l'invio del *link* in *chat* di messaggistica istantanea o pubblicazione su *social* in gruppi dedicati a genitori e attraverso l'affissione o la distribuzione di volantini con *QR code* nei poliambulatori pediatrici o presso il Pronto Soccorso (PS) pediatrico del Policlinico di Modena e in alcuni studi pediatrici della Provincia di Modena e Reggio Emilia (in base alla disponibilità volontaria del singolo PdF).

Elaborazione dei risultati

Dopo aver valutato le risposte relative alla frequenza di consumo dei vari alimenti date dai genitori, abbiamo suddiviso il campione tra chi consumava un pasto presso il proprio servizio educativo e chi no: nel primo caso abbiamo analizzato i dati tenendo conto anche dei pasti offerti dai menù scolastici.

Abbiamo quindi associato a ogni risposta relativa alla frequenza di consumo di un determinato alimento un'etichetta: "Secondo LG" nel caso la risposta coincidesse con le indicazioni di frequenza di consumo delle LG, "Inferiore LG" o "Maggiore LG" nel caso la frequenza di consumo fosse rispettivamente minore o maggiore di quanto indicato nelle LG.

Per valutare l'aderenza alle LG della dieta nella sua totalità, abbiamo da-

to un punteggio pari a 1 nel caso il consumo dell'alimento fosse "Secondo LG" e un punteggio pari a 0 nel caso la frequenza fosse "Inferiore" o "Maggiore" rispetto alle LG. In questo modo è stato possibile effettuare la somma dei punteggi associati agli alimenti ricavando un punteggio da 0 a 14 (dalla minima alla massima aderenza alle LG).

RISULTATI

Descrizione della popolazione

Il nostro campione è costituito da 1.069 famiglie. Le caratteristiche dei genitori e dei bambini del nostro campione sono indicate nella *Tabella I*.

Aderenza alle Linee Guida

Nella *Tabella II* è rappresentata l'aderenza alle LG del nostro campione delle varie categorie alimentari per i pasti consumati a casa.

I cereali sono la categoria alimentare che raggiunge i migliori livelli di aderenza (93%).

Tra le fonti proteiche l'aderenza minore è raggiunta dalla carne, con solo il 16% dei bambini che ha un consumo adeguato, mentre la migliore aderenza è raggiunta dai legumi con il 40% di bambini con un consumo in linea con le LG. Uova, pesce, formaggi si assestano tutti su un 35% circa di aderenza. Per quanto riguarda carne e formaggi, la maggior parte dei bambini che non seguono le LG ha un consumo maggiore di queste due categorie di alimenti; mentre per pesce, uova e legumi il consumo tende a essere inferiore alle LG.

Anche per quanto riguarda il consumo di frutta e verdura i risultati non sono ottimali: solo il 39% dei bambini, per quanto riguarda la verdura, e il 48%, per quanto riguarda la frutta, hanno un consumo al pari di quello indicato dalle LG; la restante parte ne fa un consumo minore.

Il 62% dei bambini consuma dolci e bevande zuccherate come indicato dalle LG, mentre il restante 38% ha un consumo maggiore. Si osserva una tendenza legata all'età, con un aumento del sovraconsumo di carne, bevan-

de zuccherate e prodotti industriali e una riduzione del consumo adeguato di pesce, legumi, verdura e frutta fresca con l'aumentare dell'età.

Nella *Tabella III* (disponibile nella versione online) è rappresentata l'aderenza alle LG considerando anche il consumo del pasto scolastico.

CARATTERISTICHE SOCIO-DEMOGRAFICHE DEL CAMPIONE (N = 1.069)

GENITORI	
Residenza	
Modena	553 (52%)
Reggio Emilia	219 (21%)
Altre province Emilia-Romagna	138 (13%)
Extra Emilia-Romagna	159 (14%)
Età / mediana (25°-75°)	38 (34-43) anni
Nazionalità	
Italiana	1.041 (97%)
Non italiana	28 (3%)
Stato civile	
Coniugati	670 (63%)
Conviventi	341 (32%)
Separati	24 (2,2%)
Single	20 (1,9%)
Divorziati	12 (1,1%)
Vedovi	2 (0,2%)
Istruzione	
Laurea	695 (65%)
Diploma professionale/secondaria superiore	331 (31%)
Diploma primaria/media inferiore/senza titolo	43 (4%)
Reddito mensile	
< 1.499 euro	44 (4%)
1.500-2.499 euro	204 (19%)
> 2.500 euro	581 (54%)
non noto	240 (22%)
Lavoro	
High class	373 (35%)
Middle class	191 (18%)
Working class	458 (43%)
Not working	47 (4,5%)
Numero di figli	
Un figlio	481 (45%)
2 figli	470 (44%)
3 o più figli	118 (11%)
BAMBINI	
Sesso	
Femminile	502 (47%)
Maschile	567 (53%)
Età	
6 mesi-1,99 anni	135 (12%)
2-3,99 anni	242 (23%)
4-6,99 anni	279 (26%)
7-10,99 anni	231 (22%)
11-13,99 anni	182 (17%)
Patologia cronica	
Assente	1.030 (96%)
Presente	39 (4%)
Allergie alimentari	
Assenti	1.030 (96%)
Presenti	39 (4%)
Consumo pasto a scuola	
Sì	738 (69%)
No	331 (31%)

Tabella I

**ADERENZA ALLE LINEE GUIDA PER UNA SANA ALIMENTAZIONE CREA 2018¹²
DEL CAMPIONE INTERO E STRATIFICATO PER FASCE D'ETÀ, CALCOLATO SUI PASTI CONSUMATI A CASA**

Popolazione	FASCIA ETÀ DEL BAMBINO					
	N totale 1.069	6m-1aa N = 135	2-3 aa N = 242	4-6 aa N = 279	7-10 aa N = 231	11-14 aa N = 182
Cereali						
Inferiore LG	76 (7,1%)	0 (0%)	12 (5,0%)	29 (10%)	21 (9,1%)	14 (7,7%)
Secondo LG	993 (93%)	135 (100%)	230 (95%)	250 (90%)	210 (91%)	168 (92%)
Maggiore LG	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Carne						
Inferiore LG	173 (16%)	31 (23%)	55 (23%)	45 (16%)	27 (12%)	15 (8,2%)
Secondo LG	174 (16%)	17 (13%)	43 (18%)	47 (17%)	42 (18%)	25 (14%)
Maggiore LG	722 (68%)	87 (64%)	144 (60%)	187 (67%)	162 (70%)	142 (78%)
Pesce						
Inferiore LG	672 (63%)	45 (33%)	121 (50%)	198 (71%)	168 (73%)	140 (77%)
Secondo LG	377 (35%)	77 (57%)	115 (48%)	80 (29%)	63 (27%)	42 (23%)
Maggiore LG	20 (1,9%)	13 (9,6%)	6 (2,5%)	1 (0,4%)	0 (0%)	0 (0%)
Legumi						
Inferiore LG	548 (51%)	35 (26%)	84 (35%)	155 (56%)	148 (64%)	126 (69%)
Secondo LG	425 (40%)	64 (47%)	128 (53%)	109 (39%)	72 (31%)	52 (29%)
Maggiore LG	96 (9%)	36 (27%)	30 (12%)	15 (5,4%)	11 (4,8%)	4 (2,2%)
Formaggi						
Inferiore LG	165 (15%)	20 (15%)	29 (12%)	41 (15%)	47 (20%)	28 (15%)
Secondo LG	383 (36%)	34 (25%)	87 (36%)	105 (38%)	89 (39%)	68 (37%)
Maggiore LG	521 (49%)	81 (60%)	126 (52%)	133 (48%)	95 (41%)	86 (47%)
Verdura						
Inferiore LG	657 (61%)	41 (30%)	143 (59%)	187 (67%)	157 (68%)	129 (71%)
Secondo LG	412 (39%)	94 (70%)	99 (41%)	92 (33%)	74 (32%)	53 (29%)
Maggiore LG	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Frutta fresca						
Inferiore LG	561 (52%)	49 (36%)	113 (47%)	144 (52%)	130 (56%)	125 (69%)
Secondo LG	508 (48%)	86 (64%)	129 (53%)	135 (48%)	101 (44%)	57 (31%)
Maggiore LG	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Frutta secca						
Inferiore LG	619 (58%)	94 (70%)	143 (59%)	148 (53%)	145 (63%)	89 (49%)
Secondo LG	174 (16%)	14 (10%)	28 (12%)	54 (19%)	45 (19%)	33 (18%)
Maggiore LG	276 (26%)	27 (20%)	71 (29%)	77 (28%)	41 (18%)	60 (33%)
Latte						
Inferiore LG	660 (62%)	115 (85%)	129 (53%)	160 (57%)	146 (63%)	110 (60%)
Secondo LG	386 (36%)	19 (14%)	100 (41%)	116 (42%)	82 (35%)	69 (38%)
Maggiore LG	23 (2,2%)	1 (0,7%)	13 (5,4%)	3 (1,1%)	3 (1,3%)	3 (1,6%)
Yogurt						
Inferiore LG	820 (77%)	107 (79%)	168 (69%)	198 (71%)	191 (83%)	156 (86%)
Secondo LG	150 (14%)	27 (20%)	39 (16%)	42 (15%)	18 (7,8%)	24 (13%)
Maggiore LG	99 (9,3%)	1 (0,7%)	35 (14%)	39 (14%)	22 (9,5%)	2 (1,1%)
Uova						
Inferiore LG	676 (63%)	113 (84%)	171 (71%)	180 (65%)	125 (54%)	87 (48%)
Secondo LG	368 (34%)	21 (16%)	68 (28%)	93 (33%)	98 (42%)	88 (48%)
Maggiore LG	25 (2,3%)	1 (0,7%)	3 (1,2%)	6 (2,2%)	8 (3,5%)	7 (3,8%)
Dolci						
Inferiore LG	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Secondo LG	660 (62%)	128 (95%)	164 (68%)	145 (52%)	111 (48%)	112 (62%)
Maggiore LG	409 (38%)	7 (5,2%)	78 (32%)	134 (48%)	120 (52%)	70 (38%)
Bevande zuccherate						
Inferiore LG	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Secondo LG	663 (62%)	128 (95%)	168 (69%)	152 (54%)	115 (50%)	100 (55%)
Maggiore LG	406 (38%)	7 (5,2%)	74 (31%)	127 (46%)	116 (50%)	82 (45%)
Prodotti industriali						
Inferiore LG	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Secondo LG	463 (43%)	120 (89%)	124 (51%)	95 (34%)	73 (32%)	51 (28%)
Maggiore LG	606 (57%)	15 (11%)	118 (49%)	184 (66%)	158 (68%)	131 (72%)

Tabella II

ADERENZA ALLE LINEE GUIDA CREA 2018¹² DEL CAMPIONE INTERO E STRATIFICATO PER FASCE D'ETÀ OTTENUTA SOMMANDO AI PASTI CONSUMATI A CASA E I PASTI CONSUMATI A SCUOLA

Popolazione	FASCIA ETÀ DEL BAMBINO					
	N totale 1.069	6m-1aa N = 135	2-3 aa N = 242	4-6 aa N = 279	7-10 aa N = 231	11-14 aa N = 182
Cereali						
Inferiore LG	18 (1,7%)	0 (0%)	4 (1,7%)	0 (0%)	1 (0,4%)	13 (7,1%)
Secondo LG	1,051 (98%)	135 (100%)	238 (98%)	279 (100%)	230 (100%)	169 (93%)
Maggiore LG	—	—	—	—	—	—
Carne						
Inferiore LG	60 (5,6%)	21 (16%)	12 (5%)	10 (3,6%)	5 (2,2%)	12 (6,6%)
Secondo LG	77 (7,2%)	13 (9,6%)	15 (6,2%)	13 (4,7%)	13 (5,6%)	23 (13%)
Maggiore LG	932 (87%)	101 (75%)	215 (89%)	256 (92%)	213 (92%)	147 (81%)
Pesce						
Inferiore LG	672 (63%)	45 (33%)	121 (50%)	198 (71%)	168 (73%)	140 (77%)
Secondo LG	377 (35%)	77 (57%)	115 (48%)	80 (29%)	63 (27%)	42 (23%)
Maggiore LG	20 (1,9%)	13 (9,6%)	6 (2,5%)	1 (0,4%)	0 (0%)	0 (0%)
Legumi						
Inferiore LG	301 (28%)	27 (20%)	20 (8,3%)	59 (21%)	81 (35%)	114 (63%)
Secondo LG	672 (63%)	72 (53%)	192 (79%)	205 (73%)	139 (60%)	64 (35%)
Maggiore LG	96 (9%)	36 (27%)	30 (12%)	15 (5,4%)	11 (4,8%)	4 (2,2%)
Formaggi						
Inferiore LG	51 (4,8%)	16 (12%)	4 (1,7%)	1 (0,4%)	7 (3%)	23 (13%)
Secondo LG	222 (21%)	19 (14%)	32 (13%)	43 (15%)	62 (27%)	66 (36%)
Maggiore LG	796 (74%)	100 (74%)	206 (85%)	235 (84%)	162 (70%)	93 (51%)
Verdura						
Inferiore LG	343 (32%)	27 (20%)	50 (21%)	76 (27%)	73 (32%)	117 (64%)
Secondo LG	726 (68%)	108 (80%)	192 (79%)	203 (73%)	158 (68%)	65 (36%)
Maggiore LG	—	—	—	—	—	—
Frutta fresca						
Inferiore LG	269 (25%)	34 (25%)	34 (14%)	39 (14%)	46 (20%)	116 (64%)
Secondo LG	800 (75%)	101 (75%)	208 (86%)	240 (86%)	185 (80%)	66 (36%)
Maggiore LG	—	—	—	—	—	—
Frutta secca						
Inferiore LG	619 (58%)	94 (70%)	143 (59%)	148 (53%)	145 (63%)	89 (49%)
Secondo LG	174 (16%)	14 (10%)	28 (12%)	54 (19%)	45 (19%)	33 (18%)
Maggiore LG	276 (26%)	27 (20%)	71 (29%)	77 (28%)	41 (18%)	60 (33%)
Latte						
Inferiore LG	660 (62%)	115 (85%)	129 (53%)	160 (57%)	146 (63%)	110 (60%)
Secondo LG	386 (36%)	19 (14%)	100 (41%)	116 (42%)	82 (35%)	69 (38%)
Maggiore LG	23 (2,2%)	1 (0,7%)	13 (5,4%)	3 (1,1%)	3 (1,3%)	3 (1,6%)
Yogurt						
Inferiore LG	820 (77%)	107 (79%)	168 (69%)	198 (71%)	191 (83%)	156 (86%)
Secondo LG	150 (14%)	27 (20%)	39 (16%)	42 (15%)	18 (7,8%)	24 (13%)
Maggiore LG	99 (9,3%)	1 (0,7%)	35 (14%)	39 (14%)	22 (9,5%)	2 (1,1%)
Uova						
Inferiore LG	299 (28%)	81 (60%)	46 (19%)	46 (16%)	54 (23%)	72 (40%)
Secondo LG	495 (46%)	42 (31%)	128 (53%)	138 (49%)	89 (39%)	98 (54%)
Maggiore LG	275 (26%)	12 (8,9%)	68 (28%)	95 (34%)	88 (38%)	12 (6,6%)
Dolci						
Inferiore LG	—	—	—	—	—	—
Secondo LG	660 (62%)	128 (95%)	164 (68%)	145 (52%)	111 (48%)	112 (62%)
Maggiore LG	409 (38%)	7 (5,2%)	78 (32%)	134 (48%)	120 (52%)	70 (38%)
Bevande zuccherate						
Inferiore LG	—	—	—	—	—	—
Secondo LG	663 (62%)	128 (95%)	168 (69%)	152 (54%)	115 (50%)	100 (55%)
Maggiore LG	406 (38%)	7 (5,2%)	74 (31%)	127 (46%)	116 (50%)	82 (45%)
Prodotti industriali						
Inferiore LG	—	—	—	—	—	—
Secondo LG	463 (43%)	120 (89%)	124 (51%)	95 (34%)	73 (32%)	51 (28%)
Maggiore LG	606 (57%)	15 (11%)	118 (49%)	184 (66%)	158 (68%)	131 (72%)

Tabella III

Quello che si evince è che il consumo di un pasto a scuola migliora l'aderenza di alcune categorie alimentari mentre peggiora l'aderenza

di altre: migliora l'aderenza per cereali (che passano dal 93% al 98%), verdura (dal 39% al 68%), frutta fresca (dal 48% al 75%) e legumi (dal 40

al 63%); peggiora invece l'aderenza di carne (dal 16% al 7,2%) e formaggi (dal 36% al 21%).

Per quanto riguarda l'aderenza totale della dieta, indicata nella *Figura 1*, quello che si evidenzia è che il punteggio ottenuto dalla popolazione generale ha una mediana di 7 (*Inter-Quartile Range*, IQR 5-8). Se andiamo a valutare le differenze tra le varie fasce d'età vediamo che il punteggio ottenuto è leggermente più alto nelle prime fasce d'età, mentre tende a calare nei bambini con età maggiore. L'aderenza alla dieta migliora se il bambino consuma un pasto a scuola (mediana 7; IQR 6-8) rispetto ai bambini che non consumano il pasto a scuola (mediana 6; IQR 4-7,25).

Abitudini di acquisto alimentare, consapevolezza sull'impatto ambientale e ruolo del pediatra

Le risposte relative alle abitudini di spesa alimentare sono riportate nella *Tabella IV*. Secondo i genitori ciò che contribuisce in maniera importante alla spesa alimentare è la salubrità del pasto, seguito dalla presenza di un cibo biologico, a chilometro zero e stagionale.

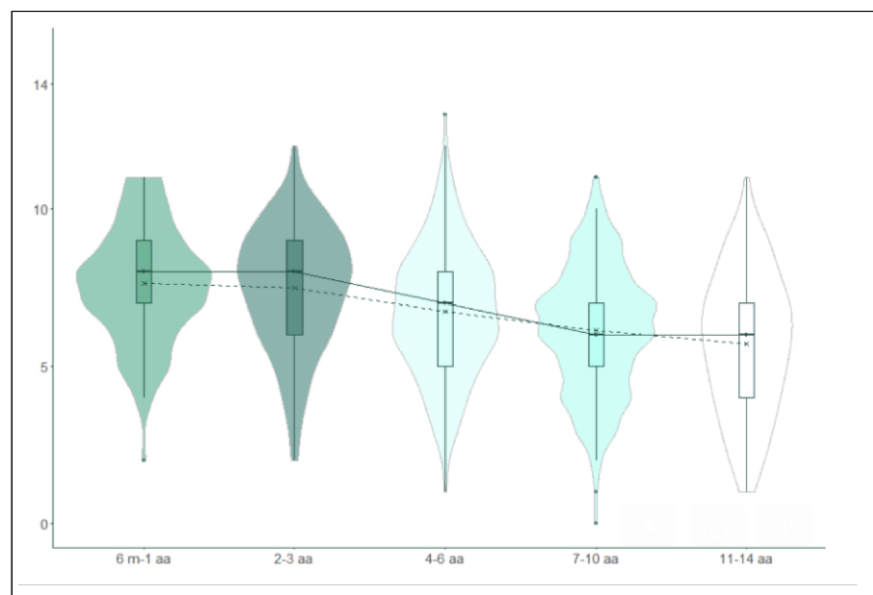


Figura 1. Punteggio di aderenza alle linee guida per una sana alimentazione CREA 2018 (ordinate stratificate per età (ascisse) (da voce bibliografica 12, modificata). Nota: Per valutare l'aderenza alle LG della dieta nella sua totalità è stato dato un punteggio pari a 1 nel caso il consumo dell'alimento fosse "Secondo LG" e un punteggio pari a 0 nel caso la frequenza fosse "Inferiore" o "Maggiore" rispetto alle LG. La somma dei punteggi associati agli alimenti va da un punteggio da 0 a 14 (dalla minima alla massima aderenza alle LG).

FATTORI CHE CONTRIBUISCONO NELLA SCELTA DI ACQUISTO DEI GENERI ALIMENTARI PER I FIGLI DA PARTE DEI GENITORI DEL CAMPIONE

Abitudini di spesa	Km 0	Stagionalità	Biologico	Imballaggi	Salubrità
Non importante	81 (8%)	12 (1%)	56 (5%)	148 (14%)	4 (0,4%)
Poco importante	283 (26%)	71 (6,6%)	209 (20%)	394 (37%)	22 (2%)
Abbastanza importante	571 (53%)	534 (50%)	575 (54%)	404 (38%)	394 (37%)
Estremamente importante	134 (13%)	452 (42%)	229 (21%)	123 (12%)	649 (61%)

Tabella IV

CONSAPEVOLEZZA DELL'IMPATTO AMBIENTALE DEI SETTORI ALIMENTARI SECONDO I GENITORI DEL CAMPIONE

	Settore alimentare	Carne rossa	Carne bianca	Alimenti vegetali	Latte e derivati	Prodotti industriali	Trasporti generi alimentari	Imballaggi
Quasi per niente	9(1%)	13(1%)	15(1%)	111(10%)	40(4%)	15(1%)	13(1%)	12(1%)
Poco	27(3%)	72(7%)	148(14%)	443(41%)	186(17%)	50(5%)	42(4%)	39(4%)
Abbastanza	368(34%)	334(31%)	542(51%)	291(27%)	491(46%)	249(23%)	277(26%)	225(21%)
Molto	554(52%)	549(51%)	258(24%)	110(10%)	233(22%)	663(62%)	656(61%)	723(68%)
Non lo so	111(10%)	101(9%)	106(10%)	114(11%)	119(11%)	92(9%)	81(8%)	70(7%)

Tabella V

**FREQUENZA CON CUI IL PDF AFFRONTA GLI ARGOMENTI
"ALIMENTAZIONE" E "SOSTENIBILITÀ AMBIENTALE" DURANTE LE VISITE**

	Alimentazione	Sostenibilità ambientale
Mai	100 (9%)	817 (76%)
Raramente	196 (18%)	137 (13%)
Saltuariamente	328 (31%)	87 (8%)
Ad ogni bilancio	445 (42%)	28 (3%)

Tabella VI

La *Tabella V* mostra la consapevolezza dei genitori rispetto a quanto le diverse fasi di produzione e distribuzione coinvolte nel settore alimentare influiscano sull'ambiente. Il 68% dei genitori ritiene che gli imballaggi abbiano un impatto elevato, dato maggiore rispetto alle carni (51% carne rossa e 24% carne bianca) e il trasporto (61%).

La *Tabella VI* mostra che nel 42% dei casi si parla di alimentazione durante ogni bilancio dal pediatra. Il 76% dei genitori riferisce di non aver mai parlato con il curante di sostenibilità ambientale.

DISCUSSIONE

I bambini valutati in questo studio hanno una scarsa aderenza alle LG per una sana alimentazione e le loro abitudini alimentari si discostano da quella che si definisce una dieta "sostenibile". Come evidenziato in precedenti studi di aderenza alla dieta mediterranea^{14,15}, anche quella rilevata in questo studio è molto più vicina a un modello di dieta "occidentale" con un alto consumo di proteine animali (in particolare carne e formaggi) e scarso consumo di alimenti di origine vegetale. La già scarsa aderenza alle LG tende a peggiorare con l'età, suggerendo una migliore *compliance* delle famiglie nei primi anni di vita.

Il pasto a scuola

Un'altra riflessione emerge dai risultati ottenuti dai bambini che consumano un pasto a scuola: si evidenzia una migliore aderenza alle LG della dieta nella sua totalità nei bambini che mangiano a scuola, ma se guar-

diamo le singole categorie alimentari vediamo che se da una parte il pasto a scuola aumenta il consumo di frutta, verdura, legumi e la variabilità dei cereali; dall'altra aumenta ulteriormente il già alto consumo di carne e prodotti caseari contribuendo al mantenimento di una dieta occidentale.

I menù scolastici sono pensati per promuovere sane abitudini alimentari volte a prevenire il sovrappeso e l'obesità e le loro conseguenze in termini di incidenza di malattie non trasmissibili. Grazie alla scuola, infatti, si assiste a una maggiore offerta di frutta e verdura, che conferma i dati disponibili in letteratura secondo cui la maggior assunzione di questi alimenti è associata all'introduzione di politiche alimentari e nutrizionali nelle scuole¹⁶.

Molti studi negli anni hanno dimostrato che la possibilità di una mensa scolastica ha contribuito sensibilmente a migliorare lo stato nutrizionale dei bambini, ma nella maggior parte dei casi si tratta di lavori condotti in Paesi in via di sviluppo in cui c'è un alto tasso di popolazione che soffre ancora di instabilità alimentare¹⁷.

Alcuni studi condotti in Paesi ad alto reddito ma non eseguiti nel contesto italiano, hanno dato risultati più discordanti: la frequentazione di una mensa scolastica in alcuni casi sembra associata a livelli di BMI più elevati^{18,19}.

Le diete scolastiche sono studiate per essere equilibrate dal punto di vista nutrizionale, ma si vanno a sommare a ciò che viene consumato a domicilio che, come abbiamo visto, si discosta molto da una dieta bilanciata. Se da una parte quindi la mensa scolastica compensa la scarsa introduzione familiare di alimenti vegetali, dall'altra

peggiora sensibilmente il già alto consumo di proteine animali.

Recenti studi stanno iniziando a valutare la possibilità di eseguire minime modifiche dei menù scolastici al fine di renderli a minor impatto ambientale pur mantenendo adeguato l'apporto nutrizionale^{20,21}. Rimane comunque essenziale una maggiore sensibilizzazione delle famiglie alle corrette frequenze alimentari con il conseguente adeguamento dell'offerta alimentare a domicilio.

Consapevolezza genitoriale

Per quanto riguarda la consapevolezza dei genitori sui temi di alimentazione, cambiamento climatico e sostenibilità della dieta, abbiamo osservato che, sebbene emerga una discreta attenzione in merito alle scelte alimentari per i propri figli, preferendo alimenti a chilometro zero, biologici e che seguano una stagionalità, e dichiarando quanto sia importante che questi alimenti siano salutari, questo non sembra tradursi concretamente in una dieta sana.

Inoltre, sebbene la maggior parte di loro sia consapevole che la carne abbia un ruolo preponderante sull'impatto ambientale del sistema alimentare, ciò non si traduce in un minor consumo da parte delle famiglie.

Il dato che appare più evidente è la percezione che imballaggi e trasporti abbiano un peso altissimo in termini di impatto ambientale, fatto che, come abbiamo visto, non corrisponde alla realtà.

Studi sulla percezione ambientale mostrano una scarsa conoscenza e sottovalutazione dell'impatto del sistema alimentare da parte dei consumatori, ostacolando diete più sostenibili²².

Altri studi mettono in evidenza uno scetticismo nella popolazione generale riguardo alle prove relative all'impatto ambientale della carne e una conseguente reticenza nel diminuirne il consumo²³; a questo si associa il ruolo culturale centrale che la carne ha nella nostra società²³.

La scarsa consapevolezza dei consumatori sulle tematiche ambientali può essere spiegata dalla scarsa presenza di questi temi sui principali mezzi di

informazione: in un'analisi di *Greenpeace* condotta nel corso del 2022 emerge che la tematica dei cambiamenti climatici nei telegiornali serali viene affrontata con una percentuale di copertura attorno allo 0,7% (96 su 14.211 notizie tra gennaio e aprile 2022).

Un altro fenomeno che può essere responsabile di una scarsa consapevolezza in merito ai cambiamenti climatici e una confusione da parte dei consumatori è quello del *greenwashing*, ossia una pratica di *marketing* sempre più frequente che ha lo scopo di far apparire un'azienda più sostenibile ed ecologica: attraverso campagne pubblicitarie *ad hoc* mostrano di attuare transizioni verso una produzione più sostenibile, che rimangono però esclusivamente di facciata (per esempio rendendo gli imballaggi biodegradabili). È facile che un consumatore poco esperto percepisca così che gli imballaggi abbiano un peso importante sull'impatto ambientale, come dimostra il nostro studio. Nonostante questo, è importante ricordare come gli imballaggi possano rilasciare composti chimici come ftalati e microplastiche, che possono avere un effetto dannoso sul neurosviluppo delle popolazioni fragili²⁴⁻²⁶.

Ruolo del pediatra di famiglia

È importante valutare il ruolo dei PdF nell'educazione alimentare. Solo il 42% dei genitori ha ricevuto consigli nutrizionali dal pediatra a ogni bilancio di salute (il 31% lo fa saltuariamente) (*Tabella IV*), risultato che potrebbe spiegare in parte la scarsa aderenza a una dieta sana.

Ma d'altra parte potrebbero sorgere anche dei dubbi relativi al fatto che i pediatri siano realmente adeguatamente formati per fare questo tipo di informazione.

Da una *survey* condotta nel 2018 dal *Nutrition and Lifestyle Working Group of the American College of Cardiology's Cardiovascular Disease Prevention Section*²⁷ si evince che il 22% dei medici intervistati ricorda di non aver ricevuto alcuna educazione nutrizionale durante il corso di laurea in Medicina e il 73% degli intervistati ha ritenuto di aver ricevuto un'istruzione

in temi di nutrizione minima o nulla durante il corso di specializzazione. È importante sottolineare che questa *survey* è stata condotta a livello globale e non specificatamente su pediatri; quindi, i risultati non si possono necessariamente riportare alla nostra realtà italiana e all'ambito pediatrico, che tuttavia potrebbe non discostarsi molto. Un altro studio del 2021 condotto in Arabia Saudita²⁸ ha confermato una scarsa conoscenza in materia di nutrizione in 443 medici intervistati con specializzazioni in cui l'assistenza nutrizionale è rilevante (tra i quali 22 pediatri), non rilevando particolari differenze tra le varie specializzazioni. I medici che avevano partecipato a corsi di nutrizione facoltativa hanno ottenuto punteggi maggiori, sottolineando quanto sia importante un costante aggiornamento sulle tematiche da parte del personale sanitario.

Il nostro studio ha rilevato che il 76% dei genitori non ha mai ricevuto informazioni sulla sostenibilità ambientale dal PdF. Questo non sorprende, dato che i medici non ricevono una formazione obbligatoria su questi temi, che rimangono di interesse solo per chi sceglie di approfondirli. A livello internazionale, esistono già progetti per integrare questo argomento nei *curricula* medici e insegnare loro una corretta comunicazione^{29,30}: questo è importante sia per poter affrontare un futuro in cui le malattie legate al clima saranno sempre più preponderanti sia perché Salute pubblica e Salute ambientale non possono più essere imprescindibili l'una dall'altra, e in quanto medici abbiamo l'obbligo di salvaguardare entrambe³¹.

CONCLUSIONI

Una popolazione umana sempre più in crescita con modelli di produzione e consumo in espansione sta guidando un rapido cambiamento ambientale globale con importanti conseguenze anche sulla salute umana.

Una delle sfide più difficili nel prossimo futuro sarà quella di riuscire a garantire diete sostenibili per tutta la popolazione pediatrica³². Anche te-

nendo in considerazione il preoccupante livello di povertà assoluta che riguarda in Italia il 10% popolazione³³.

I modelli alimentari attuali sono ampiamente insostenibili sia dal punto di vista ambientale che dal punto di vista della salute umana. Quello che si evince è che la dieta mediterranea, di per sé molto vicina a una dieta sostenibile, è stata largamente sostituita da una dieta Occidentale, caratterizzata da ampio consumo di carne e derivati animali, con tutte le conseguenze sull'impatto ambientale e sulla salute umana.

È sempre più stringente un'inversione di marcia e un'azione globale verso diete più sostenibili e il ruolo dei medici, in particolare dei pediatri, è centrale in questo: in quanto medici abbiamo la possibilità di educare le famiglie e i bambini, ma per fare ciò è necessario che siamo prima noi stessi adeguatamente formati in merito a queste tematiche.

In quanto responsabili di preservare la Salute, non possiamo più focalizzarci solo sulla salute umana, distaccata dall'insieme dei sistemi naturali da cui dipendiamo, ma è sempre più necessario che il concetto di Salute planetaria diventi la base della nostra pratica clinica.

MESSAGGI CHIAVE

- ❑ Più del packaging e il trasporto degli alimenti, è la fase produttiva degli alimenti ad avere un maggior impatto ambientale. Particolarmente impattante il consumo di alimenti di origine animale.
- ❑ L'aumento della prevalenza di una dieta occidentale, con un eccessivo consumo di carne e latticini rende la dieta non sostenibile per la salute dei bambini e del pianeta.
- ❑ La consapevolezza dei genitori nelle tematiche di sostenibilità ambientale e diete sane è limitata.
- ❑ I pediatri hanno un ruolo fondamentale nel promuovere diete sane e sostenibili, ma solo il 42% dei genitori afferma di ricevere consigli nutrizionali durante le visite pediatriche.

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5 CHILDREN AND PHTHALATES, ARE WE DOING ENOUGH?

5.0 INTRODUCTORY CHAPTER

The third chapter addressed the issue of human exposure to phthalates, chemical compounds used in everyday consumer products and some of which are known toxicants, focusing both on the legislative context and on the potential health consequences of exposure during sensitive developmental periods.

The chapter originated from two complementary studies that explored the topic from distinct but interrelated perspectives: the first aimed to systematize the European Union's regulatory framework on phthalates and their substitutes; the second investigated early-life exposure to these compounds and its possible influence on neurodevelopment in infants.

The first study analyzed the European regulatory context governing phthalates and selected substitutes (Palandri et al., 2025). Drawing on official institutional databases and documents from the European Commission, the European chemical Agency (ECHA), the European Food and Safety Authority (EFSA) and others, the study summarized existing restrictions and identified areas where regulation remained inconsistent or incomplete. Although the European Union had established one of the most advanced systems for chemical risk management, exposure to certain phthalates and alternative plasticizers persists, particularly among vulnerable populations such as children and pregnant women. The work highlighted the need for continuous legislative updating and harmonization to ensure effective protection. The second study examined early-life exposure to phthalates and its possible effects on infant neurodevelopment within the Modena Phthalates Cohort Study (MoPhCoS) (Lucaccioni et al., 2023). The study found widespread exposure and observed inverse associations between specific metabolites and developmental outcomes, particularly in male infants. These findings reinforced concerns about potential early neurotoxic effects of phthalates and the need for strengthened preventive policies.

Together, these two works framed the dual perspective of the third chapter: the *macro* dimension of environmental and regulatory determinants, and the *micro* dimension of biological and developmental consequences. By linking legislative

frameworks to biological evidence, the chapter highlighted how public health protection against endocrine disruptors requires an integrated approach combining epidemiological surveillance, laboratory research, and regulatory action. Ultimately, the chapter contributed to strengthening the rationale for preventive policies targeting maternal and child exposure, aligning scientific evidence with the European commitment to safeguarding future generations.

In what follows, I present my author contributions and the full abstract of the manuscripts. You will find the full text of the papers in the following paragraphs. All the manuscript presented in this chapter were submitted in peer-reviewed journals. The first has been accepted for publication (October 27th, 2025) while the second has been published.

5.0.1 Regulatory Framework of Phthalates and two common alternatives: a review of the European Union legislation

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Journal: International Journal of Hygiene and Environmental Health

Doi: <https://doi.org/10.1016/j.ijheh.2025.114704>

My contributions: As first and corresponding author, I conceptualized and designed the study, coordinating and supervising data collection as well as reviewing phthalate legislation. I critically analyzed and interpreted the data and contributed to the drafting of the initial manuscript.

Abstract

Background Globalized supply chains make it harder to regulate hazardous chemicals in products. These include some phthalates with reproductive and developmental toxicity that maybe found in a variety of products. The European Union (EU) was among the first economies to implement policies to limit their use, yet vulnerable populations (children, pregnant women) are exposed to restricted phthalates. Phthalates' regulation varies significantly by product or chemical compound, but literature lacks systematization of current EU legislation. **Methods** We examined EU regulatory framework for 19 major phthalates (DMP, DEP, DPrP, DiPrP, DMOEP, DBP, DiBP, DPeP, DiPeP, BBP, DHxP,

DCHP, DHpP, DEHP, DHNUP, DPHP, DnOP, DiNP, DiDP) and 2 substitutes (DINCH, DEHTP). We reviewed official institutional websites and regulatory agencies to assess uses and bans in food contact materials (FCMs), toys and childcare articles, cosmetics, and medical devices. Results The European Chemical Agency (ECHA) is the main authority supervising chemical use in the EU and regulates phthalates mainly through the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) regulation. Most reviewed phthalates are severely restricted in FCMs. Phthalates classified as toxic for reproduction are limited in toys and childcare articles above 0.1% by weight; they are banned in cosmetics and restricted in medical devices. Conclusions The EU has reduced exposure to phthalates through stringent regulations, effectively protecting newborns and infants. However, gaps remain, as many everyday items, like food packaging, may still represent sources of exposure. Ongoing regulatory revisions and international cooperation are essential to ensure safer cross-border commerce and international compliance, to further reduce phthalate exposure and protect public health.

5.0.2 Perinatal and postnatal exposure to phthalates and early neurodevelopment at 6 months in healthy infants born at term

Laura Lucaccioni, Lucia Palandri, Erica Passini, Viola Trevisani, Filippo Calandra Buonauro, Natascia Bertoncelli, Giovanna Talucci, Angela Ferrari, Eleonora Ferrari, Barbara Predieri, Fabio Facchinetti, Lorenzo Iughetti and Elena Righi

Journal: Frontiers in Endocrinology

Doi: <https://doi.org/10.3389/fendo.2023.1172743>

My contributions: As co-first author, I conceptualized and designed the study, coordinating and supervising data collection as well as contributing actively to data collection. I performed data analyses and critically analyzed and interpreted results. I contributed to the drafting of the initial manuscript.

Abstract

Background: Phthalates are non-persistent chemicals largely used as plasticizers and considered ubiquitous pollutants with endocrine disrupting activity. The exposure during sensible temporal windows as pregnancy and early childhood, may influence physiological neurodevelopment. Aims and Scope: The aim of this study is to analyze the relationship between the urinary levels of

phthalate metabolites in newborn and infants and the global development measured by the Griffiths Scales of Children Development (GSCD) at six months. Methods: Longitudinal cohort study in healthy Italian term newborn and their mothers from birth to the first 6 months of life. Urine samples were collected at respectively 0 (T0), 3 (T3), 6 (T6) months, and around the delivery for mothers. Urine samples were analyzed for a total of 7 major phthalate metabolites of 5 of the most commonly used phthalates. At six months of age a global child development assessment using the third edition of the Griffith Scales of Child Development (GSCD III) was performed in 104 participants. Results: In a total of 387 urine samples, the seven metabolites analyzed appeared widespread and were detected in most of the urine samples collected at any time of sampling (66-100%). At six months most of the Developmental Quotients (DQs) falls in average range, except for the subscale B, which presents a DQ median score of 87 (85-95). Adjusted linear regressions between DQs and urinary phthalate metabolite concentrations in mothers at T0 and in infants at T0, T3 and T6 identified several negative associations both for infants' and mothers especially for DEHP and MBzP. Moreover, once stratified by children's sex, negative associations were found in boys while positive in girls. Conclusions: Phthalates exposure is widespread, especially for not regulated compounds. Urinary phthalate metabolites were found to be associated to GSCD III scores, showing inverse association with higher phthalate levels related to lower development scores. Our data suggested differences related to the child's sex.

5.1 REGULATORY FRAMEWORK OF PHTHALATES AND TWO COMMON ALTERNATIVES: A REVIEW OF THE EUROPEAN UNION LEGISLATION

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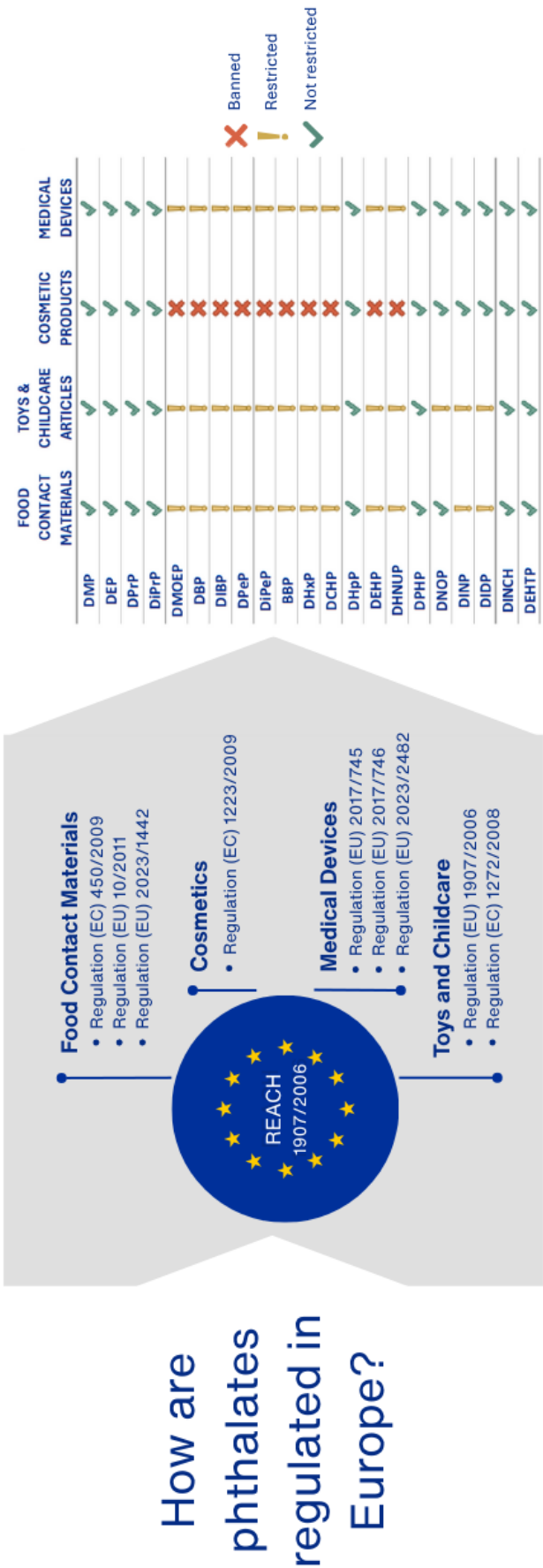
Keywords

Regulatory Framework, legislation, Endocrine disruptors, phthalates, Europe

Highlights

- EU regulates phthalates use in consumer products via REACH, supervised by ECHA.
- Phthalates are restricted in FCMs, childcare articles, cosmetics, and medical devices.
- Regulations reduce phthalate exposure in newborns/infants, but older children remain exposed.
- Ongoing regulatory revisions essential to further reduce phthalate exposure.

5.1.1 Graphical Abstract



5.1.2 Introduction

Phthalates are a class of chemical compounds, diesters of ortho-phthalic acid, used worldwide in the production of many industrial and everyday products as plasticizers, stabilizers and preservatives.

These chemicals therefore are commonly found in most plastic objects, including children's toys, childcare articles, packaging for food and drinks, and in personal care products, cosmetics, perfumes. They are also added to textiles like clothing and footwear, as well as in medical devices and pharmaceuticals. In construction, phthalates are incorporated in a variety of building materials, such as vinyl wall and floor coverings, pipes, roofing materials, and electrical cables. They are used in automotive components, lubricating oils, and paints, underlining their versatility and extensive use across multiple sectors (Table 1). As a result, they have become so integrated in our lives that avoiding being exposed to them is challenging.

Category	Uses of Phthalates and their substitutes
Plastics	Used as plasticizers to make polyvinyl chloride (PVC) more flexible and durable, employed in electrical cables, pipes, carpets, films, toys, and household products.
Food Packaging Materials	Found in food wraps, containers, and packaging to provide elasticity and transparency.
Toys and Childcare Articles	Incorporated into soft plastic toys and childcare items
Cosmetic Products	Found in perfumes, nail polishes, hair sprays, and lotions, where they help stabilize fragrances, improve the consistency of the product or are used as solvents.
Medicines and Medical Devices	Used in the plastics of some medical devices, such as blood transfusion bags, dialysis tubing, and catheters, to enhance flexibility. Used as preservatives for blood storage.
Textile Industry	Applied in the plastic coatings of waterproof fabrics, such as shower curtains, rainwear, and furniture coverings.
Building Materials	Included in products like vinyl flooring, adhesives, sealants, gaskets, and wall coverings to improve workability and durability.
Automotive Industry	Used in car interiors, including plastic trim, upholstery, sealants, and paints, to provide flexibility and resistance.
Electronics	Used in cable coatings, seals, and flexible plastic components.
Industrial Products	Added to lubricants, industrial oils, adhesives, and solvents to enhance product performance.

Table 1. Main uses of Phthalates and their substitutes in consumer products (ECHA, 2022).

Phthalates do not form chemical bonds with the products they are added to, allowing them to migrate, leach and volatilize, resulting in exposure via ingestion, inhalation or skin contact.

For instance, high molecular weight phthalates used in the manufacture of Polyvinyl Chloride (PVC) food packaging and equipment used for food processing, are lipophilic and can be detected at high concentrations in fatty food, especially meat and dairy products, and their migration into food can be accentuated by heating and prolonged use of plastic containers (Pacyga et al., 2019). A study conducted in 2021 in Portugal (Perestrelo et al., 2021), detected measurable levels of phthalates in food packaging, specifically phthalates like butyl-benzyl phthalate (BBP), di-iso-butyl phthalate (DiBP) and di-n-octyl phthalate (DnOP) showing how food contact materials (FCMs) might serve as a source of food contamination. Cosmetics might serve as an exposure source both directly and indirectly (Orecchio et al., 2015). Migration of phthalates from PVC packaging into shower and bath gels was detected in Basel showing how packaging as well might contribute to phthalate exposure (Amberg-Müller et al., 2010). Over the last decade, phthalates in medical devices have gathered significant attention, due to the potential health effects associated with these compounds. Tubing, blood bags and other equipment have been associated with higher concentrations of phthalates in critically ill patients and neonates (Jenkins et al., 2021; Malarvannan et al., 2019; Razatos et al., 2022).

Some phthalates are associated with various disorders (Lucaccioni et al., 2021), but mainly they are known as Endocrine Disruptor Chemicals (EDC) for humans, as they can mimic hormones and interfere with hormonal functions with adverse effects on reproductive health, sexual development, affecting estrogen and testosterone levels (Furr et al., 2014; Kortenkamp and Koch, 2020), and altering thyroid hormone concentrations. Prenatal exposure is related to preterm birth (Welch et al., 2022), low birth weight and gestational diabetes in their mothers (Qian et al., 2020). Given their widespread it is difficult to study their effects on health, furthermore the existence of a threshold for the adverse effect of chemicals for endocrine disruption is debated. While Belmaker et al. (Belmaker et al., 2024) suggest there is likely no safe level of exposure to EDCs, this view is

contested, by Brescia (Brescia, 2020) arguing that thresholds of adversity exist in biology and that they are applicable to EDCs.

These implications on human health underscores the need both for research and regulatory interventions about phthalates (Maffini et al., 2021).

The European Union (EU) is the second largest economy in the world according to the International Comparison Program (ICP), accounting for 18%, of the Global Gross Domestic Product (GDP) (European Parliament, 2024) and was among the first economies worldwide to restrict toxic phthalate use in consumer products, specifically children's toys with the Commission Decision 1999/815/EC (European Commission, 1999). Since then, economies worldwide have started to restrict the use of these compounds.

Even though more stringent restrictions have been implemented over time, encompassing a broader range of consumer products in the EU, phthalates regulation varies significantly depending on the product or on the chemical compound, resulting in phthalates classified as toxicants being strictly regulated while others remain unregulated as their toxicological profiles provide no justification for regulation.

Literature lacks evidence that systematizes the European regulatory framework on phthalates. To the best of our knowledge, only two studies may be found in literature. The first gives a general description on regulatory actions against phthalates but dates back to 2009 (Kamrin, 2009), the other published in 2025 contains a detailed list of the current classification and labelling status of phthalates in the EU (Kasper-Sonnenberg et al., 2025). The aim of this review, therefore, is to provide a comprehensive overview of the current state of European legislation on phthalates. By compiling, analyzing and summarizing the regulatory framework and the key phthalate regulations, the aim is to provide an informed basis for understanding the complexities of the legislation and identifying potential normative gaps that might explain the current levels of everyday exposure for the general population.

While this review focuses primarily on ortho-phthalates, we also address two common alternatives including bis(2-ethylhexyl) terephthalate (DEHP) and diisononylcyclohexane-1,2-dicarboxylate (DINCH), which possess fundamentally different chemical structures and toxicological profiles. Despite these structural

distinctions, these compounds share the comparable function as plasticizers and similar applications in consumer products.

5.1.3 Methods and Materials

To assess the relevant available regulatory information on phthalates, we conducted an online research on institutional platforms and official websites of the main specialized regulatory agencies operating in the EU including the European Commission (EC), the European Chemical Agency (ECHA), and the European Food Safety Authority (EFSA) to identify the correct regulation that applied to the selected phthalates and consumer products.

We searched for applicable regulations, guidelines for use, and specific restrictions or bans to investigate the regulatory status of nineteen of the major phthalates currently in use and two substitutes (Frederiksen et al., 2022; Gericke et al., 2024a):

- Dimethyl phthalate (DMP),
- Diethyl phthalate (DEP),
- Dipropyl phthalate (DPrP),
- Diisopropyl phthalate (DiPrP),
- Bis(2-methoxyethyl) phthalate (DMOEP),
- Dibutyl phthalate (DBP),
- Diisobutyl phthalate (DiBP),
- Dipentyl phthalate (DPeP),
- Diisopentyl phthalate (DiPeP),
- Butyl benzyl phthalate (BBP),
- Dihexyl phthalate (DHxP),
- Dicyclohexyl phthalate (DCHP),
- Diheptyl phthalate (DHpP),
- Bis(2-ethylhexyl) phthalate (DEHP),
- 1,2-Benzenedicarboxylic acid, di-C7-11-branched and linear alkyl esters (DHNUP)
- Bis(2-propylheptyl) phthalate (DPHP),
- Di-n-octyl phthalate (DnOP),
- Diisononyl phthalate (DiNP),
- Diisodecyl phthalate (DiDP),

- Diisononylcyclohexane-1,2-dicarboxylate (DINCH),
- bis(2-ethylhexyl) terephthalate (DEHP).

The main features of the investigated chemicals are reported in Table 2.

Name	Abb.	CAS-Number	IUPAC Name	Alkyl chains total carbon count	Alkyl chains length	Properties of Concern
Phthalates						
Dimethyl phthalate	DMP	131-11-3	1,2-dimethyl benzene-1,2-dicarboxylate	1	1-1	No hazards have been classified
Diethyl phthalate	DEP	84-66-2	1,2-diethyl benzene-1,2-dicarboxylate	2	2-2	No hazards have been classified
Dipropyl phthalate	DPrP	131-16-8	1,2-dipropyl benzene-1,2-dicarboxylate	3	3-3	No hazards have been classified
Diisopropyl phthalate	DiPrP	605-45-8	1,2-bis(propan-2-yl) benzene-1,2-dicarboxylate	3	2-2	No hazards have been classified
Bis(2-methoxyethyl) phthalate	DMOEP	117-82-8	1,2-bis(2-methoxyethyl) benzene-1,2-dicarboxylate	3	2-2	Toxic for reproduction. May damage the unborn child and is suspected of damaging fertility (H360Df).
Dibutyl phthalate	DBP	84-74-2	1,2-dibutyl benzene-1,2-dicarboxylate	4	4-4	Toxic for reproduction, endocrine disruptor. May damage the unborn child and is suspected of damaging fertility (H360Df). Very toxic to aquatic life (H400).
Diisobutyl phthalate	DIBP	84-69-5	1,2-bis(2-methylpropyl) benzene-1,2-dicarboxylate	4	3-3	Toxic for reproduction, endocrine disruptor. May damage the unborn child and is suspected of damaging fertility (H360Df).
Dipentyl phthalate	DPeP	131-18-0	1,2-dipentyl benzene-1,2-dicarboxylate	5	5-5	Toxic for reproduction. May damage fertility. May damage the unborn child (H360FD). Very toxic to aquatic life (H400).

Diisopentyl phthalate	DiPeP	605-50-5	1,2-bis(3-methylbutyl) benzene-1,2-dicarboxylate	5	4-4	Toxic for reproduction. May damage fertility. May damage the unborn child (H360FD). Very toxic to aquatic life (H400).
Butyl benzyl phthalate	BBP	85-68-7	1-benzyl 2-butyl benzene-1,2-dicarboxylate	4-7	4-7	Toxic to reproduction, endocrine disruptor. May damage the unborn child and is suspected of damaging fertility (H360Df). Very toxic to aquatic life (H400). Very toxic to aquatic life with long lasting effects (H410).
Dihexyl phthalate	DHxP	84-75-3	1,2-dihexyl benzene-1,2-dicarboxylate	6	6-6	Toxic for reproduction. May damage fertility. may damage the unborn child (H360FD).
Dicyclohexyl phthalate	DCHP	84-61-7	1,2-dicyclohexyl benzene-1,2-dicarboxylate	6-ring	6-ring -6-ring	Toxic to reproduction. May damage the unborn child (H360D). May cause allergic skin reaction (H317).
5.1.4 Diheptyl phthalate	DHpP	3648-21-3	1,2-diheptyl benzene-1,2-dicarboxylate	7	7-7	No hazards have been classified.
Bis(2-ethylhexyl) phthalate	DEHP	117-81-7	1,2-bis(2-ethylhexyl) benzene-1,2-dicarboxylate	8	6-6	Toxic to reproduction, endocrine disruptor. May damage fertility. May damage the unborn child (H360FD).
1,2-Benzenedicarboxylic acid, di-C7-11-branched and linear alkyl	DHNU P	68515-42-4	1,2-Benzenedicarboxylic acid, di-C7-11-branched and linear alkyl esters	7-11	6-10	Toxic for reproduction. May damage the unborn child and is suspected of damaging fertility (H360Df).
Bis(2-propylheptyl) phthalate	DPHP	53306-54-0	1,2-bis(2-propylheptyl) benzene-1,2-dicarboxylate	10	6-7	No hazards have been classified.
Di-n-octyl phthalate	DnOP	117-84-0	1,2-dioctyl benzene-1,2-dicarboxylate	8	8-8	No hazards have been classified.
Diisononyl phthalate	DiNP	(DiNP 1) 68515-48-0 (DiNP 2) 28553-12-0	1,2-bis(7-methyloctyl) benzene-1,2-dicarboxylate	8-10 9	6-10 7-9	No hazards have been classified.

Diisodecyl phthalate	DiDP	68515-49-1 26761-40-0*	1,2-bis(8-methylnonyl) benzene-1,2-dicarboxylate	9-11 10	7-11 8-10	No hazards have been classified.
Substitutes						
Diisononylcyclohexane-1,2-dicarboxylate	DINCH	166412-78-8	Di-isononyl-cyclohexane-1,2-dicarboxylate	9	7-9	No hazards have been classified
bis(2-ethylhexyl) terephthalate	DEHP	6422-86-2	1,4-bis(2-ethylhexyl) benzene-1,4-dicarboxylate	8	6-6	No hazards have been classified

Table 2. Chemical properties and health properties of concerns of the reviewed phthalates and two common substitutes (ECHA, 2022; Kasper-Sonnenberg et al., 2025). In parenthesis the hazard statement code according to Regulation (EC) No 1272/2008 (CLP)(European Commission, 2025a).Abb.: abbreviation, FCMs: food contact materials. *No longer produced in EU.

Search Strategy

The regulatory search was conducted by three independent reviewers (MM, MF, MRS), who performed an initial screening. A second screening and verification of the identified regulations were carried out by two additional reviewers (LP and CL, with oversight by LL). The search was performed on official institutional websites using specific keywords, including the name of each phthalate listed in Table 2, the term “phthalat*” or “benzene-1,2-dicarboxylic acid esters of alcohols” and the corresponding CAS numbers, which serve as unique identifiers for chemical substances. Any occurrence of the selected substances within legal or regulatory documents was documented and synthesized in the Results section.

We primarily relied on the English versions of laws, regulations, and official reports, issued by the competent agencies responsible for overseeing and regulating specific substances or materials as English is the most spoken language globally, used in 186 countries (Ethnologue, 2024).

In our review, we decided to focus specifically on the products commonly used in household settings and everyday life, excluding construction products, automotive components, lubricants, paints, and electrical cables, as these are generally governed by different regulatory frameworks. To focus on consumer goods that are more relevant for the general population, we selected four main categories, ensuring that our research addressed practical and everyday exposure to phthalates:

- a. FCMs,
- b. Toys and Childcare Products,
- c. Cosmetic Products,
- d. Medical Devices.

This study was conducted between November 1, 2023, to January 31, 2025, and updated September 15, 2025.

5.1.5 Results

The legislation governing phthalates and two common substitutes in the EU was freely accessible in multiple languages.

The result section is organized as follows: we discuss the regulatory framework governing phthalate regulation, followed by an examination of the specific regulation applied to phthalates for each investigated consumer category.

A summary of phthalate types of restrictions in the EU may be found in table 3 while table 4 reports the regulatory framework, and the specific regulations and restrictions promulgated for each consumer product category.

	FOOD CONTACT MATERIALS			TOYS – CHILDCARE ARTICLES			COSMETIC PRODUCTS			MEDICAL DEVICES		
	BANNED	RESTRICTED	NOT RESTRICTED	BANNED	RESTRICTED	NOT RESTRICTED	BANNED	RESTRICTED	NOT RESTRICTED	BANNED	RESTRICTED	NOT RESTRICTED
DMP			X			X			X			X
DEP			X			X			X			X
DPrP			X			X			X			X
DiPrP			X			X			X			X
DMOEP		X			X		X				X	
DBP		X			X		X				X	
DiBP		X*			X		X				X	
DPeP		X			X		X				X	
DiPeP		X			X		X				X	
BBP		X			X		X				X	
DHxP		X			X		X				X	
DCHP		X			X		X				X	
DHpP			X			X			X			X
DEHP		X			X		X				X	
DHNUP		X			X		X				X	
DPHP			X			X**			X			X
DnOP			X		X				X			X
DiNP		X			X				X			X

DiDP		X			X				X			X
DINCH			X			X			X			X
DEHTP			X			X			X			X

Table 3. Restrictions in the use of reviewed phthalates and two common substitutes adopted in the EU for different everyday consumers goods. For phthalates abbreviations refer to table 2. Banned: prohibited from use in specified products, Restricted: may be used only within defined concentration limits or specific conditions. Not restricted: no regulatory limitations on their use. *DiBP is not listed as an authorized substance for FCMs. However, it may co-occur with other phthalates as a consequence of its use as an aid to polymerization and is included in group restrictions. **DPHP is a plasticizer only for technical applications, not restricted but use in toys and childcare products not supported by producers (BASF, 2025; Perstorp, 2023).

Consumer Product Category	Regulation	Acts	Types of restrictions
General European Regulation	Regulation (EC) 1907/2006 (REACH)		Establishes ECHA. Regulates the production or import of phthalates into the European Economic Area
	Regulation (EC) 1272/2008 (CLP)		Implements in the EU the United Nations' Globally Harmonized System of Classification and Labelling of Chemicals (GHS), requiring companies to classify, label and package chemicals before placing them on the market
Food contact materials (FCMs) Regulation	Regulation (EC) 450/2009	Article 5(2)(c)(i)	Prohibits the use of substances classified as 'mutagenic', 'carcinogenic', or 'toxic to reproduction' in food contact active and intelligent materials, therefore: DMOEP, DBP, DiBP, DPpP, DiPeP, BBP, DHxP, DCHP, DEHP, DHNUP.
	Regulation (EU) 10/2011	Annex I	Specifies the EU list of substances that are authorized for the manufacture of plastic FCMs. DEHP and DBP may be used as plasticizer in repeated use materials and articles contacting non-fatty foods or as technical support agent in concentrations up to 0.1 % for DEHP and 0.05% for DBP in the final product. BBP, DiNP and DiDP are restricted to be only used as plasticizer in repeated use materials and articles contacting non-fatty foods, plasticizer in single-use materials and articles contacting non-fatty foods except for infant formulae and follow-on formulae or as technical support agent in concentrations up to 0.1 % in the final product.
	Regulation (EU) 2023/1442 (effective from February 1, 2025)	Annex I	Establishes the SML Amends EU Regulation 10/2011 Annex I modifying SML: DEHP: SML 0.6 (mg/kg), SML(T) group restriction n. 32: 60 mg/kg and n. 36: 0.6 mg/kg; BBP: SML 6 (mg/kg), SML(T) group restriction n. 32: 60 mg/kg and n. 36: 0.6 mg/kg; DBP: SML 0.12 (mg/kg) , SML(T) group restriction n. 32: 60 mg/kg and n. 36: 0.6 mg/kg; DiBP*, DiNP and DiDP are included in group restrictions n. 32 and 36 DiNP: not to be used in combination with FCMs substances DBP, BBP, DEHP or DiDP
Toys and Childcare Articles Regulation	Regulation (EU) 1907/2006	Annex XVII Entry 51	DEHP, BBP, DBP, DiBP are prohibited from being used, individually or in combination, at concentrations equal to or greater than 0.1% by weight of the plasticized material, which includes materials such as PVC, PVDC, PVA, polyurethanes, and surface coatings.

		Annex XVII Entry 52	DiNP, DiDP and DnOP shall not be used as substances or in mixtures, in concentrations greater than 0,1 % by weight of the plasticized material, in toys and childcare articles which can be placed in the mouth by children
	Regulation (EC) 1272/2008 (CLP)	Annex VI	DMOEP, DBP, DiBP, DPeP, DiPeP, BBP, DHxP, DCHP, DEHP, DHNUP are classified as reproductive toxicant category 1B and can be considered hazardous for the purposes of the General Product Safety and shall not be used, as substances or mixtures for supply to the general public when the individual concentration is equal to or greater than 0,1%.
Cosmetics Regulation	Regulation (EC) 1223/2009	Annex II	DMOEP, DBP, DiBP, DPeP, DiPeP, BBP, DHxP, DCHP, and DEHP are banned in all cosmetic products, sold or intended for use
Medical Devices Regulation	Regulation (EU) 2017/745	Annex I, Chapter II, Section 10.4.1 and Section 10.4.3	This regulation allows the use substances which are carcinogenic, mutagenic or toxic to reproduction or substances having endocrine-disrupting properties in medical devices at concentrations exceeding 0.1% of total weight only when there is an adequate justification provided for their use, therefore: DMOEP, DBP, DiBP, DPeP, DiPeP, BBP, DHxP, DCHP, and DEHP
	Regulation (EU) 2017/746	Annex 1, Chapter III, Section 10.3	This regulation requires that in vitro diagnostic medical devices for human use, shall be designed and manufactured to reduce to a level as low as reasonably practicable the risks posed by substances or particles that may be released from the device. Special attention shall be given to substances which are carcinogenic, mutagenic or toxic to reproduction and to substances having endocrine disrupting properties, therefore this includes: DMOEP, DBP, DiBP, DPeP, DiPeP, BBP, DHxP, DCHP, and DEHP
	Regulation (EU) 2023/2482	Annex XIV	Updated sunset date of DEHP in medical devices set up by EU Regulation 2017/745 moving it from May 26, 2025, to July 1, 2030

Table 4: Regulatory framework, regulations and restrictions for phthalates in each Consumer Product Category for the EU (last update: September, 17, 2025). For phthalates abbreviations refer to table 2.

ECHA: European Chemical Agency, SML: Specific Migration limits; SML(T): Total specific migration groups. *note: DiBP is not listed as an authorized substance for FCMs. However, it may co-occur with other phthalates as a consequence of its use as an aid to polymerization and is included in group restrictions with the assignment FCM No 1085.

5.1.5.1 EU Regulatory Framework

EU regulations related to chemical substances are complex and elaborate. The main authority supervising the registration, authorization and restriction of use of chemicals in the EU is **ECHA** (Agency of the European Union, 2025), established in 2007 and operating with the aim of safeguarding both human health and the environment.

Among the main regulatory instruments coordinated by ECHA is the **Authorization and Restriction of Chemicals (REACH) Regulation (Registration, Evaluation, Authorization and Restriction of Chemicals)** ((European Chemicals Agency) ECHA, 2024), which has been in force since June 1, 2007, under **Regulation (EC) No. 1907/2006**. The current consolidated version was published in on September 1st, 2025 (European Commission, 2025b).

REACH regulation requires chemical companies to test new chemicals for human toxicity and assess the associated risks before their approval for marketing. The aim is to strengthen the protection of human health and the environment by progressively eliminating the use of dangerous substances unless safer alternatives are unavailable, and their use must be justified for specific purposes. This regulation also establishes timelines for companies, including the latest application dates (by which companies must apply for authorization) and sunset dates (after which the substance cannot be used without authorization). Furthermore, the REACH regulation requires that substance characterization, data on annual production volume, production process, physical chemical properties as well as ecotoxicological and toxicological profiles are provided to ECHA.

Chemicals with scientific evidence of potential serious effects on human health or the environment are classified as Substances of Very High Concern (SVHCs) and require authorization prior to use (**Annex XIV of REACH**). Further, different assessment lists have been created including an Endocrine Disruptor Assessment List. Chemicals are included in the list if, starting from February 2013, an informal hazard assessment for endocrine-disrupting properties is either under development or has been completed. If there is scientific evidence

of probable serious effects to human health or the environment, endocrine disruptors may be identified as SVHCs (ECHA, 2024a).

Moreover, under the ECHA umbrella, the **Prior Informed Consent (PIC) Regulation** (ECHA, 2024b) governs the import and export of specific hazardous substances, especially those that are banned or severely restricted in the EU. To ensure clear communication of risks, the **Classification, Labelling, and Packaging Regulation (EC) No 1272/2008 (CLP)**, consolidated version on September 1st, 2025 (ECHA, 2024c; European Commission, 2025a) regulates and harmonizes the classification and labelling of chemicals, helping workers and consumers in the EU to be aware of the hazards and risks related to chemicals products. CLP implements in the EU the United Nations' Globally Harmonized System of Classification and Labelling of Chemicals (GHS). According to Annex VI - Part 3 of the CLP, a substance can be classified as carcinogenic, mutagenic or toxic for reproduction as follows:

- Category 1A: human toxicant - classification based on human evidence
- Category 1B: presumed human toxicant - classification based on animal evidence
- Category 2: suspected human toxicant (not enough evidence to be placed in Category 1A or 1B).

In addition to the comprehensive regulatory framework provided by ECHA, there are also more specific, sector-focused authorities that cooperate with it. For instance, when it comes to risks associated with the food chain, EFSA plays a key role (EFSA, 2021). Established in 2002 and funded by the EU, EFSA operates independently of EU institutions and member states to provide scientific advice and communication on food-related risks. In 2017, ECHA and EFSA established a comprehensive cooperation framework through a Memorandum of Understanding to enhance scientific collaboration, share data and expertise, coordinate risk assessments for chemical substances affecting food safety, and prevent conflicting opinions through regular consultation and joint activities.

Additionally, the EC developed the CosIng (Cosmetic Ingredients) database (European Commission, 2024a), a comprehensive and updated tool about cosmetic ingredients used in EU. Primarily, CosIng serves as a reference and regulatory tool for manufacturers and consumers, facilitating adherence to **Regulation (EC) No 1223/2009** (European Commission, 2019), the legislation governing cosmetic products in EU. This database identifies limitations, bans, or

safety assessments performed by the Scientific Committee on Consumer Safety (SCCS)(European Commission, 2025c), classifies cosmetic substances, and provides the standardized INCI (International Nomenclature of Cosmetic Ingredients) names, essential for proper cosmetic labelling within the EU, resulting in helping market surveillance, guaranteeing uniformity in ingredient labelling, and enhancing consumer protection. Furthermore, ECHA regulates drinking water since 2021 through the Drinking Water Directive. This directive established the minimum requirements for materials that are in contact with water meant for human consumption in EU (ECHA, 2025).

Together, all these regulations and directives define a complete framework within the EU, aimed at managing chemical risks across all sectors.

5.1.5.2 Phthalates, restrictions and two common substitutes

5.1.5.2.1 Classification according to REACH regulation

Phthalates are registered under **the REACH Regulation** and according to the results of the ongoing evaluations carried out under the REACH regulation umbrella (European Commission, 2024b), they are classified as follows (Table 5):

- DBP, DiBP, BBP, DEHP, are officially recognized in the EU as SVHC and included in the authorization list, under **Annex XIV of REACH**, due to their well-documented reproductive toxicity and endocrine disrupting activities,
- DMOEP, DPeP, DiPeP, DHxP and DHNUP are included in the authorization list, under **Annex XIV of REACH**, due to their documented reproductive toxicity,
- DCHP is included in the candidate list of SVHC for authorization due to its reproductive toxicity and endocrine disrupting activities,
- DCHP may cause allergic skin reactions.
- DMOEP, DBP, DiBP, BBP and DHNUP may damage the unborn child and are suspected of damaging fertility,
- DPeP, DiPeP, DHxP, DEHP may damage fertility and may damage the unborn child,
- DCHP may damage fertility or the unborn child,
- DBP, DPeP, DiPeP are recognized to be very toxic to aquatic life,
- BBP is recognized to be very toxic to aquatic life with long lasting,
- DMP, DEP, DPrP, DHpP, DPHP, DnOP, DiNP, DiDP, DINCH, DEHTP are under revision and up to now no hazards have been classified.

Based on these evaluations the uses of DMOEP, DBP, DiBP, DPeP, DiPeP, BBP, DHxP, DCHP, DEHP, DHNUP, DnOP, DiNP, and DiDP are regulated under **Annex**

XVII of REACH, which lists the restrictions on specific hazardous substances for their commercialization and use.

DMOEP, DiBP, DPeP, DiPeP, BBP, DHxP, and DHNUP are also subjected to the **Prior Informed Consent regulation (f - Annex I)** (ECHA, 2024b) and to export notification procedure from April 2018.

Furthermore, due to their hazardous classification, products containing DMOEP, DBP, DiBP, DPeP, DiPeP, BBP, DHxP, DCHP, DEHP and DHNUP must display appropriate hazard statements on their labels in accordance with the CLP Regulation (European Commission, 2025a).

DMP, DEP, DPpP, DiPrP, DHpP, DPHP, DINCH, DEHTP are not regulated by the previously mentioned regulations.

	Date of inclusion	Reason for inclusion	ECHA decision document
BBP	October 28, 2008	Toxic for reproduction (Article 57c) Endocrine disrupting properties (Article 57(f) - human health)	EU/2017/4462 ED/30/2017 ED/67/2008
DEHP	October 28, 2008	Toxic for reproduction (Article 57c) Endocrine disrupting properties (Article 57(f) - environment) Endocrine disrupting properties (Article 57(f) - human health)	EU/2017/4462 ED/108/2014 ED/30/2017 ED/67/2008
DBP	October 28, 2008	Toxic for reproduction (Article 57c) Endocrine disrupting properties (Article 57(f) - environment) Endocrine disrupting properties (Article 57(f) - human health)	EU/2017/4462 ED(2023)8585-DC ED/30/2017 ED/67/2008
DiBP	January 13, 2010	Toxic for reproduction (Article 57c) Endocrine disrupting properties (Article 57(f) - human health)	EU/2017/4462 ED/30/2017 ED/68/2009
DHNUP	June 20, 2011	Toxic for reproduction (Article 57c)	ED/31/2011
DMOEP	December 19, 2011	Toxic for reproduction (Article 57c)	ED/77/2011

DiPeP	December 19, 2012	Toxic for reproduction (Article 57c)	ED/169/2012
DPeP	June 20, 2013	Toxic for reproduction (Article 57c)	ED/69/2013
DHxP	December 16, 2013	Toxic for reproduction (Article 57c)	ED/121/2013
DCHP	June 27, 2018	Toxic for reproduction (Article 57c) Endocrine disrupting properties (Article 57(f) - human health)	EU/2018/636 ED/61/2018

Table 5. Phthalates included in the Substances of Very High Concern (SVHC) list in order of date of inclusion, registration reason and ECHA (European Chemical Agency) decision document. For phthalates abbreviations refer to table 2

5.1.5.2.2 Food Contact Materials

FCMs are defined as materials and articles intended to come into contact with food. Since 2009, the use of substances classified as ‘mutagenic’, ‘carcinogenic’, or ‘toxic to reproduction’ (e.g.: DMOEP, DBP, DiBP, DPeP, DiPeP, BBP, DHxP, DCHP, DEHP, DHNUP) has been prohibited in food-contact active and intelligent materials and articles, as specified in **Article 5(2)(c)(i) of Regulation (EC) 450/2009**. Active materials are products used in packaged food with the aim of extending their shelf life or to maintain their condition while intelligent materials are used to monitor the condition of the packaged food or the environment surrounding the food (European Commission, 2009).

Annex I of Regulation (EU) 10/2011 (European Commission, 2011), and its amendments, specifies the EU list of substances that are authorized for the manufacture of plastic FCMs and, considering phthalates, DEHP and DBP are restricted only to be used as plasticizer in repeated use materials and articles contacting non-fatty foods or as technical support agent in concentrations up to 0.1 % in the final product. BBP, DiNP and DiDP are restricted to be only used as plasticizer in repeated use materials and articles contacting non-fatty foods, or plasticizer in single-use materials and articles contacting non-fatty foods (with the exclusion of their use for infant formulae and follow-on or processed cereal-based foods and baby foods for infants and young children) or technical support agent in concentrations up to 0.1 % in the final product.

Annex I also has established for four phthalates (DEHP, BBP, DBP, DiDP and DiNP) the maximum allowable amount of a chemical substance (Specific Migration limits (SML)) or of a group of chemical substances (Total Specific Migration Limit (SML(T))) that can migrate from a material into food or other consumables under standard conditions of use, without exceeding safe levels. Limits are typically expressed in milligrams per kilogram (mg/kg) of food or beverage that comes into contact with the material. Groups of substances are identified based on similar health effects.

These SML and SML(T) have been recently revised by the **Regulation (EU) 2023/1442** (European Commission, 2023a), amending Annex I of Regulation 10/2011, published in the EU Official Journal on July 12, 2023 and in force starting from February 1 2025, based on up to date scientific opinions issued by EFSA (EFSA et al., 2022a, 2022b) that had prompted the EC to revise the list of authorized substances, improving clarity, and resolving ambiguities.

The regulation revises and expands the authorization framework for substances used in the production of plastic FCMs, particularly regarding phthalates, and adds DiBP in two group restrictions (32 and 36). Nevertheless, FCMs plastic materials that comply with the pre-amendment regulation (Annex I of Regulation (EU) 10/2011) may still be sold, even after February 1, 2025, until the current stock is depleted. The specific and group migration limits set up by the two EU regulations are reported and compared in Table 6.

Phthalate	FCM No	Annex I to Regulation (EU) 10/2011 In force up to February 1, 2025	Regulation (EU) 2023/1442 amending Annex I to Regulation (EU) 10/2011 In force starting from February 1, 2025
DEHP	283	SML: 1.5 mg/kg SML(T) group restriction n. 32: 60 mg/kg	SML: 0.6 mg/kg SML(T) group restriction n. 32: 60 mg/kg SML(T) group restriction n. 36: 0.6 mg/kg
BBP	159	30.0 mg/kg SML(T) group restriction n. 32: 60 mg/kg	6.0 mg/kg SML(T) group restriction n. 32: 60 mg/kg SML(T) group restriction n. 36: 0.6 mg/kg

DBP	157	SML: 0.3 mg/kg SML(T) group restriction n. 32: 60 mg/kg	SML: 0.12 mg/kg SML(T) group restriction n. 32: 60 mg/kg SML(T) group restriction n. 36: 0.6 mg/kg
DiBP	1085	Not listed as an authorized substance for FCMs	Not listed as an authorized substance for FCMs. However, it may co-occur with other phthalates as a consequence of its use as an aid to polymerization and is included in group restrictions n. 32 and n. 36 with the assignment FCM No 1085. SML(T) group restriction n. 32: 60 mg/kg SML(T) group restriction n. 36: 0.6 mg/kg
DiNP	728	SML(T) group restriction n.26: 1.8 SML(T) group restriction n.32: 60 mg/kg	SML(T) group restriction n..26: 1.8 mg/kg SML(T) group restriction n..32: 60 mg/kg Not to be used in combination with FCMs substances DBP, BBP, DEHP, DiBP
DiDP	729	SML(T) group restriction n.26: 1.8 SML(T) group restriction n.32: 60 mg/kg	SML(T) group restriction n.26: 1.8 SML(T) group restriction n.32: 60 mg/kg

Table 6: Specific migration limits (SML) and Total specific migration groups (SML(T)) for phthalates set up by Regulation (EU) 10/2011 and Regulation (EU) 2023/1442 amendment of Annex I to Regulation (EU) 10/2011. FCM No: substance identification number; SML: Specific Migration limits; SML(T): Total specific migration groups. For phthalates abbreviations refer to table 2.

5.1.5.2.3 Toys and childcare articles

The term childcare article refers to any product designed to facilitate sleep, relaxation, hygiene, feeding, or sucking for children such as pacifiers, baby bottles, cribs, and towels, all of which are used in the context of childcare.

To protect newborn and infant health, the most vulnerable subgroups of the population, **entry 51 of the Annex XVII to REACH Regulation** restricts the use of specific phthalates, including DEHP, BBP, DBP, and DiBP, in the manufacturing, placing on the market, and use of certain materials and products.

Specifically, these four phthalates are prohibited from being used, individually or in combination, at concentrations equal to or greater than 0.1% by weight of the

plasticized material, which includes materials such as PVC, PVDC (polyvinylidene dichloride), PVA (polyvinyl alcohol), polyurethanes, and surface coatings.

Additionally, starting from July 2020, they shall not from be placed on the market in toys or childcare articles, individually or in combination, at the same concentration threshold.

Further, **entry 52 of Annex XVII** prohibits the use of specific phthalates, including DiNP, DiDP, and DnOP, which shall not be used as substances or in mixtures, in concentrations greater than 0,1 % by weight of the plasticized material, in toys and childcare articles which can be placed in the mouth by children(e.g. teething ring or rattle), and any toy or childcare article containing these phthalates above this threshold is banned from being placed on the market (European Commission, 2024b). According to ECHA guidelines, articles “which can be placed in the mouth” are defined as those that can actually be brought to and kept in the mouth by children for sucking and chewing, with key criteria being size (generally <5 cm in at least one dimension) and accessibility during normal or foreseeable use. (ECHA, 2014).

Moreover, phthalates classified as reproductive toxicant category 1B in Part 3 of Annex VI to Regulation (EC) No 1272/2008 and listed in Appendix 6, Annex XVII to REACH Regulation, can be considered hazardous for the purposes of the General Product Safety Regulation (EU) 2023/988 (European Parliament, 2023). Therefore, DMOEP, DBP, DiBP, DPpP, DiPeP, BBP, DHxP, DCHP, DEHP and DHNUP shall not be used, as substances or mixtures for supply to the general public when the individual concentration is equal to or greater than 0,1%.

It is important to note that even if DPHP is a plasticizer only used for technical applications and is not restricted, its use in toys and childcare products is not supported by producers(BASF, 2025; Perstorp, 2023).

5.1.5.2.4 Cosmetics

Cosmetics are defined as any substance or mixture destined to be used on external surfaces of the human body (epidermis, hair, nail, lips and external genital organs) or on teeth or on the oral mucosa, with the purpose of cleaning them, perfuming them, changing their appearance, protecting them, keeping them in good condition or correcting body odors, as defined by the **Regulation**

(EU) 1223/2009 (European Commission, 2019) which is the primary regulatory framework for cosmetic products in EU.

The regulation sets safety standards for cosmetics to protect consumers health and ensure product safety considering various aspects (from manufacturing methods to ingredient control, mandatory labelling information, and expert evaluations). For example, manufacturers must prepare a safety report before product market release and identify a person responsible for ensuring compliance with the regulation and in charge of reporting serious adverse effects to the competent authorities. Further, manufacturers are required to withdrawal and recall all non-compliant products. The regulation defines, as well, that the Member States should implement dissuasive and effective sanctions for non-compliance.

Annex II of this regulation contains the list of substances that are banned for marketing or use in cosmetics within the EU. To prevent skin absorption DMOEP, DBP, DiBP, DPpP, DiPeP, BBP, DHxP, DCHP, DEHP and DHNUP, are specifically banned in all cosmetic products, sold or intended for use.

5.1.5.2.5 Medical Devices

A Medical device is defined as any instrument, apparatus, software, or material intended for diagnosing, preventing, monitoring, treating, or alleviating diseases, injuries or disabilities, modifying anatomy or physiological processes, or providing information by in vitro examination of specimens derived from the human body, without achieving its primary effect through pharmacological, immunological, or metabolic means.

Medical Devices placed on the European market must comply with **Regulation (EU) 2017/745 (Medical Devices Regulation, MDR)** (European Commission, 2017) on medical devices, which has superseded Directive 93/42/EEC and came into effect on 26 May 2021. However, Article 120 of the Regulation allows for a transitional period during which medical devices, under certain conditions (such as those placed on the market before 26 May 2021), can continue to comply with the Directive. According to the fourth paragraph of Article 120, this transitional period concludes on 26 May 2025.

In vitro diagnostic medical devices for human use on the European market must comply with **Regulation (EU) 2017/746** (European Commission, 2017), which has Directive 98/79/EC and Commission Decision 2010/227/EU.

The **Regulations (EU) 2017/745 and 2017/746** mandate the minimization of risks linked with the use of potentially harmful substances, classified as carcinogenic, mutagenic or toxic to reproduction or substances having endocrine-disrupting properties. Therefore, for phthalates, DMOEP, DBP, DiBP, DPeP, DiPeP, BBP, DHxP, DCHP, DEHP and DHNUP. This includes taking measures to limit phthalates' release to patients as much as practicably possible. Specifically, this regulation permits the use of phthalates in medical devices including their parts and materials, that are invasive and directly contact the human body, (re)administer substances, or transport/store substances for (re)administration to the body, at concentrations exceeding 0.1% of total weight only when there is an adequate justification provided for their use (**Annex I, Chapter II, Section 10.4.1**). According to MDR 2017/745 guidelines must be updated at least every five years, based on the latest scientific evidence (**Annex I, Chapter II, Section 10.4.3**).

Manufacturers are also required to provide clear labelling and information about the presence of DEHP in their products while they are encouraged to seek safer alternatives. Additionally, for medical devices containing DEHP, manufacturers must conduct a clinical risk assessment to evaluate exposure impact on patients' health, with the benefits of using DEHP that must balance the potential risks to patient safety.

This regulation took full effect starting January 1, 2025; however, manufacturers are allowed to sell their products previously produced until their stock is depleted.

Noteworthy, **Regulation (EU) 2023/2482** (European Commission, 2023b) amendment to **Regulation (EC) No 1907/2006**, released on November 13, 2023, changed the sunset date for use of DEHP in medical devices postponing it from May 26, 2025, to July 1, 2030, allowing therefore a longer transitional period for medical devices, under specific condition, to comply with the regulation.

5.1.6 Discussion

This study focuses on the EU legislation regulating the use of the nineteen phthalates and two substitutes commonly involved in the production of different

everyday goods categories highlighting, as well, both the significant differences and the shared features of the regulations in force. Our work, therefore, provides environmental researchers and epidemiologists with a clearer perspective on the regulatory framework, to help them better understand what they may encounter when assessing phthalate exposure and their common alternatives in European populations.

The EU was among the first economies implementing stringent restrictions to avoid exposure from consumer products, particularly from toys. Through ECHA, the EU provides comprehensive and structured directives, primarily by coordinating the REACH program, which supervises chemical compounds and ensures regulatory control. Additionally, under ECHA's advice and guidance, the EC and the EU Parliament design more specific, sector-focused regulations to manage chemical risks across specific sectors. EU regulations adopt a precautionary approach to protect human health and the environment, strictly restricting phthalates considered hazardous. Despite progressively broader measures over time, regulation still differs across compounds or product types, with those recognized as hazardous, tightly controlled and others unregulated due to limited toxicological evidence. .

Although the European regulatory framework sets strict limits on toxic phthalate concentration and bans specific molecules, a critical issue lies in the control and monitoring of products. Researchers have recently found significant phthalate contamination in everyday items on the EU market, including food packaging, demonstrating a gap between regulatory purposes and practical outcomes (García Ibarra et al., 2018; Iannone et al., 2024; Perestrelo et al., 2021).

The case of DHxP exposure through contaminated UV filters exemplifies the complexity of chemical exposure pathways. Despite strict regulations on this compound, biomonitoring studies in Denmark and Germany showed significant urinary concentrations of its metabolite, particularly during summer months. Sunscreen formulations containing the UV filter diethylamino hydroxybenzyl hexyl benzoate (DHHB) were identified as a significant source of DHxP exposure, due to contamination (Frederiksen et al., 2025; Scherer et al., 2025). In response to these findings, the SCCS established a maximum safe level of 0.026% (260 ppm) for DHxP contamination in DHHB, while recommending a target level of 1 ppm where technically feasible (SCCS, 2025).

These findings underline that exposure to phthalates in Europe remains ubiquitous and a significant proportion of children and teenagers can reach levels potentially impacting human health.

European biomonitoring studies over the past decade have consistently described different levels of exposure in children and adolescents depending on sampling age. Concentrations appear low during the first months of life (birth to approximately 6 months when weaning begins), rise in toddlerhood to then decrease once more in adolescence and youth.

Multiple studies report this trend. Carlstedt and colleagues found that all phthalate metabolites except MEP and MBP were higher at 6 months compared to 2 months of age (Carlstedt et al., 2013). Similarly, Frederiksen and colleagues reported higher concentrations in infants consuming mixed diets versus those exclusively breastfed (samples collected 2.5-12.5 months prior to weaning) (Frederiksen et al., 2022). Comparable results have been documented in Finnish infants (1-14 months) (Frederiksen et al., 2014), and Italian infants (0-6 months) as well (Lucaccioni et al., 2023). This pattern changes when comparing toddler concentrations to adolescents or adults, resulting in lower concentrations in the latter (Den Hond et al., 2015; Govarts et al., 2023; Schwedler et al., 2020; Vogel et al., 2023c).

Lower concentrations observed in early infancy suggest that regulatory restrictions on toys and childcare products likely reduce exposure in newborns and infants, who primarily remain in controlled environments such as cribs or designated nursery spaces with regulated materials. However, these protective measures become less effective as toddlers gain mobility, begin environment autonomous exploration and interact with a broader range of materials. With age, mouthing behaviors and dust intake by playing near the ground decreases, which may account for the lower phthalate levels in adolescence.

Several factors may explain the gap between exposure levels and regulatory restrictions. Legacy products manufactured during periods with fewer or no phthalate restrictions remain present in many domestic environments over time. Additionally, building materials, decorative items, and furniture, which face less stringent phthalate regulations, are commonly found in indoor spaces where children spend time.

These discrepancies between the intended protective effects of regulatory restrictions and actual exposure levels highlight the need for more comprehensive research that integrates legislative analysis with biomonitoring data to better protect vulnerable populations.

Nevertheless, the documented decline in phthalate concentrations observed across the aforementioned cohorts and other studies (Gerofke et al., 2024b; Vogel et al., 2023a, 2023b) over recent decades demonstrates the importance and effectiveness of ongoing legislative efforts. Another critical issue to consider is the search for safe phthalate substitutes. The same research by Vogel and colleagues also revealed how this regulatory success has been accompanied by concurrent increases in substitute levels such as DINCH and DEHP, reflecting the market's rapid adaptation to regulatory restrictions. These two substitutes are classified as non-hazardous under CLP and have undergone extensive independent assessments by regulatory authorities including EFSA, ECHA, ANSES, NSF International, and CPSC. Recent human biomonitoring data demonstrate that exposure to these substitutes, while increasing with greater market use, remains well below established safe reference values, indicating adequate safety margins for their current applications (Ball et al., 2012; CPSC, 2018a, 2018b; ECHA, 2024d, 2024e; EFSA, 2006; France, 2016a, 2016b).

Further, it is important to emphasize the significant role played by watchdog systems operating in the EU across various areas of concern. One such system is the Safety Gate system (European Commission, 2018), a rapid alert mechanism for dangerous non-food products, established by the General Product Safety Directive and operative since 2024 (Directive 2001/95/EC). Previously known as the RAPEX Network, renamed in 2018, its primary aim is to facilitate the exchange of information and cooperation on product safety regarding hazardous non-food products among national authorities within the European Community. Its counterpart, the RASFF System (Rapid Alert System for Food and Feed), serves as a dedicated alert system for ensuring the safety of food and feed products (European Commission, 2025d).

The latest RAPEX report highlights the proliferation of fraudulent products, many of which fail to comply with safety standards. The RAPEX findings underscore the gap between regulation and enforcement, and this disconnection highlights the need for more robust instruments to ensure compliance at every stage of the commerce chain.

To ensure consumer safety on a global scale, regulations are important to ensure and maintain appropriate control and enforcement throughout the distribution chain, especially in the global market, where products cross countries every day. Different attempts have been made to ease this process. For instance, noteworthy is the SPEAC Project (Safe Non-food Consumer Products in the EU and China), an information and training program designed to help Chinese manufacturers to enhance product safety standards and sell safely to the EU. Its primary goal was to assist and instruct Chinese producers in complying with European safety regulations for non-food items, including toys, electronics, and household furnishings. The initiative aimed to safeguard consumers by reducing the risk of hazardous products entering the European market. To improve enforcement and accelerate compliance processes for Chinese producers, the program also promoted communication and collaboration between EU and Chinese regulatory authorities by creating guidelines and hosting seminars to help companies understand and adhere to European legislation. The project will run until November 2025, but its impact is likely to continue influencing product safety policies in the years to come. The SPEAC initiative between the EU and China demonstrates the potential of collaborative efforts in addressing regulatory gaps(SPEAC, 2025).

The ongoing internationalization of trade markets and the rise of domestic e-commerce increase the likelihood of using products being regulated under different frameworks, therefore aligning regulations on hazardous substances in international commerce is essential. Despite efforts to restrict their use, legislation regarding phthalates remains fragmented across different economies and nations. When considering two of the largest economies in the world, as USA and China, the different regulatory framework and regulation in place pose a significant barrier to achieving this harmonization.

The regulatory landscape in the USA is notably fragmented, primarily due to the federal structure of the states. The United State Congress implemented their first

restrictions with the Consumer Product Safety Improvement Act (CPSIA) in 2008, although some states had previously implemented their own initiatives to restrict phthalates (California started restricting DEHP in 1988 listing it in the Safe Drinking Water and Toxic Enforcement Act of 1986). The regulatory framework is complex, involving multiple agencies such as the Environmental Protection Agency (EPA), the Food and Drug Administration (FDA), and the Consumer Product Safety Commission. Federal oversight is mainly governed by the EPA and FDA, which strive to harmonize with state-level regulations like California's Proposition 65, known for its rigorous standards. Despite this complexity, the USA maintained a framework that emphasizes control, safety, and transparency. However, the regulatory measures are less comprehensive compared to the EU framework. The country imposes strict regulations on food FCMs, toys, childcare articles, and medical devices, while cosmetic products are subject to less stringent oversight.

China is still developing but making efforts to align with global safety standards. As with other restriction areas, China recognizes phthalates and certain environmental priority control pollutants (Wang et al., 2017), yet the enforcement regulations are not as robust as those in the EU or the USA. However, regulation comparison is faced with considerable difficulties in terms of regulatory transparency and free accessibility, especially for non-Chinese speaking stakeholders.

Overall, our study highlights the need to conduct further research to compare EU legislation with other regulatory frameworks and to find ways to harmonize it worldwide.

Further, it is important to invest in research assessing phthalate exposure in different populations, to describe potential associations between legislation and phthalate levels, reveal patterns of exposure, and identify high-risk populations, to guide both policy adjustments, and enforcement strategies. This is the pathway defined by the European Human Biomonitoring Initiative (HBM4EU), an innovative European Joint Program co-funded by the EU under Horizon 2020 focusing on methods to facilitate science-to-policy transfer and proposing a new set of human biomonitoring indicators to convey information on exposure in different age groups, sexes, geographical time points to help answer key policy questions (Gerofke et al., 2023). Beyond indicator development, HBM4EU has

also generated methodological recommendations for integrating human biomonitoring into chemical risk assessment (Santonen et al., 2023) and derived human biomonitoring guidance values (HBM-GVs) for selected phthalates and substitute plasticizers that enable direct interpretation of biomonitoring data in a regulatory context (Lange et al., 2021) . These advances, together with the strategic vision for human biomonitoring as part of Europe's exposure science agenda (Zare Jeddi et al., 2022), are being transferred to and further developed under the Partnership for the Assessment of Risks from Chemicals (PARC), ensuring that biomonitoring data are increasingly aligned with regulatory needs and contribute directly to evidence-based policymaking. Finally, to minimize exposure, actions aimed at strengthening public health communication skills and increasing information literacy in consumers and professionals are essential (Koester et al., 2021; Lugli et al., 2024; Palandri et al., 2024b).

5.1.7 Conclusion

The EU is showing its commitment to reducing exposure to chemicals associated with potential health risks, such as phthalates. The EU has been a pioneer in implementing stringent restrictions on phthalates, particularly through the REACH program, ECHA and sector-specific regulations. These measures have been effective in reducing phthalate exposure related to certain products, especially toys and childcare items, as evidenced by recent biomonitoring studies in newborns and infants, the most vulnerable populations.

However, phthalates, even those restricted, are still contained in articles with long shelf-lives, revealing a gap between regulatory intentions and practical outcomes. This discrepancy is further highlighted by the same biomonitoring studies showing increased phthalate concentrations in toddlerhood, suggesting that current regulations may lose effectiveness in this delicate period.

This been said declining phthalate levels documented in numerous studies provide strong evidence of the long-term success of legislative actions in reducing exposure. The ongoing revision of regulations marks a positive trend, but more must be done to integrate regulatory procedures, particularly in facilitating safer cross-border commerce and ensuring continued international compliance between nations. On this note, international cooperation is crucial, and any attempt to standardize safety standards, to increase data accessibility,

and strengthen enforcement strategies is essential for reducing phthalates' exposure worldwide.

Integrating HBM4EU outputs (methodological guidance and HBM-GVs) and their ongoing translation via PARC will improve the use of biomonitoring evidence in European chemical risk management. Finally, strengthening public health communication and increasing consumer health literacy are also vital steps towards minimizing phthalate exposure and protecting human health.

5.1.7.1 Statements & Declarations

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Author Contributions

LP, ER conceptualized and designed the study, coordinated and supervised data collection. MM, LP, MRS, CL, MF, LL, reviewed phthalate legislation. LP, MM, MRS, MF performed legislation synthesis, supervised by ER. LP, CL, LL, ER critically analysed and interpreted data. LP, MM and MRS. drafted the initial manuscript, ER, CL and LL reviewed and revised the manuscript. All authors critically reviewed the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. All authors contributed to the article and approved the submitted version. All authors have read and agreed to the published version of the manuscript.

Ethics approval

This study did not require the approval of an ethical committee because this study did not require data collection from the participants using questionnaire, interview, focus group study, observation, experiment, interview techniques, the use of humans and animals (including material/data) for experimental or other scientific purposes.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used Microsoft Copilot and Claude to improve language and readability. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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5.2 PERINATAL AND POSTNATAL EXPOSURE TO PHTHALATES AND EARLY NEURODEVELOPMENT AT 6 MONTHS IN HEALTHY INFANTS BORN AT TERM

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Perinatal and postnatal exposure to phthalates and early neurodevelopment at 6 months in healthy infants born at term

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Background: Phthalates are non-persistent chemicals largely used as plasticizers and considered ubiquitous pollutants with endocrine disrupting activity. The exposure during sensible temporal windows as pregnancy and early childhood, may influence physiological neurodevelopment.

Aims and Scope: The aim of this study is to analyze the relationship between the urinary levels of phthalate metabolites in newborn and infants and the global development measured by the Griffiths Scales of Children Development (GSCD) at six months.

Methods: Longitudinal cohort study in healthy Italian term newborn and their mothers from birth to the first 6 months of life. Urine samples were collected at respectively 0 (T0), 3 (T3), 6 (T6) months, and around the delivery for mothers. Urine samples were analyzed for a total of 7 major phthalate metabolites of 5 of the most commonly used phthalates. At six months of age a global child development assessment using the third edition of the Griffith Scales of Child Development (GSCD III) was performed in 104 participants.

Results: In a total of 387 urine samples, the seven metabolites analyzed appeared widespread and were detected in most of the urine samples collected at any time of sampling (66-100%). At six months most of the Developmental Quotients (DQs) falls in average range, except for the subscale B, which presents a DQ median score of 87 (85-95). Adjusted linear regressions between DQs and urinary phthalate metabolite concentrations in mothers at T0 and in infants at T0, T3 and T6 identified several negative associations both for infants' and mothers

especially for DEHP and MBzP. Moreover, once stratified by children's sex, negative associations were found in boys while positive in girls.

Conclusions: Phthalates exposure is widespread, especially for not regulated compounds. Urinary phthalate metabolites were found to be associated to GSCD III scores, showing inverse association with higher phthalate levels related to lower development scores. Our data suggested differences related to the child's sex.

KEYWORDS

neurodevelopment, phthalates, perinatal exposure, endocrine disruptors, infants, newborns, Griffiths development scales

1 Introduction

Phthalates are synthetic chemical compounds obtained through a process of esterification between phthalic anhydride and an alcohol of variable size, from methanol to tridecanol. This family of non-persistent chemicals are generally used as plasticizers to give flexibility, malleability and temperature tolerance to several materials, such as polyvinylchloride (PVC) (1).

Phthalates have a weak interaction with the polymer matrix where they are dispersed and so they are quickly released from their plastic embodiment into the environment. Since they are used in a wide range of everyday consumer products, these compounds are considered ubiquitous pollutants. Consequently, the potential human exposure occurs through multiple sources and is widespread, as well as continuous over time (2–4). One of the main sources of exposure during neonatal life is represented by breast or formula milk. During weaning, exposure due to food contamination is also frequent. Moreover, in the first months and years of life, ingestion from non-food origin occurs due to some typical newborn and toddler behaviors (use of pacifiers and teethingers, frequent hand-to-mouth contact, crawling on vinyl and household floors) (5, 6). Phthalates are easily absorbed, distributed by circulation and quickly metabolized by intestinal lipase and esterases into their respective primary and secondary metabolites, and finally eliminated, mainly in the urine (7, 8).

Phthalates are classified as Endocrine-disrupting Chemicals (EDCs) because they may interfere with the regular hormonal activity. In particular, phthalates compete with endogenous hormones-receptor binding and with hormone transport proteins modifying normal gene expression within the cell (9–13). For this reason, over the past decades, European and international regulations have worked on restricting their use in products such as toys, childcare products, food packaging materials and so on (14).

Early life exposure to EDCs, and in particular to phthalates, is suspected to affect child health including neurodevelopment (15–19). The risk is higher when exposure occurs during windows of vulnerability, such as prenatal, perinatal, and early childhood life. In fact, during the third trimester of pregnancy the brain growth spurt (BGS) occurs. Moreover, the development of the central nervous

system (CNS) is completed within the first two years after birth. During this time, the CNS is particularly susceptible to external stressors, which if present, can influence neurodevelopment in different domains (i.e. sensory, motor and cognitive functions) (20–24). Several epidemiological studies have described harmful associations between prenatal exposure to phthalates and child behavior or cognition (25, 26).

The aim of this study is to analyze the relationship between the urinary levels of phthalate metabolites and the global development measured by the Griffiths Scales of Children Development (GSCD) at six months.

2 Methods

2.1 Participants and sample collection

Participants were recruited as part of the Modena cohort study, a longitudinal cohort study started in 2019 with the aim of investigating the relationship between peri and postnatal exposure to phthalates and the possible relationship with hormonal, anthropometric and neurocognitive development, in healthy Italian children during the first 3 years of life. Mothers were recruited during their hospital stay in the Obstetric ward between March 2019 and October 2020, as soon as possible after delivery. Newborns with mothers of legal age (>18 years old) at delivery, who understood the Italian language and had a singleton pregnancy were eligible for participation in the main cohort study. Other inclusion criteria were: at term delivery (37–41 weeks), appropriate-for-gestational-age (AGA) infant, Apgar score >7 five minutes after birth.

The study was approved by Area Vasta Emilia Nord Ethics Committee (2018/num715). Informed consent to participation and publication of the data was obtained from caregivers of all individual participants included in the study.

The study is a sub-sample of the Modena cohort study. The eligibility criteria were: 1. having at least one urine sample for exposure assessment from birth to 6 months or from the mother within a few days from delivery and 2. having completed the global

development assessment with GSCD at six months. Sample size calculation was performed for the main study, and it was estimated that about 200 newborns were needed. Therefore, we enrolled 197 mothers and child pairs. Among them, 104 infants completed the global development assessment at 6 months, and this determined the sample size for the present sub-study.

2.2 Urine sampling for phthalate exposure assessment

Children underwent consecutive examinations, from birth to sixth month of age, at respectively 0 (T0), 3 (T3), 6 (T6) months. At each evaluation spot urine samples were collected.

Urine samples were chosen as preferred biological matrix to assess phthalate metabolites concentration in mothers and children (27). Children spot urine samples were collected, using phthalate-free pediatric urine bags attached to the skin of external genitalia. Mothers were asked to provide a spot urine sample in phthalate-free plastic containers within a few days from delivery. Urine samples obtained by newborns were collected by trained hospital personnel during their hospital stay, as well as during follow-up visits, until the COVID pandemic outbreak. From that moment on, parents were instructed on correct at-home sampling techniques and were provided with tested phthalate-free urine sampling kits. Once the sample was obtained, it was collected by researchers and immediately labeled and stored in glass vials at -20°C until extraction and analysis procedures.

2.3 Phthalate analysis

Urine samples were analyzed for a total of 7 major phthalate metabolites of 5 of the most commonly used phthalates (Table 1).

Urine sample preparation was performed in the laboratories of the Department of Biomedical, Metabolic and Neural Sciences, while phthalate qualitative and quantitative determination was conducted at the CIGS (Centro Interdipartimentale Grandi Strumenti) of the University of Modena and Reggio Emilia. Abbreviation on phthalates, metabolites and their characteristics may be found in Table 1. Analytical procedures for sample preparation were optimized following published methods by the USA Centers for Disease Control and Prevention (CDC)_Environmental Health Department. Urine samples were defrosted at room temperature sampling 1 ml of urine. β -glucuronidase enzyme was used to hydrolyze the glucuronidated phthalate metabolites (adding 200 μ L of 6% β -glucuronidase enzyme in 6.5 pH acetate buffer and then using 10 ppb of internal standard). They were incubated for 120 minutes at 38°C to allow the cleavage of monoester glucuronides by the enzyme. The reaction was blocked by adding glacial acetic acid and 5% acetonitrile in ultrapure water to the sample solution. The samples were then purified by solid phase extraction (SPE), in order to prevent impurities that may affect matrix compounds and alter the sample selectivity and specificity. The cartridges were conditioned with 2 mL of methanol and 2 mL ultra-pure water. Urine sample was then loaded into the cartridge phase which aims to block interferents and phthalates. The cartridge was then washed with 2 mL of 0.1% acetic acid in ultra-pure water. The samples were eluted with 1 mL of 0.1% acetic acid in acetonitrile. All phthalate metabolites were quantified using reversed-phase-high-performance liquid chromatography–mass spectrometry (RP-HPLC–MS).

2.4 Assessment of neurocognitive development

From 6 months onwards, the study design included a global child development assessment of the enrolled children using the third

TABLE 1 Names, abbreviations, molar weight and limit of detection (LOD) of investigated phthalate parents and their metabolites.

Phthalate diester	Urine metabolites	Abbreviation	Molar weight (g/mol)	LOD (ppb)
Di-methyl phthalate		DMP	194.18	
	Mono-methyl phthalate	MMP	184.18	0.1
Di-ethyl phthalate		DEP	224.24	
	Mono-ethyl phthalate	MEP	194.18	0.1
Di-n-butyl phthalate		DnBP	278.34	
	Mono-n-butyl phthalate	MnBP	222.24	0.05
Butylbenzyl phthalate		BBzP	312.36	
	Mono-benzyl phthalate	MBzP	256.257	0.05
Di-(2-ethyl-hexyl) phthalate		DEHP	390.56	
	Mono-(2-ethyl-hexyl) phthalate	MEHP	278.34	0.25
	Mono-(2-ethyl-hydrohexyl) phthalate	MEOHP	292.33	0.05
	Mono-(2-ethyl-oxohexyl) phthalate	MEHHP	294.34	0.05

Ppb, parts per billion.

edition of the Griffith Scales of Child Development (GSCD III) (28, 29). This widely used specialistic tool explores five key evolutionary areas: foundations of learning (scale A), language and communication (scale B), eye and hand coordination (scale C), personal-social-emotional (scale D), and gross motor (scale E). Subscale scores and a total score, the so called General Development Score (GDS), were calculated. Subscale and GDS raw scores were standardized for sex and age according to GSCD normative scoring tables and guidelines, and standardized “Developmental Quotient (DQ)” scores were produced. In the present study, we used the Italian validated version GSCD questionnaire addressed to 0–12 months children and the normative scoring tables produced for the Italian population (30, 31).

According to the Griffiths III administration manual, the observed standardized DQ can be divided into seven categories for score interpretation: Extremely High (DQ ≥ 130), High (DQ = 120–129), Above Average (DQ = 110–119), Average (DQ = 90–109), Below Average (DQ 80–89), Borderline (DQ = 70–79), Extremely Low (DQ ≤ 69). In the present study, a trained team of pediatricians and a psychologist administered the GSCD at the six-month follow-up visit. After February 2020 due to pandemic restrictions, some of the 6-month follow-up visits were performed online. Staff and families were trained to accurately reproduce the procedures and assessments of in-person GSCD visits.

2.5 Covariates

Given that child development is a complex process due to the interaction with multiple factors derived from the environment, society and the family background, we collected as covariates the items that majorly interact with the GSCD paradigm of development, and which are related to social-economical-cultural background of the parents (31). Data on socio-demographic characteristics of caregivers was collected during the enrollment visit. To specifically examine the relationship between the parents’ cultural background and the baby’s cognitive performance according to the GSCD scales, we defined three educational levels (1 = up to middle school; 2 = high school; 3 = bachelor or more). Working groups were defined according to European Socio-economic Groups (ESeG) (32) classification composed of 3 classes of 9 categories: high class (managers, professionals), middle class (technicians and associated professionals employees, small entrepreneur), working class (clerks and skilled service employees, skilled industrial employees, lower status employees) and not working. Maternal age at delivery, pre-gravidic weight, weight at delivery and height were collected for each mother and pre-gravidic BMI was calculated. Lifestyle habits of mothers during pregnancy were collected. Finally data on whether the evaluation was conducted before or after the pandemic outbreak was collected. Variable details are described in Table 2.

2.6 Study size

The Present study involves 104 participants.

2.7 Statistical analysis

Categorical variables characteristics were summarized by absolute and relative frequencies. Median and interquartile range (IQR) were used to summarize continuous variables. Phthalate concentrations below the respective level of detection (LOD) are expressed as the LOD value divided by the square root of 2 ($<LOD = LOD/\sqrt{2}$). LOD values for each metabolite are reported in Table 1. Metabolites of DEHP were expressed combined as the sums $\Sigma DEHP_m$, by using equation (1):

$$\Sigma DEHP = \left[\left(\frac{UC_{m1} \left(\frac{ng}{mL} \right)}{MW_{m1} \left(\frac{ng}{mmol} \right)} \right) + \left(\frac{UC_{m2} \left(\frac{ng}{mL} \right)}{MW_{m2} \left(\frac{ng}{mmol} \right)} \right) + \dots \right] \times MW_p \left(\frac{ng}{mmol} \right)$$

where $\Sigma DEHP_m$ is the summed urinary concentration of metabolites of DEHP (MEHP, MEHHP, MEOHP) expressed as the urinary concentration of parent compound; UC_{m1} , UC_{m2} etc. are the urinary concentration of the individual metabolites and MW_{m1} , MW_{m2} etc. indicate molecular masses of each metabolite, respectively, while MW_p is the molecular mass of the parent compound. Molecular masses are reported in Table 1.

When considering phthalate metabolite concentration, aside from descriptive analyses, statistical analyses were conducted after natural logarithmic transformation to minimize the influence of highly skewed data. Pearson’s chi-square test or Fisher’s exact test was used to compare categorical variables. T-student test or Wilcoxon rank sum test (also known as Mann Whitney U test) were used to analyze differences in two groups of numeric variables depending on their distribution. We examined potential confounding variables by literature search and included those factors likely to be associated both with phthalate exposure and adverse neurodevelopment (details in Table 2). Given the relatively small sample size, we ran regression models with all candidate covariates and no exposure with each GSCD score. Covariates with p-values less than 0.20 in at least one of the models were retained in all final models. The retained covariates were: child sex, gestational age at delivery, delivery mode, mother’s educational level, father’s educational level and if GSCD was performed before or after the pandemic outbreak.

Several studies reported effect modification for numerous neurodevelopmental outcomes depending on the sex of the child (34–40). We performed regression models stratifying population by sex.

Finally, some of the visits (n:35) were conducted online due to pandemic restrictions. Staff attempted to replicate the procedures and assessments of in-person GSCD visits as accurately as possible; however, given the possibility of bias in test evaluation during online visits, as well as the higher variability of the scores producing some outlier scores, we performed a subgroup analysis on infants visited exclusively in presence. This affected our sample size, but it allowed us to exclude outliers from the analysis. False discovery rate was controlled by using the Benjamini-Hochberg procedure.

Missing data were dealt with pairwise-case data analysis. Statistical software IBM SPSS Statistics®, version 27 and the R software version 4.2.1 (The R Foundation for Statistical Computing) for plotting and advanced statistical analysis, with packages including tidyverse, ggplot2, ggh4x, gtsummary. Code for linear model figure plotting was adapted from Rolland et al. (41).

TABLE 2 Demographic-socio-economic characteristics of infants and caregivers.

		Overall N = 104 ¹
Child characteristics		
Child sex	female	43 (41%)
	male	61 (59%)
Gestational age at delivery	(weeks)	39 (39, 40)
	Not specified	1
Delivery mode	Caesarean	23 (22%)
	Natural	81 (78%)
Weight Percentile at birth*		57 (35, 72)
Height Percentile at birth*		60 (47, 74)
Head Circumference Percentile at birth*		83 (54, 83)
Maternal characteristics		
Mother's age at delivery	(years)	34 (31, 37)
Mother Citizenship	Italian	98 (94%)
	Not Italian	6 (5.8%)
Mother's Educational level	Up to Middle School	1 (1.0%)
	High School	29 (28%)
	Bachelor or more	74 (71%)
Mother's Working status**	High class	35 (34%)
	Middle class	19 (18%)
	Not working	13 (12%)
	Working class	37 (36%)
Mother's BMI before pregnancy	<18.5	4 (3.9%)
	18.5-<25	77 (75%)
	25-<30	16 (16%)
	>=30	6 (5.8%)
	Not specified	1
Smoking during pregnancy	No	98 (95%)
	Yes	5 (4.9%)
	Not specified	1
Alcohol consumption during pregnancy	No	80 (77%)
	Yes	24 (23%)
Paternal characteristics		
Father's age	(years)	37 (34, 41)
Father Citizenship	Italian	100 (96%)
	Not Italian	4 (3.8%)
Father's Educational level	Up to Middle School	4 (4.2%)
	High School	49 (51%)
	Bachelor or more	43 (45%)

(Continued)

TABLE 2 Continued

		Overall N = 104 ¹
	Not specified	8
Father's Working status**	High class	25 (27%)
	Middle class	11 (12%)
	Not working	1 (1.1%)
	Working class	56 (60%)
	Not specified	11

n(%) or median (IQR). *Antropometric percentiles according to WHO (33) **According to the European Socio-economic Groups (ESeG) classification (32). ¹number of participants.

3 Results

3.1 Description of the population

Table 2 describes the overall population of our study involving 104 children, with regards to demographic-socio-economic characteristics of infants and caregivers.

The comparison between the 104 children who underwent the GSCD III evaluation at T6 and were included in the present study (the 'included' group), and those who were not is described in Supplementary Table S1. Significant differences between the two groups were detected for mother's scholarization (higher educational level in the included group), pre-gravidic BMI (higher normo-BMI in the included group) and smoking habit during pregnancy (lower smoking in the included group). No differences were found for the paternal socio-economic characteristics.

3.2 Urinary phthalate metabolite concentrations

For the present study we collected 387 urine samples from 103 mothers, 95 newborns and respectively 92 and 97 infants of three and six months.

Metabolite concentrations detected in urine samples of mothers and children overtime are presented in Table 3. In a total of 387 urine samples, the seven metabolites analyzed appeared widespread and were detected in most of the urine samples collected at any time of sampling (66-100%).

Comparison between 'included' and 'not included' groups are shown in Supplementary Table S2. Overall, the characteristics and urinary concentrations of the 'included' group, did not differ significantly from the 'not included'.

3.3 Assessment of child development

Developmental quotients at 6 months, expressed as median and IQRs, are shown in Table 4. Due to the pandemic restrictions

TABLE 3 Phthalate metabolite concentration (ng/mL) in 387 urine samples from mothers close to delivery, and in their children at birth, three and six months.

	% > LOD	Median (IQR)
Mother samples at delivery (M) - n: 103		
Sampling time from delivery (days)		1.00 (0.00, 1.00)
MMP	66	0.22 (0.07, 0.42)
MEP	100	15 (5, 30)
MnBP	92	5 (2, 10)
MBzP	99	2.46 (1.13, 5.56)
ΣDEHP	100	4 (2, 8)
Newborn samples at birth (T0) - n: 95		
Sampling time from birth (days)		1.00 (0.00, 1.00)
MMP	67	0.18 (0.07, 0.34)
MEP	100	15 (9, 31)
MnBP	92	7 (3, 14)
MBzP	99	4 (1, 8)
ΣDEHP	97	3.0 (1.6, 5.2)
Infant samples at 3 months (T3) - n: 92		
Sampling time from birth (days)		96 (90, 103)
MMP	87	0.19 (0.13, 0.42)
MEP	100	14 (8, 36)
MnBP	100	2.5 (1.5, 4.5)
MBzP	95	0.64 (0.25, 1.56)
ΣDEHP	100	2.2 (1.2, 4.8)
Infant samples at 6 months (T6) - n: 97		
Sampling time from birth (days)		196 (189, 210)
MMP	96	0.40 (0.21, 0.76)
MEP	100	19 (8, 57)
MnBP	100	3.9 (2.2, 6.9)
MBzP	98	1.2 (0.6, 2.8)
ΣDEHP	100	5 (3, 12)

Phthalate abbreviations are explained in Table 1.

TABLE 4 Griffiths III Scales of Child Development results stratified by child sex.

	Overall, N=104 ¹	Female, N=43 ¹	Male, N= 61 ¹	p-value ²
General Development Score *	97 (92, 100)	95 (90, 97)	98 (93, 100)	0.028
Scale A: Foundation of Learning	105 (101, 114)	101 (94, 106)	111 (105, 114)	<0.001
Scale B: Language and Communication	87 (85, 95)	87 (81, 88)	91 (85, 97)	0.2
Scale C: Eye and Hand Coordination*	101 (95, 106)	106 (98, 106)	101 (95, 103)	0.005
Scale D: Personal-Social-Emotional*	90 (85, 97)	86 (81, 90)	93 (87, 99)	<0.001
Scale E: Gross Motor*	100 (95, 109)	101 (95, 109)	100 (96, 106)	0.6

¹Median (IQR); ² Wilcoxon rank sum test. *Missing data for Griffiths III Scales of Child Development: 3 for General Development Score (GDS) given by 2 missing data in subscale D and E, and 1 in subscale C

35 evaluations (33.7%) were performed online, while the ‘in-person’ evaluations were 69 (66.3%). Less than 3% of the study participants had missing outcome data. According to Table 2 most of the DQs fall in average range, except for the subscale B, which present a DQ median score of 87 (85–95). In particular, 46 infants (44%) scored in average or above, while 46 (44%) below average, 8 (7.7%) borderline and 4 (3.8%) extremely low. Table 4 shows the standardized scores obtained at 6 months for the overall population and categorized by children’s sex. The General development and the scales A and D scores, are significantly higher in males; while the scale C had significantly higher score for females. For scale D there is a median score of 93 in boys, which is in average, while in girls there is a median score of 86, which falls below average.

3.4 Adjusted associations between urinary phthalate metabolite concentrations and Griffith’s developmental quotients scores

Figure 1 shows the adjusted linear regressions between Griffith’s developmental quotients scores and urinary phthalate metabolite concentrations in mothers at T0 and in infants at T0, T3 and T6. Several trends both for infants’ and mothers concentrations were found, for each exposure period. Numerical betas and confidence intervals are shown in Supplementary Table 4.

Maternal urinary MnBP concentrations showed a negative trend with the scale C scores at six months while MBzP concentrations showed a negative trend with scale B, scale C and scale E scores. Maternal DEHP concentrations were negatively associated to scale B scores at six months.

At T0, neonatal concentrations of MBzP and DEHP metabolites showed an inverse trend to the scale B at T6. MBzP also showed negative trends with scale A scores. Neonatal MEP concentrations at T0 were positively associated to scale D scores.

MnBP urinary concentrations at T3 showed positive trends with scale E at three and six months; MBzP for all sampling timings was negatively associated to subscale B scores.

Figure 2 shows the adjusted linear regressions between Griffith’s developmental quotients scores and urinary phthalate metabolite concentrations in mothers at T0 and in infants at T0, T3 and T6 stratified by children’s sex. Numerical betas and confidence intervals are shown in Supplementary Table 5 for female and in Supplementary Table 6 for male.

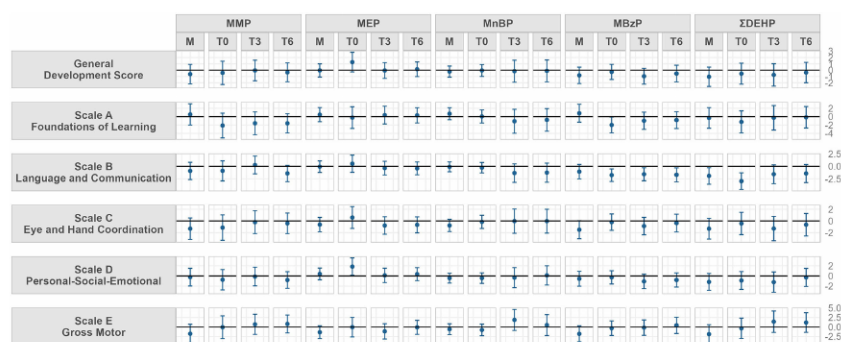


FIGURE 1

Model adjusted for child sex, gestational age at delivery, delivery mode, mother's educational level, father's educational level and if GSCD was performed before or after the pandemic outbreak. Beta and 95% confidence interval of adjusted linear regression models between urinary concentrations of phthalate metabolite and parent compound and Griffith Scales of Child Development (GSCD) measured at 6 months in the Modena cohort study, stratified by sampling timing (from mothers close to delivery, M, and in their children at birth, T0, three, T3, and six months, T6). Values may be found in [Supplementary Material; Table S4](#). Phthalate abbreviations are explained in [Table 1](#).

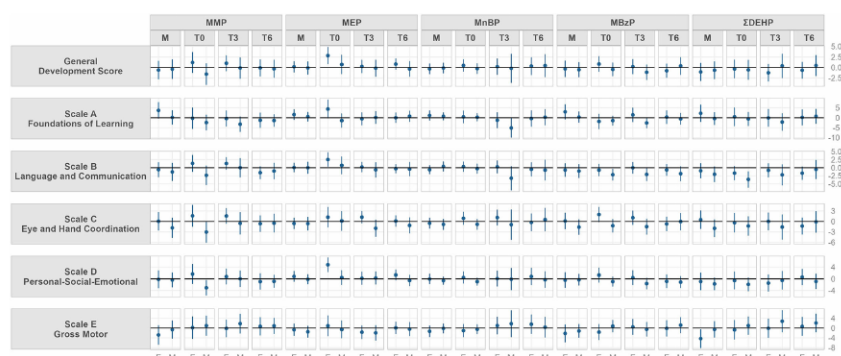


FIGURE 2

Model adjusted for gestational age at delivery, delivery mode, mother's educational level, father's educational level and if GSCD was performed before or after the pandemic outbreak. Beta and 95% confidence interval of adjusted linear regression models stratified by sex between urinary concentrations of phthalate metabolite and parent compound and Griffith Scales of Child Development (GSCD) measured at 6 months in the Modena cohort study, stratified by sampling timing (from mothers close to delivery, M, and in their children at birth, T0, three, T3, and six months, T6). Values may be found in [Supplementary Material; Table S5, 6](#). Phthalate abbreviations are explained in [Table 1](#).

Maternal urinary concentrations had a positive relationship with female scale A scores for MMP and MBzP, while showed a negative association to scale E for DEHP. In boys, negative trends were found for scale C and maternal MMP, MBzP and DEHP concentrations, and for scale B and D and DEHP concentrations.

Neonatal urinary concentrations (T0) showed a positive trend in females with: scale C for MMP, General development score, scale A, B, C and D for MEP, scale C for MBzP. Moreover, in girls a negative trend was found between scale E and MBzP.

In males, neonatal urinary concentrations (T0) were found to be negatively associated to: scale B, C and D for MMP; scale B for MBzP and for DEHP.

At three months of age (T3) a positive trend between female urinary MMP concentrations and scale C was found.

In males, negative associations at T3 was found between MnBP and MBzP and scale A and B.

Urinary phthalate concentrations at T6 did not show relevant trends with DQs at six months in girls and boys.

Finally, given the possible bias in test evaluation during online visits, we performed a subgroup analysis on infants visited exclusively in presence. Even if due to sample size reduction relationships appear less strong, overall associations and patterns were similar to those found in the main models.

4 Discussion

4.1 Main findings

The present study evaluates peri- and postnatal exposure to phthalates in an Italian pediatric cohort of full term babies and their mothers and its possible associations with the child's neurodevelopment. The population showed homogeneous characteristics: all the babies were born from a single center, at term, with no perinatal complications. There is a relatively equal division between males and females and the anthropometric characteristics were in line with healthy newborns for both sexes.

As shown in **Supplementary Material**, few differences between ‘included’ and ‘not included’ groups were found, in particular for mothers (educational status, pre-gravidic BMI and smoking habits). Despite these differences, phthalate metabolites concentrations resulted almost equally distributed within the two groups (as shown in **Supplementary Table S2**). Our results showed that infants and mothers were exposed to several phthalates during the whole study period.

4.1.1 Neurocognitive development

The neurocognitive assessment performed for 104 children at six months through the Griffith Scales of Child Development (GSCD III) showed scores within the normal range for General development score and scales A, C, D, and E. This was expected because the children involved in our study had no significant neurodevelopment risk factors, due to the study inclusion criteria.

For scale B, 46% of our population scored below average. This result could therefore be justified due to the social distancing measures introduced by the pandemic outbreak and the consequent prolonged reduced socialization (42–44). In addition, the use of the facial mask may have influenced and slowed learning, since it hinders labial vision. The evidence that COVID-19 somehow affected children’s neurocognitive development was shown in a recent cross-sectional study. In fact, significantly lower scores in both general development and subscales scores were observed in children assessed during the pandemic period (31).

The surrounding environment, external cues, and lifestyle habits are very important in determining and eliciting neurocognitive development in children. In a study conducted on Filipino children, the Griffith’s Mental Developmental Scales were evaluated by comparing the performance of 742 Filipino children longitudinally at 6, 12 and 24 months old to those of their British counterparts.

Although the performance of the Filipino children in the Griffiths test were within average for age, their performances on developmental sub quotients at later ages of 12 and 24 months were significantly lower than British children and may have been influenced by differences in ethnicity, cultural traditions and limited environmental resources (44).

Our results have also shown differences in the GSCD III scores according to sex, although scores are adjusted for age and sex.

In particular, males reported higher scores in scale A (Foundations of Learning) in scale D (Personal-Social-Emotional) and in General developmental score; while girls, reported higher scores in scale C (hand-eye coordination). From an overall view, in our population boys have higher scores than girls in different areas of development. It is known that there are anatomical and functional differences between the central nervous system maturation of males and females. Hormonally dependent, sex-specific changes in the ultrastructure of the developing central nervous system are known. Higher prenatal androgens in males than in females modulates the masculinization of external genitalia, the developing neural system, and the behavioral development. In particular, the androgen levels during critical periods in early development are thought to contribute to the between- and

within-sex variability in human social and cognitive behavior (4, 45). In literature, data comparing the differences between neurodevelopmental assessment of male and female are present, especially using a different tool compared to our study, the Bayley III scales (40). From a general overview, females present higher scores for language and fine motor performance, while males for gross motor functions and oculo-manual coordination, although these differences are quite clear from 12 months onwards (46).

In a 2019 Danish study (45), the authors investigated whether gender differences were present in Bayley-III scores and behavior in a sample of typically developing children at ages 4, 7, 10, 13, 24 and 36 months. The results demonstrated the existence of gender differences in test scores, but the pattern of differences varied across scales and subtests. In the cognitive scale, gender differences were found at 24 and 36 months with higher scores in girls rather than boys; in the language scale at 10, 13, 24 and 36 months, which found girls’ performances to be superior to those of the boys as well as in the motor scale at 36 months. In a Chinese study, conducted in 2019 to detect possible sex differences in term children using the Bayley-III cognitive scales, 1486 children aged 16 days to 42 months were analyzed. In this study, it was found that girls in the 0-5, 6-11, 12-17 and 18-23-months ranges reported higher scores than boys, although the only significance was reported in the 18-23 months range (38). It is therefore necessary to investigate further, particularly with regard to the use of the GSCD III in the assessment of healthy, term-born children.

4.1.2 Possible associations between phthalates exposure and neurocognitive development

This study detected several possible associations between urinary phthalate concentrations in mothers and children, at three different time points, and GSCD III scores conducted at 6 months.

A large number of tests were carried out, hence, we cannot exclude that some statistically significant results were random. Furthermore, the small sample size may account for the change in significance observed between the unadjusted and adjusted model. For this reason, attention should be focused mainly on the more consistent associations.

As shown in **Figure 1**, MBzP and DEHP metabolites seem to be the most negatively associated to GSCD III, in particular to scale B and C. MBzP itself also showed a negative association with scale A and E. As previously mentioned, these are two of the most regulated phthalates due to their anti-androgenic and endocrine disrupting effects. Although found at low concentrations, both MBzP and DEHP metabolites have shown significant negative associations with different scales of development, confirming previous literature data (47).

MMP, MnBP, DEHP showed positive relation with scale E. The positive association to the gross motor function may be explained with the tendency at six months, for good scale-E performers, to bring objects to the mouth, to suck toys and to start exploring the playground. Maternal levels of MnBP were also found to be negatively associated to scale C, enforcing the negative effect of MBzP and DEHP on neurodevelopment (48).

MEP at T0 was found to be positively associated to scale D performed at six months. MEP is a metabolite of one of the not restricted phthalate (DEP) currently used mainly in self-care products. Our personal interpretation of this direct association with scale D, is linked to the high level of personal care and hygiene that families of babies with high scores at scale D may present. The more the baby is keen to socialization, the more probably the parent are keen to care themselves and the baby and vice-versa. However no results in literature are available to confirm this possibility (49). Child development is an ongoing process within the first years of life, influenced by several different factors as: the relationship with parents and care-givers, appropriate sensorial stimulations or unappropriated deprivation, energy intake, quality of sleep etc. Being able to detect an association within phthalates exposure and GSCD III scores at six months of age in otherwise healthy children with no apparent neurodevelopmental risk factors, brings us to be very careful in results interpretation. However, as clinicians, we need to consider these findings as an alert for the future child development. We need to ask ourselves if GSCD III lower scores are due to a delayed acquisition of the development milestones or to a proper modulation of the neurodevelopment process. Moreover, seen that phthalates are ubiquitous, our children will experienced a prolonged exposure to chemical compounds during a very vulnerable temporal window, leading to a possible summatory effect. Longitudinal follow up of children becomes a priority for brain health.

Once we stratified the population according to sex, associations between GSCD III scores and phthalates concentrations changed. In particular, from an overall view of Figure 2 we detected positive associations in female, while negative associations in male.

MMP, MnBP, MBzP and DEHP metabolites showed several negative associations with all the scale of GSCD III in male, during all the different timing of the study.

These negative associations were previously detected in literature, indicating that there is a negative influence of these compounds on neurodevelopment, especially in males, probably linked to the anti-androgenic effects of many of them.

A recent study suggested that prenatal exposure to phthalates could be inversely associated with the MDI and PDI of infants, particularly in males, at 6 months (34). Other studies (35–40) showed a negative correlation between phthalate levels and neurodevelopment: in all cases a significant inverse associations between prenatal exposure to DBP and cognitive and psychomotor development was found.

On the contrary, positive associations between GSCD III scores in females and urinary phthalates concentrations were found. This was seen especially for MEP, who showed associations with general development score, scale A, B and D for neonatal urinary concentrations.

In females, negative association were found with scale E and MBzP and DEHP concentrations.

Similar associations were previously found by Hyland C et al, who found slightly higher IQ scores in girls with higher phthalates concentrations (50) compared to boys, although age of assessment and urinary collection was completely different from our study. In fact, we need to remember how, in our population, general quotient, scale A and scale D scores were higher in male.

The positive associations in girls may depend on the different body composition of female neonates and children, who present an higher percentage of body fat mass, than male peers.

Differences in body composition between female and male neonates are confirmed, with girls having a higher fat mass divided by total body mass (%) (11.1% vs. 9.6%) and lower free fat mass (2827 g vs. 2979 g), which seems to be maintained throughout life (51, 52).

Full term males are heavier at birth and have a higher lean body mass, whereas females have more subcutaneous fat (53). These sex-related differences have been primarily attributed to the action of fetal sex steroid hormones, which presumably enhances lean body mass growth *in utero* and later during the first months of life, determining a metabolic imprinting of the body fat mass in males (54).

Boys may be more vulnerable to the neurotoxicity in several areas of development, due to anti-androgenic effects of phthalates, although their global scores were within the normal range except for scale B (55–57).

Females may be keener to the accumulation of phthalates in body fat mass. This may lead to a positive association within phthalates concentrations and different developmental domains, although lower scores than males were often found, except for scale C.

4.2 Strengths and limitation

The small number of subjects enrolled in the study is strictly dependant by the complexity of urine sampling in newborn during their very first days of life, which is especially true when conducting stratification by sex. Given this problem, even if the sample appears small, this study is one of the few European studies to assess exposure at this timepoint and, at the moment, one of the largest (34–39). COVID-19 disruption of study protocol affected timing and logistic of sampling collection. After the outbreak, caregivers were asked to collect urine samples. To avoid contamination, we carefully trained them on proper sample techniques and provided them with phthalate-free sampling kits. Finally, researchers collected and stored urine samples as quickly as feasible after sampling. While attempts were made to minimize contamination in our investigation, the chance of contamination exists. Secondly, the use of single spot urine, especially with short half-life compounds, limits the generalizability of our findings to everyday life or chronic exposure. The use of multiple single spot urine over the first six months of life enabled us to assess time trends in early life exposure to phthalates. Furthermore, some authors argued that a single sample may also reasonably predict average metabolite concentrations over a period of several months (58–60). Even though the first year of life is a critical period for brain development, very few studies assessed phthalate concentrations during the first year of life (41, 61), hence the collection of three sample points in the first six months of life is a great strength of our study.

It is noteworthy that the associations of urinary phthalate metabolites collected at 6 months and the GSCD scores collected at the same timing are cross-sectional and need to be interpreted with caution.

Due to the presence of many exposures as well as outcomes, multiple comparisons were performed and we cannot exclude that the some of the association we found were due to chance. Associations found with MMP must be interpreted cautiously, given that the percent of detected samples but lower than LOD was lower than 90%.

Finally, the collection of information regarding the family's socio-economical-cultural background, perinatal and child factors, allowed us to adjust for potential confounder. However, given the complexity of environmental exposure, there may be confounding from residual covariates.

5 Conclusion

Our results highlighted how phthalates exposure in the restricted geographic area analyzed, is widespread. At six months of age, our population of healthy term newborn scored within the normal range in all the different domains of development, except for the language development. This could be related to the social distancing and the use of masks due to pandemic restrictions.

Urinary phthalate metabolites were found to be associated to GSCD III scores, showing negative associations within 'language' and 'hand-eye coordination' and MBzP and DEHP concentrations. The impact of phthalates on neurodevelopment showed a clear sex-related difference with several negative associations in boys within GSCD III scores and anti-androgenic phthalates, while several positive associations in girls, especially with non-regulated compounds.

As phthalates are almost ubiquitous compounds and it is therefore quite impossible to avoid them in daily life, some precautions can be used to minimize exposure. Intervention strategies to reduce the exposure to phthalates in children may include: to prefer fresh foods, to avoid the use of environmental deodorants or cosmetics and personal care products if not phthalates-free; to pay attention to the labels of products purchased, making sure they are phthalate-free; to dispose of older toys or food contact materials that were made prior to the introduction to phthalate regulations, preferring the use of materials that come from countries that currently have in place regulations that limit the use of such compounds (I.e.: European Union)t (62).

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Comitato Etico Area Vasta Emilia Nord. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

LL, LP, ER conceptualized and designed the study, coordinated and supervised data collection, drafted the initial manuscript, and reviewed and revised the manuscript. EP, VT, FC, EF, GT and NB collected data. AF analyzed urinary samples. LL, LP and ER critically analyzed and interpreted data. FF, BP and LI critically reviewed the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. LL and LP have contributed equally to this work and share first authorship. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fendo.2023.1172743/full#supplementary-material>

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6 DISCUSSION AND CONCLUSION

6.1 DISCUSSION

This dissertation integrated epidemiological and environmental perspectives to investigate how environmental, social, and policy determinants shape health across the life course, with a particular focus on the COVID-19 pandemic, sustainable nutrition, and chemical exposure in children. Collectively, the eight articles underscored the interconnectedness of human and planetary health and highlighted how preventive strategies rooted in environmental epidemiology can guide public health policy.

6.1.1 Synthesis of Findings

Across its three thematic chapters, the dissertation advanced a coherent framework for understanding how contextual factors influence both infectious and non-infectious health outcomes. The first chapter, focusing on the COVID-19 pandemic, demonstrated that spatial, environmental, and socio-demographic variables substantially conditioned the spread and severity of SARS-CoV-2. Geography, climate, and population structure shaped exposures, and public health interventions and vaccination modified outcomes. These findings reinforced the need for adaptive, place-based approaches to epidemic preparedness and response.

The second chapter addressed early childhood nutrition and its implications for planetary health. The studies showed that children's diets in two provinces in Northern Italy were frequently unbalanced and environmentally unsustainable, characterized by excessive consumption of animal-based and processed foods. Limited parental awareness and insufficient institutional support pediatricians should be addressed to help the transition toward healthier dietary patterns. The evidence pointed to the need for integrated policies that promote sustainable diets beginning in early life, aligning nutritional, environmental, and educational goals.

The third chapter examined children's exposure to phthalates, combining regulatory analysis with empirical data on early-life exposure and neurodevelopment. Despite advances in European chemical regulation, results indicated that exposure remains widespread and potentially harmful. The work

highlighted the strengths of current regulatory frameworks, emphasizing though the importance of promoting continuative chemical safety policies, especially for vulnerable populations such as infants and pregnant women.

6.1.2 Methodological and Conceptual Contributions

Methodologically, the dissertation applied multi-domain models that combined environmental, geographic, behavioral, and policy variables. It demonstrated how integrating diverse datasets, from spatial and climatic information to biomonitoring and dietary assessments, can reveal complex determinants of health. Conceptually, the work promoted a preventive paradigm that situates human health within environmental systems. It emphasized that population and pediatric health cannot be fully understood without considering ecological and social contexts.

6.1.3 Policy Implications

The findings have direct relevance for public health and environmental policy. First, spatial and environmental data should inform local epidemic surveillance and emergency preparedness. Second, promoting sustainable diets from infancy should become a cross-sectoral priority involving health, education, and agricultural policies. Third, chemical regulation requires continuous updating based on emerging evidence of low-dose and mixture effects. Policymakers should adopt precautionary approaches, ensuring that children's environments are free from harmful exposures.

6.2 CONCLUSIONS AND FUTURE DIRECTIONS

This dissertation provided an empirical and conceptual framework that emphasizes how environmental determinants operate across scales, from the planetary to the individual and that health equity and environmental sustainability are inseparable. Future research should further develop integrative exposure models, longitudinal pediatric cohorts, and participatory approaches that engage families, educators, and clinicians in preventive strategies. Strengthening data integration and communication between environmental and health sectors will be essential to advance the planetary health agenda. Ultimately, protecting children's health and reducing environmental burdens must be regarded as convergent goals at the core of 21st-century public health policy.

7 MANUSCRIPT PUBLICATION PERMISSIONS

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Conditioning factors in the spreading of Covid-19 – Does geography matter?

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8 STATEMENTS

8.1 COMPETING INTERESTS

The author of the present dissertation has no relevant financial or non-financial interests to disclose that are relevant to the content of the present dissertation.

8.2 DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of the present dissertation work the author used ChatGPT and Claude to improve language and readability. After using this tool/service, the author reviewed and edited the content as needed and takes full responsibility for the content of this dissertation.

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