Interdisciplinary Note

Advancing childhood health: The role of transdisciplinary research in understanding the effects of prenatal environmental exposures on respiratory and allergic diseases

Thesis title: Effects of pregnancy exposure to air pollution and surrounding residential greenness on childhood asthma, rhinitis, eczema, and their comorbidity: findings from the French mother-child cohort Pélagie.

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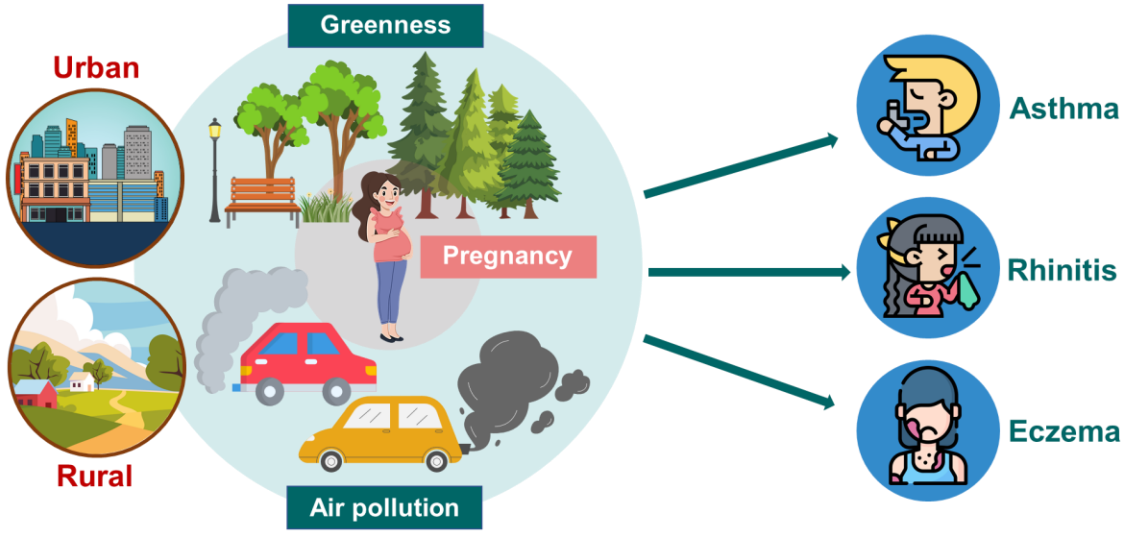
Abstract

Associations of prenatal exposure to air pollution and greenness with childhood asthma, rhinitis, eczema, and their multimorbidity remain inconsistent. As illustrated in the graphical summary, the overarching objective of my thesis was to examine these associations using data from the Pélagie mother-child cohort from Brittany, France, which primarily consists of rural participants. Additionally, I explored how the degree of urbanization modifies these associations.

Overall, the results of this thesis contribute to a better understanding of the effects of prenatal air pollution and surrounding residential greenness on childhood asthma, rhinitis, eczema, and their multimorbidity. While no strong associations were found, observed tendencies for asthma, eczema, and the multimorbidity highlight the need for further investigation. This research reinforces the importance of studying environmental exposures, even in regions with relatively low pollution levels and high greenness. **A transdisciplinary approach, integrating epidemiology, biology, toxicology, medicine, statistics, and social sciences, is essential to fully understand the complex interactions between environmental exposures** such as air pollution and green spaces, **and their effects on health.** Insights from these diverse fields will support evidence-based health policies aimed at minimizing environmental risks and improving long-term public health outcomes.

This interdisciplinary note aims to explore the broader impact of this thesis's findings on epidemiology and public health, emphasizing the role of multiple disciplines in understanding the effects of prenatal environmental exposures. We discuss various research perspectives on prenatal exposure to air pollution and greenness, highlighting the necessity of future transdisciplinary studies to advance knowledge on their effects on childhood respiratory and allergic diseases.

Objectives graphical summary. To investigate the associations of prenatal exposure to air pollution and greenness with childhood asthma, rhinitis, eczema, and their multimorbidity.



1. Introduction

In recent decades, the prevalence of childhood asthma, rhinitis, and eczema increased (1). These three diseases, which often coexist in the same individual, are heterogeneous conditions and their development and progression depend on a variety of factors such as genetics, and environmental exposures (2,3).

According to the developmental origins of health and disease (DOHaD) hypothesis, the fetal and neonatal periods are key windows of susceptibility (4). Growing evidence suggests that an important proportion of childhood asthma, rhinitis, and eczema occurrence is influenced by different environmental exposures during pregnancy and childhood, including outdoor air pollution and green spaces (5,6).

Regarding outdoor air pollutants, fine particulate matter (aerodynamic cut-off diameter of ≤2.5 micrometers, $PM_{2.5}$) and nitrogen dioxide (NO_2), which belong to the traffic-related air pollutants (TRAP), have been of interest in environmental epidemiology for their detrimental effects on children's respiratory health and allergies (4). A number of studies have linked exposure to $PM_{2.5}$ and NO_2 during pregnancy and childhood with the development of childhood asthma, the exacerbation of asthma symptoms, and increased allergic sensitizations (7). However, research specifically examining exposure during pregnancy is more limited regarding their effects on childhood rhinitis and eczema. Furthermore, little evidence exists on outdoor air pollution effects among rural populations, where sources and composition of air pollution widely differ from urban areas (8).

Conversely, green spaces, including parks, forests, and urban green areas, are often associated with various health benefits (9). These areas contribute to air quality improvement and temperature modulation, but also promote and facilitate physical activity, stress reduction, and overall well-being improvement (9). Furthermore, exposure to natural environments can enhance immune function and reduce inflammation, potentially lowering the risk of asthma and allergic diseases (9,10). However, green spaces can also be sources of allergens like pollen, which may trigger allergic reactions (9). Thus, the literature on the effects of green spaces on childhood asthma, rhinitis, and eczema reports contrasting results, showing that the relationship between green spaces and respiratory health and allergies is complex.

In this context, the **main objective** of my thesis was to investigate the associations of exposures to **outdoor air pollution** and surrounding **residential greenness** during pregnancy on **childhood asthma, rhinitis, eczema,** and their **comorbidity**.

2. Summary of findings

Our main analyses did not reveal significant associations between prenatal exposure to outdoor air pollution ($PM_{2.5}$ and NO_2) and childhood respiratory or allergic diseases at 6- or 12-year follow-ups. However, children with a single disease at 6 years showed significantly increased odds in association with NO_2 exposure, while tendencies ($p \leq 0.10$) were observed for eczema at 6 years and for asthma and multimorbidity at 12 years. Stratified analyses by urbanization degree showed significant increased odds for eczema and single-disease cases at 6 years in urban areas in association with $PM_{2.5}$ and NO_2, whereas rural areas suggested a protective effect, significant only for $PM_{2.5}$ and eczema. No significant associations were found in urbanicity-stratified analyses at 12 years. These findings partially support our hypothesis that urban air pollution exposure has stronger effects, though null results for asthma and rhinitis may be influenced by low pollution levels and small sample size.

Regarding prenatal exposure to surrounding greenness, no associations were found with asthma or rhinitis at 6 years, but a protective effect was observed for eczema and single-disease cases. Stratified analyses suggested a protective effect of greenness in rural areas for single-disease cases, while a borderline protective effect for eczema was observed in urban areas. No significant associations were found at 12 years. These results partially align with our hypothesis that greenness effects differ by urbanization level, with some early protective associations for eczema. However, further research is needed to clarify the role of prenatal greenness exposure in childhood respiratory and allergic health outcomes.

3. Research perspectives

3.1. Economic and social burden of childhood asthma, rhinitis, and eczema in France and Europe: A need for further research.

In spite of the high prevalence of childhood asthma, rhinitis, and eczema, evidence on their economic and social burden in France and Europe is limited.

Asthma, particularly during childhood, significantly impacts quality of life due to recurrent exacerbations, leading to missed school days, reduced physical activity, and increased hospitalizations. The economic burden of childhood asthma is considerable, with direct costs, such as hospitalizations and medications, accounting for 50–80% of the total impact (11). In Europe, costs vary across countries due to healthcare systems and socio-economic conditions (12). In France, the average six-month cost for a child with severe asthma is €3,982, driven primarily by medication, especially biologics (13). Long-term effects include reduced educational attainment and productivity, leading to lower lifetime earnings and greater reliance on healthcare services (12).

Childhood rhinitis is often regarded as a less severe condition than asthma, but still represents a significant global health burden. Particularly when untreated or poorly managed, it can have long-term consequences, affecting cognitive development and educational outcomes (14). Regarding its economic burden, we found no specific studies on children.

Childhood eczema also imposes a significant economic and humanistic burden. In France, costs for pediatric patients range from €1,812 for mild cases to €5,861 for severe cases (15). Families face additional out-of-pocket expenses averaging €927 annually, mostly for emollients and non-reimbursed medications (16). Moderate-to-severe eczema severely impacts quality of life, with children experiencing more missed school days, sleep disruption, and social stigma, further affecting their well-being and development (17).

Despite these findings, further research is needed to fully assess the **social and financial impact** of these diseases in childhood across different contexts and European countries. **This requires collaboration among epidemiologists, health economists, and social science experts to generate evidence that can effectively guide healthcare policies in France and Europe.**

3.2. Studying green spaces is a challenge

3.2.1. Defining green spaces

The Normalized Difference Vegetation Index (NDVI) is the metric most widely used in epidemiology to study the effects of green spaces. However, this metric, as other vegetation indexes, still have limitations in capturing fine-scale variability and is influenced by contextual factors like vegetation density, type, and temporal changes (18,19). To better assess the health effects of green space, future research should refine exposure assessments using high-resolution satellite imagery and dynamic longitudinal data, while incorporating diverse indicators such as biodiversity, canopy coverage, and subjective green space measures. **This would require collaboration across multiple disciplines, including remote sensing, environmental epidemiology, ecology, urban planning, data science, public health, and climate sciences.**

3.2.2. Underlying biological mechanisms on respiratory health and allergies

The biological pathways implicated in the effects of green spaces on respiratory health and allergies as well as other health outcomes remain poorly understood, and findings are inconsistent across various health outcomes. These uncertainties underscore the urgent need for more studies assessing the pathways and biomarkers through which green spaces may influence health.

Research investigating DNA methylation (a key epigenetic mechanism) has begun to explore potential biological mediators linking green space exposure to health. One such study, pooling data from eight

European birth cohorts, examined the association between residential greenness and DNA methylation in cord and child blood (20). Despite identifying associations between greenness and differential methylation regions (DMRs) in genes such as ADAMTS2 (linked with connective tissue disorders and brain diseases), KCNQ1DN (associated with aging), SLC6A12 (cellular uptake of betaine and Gamma-Aminobutyric Acid (GABA) in a sodium-and chloride dependent process), and SDK1 (implicated in the cell junction organization), the overall evidence was limited, with no statistically significant results for individual methylation positions after correction for multiple testing (20). These findings, while suggestive, require replication in future studies to confirm their biological relevance and identify potential health-related pathways (20). **A transdisciplinary approach including epidemiology, genetics, biology, and ecology is necessary.**

3.3. Joint effects of air pollution and green spaces

In this thesis, due to the overall non-significant results, we were unable to investigate the mediation effects between air pollution and greenness. However, the relationship between these two factors remains poorly understood, as the beneficial effects of green spaces may be diminished or amplified by high levels of pollution, and these relationships can vary depending on environmental context, geography, and the socio-economic characteristics of exposed populations (21,22).

Green space location and characteristics are crucial in mitigating health risks associated with air pollution. For example, parks near major traffic routes or industrial areas may have limited protective effects due to persistent pollution exposure (21). Additionally, green spaces can enhance immune health through microbial biodiversity, but certain vegetation types, such as pollen-producing plants, may worsen asthma and rhinitis symptoms, especially in polluted urban areas (9). The role of pollen in mediating green space effects on respiratory and allergic diseases requires further exploration, including seasonal variations in pollen levels (9). Studies have also examined the interaction between air pollution, green space, and stress biomarkers like cortisol (23). Research suggests that access to green spaces may mitigate the stress-related effects of air pollution, but the underlying mechanisms are still unclear (23). Furthermore, green spaces help alleviate the urban heat island effect, which exacerbates air pollution's health impacts (9). However, their effectiveness depends on vegetation type and pollution levels, as green spaces in highly polluted areas may not fully counteract these harmful effects (21).

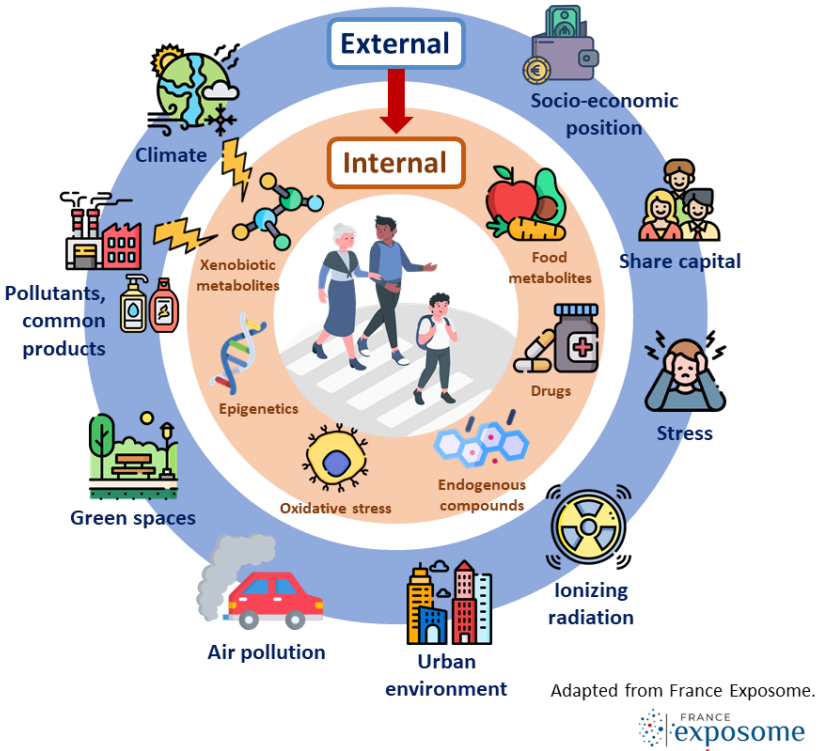
Understanding these interactions is vital for urban planners and policymakers to design green spaces that maximize health benefits while minimizing risks. **A holistic, risk-based approach informed by interdisciplinary research** should guide the planning of context-specific, accessible, and diverse green spaces that address environmental and public health challenges, enhancing well-being, social cohesion, and environmental quality.

3.4. The exposome approach

The exposome concept, introduced in 2005 by Wild (24), emphasizes the cumulative environmental exposures from conception onwards, which encompass not only air pollution and green spaces but a broad range of factors such as occupational exposures, psychosocial stressors, and lifestyle (Figure 1). This approach allows for a more holistic understanding of how various environmental, social, and biological factors interact to shape health outcomes (25). This approach could be particularly relevant in understanding conditions like asthma, rhinitis, or eczema, where multiple individual and environmental factors such as diet, chemical pollutants, pollen, and climate may interact and influence disease onset and progression (26,27). The challenge of studying the exposome lies in its complexity, as it requires capturing a wide range of environmental and behavioral exposures throughout life and processing this data using advanced statistical methods (28).

Moreover, **the exposome framework is inherently transdisciplinary, demanding the integration of diverse fields such as epidemiology, biology, toxicology, social sciences, and data science** (29). The role of social determinants of health, such as socioeconomic status and cultural factors, must be considered, as they significantly impact both environmental exposures and health outcomes, where the more disadvantaged populations are usually the more exposed to environmental hazards or the ones exhibiting poorer health outcomes (30). Technological advancements in environmental monitoring, genomics, and microbiome research will also play a key role in uncovering the mechanisms through which these exposures influence health (29).

Figure 1. The Human Exposome: A holistic approach for the environmental influences on health and well-being.



4. Conclusion

This thesis contributes to the growing body of research on the effects of prenatal exposure to air pollution and surrounding greenness on childhood respiratory and allergic diseases, notably in rural populations, which are often underrepresented in environmental health studies. Moreover, it highlights the complex relationship between prenatal exposure to air pollution, surrounding residential greenness, and childhood respiratory and allergic diseases, particularly asthma, rhinitis, and eczema. We aimed to investigate the potential links between two major traffic-related air pollutants ($PM_{2.5}$ and NO_2) and the presence of greenness, examining how these environmental factors might contribute to the development of allergic diseases, including multimorbidity in childhood.

Our research found no statistically significant associations overall between prenatal exposure to $PM_{2.5}$, NO_2, and greenness exposure and asthma, rhinitis, or eczema. However, we observed some tendencies that suggest potential deleterious effects of air pollution, particularly on asthma and the multimorbidity, with stronger effects observed in urban settings. A potential protective role of residential greenness was observed, particularly for eczema and single-disease multimorbidity at 6 years of follow-up, though these findings were not consistent across follow-up periods.

These findings underscore the complexity of environmental influences on childhood health and highlight the necessity for further research to clarify exposure-related risks and protective factors. Future studies should employ refined methodologies to better assess exposure to green spaces, incorporating diverse indicators such as biodiversity and vegetation structure. Additionally, investigating the biological mechanisms underlying these associations, including the role of epigenetics and immune system modulation, will be essential for a deeper understanding of disease etiology.

Given the significant economic and social burden associated with childhood asthma, rhinitis, and eczema in France and Europe, **interdisciplinary research involving epidemiologists, health economists, and urban planners is critical to inform public health policies.** Moreover, exploring the interplay between air pollution, green spaces, and broader exposome factors will be crucial in developing targeted interventions that promote respiratory and allergic health in children. Ultimately, **integrating environmental and public health perspectives in urban planning and policy-making** will be key to fostering healthier living environments for future generations.

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