The exposome in respiratory diseases: multiple preventable risk factors from early life to adulthood

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The increasing global burden of respiratory diseases over recent decades raises questions about the lifelong impact of environmental factors during industrialisation and urbanisation. There is a clear need for action in primary and secondary prevention. https://bit.ly/3lv14zJ

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Abstract
The increasing global burden of respiratory diseases over the last decades raises questions about the impact of environmental factors during industrialisation and urbanisation. Although the knowledge of environmental epidemiology is growing, it is still unclear what the most critical exposure windows are for respiratory health. In addition, the relationships between different environmental exposures can be complex. The exposome approach investigating all non-genetic factors on health has been developed in recent years but has been little applied in respiratory health to date. This journal club article reviews three recent publications investigating the effects of environmental exposures, considered separately or in an exposome approach with different exposure windows, on respiratory health outcomes. These three studies highlight targets for action in primary and secondary prevention. Two studies, using data from the INMA and RHINESSA cohorts, support the regulation and reduction of phthalates and air pollution, respectively. Moreover, the exposome approach conducted in the NutriNet-Santé cohort emphasises that risk reduction must involve a multi-interventional approach targeting both specific early-life risk factors and promotion of a healthy lifestyle in adulthood. These three articles also present research perspectives in environmental epidemiology.

Commentary on:
- Bosch de Basea M, *et al*. Gestational phthalate exposure and lung function during childhood: a prospective population-based study. *Environ Pollut* 2022; 312: 119833.
- Nordeide Kuiper I, *et al*. Lifelong exposure to air pollution and greenness in relation to asthma, rhinitis and lung function in adulthood. *Environ Int* 2021; 146: 106219.
- Guillien A, *et al*. Exposome profiles and asthma among French adults. *Am J Respir Crit Care Med* 2022; 206: 1208–1219.

Context
The end of the 20th century and the beginning of the 21st century have been marked by increased global industrialisation and urbanisation, causing profound changes in our lifestyle choices and the living environment. The increase in the prevalence of respiratory diseases over the last few decades has mirrored the urbanisation process, which raises questions about the impact of environmental factors on the lungs [1]. The lungs develop from the embryonic phase until young adulthood [2], making them particularly vulnerable to adverse environmental exposures during this critical developmental period. A growing body of research has advanced our scientific understanding of how exposures occurring during prenatal and childhood periods may have lifelong implications on respiratory health [3]. However, knowledge is still

inadequate to fully understand the most critical exposure windows for different environmental exposures such as phthalates, air pollution or green spaces [4, 5]. The classical approach in epidemiology is to study each exposure–outcome relationship separately. While this approach is valuable to generate important evidence for environmental policy-making (*e.g.* setting threshold-based air quality guidelines), it does not always consider that different exposures are sometimes linked, and complex, from a life-course perspective. In this context, the "exposome" concept has been a major development in recent years. It was proposed in 2005 by Wild [6], and refers to the wide environmental (*i.e.* non-genetic) determinants on health and diseases from conception and onwards. To investigate multiple external exposures–outcome relationships, several types of statistical approaches have been reported in the literature: single-exposure regression-based methods (*e.g.* exposome-wide association study (ExWAS)), multiple-exposures regression-based methods (*e.g.* weighted quantile sum (WQS) regression), supervised clustering approaches (*e.g.* latent class analysis) or analysis accounting for the hierarchical structure of the data (*e.g.* Bayesian kernel machine regression) [7]. These methods can be combined, for example, by applying an ExWAS followed by a cluster analysis on a restricted set of the relevant exposures from ExWAS results [7]. These approaches are complemented by analyses of a wide range of biological responses in the internal environment using the "omics" technologies. The exposome research into respiratory diseases is still in its infancy. However, as a wide array of environmental exposure as well as personal biological data are being collected, along with the technological advances, we start to move towards better understanding of the exposome on some major respiratory diseases such as asthma [7].

In this journal club, we put into perspective three publications investigating the effects of environmental exposures considered separately or in an exposome approach, with different exposure windows, on respiratory outcomes. These three studies involved different populations, respiratory outcomes, exposures and statistical methods, which provides a comprehensive view of what can currently be done in environmental epidemiology. Far from showing that there is a preferable design and method, each of these studies presents their strengths and limitations and brings complementary results to better understand the effects of environmental exposures on respiratory health.

Methods

Table 1 and figure 1 summarise the three studies included in this journal club.

INMA study (phthalate)

Bosch de Basea *et al.* [4] investigated the associations between phthalate exposure during pregnancy and lung function during childhood. The authors used data from the Sabadell and Gipuzkoa cohorts within the Spanish INMA study (INfancia y Medio Ambiente – Environment and Childhood).

Lung function parameters were measured by spirometry at ages 4, 7, 9 and/or 11 years, with pre-bronchodilator measurements for forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1), based on which the FEV_1 to FVC ratio (FEV_1/FVC) was subsequently derived.

Nine phthalate metabolites (mono-ethyl phthalate (MEP), mono-iso-butyl phthalate (MiBP), mono-n-butyl phthalate (MnBP), mono-2-carboxymethyl hexyl phthalate (MCMHP; only measured in the Gipuzkoa cohort), mono-benzyl phthalate (MBzP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP), and mono-(2-ethyl-hexyl) phthalate (MEHP)) were measured in urine samples collected in both the first and third trimesters of pregnancy from the participating women.

Multivariable linear regression models were used to assess the association between phthalates and each lung function marker at each visit, whilst linear mixed regression with the participant as a random intercept was used to assess the association across all visits. WQS regression, an approach that is designed to estimate the effect of correlated chemical mixtures on health outcomes [8], was used to assess the effect of the phthalate metabolites mixture on the children's lung function at each study visit.

RHINESSA study (air pollution and greenness)

Nordeide Kuiper *et al.* [5] investigated the associations between air pollution and greenness and respiratory health during different exposure windows. The authors used data from the Respiratory Health in Northern Europe, Spain and Australia (RHINESSA) study.

Diagnosis of allergic and non-allergic asthma, asthma attack in the last 12 months and rhinitis were defined by questionnaire during the study period 2013–2015. FEV_1 and FVC were measured by pre-bronchodilator

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TABLE 1 Summary of the three included studies

	Study design	Population	Exposures	Outcomes	Statistical methods	Key findings
INMA study [4]	Cohort study	641 mother–child pairs from Spain	9 phthalate metabolites (MEP, MiBP, MnBP, MCMHP, MBzP, MEHHP, MEOHP, MECPP, MEHP) in the urine of gestating women	Lung function of children: FVC, FEV_1 and FEV_1/FVC at ages 4, 7, 9 and 11 years	For each phthalate, linear regression for each study visit and mixed linear regression with a random intercept for subject for overall childhood Phthalate metabolites mixture effect assessed using a WQS regression	Gestational exposure to phthalates was associated with children's lower FVC and FEV_1, especially in early childhood
RHINESSA study [5]	Retrospective cohort study	3428 adults from Norway and Sweden (mean age 28 years)	Air pollution (NO_2, PM_{10}, $PM_{2.5}$, black carbon, O_3) and greenness (NDVI) at residential address averaged across susceptibility windows: 0–10 years, 10–18 years, lifetime, and year before study participation	Physician-diagnosed asthma Asthma attack Current rhinitis LLN lung function (FEV_1, FVC and FEV_1/FVC)	Logistic regression for asthma attack, rhinitis and LLN lung function Conditional logistic regression with a matched case–control design for physician-diagnosed asthma	Air pollutants in different susceptibility windows were associated with increased risk of asthma attacks, rhinitis and LLN lung function Greenness was not associated with asthma or rhinitis, but was a risk factor for LLN lung function
NutriNet-Santé study [9]	Cross-sectional analysis from a web-based cohort study	20 833 adults from France (mean age 56 years)	Exposome (87 factors) covered four domains: socioeconomic, external environment, early-life environment, lifestyle-anthropometric	Asthma symptom score Asthma control	ExWAS followed by a latent class model within each exposome domain Negative binomial (asthma symptom score) and logistic regressions (asthma control) per exposome domain	Three early-life and one lifestyle exposure profiles were associated with increased risk of asthma

MEP: mono-ethyl phthalate; MiBP: mono-iso-butyl phthalate; MnBP: mono-n-butyl phthalate; MCMHP: mono-2-carboxymethyl hexyl phthalate; MBzP: mono-benzyl phthalate; MEHHP: mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP: mono-(2-ethyl-5-oxohexyl) phthalate; MECPP: mono-(2-ethyl-5-carboxypentyl) phthalate; MEHP: mono-(2-ethyl-hexyl) phthalate; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; WQS: weighted quantile sum; NO_2: nitrogen dioxide; PM_x: particulate matter with aerodynamic diameter <x µm; O_3: ozone; NDVI: normalised difference vegetation index; LLN: lower limit of normal; ExWAS: exposome-wide association study.

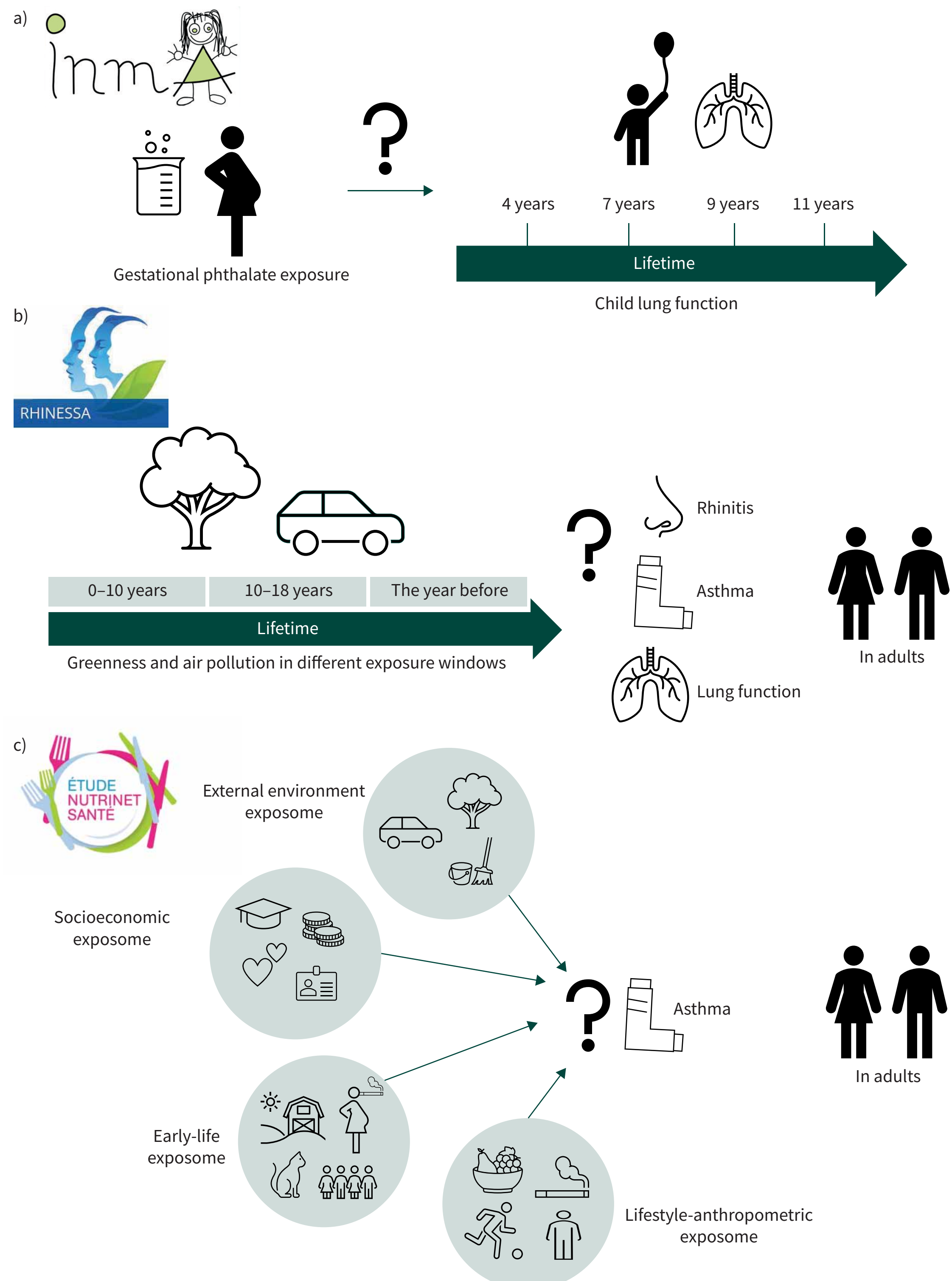

FIGURE 1 Summary of the three included studies: a) INMA study [4], b) RHINESSA study [5], and c) NutriNet-Santé study [9].

spirometry in a subsample of the population. Impaired lung function was defined as lung function below the lower limit of normal (LLN) defined as a z-score <1.64 standard deviations.

Annual mean exposures were estimated for each participant's residential address based on residential history. Nitrogen dioxide (NO_2), particulate matter with aerodynamic diameter <10 µm and <2.5 µm (PM_{10} and $PM_{2.5}$), black carbon and ozone (O_3) estimates were based on land use regression models for the year 2010 (except PM_{10}, which was for 2007). Greenness was estimated by the normalised difference vegetation index (NDVI) from satellite measurements at 300 m buffer. Exposures were averaged across different susceptibility windows: age 0–10 years, age 10–18 years, lifetime, and the year before study participation.

For asthma diagnosis, conditional logistic regressions were performed using cumulative exposures for each year up to the age of asthma diagnosis using a matched case–control design. For asthma attack, rhinitis and impaired lung function, logistic regressions for the different exposure windows were performed.

NutriNet-Santé study (exposome profiles)

The NutriNet-Santé study [9] aimed to investigate the influence of the exposome in asthma by analysing the association between combined socioeconomic, external environment, early-life environment and lifestyle-anthropometric factors and asthma phenotypes. The study population was selected from volunteers of the French NutriNet-Santé cohort, a web-based cohort aiming to evaluate relationships between health and nutrition [10]. For asthma, the authors chose to use the validated asthma symptom score (a continuous measure of respiratory symptoms during the past 12 months, with score range 0–5) and a variable called "asthma control" (never asthma, controlled asthma and uncontrolled asthma). They considered 87 exposure variables belonging to four domains of the exposome: socioeconomic, external environment, early-life environment and lifestyle-anthropometric. All exposures were either self-reported or assessed through a geographic information system (GIS)-based technique involving the residential address of the participants.

For statistical analysis, an ExWAS was performed with an independent negative binomial regression (asthma symptom score) and multinomial logistic regressions (asthma control) for each of the 87 exposure variables, adjusted for age, sex and administrative region. Variables showing an association ($p<0.20$) with one or more of the two asthma outcomes were selected. Factors highly correlated were excluded. The second part of analysis was a cluster analysis within each exposome domain to define three or four profiles of exposure. Negative binomial (for the asthma symptom score) and multinomial logistic (for asthma control) regressions per exposome domain, including the profiles and adjustment for age, sex and region, were performed to assess the association between each of these profiles and asthma.

Main results

INMA study (phthalate)

The analysis included 641 gestating mother–child pairs. Overall, phthalate metabolites were associated with lower FVC and FEV_1 at all age points; however, most of the associations did not reach statistical significance. The associations between MiBP and MBzP and reduced lung function were generally observed only at younger ages (for example, FEV_1 z-score coefficient at age 4 years was −0.024 (95% CI −0.041 to −0.008) for 10% increase in MiBP, and −0.018 (95% CI −0.032 to −0.004) for 10% increase in MBzP), but not beyond 4 years. WQS regression consistently identified MBzP as an important contributor to the phthalate mixture effect.

RHINESSA study (air pollution and greenness)

Among the 5295 Norwegian and Swedish participants, 3428 (555 with lung function data) were included in the analyses. Air pollutants and NDVI were not associated with diagnosed asthma. All air pollutants were associated with an increased risk of asthma attack for the "year before the study" exposure window (adjusted OR 1.60–2.46); NO_2, O_3 and PM_{10} were also associated for other exposure windows (adjusted OR 1.29–2.25). Air pollutants, except O_3, were associated with an increased risk of rhinitis but only for the "year before the study" exposure window (adjusted OR 1.25–1.50). Only $PM_{2.5}$ and O_3 exposures during childhood and adolescence were associated with FEV_1 and FVC <LLN (adjusted OR 2.65–5.95).

No associations between NDVI and asthma or rhinitis were found, but increased NDVI was associated with FEV_1 and FVC <LLN in the 10–18 years and lifetime exposure windows (adjusted OR 1.68 and 1.53, respectively).

NutriNet-Santé study (exposome profiles)

A total of 20 833 adults were included (mean±SD age 56.2±13.2 years; 72% women). Among them, 5546 (27%) individuals had an asthma symptom score >1, and 18 393 (93%), 1206 (6%) and 194 (1%) had never, controlled and uncontrolled asthma, respectively. Three early-life exposure profiles ("high passive smoking–own dogs", "poor birth parameters–daycare attendance–city centre" or ">2 siblings–breastfed" compared with "farm–pet owner–moulds–low passive smoking") and one lifestyle-anthropometric profile ("unhealthy diet–high smoking–overweight" compared with "healthy diet–nonsmoker–thin") were associated with more asthma symptoms (mean score ratio 1.11–1.96) and uncontrolled asthma (OR 1.45–2.88). A dose–effect response was found for all early-life profiles, and the "unhealthy diet–high smoking–overweight" profile.

Commentary

These three studies are each innovative and provide complementary knowledge in environmental epidemiology relating to respiratory diseases, covering a wide range of environmental exposures from early life to adulthood. Together, they show that for a better understanding of the aetiology of chronic respiratory diseases, we will need to consider the interplay between multiple factors (*e.g.* up to 87 potential determinants considered in the NutriNet-Santé study) and different exposure windows (adult *versus* childhood exposures as in the RHINESSA study, and up to the prenatal period as in the INMA study).

One of the main strengths of the three studies included in this journal club is the extensive characterisation of respiratory health and exposures. In the INMA study, repeated spirometry measures were available, covering four time-points in childhood. This allowed the authors to test whether specific age periods are more sensitive to the effects of gestational exposure to phthalates and to evaluate whether effects persist or remit over time. While the study results are in agreement with several previous studies investigating at a single time-point, which have showed statistically nonsignificant inverse associations or null associations, this study is one of the first to assess the association over multiple time-points throughout childhood (*i.e.* pre-adolescence). Since then, FOONG *et al.* [11] investigated whether prenatal exposure to phthalates was associated with lung function outcomes at three time-points from early childhood into young adulthood (age 5–22 years) and contrarily found it to be associated with improved lung function. However, the differences in age groups and differing methods of phthalate measurement make direct comparisons difficult.

The RHINESSA study is one of the first studies with such detailed calculations of exposures during different susceptibility windows throughout the entire lifespan of adults, and extensive respiratory health characterisation. This is also one of the first studies to investigate the effects of greenness on respiratory health in adults. The authors hypothesised that the deleterious effect of greenness could be due to pollens. However, as the NDVI does not differentiate the types of vegetations, considering pollens and/or using land cover could provide additional information to study the health impacts.

The NutriNet-Santé study is the first study investigating the association between exposome and asthma in a large population of adults. The main strength of the study is the holistic approach, considering simultaneously multiple exposures and early-life exposures, which are critical windows of vulnerability, to explore a multifactorial chronic disease. They identified profiles of combined exposures from early life and lifestyle that were at risk for asthma in adults. One of the difficulties of the exposome approach is the interpretability of the results, which is why it is always interesting to couple their interpretation with studies that focus on a specific exposure. The results are in line with those previously described in the literature; however, a validation cohort would have been interesting to evaluate the validity of the results.

The three studies employ different and complementary statistical methods. The multivariate logistic regressions used in the RHINESSA study are certainly the most classical methods and allow for a simple interpretation of the results, in particular the dose–response relationship. Results based on these classical methods can be more easily compared among different studies. However, it is still difficult to disentangle the individual health impacts within a multi-exposure framework or pollutants mixture using these classical methods. In the INMA study, the use of WQS regression allowed the authors to evaluate the phthalate metabolites mixture effect, leading to an interesting finding that perhaps MBzP could be a main driver of the observed association with reduced lung function during childhood. Novel statistical approaches such as WQS regression could be extremely useful to quantify individual health risk of environmental pollutants mixtures, which will provide targeted public health interventions [12]. Finally, in the NutriNet-Santé study, the authors performed an exposome approach by combining an ExWAS approach with a latent class analysis.

The three studies acknowledged a number of methodological limitations. The INMA study was limited by a relatively small sample size at each time-point, the difficulties in obtaining spirometry measurements in young children and the fact that the included sample differed in some sociodemographic characteristics to those excluded. Another limitation is that childhood exposure to phthalates has not been accounted for.

The response rate of RHINESSA was low (~40%), which could possibly have led to a selection bias. The authors acknowledged that it was difficult to know which was the most important window of exposure, given that they were highly correlated. Interestingly, for asthma attack in the last 12 months and rhinitis, the most recent exposure windows are those with the strongest associations. This could be explained by fewer measurement errors but also by the fact that these diseases are perhaps more associated with more recent exposures. Although the statistical method used allows a simple interpretation of the results, it may be of interest in future analyses in RHINESSA to apply methods similar to those used in the INMA and NutriNet-Santé studies, to address the health impacts from highly correlated environmental variables. The authors did not perform multi-pollutant models between NO_2, $PM_{2.5}$, PM_{10} and black carbon as these pollutants were highly correlated. Multi-pollutant models are complex to perform and interpret given the relationship of air pollutants to each other [13]. However, an analysis considering all pollutants, such as the WQS regression approach performed in the INMA study, could be interesting. In this study, the authors mutually adjusted air pollution and NDVI. As the relationship between these exposures is complex [14], it would be interesting to test their interaction and/or to perform mediation analyses, although this would usually require a relatively large sample size.

The French NutriNet-Santé cohort also has several limitations. First, participants are known to have more health-conscious behaviours and better occupational status and education level, compared to the general population. The excluded population (those who did not complete the early-life and adulthood environmental exposures questionnaire) was younger and more often women, in contrast to the study population. Therefore, the results are not necessarily generalisable to the whole population, including other ethnic populations. Secondly, some important exposures for respiratory health could not be taken into account, such as aeroallergens (pollens), indoor environment (dampness) or built environment factors (facilities density). Finally, the authors opted not to use a binary criterion to define asthmatic disease, which seems to be methodologically justified in epidemiological studies [15]; it could however induce a classification bias that may nonetheless lead to confusion with other respiratory diseases, as cough is a nonspecific symptom.

Overall, the INMA and RHINESSA studies provide new insights into the effects of phthalates, air pollution and greenness that are complementary to those of the NutriNet-Santé study, which considered these exposures together in an exposome approach.

Implications for practice and research

These three studies highlight targets for action in primary and secondary prevention. The INMA and RHINESSA studies support the regulation and reduction of phthalates and air pollution. Beyond these specific risk factors, the exposome approach conducted in the NutriNet-Santé study emphasises that risk reduction must involve a multi-interventional approach targeting both early-life risk factors and promotion of a healthy lifestyle in adulthood.

Because environmental exposures are ubiquitous and can be difficult to avoid, it may seem difficult to make an impact in clinical practice on these exposures. However, the role of health professionals is crucial for the prevention and management of environmental exposures. First, a detailed clinical examination of the patient's living environment is necessary to apply the most effective adaptation strategies [16]. In addition, health professionals are in the front line in providing patients with reliable scientific information about the adverse health effects of specific environmental exposures [17]. Finally, health professionals have the opportunity to make their voices heard by health policy makers through the scientific societies to which they may belong [17]. For example, the European Respiratory Society has on several occasions taken a position and called on the European Union to take measures to reduce air pollution levels [17].

All of these points imply initial and ongoing training of health professionals on the health impacts of environmental factors. They also imply the development of scientific knowledge in the field, as there are still many gaps in the quantification of the effects of environmental exposures. The three articles discussed in this journal club allow establishment of research perspectives in the quantification of exposures to phthalates, air pollution and green spaces from early life to adulthood in the context of lung health, as well as the application of the exposome approach in studying multifaceted respiratory diseases. These articles also put into perspective the complexity of the associations between environmental exposures and different methods that can be used to address them.

Conflict of interest: The authors declare no potential conflicts of interest in connection with this article.

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