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Full length article

Prenatal dietary exposure to chemicals and allergy or respiratory diseases in children in the EDEN mother–child cohort

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ABSTRACT

Introduction: Maternal exposure to food chemicals may increase the risk of allergy and respiratory disorders in offspring. We aimed to assess the association of prenatal dietary exposure to single chemicals and chemical mixtures with allergy or respiratory events reported before age 8 y in children.

Methods: We included 1428 mother–child pairs enrolled in the EDEN mother–child cohort. Maternal dietary exposure to 209 chemicals and eight associated mixtures was investigated. Allergic and respiratory diseases (wheezing, asthma, allergic rhinitis, eczema and food allergy) were reported by parents between birth and age 8 y. Associations with the studied outcomes were evaluated with three approaches based on adjusted logistic regression, estimating odds ratios (ORs) and 95 % confidence intervals (CIs). First, food chemicals were considered individually, with correction for multiple testing. Second, chemicals selected by elastic net regression were considered simultaneously in a multiple exposure model. Third, predefined mixtures were introduced in the same adjusted logistic regression. Results are expressed as odds ratio (OR[95 % CI]).

Results: Prenatal single exposure to 74 food chemicals was associated with higher risk of allergic rhinitis. Prenatal single exposure to 11 chemicals was associated with higher risk of wheezing. In the multi-exposure approach, risk of wheezing was associated with the pesticides diazinon and triadimenol, and polycyclic aromatic hydrocarbon 5-methylchrysene. Phytoestrogen resveratrol was negatively associated with lower risk of both wheezing and allergic rhinitis, and mycotoxin monoacetoxyscirpenol was negatively associated with risk of eczema. Finally, a chemical mixture composed mainly of trace elements, furans and polycyclic aromatic hydrocarbons, was associated with higher risk of allergic rhinitis (1.33 [1.02;1.73]).

Conclusion: Prenatal dietary exposure to chemicals was associated with risk of allergic rhinitis or wheezing up to age 8 y. A few chemicals were associated with other allergic and respiratory diseases. Larger prospective studies are needed to confirm these findings.

1. Introduction

Allergic disease prevalence has considerably increased during the last decades (Annesi-Maesano et al., 2021), which suggests a role for environmental factors inducing epigenetic modifications in allergy occurrence (Bégin and Nadeau, 2014). In this context and because of the

immaturity of the fetus immune system and the ability of numerous chemicals to cross the placental barrier (Sarron et al., 2020), the prenatal period seems a critical window to explore the effect of exposure to environmental chemicals on allergic and respiratory events in children.

Furthermore, food represents a major source of exposure to a large set of chemicals (Papadopoulou et al., 2019), and some of these

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substances have been associated with allergic and respiratory disorders (Grados et al., 2022). In a recent systematic review (Buralli et al., 2020), pre- and postnatal exposure to pesticides was associated with an increase in respiratory and allergic symptoms in childhood. Prenatal exposure to polychlorinated biphenyls (PCBs) was associated with higher risk of eczema, allergic rhinitis and asthma (Parker-Lalomio et al., 2018). Similar associations were highlighted between prenatal exposure to polycyclic aromatic hydrocarbons (PAHs) and allergic diseases in early childhood (Koh et al., 2021). In contrast, in a Japanese cohort, prenatal exposure to perfluoroalkyl acids (PFAAs) was associated with an immunosuppressive effect and reduced risk of allergies up to age 4 y (Goudarzi et al., 2016). Finally, positive and negative associations were found between early life exposure to some metals and allergic outcomes in childhood (Wang et al., 2022).

These studies mostly used biological concentrations of chemicals in maternal tissues (serum, urine etc.) during pregnancy. However, to be able to conduct preventive studies, it is of interest to identify the part of each route of exposure (oral, inhalation, dermal, etc.) combined to the part of chemicals crossing the placental barrier in the associations with child's health. Moreover, most studies have focused on a single substance, sometimes one or two families of chemicals, but individuals are simultaneously exposed to several substances (Haug et al., 2018). Only a few studies have focused on the effect of early exposure to chemical mixtures. In one study (Berger et al., 2019), maternal urinary concentrations of 20 substances showed additive and antagonistic effects of some chemicals on respiratory allergies. Another study, focused on prenatal exposure to 11 metals and atopic dermatitis (Tsai et al., 2021), found a positive association with cadmium but only when considering co-exposure to other metals. The European Human Early-Life Exposome study explored the simultaneous effects of 85 prenatal exposures to urban, chemical, and lifestyle factors on lung function, demonstrating high prenatal exposure to certain PFAAs associated with low lung function (Agier et al., 2019).

In this context, the objective of our study was to explore the link between dietary exposure to a large number of chemicals, considered individually, jointly or as mixtures, and the incidence of allergic and respiratory diseases during childhood.

2. Materials and methods

2.1. Study design

The EDEN mother-child cohort (Heude et al., 2016) enrolled 2002 pregnant women between February 2003 and January 2006 at the end of their first trimester of pregnancy in two university maternity centers in Nancy and Poitiers (France). Pregnant women presenting before 24 weeks of amenorrhea, without multiple pregnancies and able to read and speak French were invited to participate. Children were followed up to age 8 y by questionnaires completed by parents. The study was approved by the ethics committee of the university hospital of Kremlin-Bicêtre (ID 0270, December 12, 2002) and data files were declared to the National Committee for Processed Data and Freedom (CNIL, ID 902267, December 12, 2002). Written consent was obtained from both parents.

2.2. Maternal exposure to food chemicals

Maternal exposure to food chemicals during the last 3 months of pregnancy was previously described (Traoré et al., 2018). Briefly, maternal dietary intake during the last trimester of pregnancy was recorded at delivery by use of a validated food frequency questionnaire (Deschamps et al., 2009), and frequencies and portion sizes were combined to assess the individual daily intake of 137 food items. Then, these intakes were combined with the concentrations of chemicals assessed in food items in the second French Total Diet Study (TDS2) (Chan-Hon-Tong et al., 2013; Bemrah et al., 2012; Chekri et al., 2012; Millour et al., 2012; Millour et al., 2011; Noël et al., 2012; Nougadère et al., 2012;

Rivière et al., 2014; Sirot et al., 2013; Sirot et al., 2012; Veyrand et al., 2013; Sirot et al., 2012). In our study, the lower bound scenario was applied. According to this scenario, non-detected values were replaced by 0, whereas detected values unable to be quantified were replaced by the limit of detection. Thus, from the 446 food chemicals assessed in TDS2, 225 substances were considered not detected in our study population. We also excluded 12 sums of chemicals, which left 209 single food chemicals considered in this study (Supplementary Table 1): 71 pesticides, 23 trace elements, 20 PAHs, 12 PFAAs, 17 dioxins and furans, 18 PCBs, 18 mycotoxins, 14 brominated flame retardants (BFRs), 11 phytoestrogens, Three food additives, acrylamide and bisphenol A.

Moreover, mixtures of chemicals were previously identified with the sparse non-negative matrix under-approximation (SNMU) method. This method of dimension reduction is specific to non-negative matrices and thus is suitable for nutritional exposure data consisting of positive values with many zero values (Béchaux et al., 2013). Eight mixtures to which EDEN mothers may have been exposed through diet were identified and named according to substances contributing the most to their composition (Supplementary Table 2) (Traoré et al., 2018):

- *TE-F-PAH*: 11 trace elements - 5 furans - pyrene - BghiP
- *Mixt-2*: 12 PCBs - 2 BFRs - 7 PAHs - inorganic Hg - TCDF-2378 - bisphenol A - T2 toxin
- *Pest-1*: 4 carbamates - 4 organophosphorus pesticides (OPs) - 2 dicarboximides - 3 benzoylureas - 7 other pesticides - patulin
- *Pest-2*: 2 pyrethroids - 2 strobilurins - 3 OPs - 2 dicarboximides - 7 other pesticides
- *Pest-3*: 2 pyrethroids - 3 triazoles - 2 carbamates - 9 other pesticides
- *PCB-BFR-Aso-MeHg*: 6 PCBs - 7 BFRs - organic arsenic - methyl mercury - 3 PFAAs
- *Myc-Pest-PAH*: 8 mycotoxins - 3 pesticides - 4 PAHs
- *PFAA-Ge-Li*: 8 PFAAs - germanium - lithium - 6 other trace elements - 5 phytoestrogens

2.3. Allergic and respiratory events

Data on allergies were collected with the International Study on Asthma and Allergies in Childhood (ISAAC) questionnaire (Asher et al., 1995) completed by parents at the 8-month and 1-, 2-, 3-, 4-, 5- and 8-year follow-ups. In this study, allergy outcomes considered were eczema and food allergies up to age 8 y. Respiratory-related outcomes were wheezing up to age 8 y, current asthma up to age 8 y, and allergic rhinitis from age 2 to 8 y. Children were defined as having current asthma if they fulfilled at least one of the following three criteria: (1) ever asthma combined with current wheezing, (2) ever asthma combined with current use of a bronchodilator (β agonists or anticholinergics) and (3) current use of specific asthma medication. Eczema was defined as a positive answer to three items ("Has your child ever been diagnosed with eczema?"; "[Since last follow-up], has your child had an itchy rash (red patches, pimples etc.) on the skin that appears and disappears intermittently?"; "Has this itchy rash affected any of the following areas: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, around the neck, around the eyes or ears?"). Allergic rhinitis was defined as a positive answer to two items: "[Since last follow-up] has your child had sneezing, a runny nose or a stuffy nose without respiratory infection (no cold, no rhinopharyngitis, no flu etc.)? Were these nose problems accompanied by watering (crying) or itching (scratching) of the eyes?" (Anto et al., 2017).

In this study, children were considered to have ever wheezing, ever eczema, ever food allergy, ever asthma or ever allergic rhinitis if the parents reported at least once the considered health event during the follow-up.

2.4. Statistical analysis

Included and excluded populations were compared by chi-squared

and Student *t* tests for categorical and continuous variables, respectively. Daily exposure to each food chemical was log-transformed to account for skewed distributions and then standardized to allow comparison of effect size across chemicals. For 110 chemicals with very low proportion of exposed mothers, we performed tercile categorization, then exposure levels were grouped as low exposure (1st tercile) and medium/high exposure (2nd and 3rd terciles).

To examine associations between prenatal dietary exposure to chemicals and allergy/respiratory diseases in childhood, we used three complementary approaches: a single-exposure approach, a multiple-exposure approach and a mixture approach, as explained below:

- 1- Single-exposure approach:** each food chemical was analyzed separately for association with allergic or respiratory diseases with an adjusted logistic regression model ($P < 0.05$ considered statistically significant). To deal with multiple testing issues, we used the false discovery rate (FDR) procedure (SAS, PROC Multtest); $Q < 0.1$ was considered statistically significant.
- 2- A multiple-exposure approach:** the elastic net penalized regression model was used to select the most contributive variables to be introduced in the final multiple-exposure logistic regression model. Elastic net is suitable for variable selection when multiple collinearity between variables is an issue (Friedman et al., 2010). We used a 10-fold cross-validation approach, repeated 100 times, to determine the optimal degree of penalization (Berrar et al., 2019). All chemicals associated with a given allergic or respiratory disease with $P < 0.1$ on the single-exposure approach were introduced in the elastic net selection.
- 3- Mixtures approach:** the associations between prenatal exposure to the eight described food chemical mixtures and risk of allergy or respiratory diseases were examined by adjusted logistic regression considering simultaneously the individual scores of exposures to each of the eight mixtures.

Potential confounding factors were first identified based on literature findings, then selected with the directed acyclic graph method (Shrier and Platt, 2008) (Supplementary Fig. 1). All regression models described above were adjusted for the minimal sufficient adjustment set identified by the DAG: maternal age, education level, household income, primiparity, maternal smoking during pregnancy, region (recruitment center), maternal diet quality (PANDiet score) (Kadawathagedara et al., 2017) and family history of allergies. Additionally, we decided to adjust on some child's characteristics (child sex, and mode of delivery) that are not in the causal pathway from food chemical exposure to allergies.

Our main analyses were performed on the complete-case sample. In sensitivity analyses, multiple imputations models were used to account for missing data on confounding factors.

Multiple imputation data are presented in Supplementary Table 3. Data were assumed to be missing at random, and five independent datasets were generated with the fully conditional specification method (MI procedure, FCS statement, NIMPUTE option), then pooled effect estimates were calculated (SAS MIANALYSE procedure). Continuous variables were imputed with predictive mean matching, and logistic regression was used for categorical variables.

Elastic net analyses were conducted with the "glmnet" package in R v4.2.1. All other analyses were conducted with SAS v9.4 (SAS Institute, Cary, NC, USA).

2.5. Study sample

From the 2002 women included in the EDEN mother-child cohort, we excluded mothers with missing data on food chemical exposure ($n = 336$) and children with missing data on the studied outcome ($n = 123$ for eczema, 126 for food allergy, 123 for wheezing, 226 for allergic rhinitis and 122 for asthma). For complete-cases analysis, we also excluded individuals with missing data for at least one adjustment variable ($n =$

116), which left 1427, 1424, 1427, 1324, and 1428 mother-child pairs for eczema, food allergy, wheezing, allergic rhinitis and asthma, respectively (Supplementary Fig. 2).

3. Results

3.1. Population description

As compared with excluded mothers, included mothers had higher education level (34.9 % vs. 22.6 % with at least a 5-y university degree, $p < 0.0001$) and higher income (29.6 % vs. 19.6 % with more than 3.000 €/month, $p < 0.0001$), less frequently smoked during pregnancy (24.2 % vs. 32.9 %, $p = 0.0004$), and reported more family history of allergies (53.2 % vs. 47.5 %, $p = 0.03$). In the included sample, 54.1 % of mothers were primiparous, 53.2 % of children were male and 15.3 % of children were born by cesarean section. The prevalence of any wheezing, asthma, allergic rhinitis, eczema and food allergy up to age 8 y was 39.2 %, 15.5 %, 19.8 %, 25.6 %, and 10.9 %, respectively.

3.2. Prenatal exposure to food chemicals and eczema

In the single-exposure approach (Supplementary Fig. 3), prenatal dietary exposure to four pesticides was positively associated with risk of eczema up to age 8 y, but none of the observed associations persisted after correction for multiple testing (Supplementary Table 4). In the imputed model, only two of the previous pesticides were positively associated and did not persist after multiple testing correction (Supplementary Table 4).

In the multiple-exposure approach, considering simultaneously the seven chemicals selected by the elastic net method (Nickel, monoacetoxyscirpenol [MAS], azoxystrobin, chlorpyrifos-methyl, cyproconazole, flutriafol and lindane). Prenatal dietary exposure to one mycotoxin (MAS) was negatively associated with risk of eczema (Fig. 1). In the mixture approach, none of the eight mixtures was related to risk of eczema (Table 1).

3.3. Prenatal exposure to food chemicals and food allergy

In the single-exposure approach (Supplementary Fig. 4), prenatal dietary exposure to the pesticide malathion was negatively related to risk of food allergy. This association did not persist after multiple testing correction. In the imputed model, we additionally identified ten chemicals (five dioxins, one furan, two pesticides and two trace elements) positively associated with the risk of food allergy but none of these

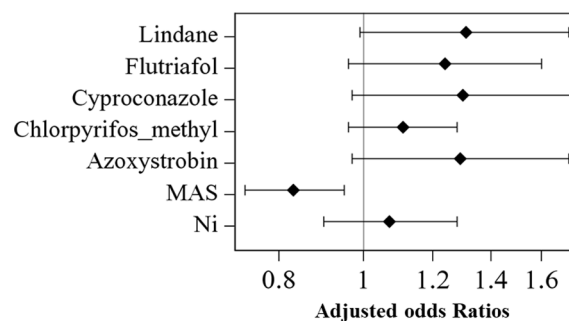


Fig. 1. Association between prenatal multiple dietary exposure to chemicals (selected by elastic net) and eczema in children up to age 8 y ($n = 1427$). Values are odds ratios (95 % CI) from a logistic regression model adjusted for maternal characteristics (age, education level, household income, primiparity, smoking during pregnancy, diet quality), child and birth characteristics (sex, mode of delivery, family history of allergies) and study center. All food chemicals selected by an elastic net penalized regression (cross-validated optimum penalization: $\alpha = 0.1$, $\lambda = 0.04495028$) were considered simultaneously in the same logistic regression model. MAS, monoacetoxyscirpenol.

Table 1
Associations between maternal dietary exposure to chemical mixtures during pregnancy and allergic or respiratory diseases in offspring up to 8 y.

	Wheezing (N = 1427)	Eczema (N = 1427)	Food allergies (N = 1424)	Allergic rhinitis (N = 1324)	Asthma (N = 1428)
TE-F-PAH	1.14 [0.93; 1.41]	1.18 [0.93; 1.49]	1.34 [0.98; 1.83]	1.33 [1.02; 1.73]	1.09 [0.83; 1.44]
Mixt-2	0.93 [0.66; 1.31]	0.86 [0.59; 1.25]	0.67 [0.41; 1.12]	0.92 [0.60; 1.40]	1.05 [0.67; 1.65]
Pest-1	1.05 [0.94; 1.18]	0.90 [0.79; 1.03]	0.95 [0.80; 1.14]	1.13 [0.99; 1.29]	1.04 [0.90; 1.20]
Pest-3	1.06 [0.94; 1.19]	1.08 [0.95; 1.22]	0.89 [0.72; 1.11]	0.99 [0.85; 1.15]	1.07 [0.92; 1.23]
PCB-BFR-Aso-MeHg	1.01 [0.81; 1.25]	1.00 [0.79; 1.27]	1.27 [0.94; 1.70]	1.04 [0.80; 1.35]	0.98 [0.73; 1.31]
Pest-2	0.95 [0.84; 1.08]	1.02 [0.89; 1.17]	1.07 [0.89; 1.28]	0.93 [0.79; 1.09]	0.97 [0.83; 1.14]
Myc-Pest-PAH	0.96 [0.85; 1.08]	1.03 [0.91; 1.18]	0.90 [0.74; 1.09]	1.03 [0.89; 1.20]	0.88 [0.74; 1.06]
PFAA-Ge-Li	0.93 [0.82; 1.06]	0.99 [0.86; 1.14]	0.95 [0.77; 1.16]	0.95 [0.8; 1.120]	0.85 [0.71; 1.03]

Values are odds ratios [95 % CI] from a logistic regression model including the eight mixtures simultaneously and adjusting for maternal characteristics (age, education level, household income, primiparity, smoking during pregnancy, diet quality), child and birth characteristics (sex, mode of delivery, family history of allergies) and study center. Abbreviations: TE-F-PAH, trace elements-furans-polycyclic aromatic hydrocarbons; Mixt-2, mixture-2; Pest-1, pesticides-1; Pest-2, pesticides-2; Pest-3, pesticides-3; PCB-BFR-Aso-MeHg, polychlorobiphenyls-brominated flame retardants-organic arsenic-methylmercury; Myco-Pest-PAH, mycotoxins-pesticides-polycyclic aromatic hydrocarbons; PFAA-Ge-Li, perfluoroalkyl acids-germanium-lithium.

associations persisted after multiple testing correction (Supplementary Table 5).

In the multiple-exposure approach, considering simultaneously the six chemicals selected by elastic net (Tin, PFOS, HCDF-123789, procymidone, metalaxyl, and malathion), prenatal dietary exposure to one pesticide (malathion) was negatively associated with risk of food allergy

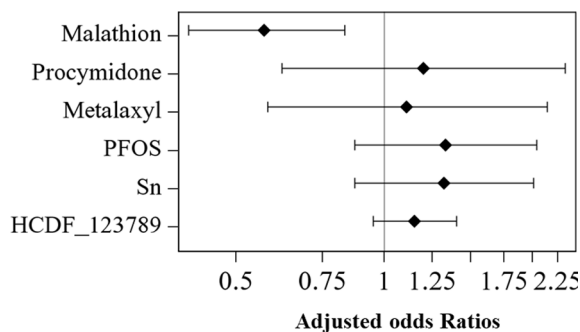


Fig. 2. Association between prenatal multiple dietary exposure to chemicals (selected by elastic net) and food allergy in children up to age 8 y (n = 1424). Values are odds ratios (95 % CI) from a logistic regression model adjusted for maternal characteristics (age, education level, household income, primiparity, smoking during pregnancy, diet quality), child and birth characteristics (sex, mode of delivery, family history of allergies) and study center. All food chemicals selected by an elastic net penalized regression (cross-validated optimum penalization: $\alpha = 0.1 \lambda = 0.01927628$) were considered simultaneously in the same logistic regression model. PFOS, perfluorooctane sulfonate.

(Fig. 2).

In the mixture approach, none of the eight mixtures was associated with risk of food allergy in the principal model (Table 1). However, in multiple imputations analysis, the “Te-F-PAH” mixture was positively associated with risk of food allergy (Supplementary Table 9).

3.4. Prenatal exposure to food chemicals and wheezing

In the single-exposure approach, prenatal dietary exposure to 19 chemicals was positively related to the risk of wheezing up to 8 y: acrylamide, 2 PAHs, 1 trace element, 1 mycotoxin, and 14 pesticides (Supplementary Fig. 5). 11 of the observed associations persisted after multiple testing correction: acrylamide, 5-methylchrysen, DbahP and 8 pesticides. In the multiple imputation model, we observed 14 of the previous associations and ten additional associations: eight positive associations with five pesticides, one furan, one PAH and one mycotoxin, and negative associations with two phytoestrogens. All of associations observed in the multiple imputation model persisted after multiple testing correction (Supplementary Table 6).

In the multiple-exposure approach, 14 chemicals were selected by elastic net and analyzed simultaneously (resveratrol, HCDF-123789, DbaeP, 5-methylchrysen, Fumonisin-B2, DON15, permethrin, azoxystrobin, cyproconazole, metalaxyl, triadimenol, diazinon, mepanipyrim, and formononetin). Only two pesticides (diazinon and triadimenol) and 5-methylchrysen were associated with increased risk of wheezing. By contrast, prenatal dietary exposure to the phytoestrogen resveratrol was negatively associated with risk of wheezing (Fig. 3).

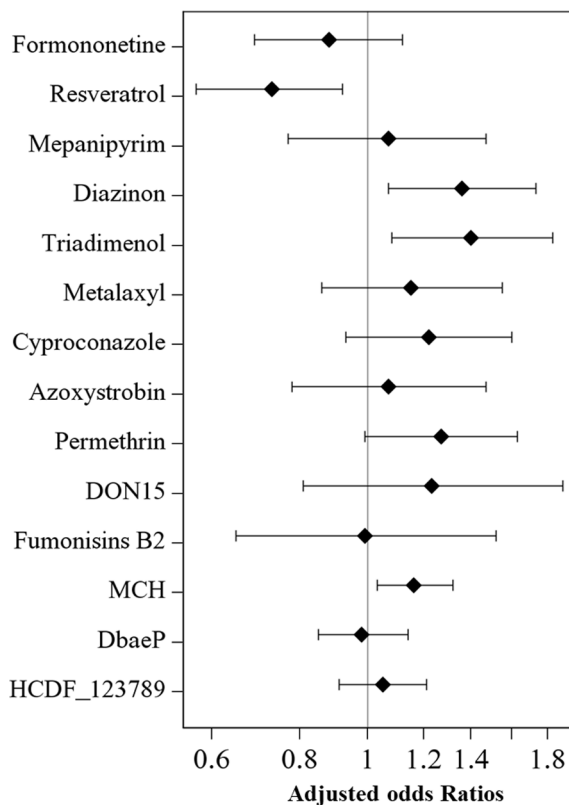


Fig. 3. Association between prenatal multiple dietary exposure to chemicals (selected by elastic net) and wheezing in children up to age 8 y (n = 1427). Values are odds ratios (95 % CI) from a logistic regression model adjusted for maternal characteristics (age, education level, household income, primiparity, smoking during pregnancy, diet quality), child and birth characteristics (sex, mode of delivery, family history of allergies) and study center. All food chemicals selected by an elastic net penalized regression (cross-validated optimum penalization: $\alpha = 0.2 \lambda = 0.02288197$) were considered simultaneously in the same logistic regression model. MCH, methylchrysen.

In the mixture approach, none of the eight mixtures was related to risk of wheezing (Table 1).

3.5. Prenatal exposure to food chemicals and asthma

In the single-exposure approach, prenatal dietary exposure to 20 chemicals was positively associated with risk of asthma up to age 8 y: five dioxins, five furans, one PCB, and nine pesticides (Supplementary Fig. 6). By contrast, prenatal dietary exposure to eight pesticides and phytoestrogen matairesinol was negatively associated with risk of asthma. None of the observed associations persisted after multiple testing correction (Supplementary Table 7). In the imputed model, we observed 12 of the previous positive associations, together with six additional pesticides and phytoestrogen resveratrol, but none of these associations persisted after multiple testing correction.

In the multiple-exposure approach, 25 chemicals selected by elastic net were considered simultaneously: acrylamide, PBDE209, PCB-126, HCDD-1234678, TCDD, HCDF-123789, HCDF-234678, DbaeP, pyrene, penconazole, iprodione, azoxystrobin, cyproconazole, fludioxonil, metalaxyl, myclobutanil, phosmet, pyrimicarb, procymidone, diazinon, fenhexamid, hexachlorobenzene, PFHxS, resveratrol and matairesinol. None of the food chemicals was associated with risk of asthma (Fig. 4).

In the mixture approach, none of the eight mixtures was associated with risk of asthma (Table 1).

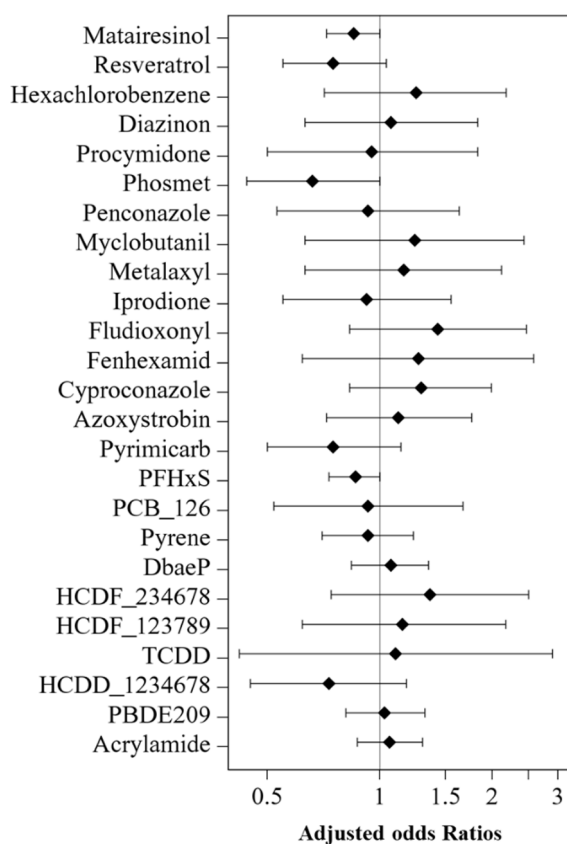


Fig. 4. Association between prenatal multiple dietary exposure to chemicals (selected by elastic net) and asthma in children up to age 8 y (n = 1428). Values are odds ratios (95 % CI) from a logistic regression model adjusted for maternal characteristics (age, education level, household income, primiparity, smoking during pregnancy, diet quality), child and birth characteristics (sex, mode of delivery, family history of allergies) and study center. All food chemicals selected by an elastic net penalized regression (cross-validated optimum penalization: $\alpha = 0.5 \lambda = 0.00775231$) were considered simultaneously in the same logistic regression model. DbaeP, dibenzo[a,e]pyrene; TCDD, tetrachlorodibenzo-p-dioxine.

3.6. Prenatal exposure to food chemicals and allergic rhinitis

In the single-exposure approach, (Supplementary Fig. 7), prenatal dietary exposure to 74 chemicals was positively associated with risk of allergic rhinitis up to age 8 y: acrylamide, one additive, six BFRs, seven dioxins, 10 furans, 15 PAHs, 13 trace elements, six mycotoxins, 11 PCBs and three pesticides (two organophosphates and one pyrethroid). Prenatal dietary exposure to one phytoestrogen (resveratrol) and one pesticide (fenbuconazole) was negatively associated with risk of allergic rhinitis. All of these associations persisted after multiple testing correction (Supplementary Table 8). In the imputed model, we observed 33 of the previous positive associations and one negative association with resveratrol and pesticide imazalil.

In the multiple-exposure approach, considering simultaneously the 21 chemicals selected by elastic net (nitrites, resveratrol, HBCDalpha, HBCDbeta, DBahA, pyrene, BaA, BaP, Ga, Al, Co, deoxynivalenol, FB2, PCB-81, dimethoate, fenbuconazole, imazalil, pirimiphos-methyl, PFDA, PFOA, and HCDF-123789), only prenatal dietary exposure to the pesticide imazalil and the phytoestrogen resveratrol was associated negatively with risk of allergic rhinitis (Fig. 5).

In the mixtures approach, the “Te-F-PAH” mixture was positively associated with risk of allergic rhinitis up to age 8 y (OR, 1.33 [95 % CI: 1.02; 1.73] for 1 SD increase in mixture pattern) (Table 1). This association was not significant in the multiple imputation model (Supplementary Table 9).

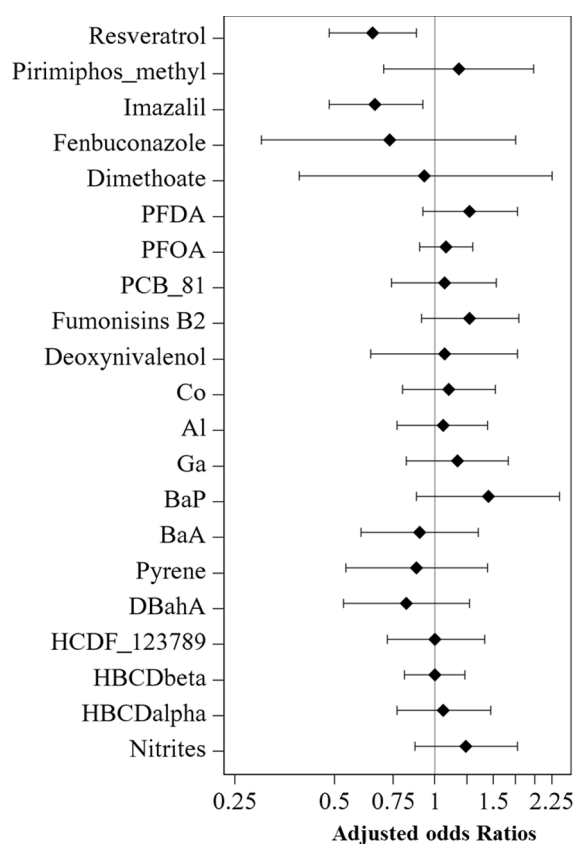


Fig. 5. Association between prenatal multiple dietary exposure to chemicals (selected by elastic net) and allergic rhinitis in children up to age 8 y (n = 1324). Values are odds ratios (95 % CI) from a logistic regression model adjusted for maternal characteristics (age, education level, household income, primiparity, smoking during pregnancy, diet quality), child and birth characteristics (sex, mode of delivery, family history of allergies) and study center. All food chemicals selected by an elastic net penalized regression (cross-validated optimum penalization: $\alpha = 0.1 \lambda = 0.03890491$) were considered simultaneously in the same logistic regression model. PFDA, perfluorodecanoic acid; OCDD, octachlorodibenzodioxine.

4. Discussion

In the present study, we assessed associations between prenatal dietary exposure to chemicals and allergic/respiratory diseases. We found several exposures associated with risk of allergic rhinitis and wheezing but few significant associations for other allergic and respiratory diseases in childhood.

Three complementary approaches were used to explore the associations between prenatal dietary exposure to chemicals and allergies or respiratory diseases during childhood. Food chemicals were first considered individually in a single-exposure approach, as is commonly used in the literature, to facilitate comparison and representation. However, the specificity of this approach is limited, notably when a large number of variables are considered. To deal with this issue, we used FDR correction to account for multiple testing. In our individual exposure analyses, few of the studied prenatal dietary exposures to chemicals was associated with risk of food allergy, eczema, or asthma in childhood. In contrast, we found increased risk of allergic rhinitis after prenatal dietary exposure to a large panel of PAHs, dioxins/furans, PCBs and trace elements, and increased risk of wheezing after prenatal dietary exposure to acrylamide, two PAHs and several pesticides. Some of these associations have been reported in previous studies, such as PAHs and allergic diseases at 6 months (Koh et al., 2021), metals and allergic rhinitis up to age 4 y (Ruan et al., 2022), and PCBs and allergic rhinitis at any age (Parker-Lalomio et al., 2018). Prenatal exposure to pesticides was associated with a higher risk of rhinitis and watery eyes reported without cold in the first year (Perzanowski et al., 2019), wheezing and physician-diagnosed asthma at age 5 y (Islam et al., 2022), and asthma in children and adolescents (Rodrigues et al., 2022; Raanan et al., 2015).

Findings from single-exposure analysis have the advantage of being easy to interpret and summarize; nevertheless, this approach is not appropriate to account for effects of co-exposure to multiple chemicals (Guillien et al., 2021). To address this issue, we used a multiple-exposure approach based on variable selection. We chose elastic net penalized regression, which enabled selection of the most contributive variables to be introduced in a most parsimonious multiple-exposure model while accounting for multicollinearity and confounding by co-exposures (Friedman et al., 2010).

In our multiple exposure analysis, the risk of wheezing was positively associated with prenatal dietary exposure to two pesticides (diazinon and triadimenol) and one PAH (5-methylchrysene), and negatively associated with the phytoestrogen resveratrol. To our knowledge, no other study has focused specifically on these chemicals in relation to the studied diseases. However, some previous studies reported increased risk of wheezing in children prenatally exposed to other chemicals from the same families (PAHs (Jedrychowski et al., 2010) or pesticides (Mamane et al., 2015), but these studies did not control for co-exposure to other groups of chemicals.

Prenatal dietary exposure to the mycotoxin MAS and the pesticide malathion was negatively associated with eczema and food allergy, respectively. We also found a negative association between prenatal dietary exposure to resveratrol and the pesticide imazalil and allergic rhinitis. Previous studies did not focus on the dietary route, but inverse associations between prenatal exposure to some environmental chemicals and allergic or respiratory disease have been reported (Luo et al., 2020; Ye et al., 2018; Ochiai et al., 2014). Negative associations can be explained by an immunosuppressive effect exerted by some chemicals, such as the pesticide malathion (Yonar et al., 2014) or some mycotoxins (Pinton et al., 2006). Another explanation could be a high correlation between some of these exposures and maternal fruit and vegetable intake. For instance, in our study, prenatal exposure to the pesticide imazalil was highly correlated with maternal intake of citrus fruits ($r = 0.94$). A protective effect of fruit consumption on asthma and allergies among children was reported (Hosseini et al., 2017). To our knowledge, no other study has examined prenatal exposure to phytoestrogens and allergies, but our results agree with a study reporting the anti-allergic

effect of resveratrol on allergic rhinitis in a mouse model (Zhang et al., 2020).

Compared to single-exposure analysis, multiple-exposure models retained only a few significant associations. Thus, associations observed in single-exposure analysis may represent false positive results due to a high correlation between variables.

A few studies used a multiple-exposure approach to explore the associations between exposure to chemicals during the prenatal period and allergies in childhood. In the HELIX European study, a deletion-substitution-addition algorithm was used to examine the co-exposure effect of several prenatal lifestyle and environmental factors on allergy-related outcomes in children. Exposure to one phthalate was associated with increased risk of rhinitis and exposure to another with reduced risk of itchy rash in the multi-exposure model (Granum et al., 2020). In another study examining associations between prenatal exposure to 18 chemicals and childhood allergic and respiratory symptoms, Bayesian Kernel Machine Regression was used to fit biomarkers into one model as joint independent variables. Higher exposure to monocarboxyisooctyl phthalate and 2,4-dichlorophenol was associated with higher risk of asthma and poor lung function, and higher exposure to mono(3carboxypropyl) phthalate and bisphenol A was associated with aeroallergies (Berger et al., 2020).

One limitation of the multiple-exposure models is that potential effects of the included chemicals are considered independently of one another and thus the models do not consider potential mixture effects such as additive, synergistic and antagonistic effects, which can lead to error of interpretation and estimation (Billionnet et al., 2012). Moreover, this approach may not be representative of the real-life exposure to food chemicals in our population. Therefore, considering mixtures of chemicals may be a good approach for exploring the co-exposure to environmental chemicals effect.

In this study, prenatal dietary exposure to the mixture composed mainly of trace elements, furans and PAHs was associated with risk of allergic rhinitis. None of the other mixtures was significantly associated with risk of allergic or respiratory diseases. These findings agree with those observed in our single-exposure analysis. In fact, 23 chemicals of the 30 most contributive contaminants in the mixture TE-F-PAH were individually associated with risk of allergic rhinitis. In contrast, the few chemicals in the multiple exposure models associated with allergic or respiratory outcomes, such as MAS, diazinon, or malathion, were not important contributors to any mixture or were present in separate mixtures, which can explain the lack of associations with these mixtures.

In the INUENDO birth cohort, 16 chemicals were assessed in maternal serum samples during pregnancy, and principal component analysis was used to identify mixtures of chemicals. The study found a modest inverse association between the principal component reflecting maternal exposure to diisononyl phthalates (DiNP) and offspring current eczema (Smit et al., 2015). In two other studies, Bayesian Kernel Machine Regression was used to estimate the overall joint association of exposure to several chemicals during pregnancy and allergies in childhood. The first study found a synergistic effect of prenatal exposure to bisphenol A and phthalates on atopic dermatitis at 6 months (Lee et al., 2021). The second study examined prenatal co-exposure to seven metals and found positive associations with allergic rhinitis (Ruan et al., 2022). However, the main limitation of this mixture approach is the difficulty to compare findings with previous literature because the chemical mixture may be specific to the studied population.

The underlying mechanisms involved in prenatal exposure to environmental chemicals and the resulting increase in allergies remain unclear. The innate immune system can be altered, such as inducing lymphocyte activation (increased B-cell and IgG production) or decreasing proinflammatory cytokine response (TNF α , IL-6, IL-33) in neonates (García-Serna et al., 2021). Also, oxidative stress and inflammation mechanisms resulting in decreased placental blood flow and reduced transfer of nutrients to the fetus have been suggested as an explanation of respiratory diseases in childhood (Deng et al., 2016).

Furthermore, epigenetic regulation mechanisms may contribute to the etiology and pathogenesis of asthma and allergic pathway diseases (Yang, 2014).

In our study, more consistent associations were observed between chemicals belonging to PAH, furans and trace elements. PAHs and furans are both persistent organic pollutants that act like agonist for aryl hydrocarbon receptor that plays a critical role in the development and function of adaptive and innate immune response (Esser et al., 2018). Prenatal exposure to mercury, arsenic and cadmium have been associated to a decreased number of T naive cells, increased number of Th2-related T cells and increased Th2 response in newborns, all characteristic of the allergic response (García-Serna et al., 2021).

To our knowledge, this is the first study exploring associations between prenatal dietary exposure to a large set of chemicals and their mixtures and risk of allergy or respiratory diseases in childhood. In the EDEN mother-child cohort, included mothers have higher socioeconomic position than the French population (Heude et al., 2016). However, in the Norwegian Mother and Child Cohort Study (MoBa), potential bias due to self-selection was evaluated by comparing the differences between the MoBa participants and all women giving birth in Norway, in prevalence estimates of 23 variables and eight well-known exposure-outcome association measures. Significant differences between the MoBa participants and the total population, were reported for prevalence estimates of exposures and outcomes, but not for the association measures (Nilsen et al., 2009). Then, we considered that the selection bias has a limited impact on our findings.

In addition, the study design gave us access to a wide range of potential confounding factors, such as family history of allergies or sociodemographic characteristics of the family that were considered here. Regardless, we cannot exclude residual confounding. Allergic and respiratory diseases were declared by parents, but the validated ISAAC questionnaire (Asher et al., 1995) was used, which might reduce misclassification bias. Furthermore, the prospective design of the EDEN mother-child cohort and the regular follow up of children from birth to 8 y limit potential memory bias. Finally, some of the chemicals significantly associated with risk of allergic or respiratory events were strongly related to intake of a specific food item (pork-meat products, meat, fish, grapes), so distinguishing the effect of the chemical from the effect of other components of the food item is difficult. Nevertheless, none of the concerned food items were previously found associated with risk of allergic or respiratory events (Donovan et al., 2020).

The present study was focused specifically on the dietary route of exposure to chemicals. In fact, as a crucial pathway of exposure to chemicals, the part of diet in the potential effects on population health must be assessed to better target prevention measures and regulations. However, diet is not the only route of exposure and studies considering independently the different routes may be of great importance to determine which one could have the most deleterious effect. Furthermore, although the food frequency questionnaire used in the study of dietary intake was validated (Deschamps et al., 2009), we cannot exclude residual recall bias. Moreover, dietary exposure to food chemicals was assessed by combining individual data on food intake with data on food chemicals content from the French total diet study (TDS2), established at the population level (Chan-Hon-Tong et al., 2013). These exposure estimations may then suffer from some uncertainties. Studies based on biomarkers of chemical exposure provide a more accurate estimate of individual exposure, but cannot distinguish between the different routes of exposure, and so cannot be used to make specific recommendations. Moreover, in studies using such biomarkers, biological samples are usually collected at a single time point during pregnancy, which may not be representative of exposure to some chemicals over the course of pregnancy (Kamai et al., 2019). Also, analyses costs, relative short half-lives, and the choice of the appropriate matrix are limits in the use of biomonitoring data to assess environmental multiple exposures (Scheepers, 2008). Nevertheless, it would be of great interest to benefit from further studies examining simultaneously the different

sources of exposure, such as atmospheric sources, domestic pollution, or use of care products during pregnancy, to establish their relative part on allergic disease development.

Finally, in this study we focused on the prenatal period of exposure to food chemicals. However, the postnatal period is also important in the maturation of the immune system (Dietert and Zelikoff, 2008). Thus, for future studies, it would be interesting to distinguish the potential effect of food chemicals exposure during both the prenatal and the postnatal period on allergic and respiratory diseases in childhood.

5. Conclusion

The present study, combining three complementary approaches, found associations between prenatal dietary exposure to a large set of chemicals and risk of allergic rhinitis and between acrylamide, two PAHs and several pesticides and wheezing, up to age 8 y in offspring. Few associations were highlighted for eczema, food allergy, or asthma but were less consistent across analyses and need to be interpreted with caution. Further studies are needed to explore more deeply the effect of early life exposure to mixtures of chemicals on allergic and respiratory health.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Barbara Heude and Marie Aline Charles reports financial support was provided by French Dairy Interbranch Center.

Data availability

The data underlying the findings cannot be made freely available for ethical and legal restrictions imposed, because this study includes a substantial number of variables that, together, could be used to re-identify the participants based on a few key characteristics and then be used to have access to other personal data. Therefore, the French ethics authority strictly forbids making these data freely available. However, they can be obtained upon request from the EDEN principal investigator. Readers may contact barbara.heude@inserm.fr to request the data. The analytic code will be made available upon request pending application and approval.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2023.108195>.

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