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Master thesis

Maternal diet may modify associations of prenatal air pollution with allergy and lung function in the offspring

Eleni Athanasaki
Nutritionist-Dietitian

Supervisor:

1. **Christos Lionis, Professor of General Practice and Primary Health Care, Clinic of Social and Family Medicine, , Division of Social Medicine, Faculty of Medicine, University o Crete**

2. **Marina Vafeiadi, Postdoctoral Researcher, Divisio of Social Medicine, Faculty of Medicine, University of Crete**

Co-supervisor:

3. **Despo Ierodiakonou, MD, MSc, PhD, Research collaborator, Dep. Of Social Medicine, School of Medicine, University of Crete**

Advisor committee

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Στην οικογένειά μου

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Ευχαριστίες

Πρώτα από όλα θα ήθελα να ευχαριστήσω τον επιβλέποντα καθηγητή μου κύριο Λιονή Χρήστο για τον χώρο και τον χρόνο που μου έδωσε να εργαστώ όντας πάντοτε αρωγός, αλλά κυρίως να τον ευχαριστήσω που πάντα με ενθαρρύνει να προχωρήσω, που είναι τόσο άμεσος και προσιτός και που πάντοτε αφήνει χώρο σε όλους όσους είναι κοντά του να αναπτύξουν τις ιδέες τους.

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Περίληψη Μεταπτυχιακής Εργασίας

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Της: Αθανασάκη Ελένη

Υπό τη επίβλεψη των: Λιονή Χρήστο, Βαφειάδη Μαρίνα, Ιεροδιακόνου Δέσπω

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Εισαγωγή: Η έκθεση της μητέρας σε περιβαλλοντικούς παράγοντες κατά την διάρκεια της εγκυμοσύνης, έχει συνδεθεί με την εμφάνιση αλλεργιών αλλά και την μειωμένη πνευμονική λειτουργία σύμφωνα με την μέχρι σήμερα βιβλιογραφία. Όμως δεν έχει μελετηθεί η δράση της μεσογειακής δίαιτας κατά την διάρκεια της εγκυμοσύνης σαν τροποποιητικός παράγοντας όταν υπάρχει παράλληλη έκθεση σε αιωρούμενα σωματίδια και ο πιθανός προστατευτικός της ρόλος στην εμφάνιση αλλεργιών και την πνευμονική λειτουργία του παιδιού.

Υπόθεση: Εάν η συμμόρφωση της μητέρας στην μεσογειακή δίαιτα, κατά την διάρκεια της εγκυμοσύνης, μπορεί να λειτουργήσει σαν προστατευτικός παράγοντας έναντι της εμφάνισης εκζέματος, αλλεργικής ρινίτιδας, άσθματος αλλά και της μειωμένης πνευμονικής λειτουργίας όταν υπάρχει έκθεση σε αιωρούμενα σωματίδια.

Στόχος: Ο στόχος της μελέτης είναι να διερευνήσει την πιθανή συσχέτιση της έκθεσης σε περιβαλλοντικούς παράγοντες κατά την διάρκεια της εγκυμοσύνης με την εμφάνιση αλλεργιών στην παιδική ηλικία, και να εκτιμήσει εάν η συμμόρφωση, κατά την διάρκεια της εγκυμοσύνης, στην μεσογειακή δίαιτα μπορεί να τροποποιήσει την συσχέτιση.

Μέθοδος: Πραγματοποιήθηκαν μετρήσεις σε 744 παιδιά στην ηλικία των 4 ετών και σε 540 στην ηλικία των 6 ετών, των οποίων οι μητέρες συμμετέχουν στην μελέτη μητέρας-παιδιού ΡΕΑ.

Αποτελέσματα: Η έκθεση σε αιωρούμενα σωματίδια με διάμετρο 2,5 σχετίζεται με την εμφάνιση εκζέματος και αλλεργικής ρινίτιδας, αλλά όχι με την εμφάνιση άσθματος και με την πνευμονική λειτουργία. Η μεσογειακή δίαιτα ως τροποποιητικός παράγοντας έδειξε να έχει προστατευτική δράση έναντι της εμφάνισης εκζέματος, της αλλεργικής ρινίτιδας και του άσθματος όταν μετρήθηκε σε συγκεκριμένες χρονικές στιγμές της εγκυμοσύνης αλλά και σε συγκεκριμένη ηλικία των παιδιών.

Η έκθεση σε αιωρούμενα σωματίδια με διάμετρο 10 σχετίζεται με την εμφάνιση εκζέματος και αλλεργικής ρινίτιδας, αλλά όχι με την εμφάνιση άσθματος ή με την πνευμονική λειτουργία. Η μεσογειακή δίαιτα ως τροποποιητικός παράγοντας έδειξε να έχει προστατευτική δράση στην εμφάνιση εκζέματος και ρινίτιδας.

Συμπεράσματα: Τα ευρήματα δείχνουν μια αλληλεπίδραση μεταξύ την έκθεσης σε αιωρούμενα σωματίδια κατά την εγκυμοσύνη, της συμμόρφωσης με την μεσογειακή δίαιτα και την ανάπτυξη αλλεργιών (έκζεμα, ρινίτιδα και άσθμα) και στην

πνευμονική λειτουργία στο παιδί. Τα δεδομένα που παρουσιάστηκαν υποστηρίζουν πως πιθανές παρεμβάσεις στην διάτα της μητέρας κατά την διάρκεια της εγκυμοσύνης θα μπορούσαν να μετριάσουν τον κίνδυνο εμφάνισης αλλεργιών όταν υπάρχει έκθεση σε περιβαλλοντικούς ρυπαντές στην εγκυμοσύνη.

Abstract

Title: Maternal diet may modify associations of prenatal air pollution with allergy and lung function in the offspring.

By: Athanasaki Eleni

Supervisors: Lionis Christos, Vafeiadi Marina, Ierodiakonou Despo

Date: August 2020

Introduction: Maternal exposure to air pollution during pregnancy is associated with the occurrence of allergies and lung malfunction. Studies result that maternal exposure may affect the outcome and that maternal adherence to Mediterranean diet during pregnancy has a protective role against PM effect. To date no studies asses the possible protective effect of maternal Mediterranean diet with PM exposure and the possibility of allergies and lower lung function in the offspring during childhood.

Hypothesis: If maternal adherence to Mediterranean diet during gestation, may modify the outcome of allergy (eczema, allergic rhinitis, asthma) and lung function in the offspring, during childhood when there is PM exposure during pregnancy.

Aim: The aim of the present study was to investigate the associations of prenatal exposure to air pollution with allergy-related outcomes in childhood, and to assess whether maternal adherence to Mediterranean diet during pregnancy modifies these associations.

Methods: Measurements were taken on 744 children at the age of 4 and on 540 at the age of 6 whose mothers are participating in the Rhea mother-child cohort study.

Results: PM2.5 exposure is associated with eczema and allergic rhinitis occurrence, but not with the occurrence of asthma or with lung function. Effect modification by Mediterranean diet showed a protective role against the occurrence of eczema, allergic rhinitis and asthma in specific time points of pregnancy and age of children.

PM10 exposure is associated with the occurrence of eczema, allergic rhinitis, but not with asthma and lung function. Effect modification by Mediterranean diet showed a protective role against eczema and allergic rhinitis, but not asthma and lung function.

Conclusion: The findings suggest interplay between prenatal PM exposure adherence to MD on the development of allergies (eczema, rhinitis and asthma) and lung function in the offspring during childhood. The data presented could support dietary interventions during gestation for mitigating offspring risk of allergies against prenatal exposure to air pollution.

Key words: Mediterranean diet, PM, Eczema, Allergic Rhinitis, Asthma, Lung function

1. Introduction

1. Associations of air pollution exposure in early life with allergies and lung function and the developmental origins of health and disease.

The Developmental Origins of Health and Disease hypothesis **(DoHAD)** postulates that exposure to certain environmental influences during critical periods of development and growth may have significant consequences on an individual's short-and long-term health (1).

Asthma, rhinitis and eczema are among the most common chronic diseases, especially in childhood (2). One of their most challenging characteristics is their complexity, with the interplay of multiple genetic environmental factors (3). These diseases generally begin very early in life and can persist into adult life (4). Early life exposure to air pollution has been associated with incidence of childhood asthma, allergic rhinitis and eczema in birth cohorts, with significant results varying by pollutant, outcomes and age at outcome (5–7). Furthermore, residential traffic related air pollution exposure at birth is reported to be associated with reduced expiratory flows in school children, and children relocating to areas with differing air pollution levels experience changes in lung function that mirrored changes in PM exposures (8).

An association was found between eczema and traffic-related air pollution exposure in a study in elementary schools in Seoul (9). Indoor and outdoor air pollutants have been considered potential risk factors for the development or exacerbation of eczema, by causing further damage to the skin barrier or immune responses (9) . A number of cross-sectional and birth cohort studies have shown that a long-term exposure to PM for 3 years or more, influences the prevalence of eczema in children from 6 to 14 years of age (10) **.** However, systematic reviews and meta-analyses found no evidence to support the hypothesis that long-term air pollution is associated with eczema (11–13).

Furthermore, epidemiological and toxicological research suggests a relationship between air pollution and the increased incidence of allergic rhinitis (14–16). These especially include PMs produced by traffic-related and industrial activities (8) . Meta-analysis of cross-sectional and cohort studies concludes that exposure to air pollution, including PM10 and PM2.5, is a risk of childhood allergic rhinitis (17–19)**.** Meta-analysis also showed an association between increased PM2,5 and PM10 exposure with asthma development in different geographic areas (20) . Furthermore, a meta-analysis of five European birth cohorts within ESCAPE showed associations mainly with exposures at the current address and lung function at 6-8 years of age (21) , and in a birth cohort associations with PM10 exposure were also observed with lung function in older children e.g., 8-16 years old (22) .

1.3 Association of prenatal air pollution and the risk of allergy and lung function in offspring

The impact of air pollution exposure on maternal health can directly impact neonatal growth and the developmental of the fetal immune system (23) . A prospective cohort study showed that maternal exposure to traffic-related air pollution during pregnancy was associated with incidence of allergic diseases in preschool children (24). They result in a hypothesis that childhood allergic diseases originate in fetal life and are triggered by traffic related air pollution during sensitive trimester.

Perinatal conditions have been found to be important for the development of eczema (25)(26) . A study suggests that exposure to fine particulate matter and tobacco smoke during pregnancy doubled the risk of eczema symptoms occurring at any point in the first year of life (27) . Another study in 2589 children in China examined the association between prenatal exposure to outdoor air pollution and some indoor environmental factors in childhood allergic diseases or symptoms. They concluded that outdoor and indoor factors were associated with childhood eczema, allergic rhinitis and asthma during different times of exposure during pregnancy (28) .

Toxic exposures in critical developmental windows my result in permanently altered changes in respiratory system. Prenatal development of the respiratory system is a multi-event process, progressing from early gestation, thus toxins may have variable impact depending on timing of exposure and the fetus is particularly vulnerable due to immature system (29) . There is strong scientific support for a relationship between in utero exposures such as environmental pollution during pregnancy and lung growth and development (30) . A systematic review and meta-analysis of 18 studies from 2004 to 2017 investigated the association between prenatal exposure to various air pollutants and subsequent development of asthma (31) .

Overall, information on the effect of air pollution exposure during pregnancy on allergic diseases other than asthma is still growing. Furthermore, studies investigating specific pregnancy sensitivity windows (trimesters) are limited (30) .

1.4 Association of Mediterranean Diet in children and allergies and lung function

The Traditional Mediterranean diet provides foods sources rich in antioxidants such as vegetables, legumes, fruits, and nuts, cereal and fish, a high monounsaturated-to-saturated fat ratio mostly from olive oil, low fat dairy products and a low intake of meat and poultry(32) . Epidemiological studies have reported associations between dietary antioxidant and lipid intakes and atopic diseases (33) . An international study of 70795 children showed association between adherence to Mediterranean diet during childhood and allergic diseases including eczema, allergic rhinitis and asthma (34). In another study high level of adherence to the Mediterranean diet showed protective effect on eczema (35).

A study in Mexican children showed that adherence to Mediterranean diet is associated with lower allergic rhinitis occurrence (36) . Similarly, a cross sectional study in Crete showed that adherence to Mediterranean diet during childhood had a protective effect against allergic rhinitis although it was not statistically significant (35) .

A study in Peruvian children 9-19 years of age, compared a Peruvian diet to Mediterranean diet and examined the relationship between diet and asthma status, and showed that moderate adherence to Mediterranean diet was associated with a lower odds of having asthma (37) . Mediterranean diet pattern was also associated with less asthma in Mexican children (36) . Systematic reviews and meta-analyses reported an association between high adherence to Mediterranean diet and the childhood asthma development (38) and with lower asthma symptoms (39) . Moreover, evidence suggest that adherence to Mediterranean diet is also associated with improved lung function (39) .

1.5 Association of prenatal Mediterranean diet and the risk of allergy and lung function in offspring

Mounting evidence suggests that prenatal and early life exposures affect the development of allergy and asthma, with a possible role of diet during pregnancy and early life (40) . Maternal diet during pregnancy could modulate the development of allergy and asthma by influencing airway and/or immune development of fetus (41)(33) . Associations between aspects of maternal diet during pregnancy and childhood allergic outcomes have been reported in birth cohort studies (42) that evaluated maternal adherence to Mediterranean diet and allergic outcomes in children (43) . Multiple systematic reviews and meta-analyses of observational studies assessing the relationship between Mediterranean diet during pregnancy and asthma in the offspring reported that a significance was observed only in a few studies (44) , Suggesting that the link between maternal adherence to Mediterranean diet and incidence of asthma and/or allergy disease in the offspring is poor. Other reviews of the literature showed that adherence to Mediterranean diet by mother during pregnancy might have some protective effect on asthma symptoms in the offspring only during their first year of life but the evidence about eczema are spurious (39) . Further studies are needed to better understand the mechanisms of a protective effects (40)

1.5 Effect modification by Mediterranean diet and its mechanisms in oxidative stress

Air pollutants are potential oxidants that are able to induce oxidative stress which can lead to inflammation. Airway and systematic inflammation as well as oxidative stress are recognized mechanisms involved in the pathogenesis of asthma and allergic disease (29) . Antioxidants reduce reactive oxygen species and epidemiological studies have reported inverse associations between diets rich in antioxidants and allergic diseases (45) . Nevertheless, evidence on effect modification of air pollution on allergies by Mediterranean Diet is limited, especially for exposures during the prenatal period. (46) .

2. Aim

The overall aim of the present study was to investigate the associations of prenatal exposure to air pollution with allergy-related outcomes in childhood, and to assess whether maternal adherence to Mediterranean diet during pregnancy modifies these associations.

3. People, material and methods

3.1 Study population

The present study is part of the prospective “Rhea” mother-child cohort. The Rhea project examines pregnant women and their children, at the prefecture of Heraklion, Crete (47). Briefly, female residents (Greek and immigrants) who became pregnant during a period of one year starting in February 2007 were contacted and asked to participate in the study. The first contact was made at the time of the first comprehensive ultrasound examination (mean ± SD 11.96 ± 1.49 weeks) and several contacts followed (6^{th} month of pregnancy, at birth, 9 months, 1^{st} year, 4 and 6 years after birth). To be eligible for inclusion in the study, women had to have a good understanding of the Greek language and be older than 16 years of age. Face-to-face structured questionnaires along with self-administered questionnaires and medical records were used to obtain information on several psychosocial, dietary, and environmental exposures during pregnancy and early childhood. The sample size of the present study was 1197 mother-child pairs with full data (774 at age 4 and 540 at age 6).

3.2 Maternal dietary assessment

Information on maternal dietary habits was collected during mid-pregnancy (14th–18th week of gestation) using a validated, semi-quantitative food frequency questionnaire (FFQ) of 250 food items (48). These food items were aggregated into seventeen food groups ('cereals and cereal products', 'meat and meat products', 'fish and seafood', 'dairy products', 'eggs', 'vegetable–animal fats except olive oil', 'olive oil', 'potatoes and other starchy roots', 'pulses', 'vegetables', 'nuts', 'fruits', 'sweets and deserts', 'non-alcoholic beverages', 'alcoholic beverages', 'salty snacks' and 'miscellaneous'). For each food item, participants were asked about both frequency of consumption and average portion size. The frequency of consumption was given per day, per week and/or per month, depending on the food item. Photographs were used to visualize small, medium and large portion sizes for each food item and respondents had to choose one out of three pictures. To estimate the intake of each food item in grams, portion sizes were multiplied by daily frequencies of intake. For complex items (such as mixed dishes), standard recipes were used as described in the Composition Tables of foods and Greek dishes by Antonia Trichopoulou, 3rd edition. Individual portion sizes and recipes were used to calculate daily energy intake on the basis of the UK food tables (McCance and Widdowson's The Composition of Foods, 6th summary edition).

3.3 Adherence to Mediterranean Diet

To evaluate adherence to Mediterranean diet during pregnancy, we used a score applied in a large cohort study (European Prospective Investigation into Cancer and Nutrition; EPIC) in adults. For beneficial components (vegetables, legumes, fruits and nuts, cereals, fish and seafood, and dairy products), women whose consumption was below the median (cohort-specific median) were assigned a value of 0 and women whose consumption was at or above the median were assigned a value of 1. For components presumed to be detrimental (meat, including all types of meat), women whose consumption was below the median were assigned a value of 1, whereas women whose consumption was at or above the median were assigned a value of 0. For fat intake (the eighth food category), we used the ratio of daily consumption of monounsaturated lipids to that of saturated lipids. Because the score had been developed for adults and the present study population involved pregnant women, we presumed dairy products to be protective and not detrimental dietary compounds and did not include alcohol consumption in the score. The total MD score ranged from 0 (minimal adherence to the traditional MD) to 8 (maximal adherence). The score was categorised to reflect two levels of adherence: 0-3 low, 4-8 high MD quality.

3.4 Exposure assessment

Back extrapolation was used to estimate the PM exposure. More specifically ESCAPE ratio method procedure was used in order to clarify the exposure assessment back in time for every trimester of the pregnancy. Outdoor air concentrations of particulate matter (PM) with an aerodynamic diameter between 2.5 μm and 10 μm were measured between February 2009 and 2010 in Heraklion. Measures were collected in 40 different sites during two weeks period in three different seasons (cold, warm and intermediate). Measured average concentrations were combined with geographic predictors to develop land use regression (LUR) models following the protocols developed as part of the European Study of Cohorts for Air Pollution Effects, Annual mean concentrations between February 2009 and 2010 were estimated at maternal home address assuming that annual mean estimations are stable from year to year.

3.5 Childhood allergy-related outcomes

Information on asthma, rhinitis and eczema occurrence was obtained by questionnaires adapted from the International Study on Asthma and Allergy in Childhood (ISAAC) (46) at 4 and 6 years of age. Doctor diagnosed asthma was defined as a positive answer to both ever-reported diagnosis of asthma and presence of wheezing or whistling in the chest in the past 12 months (47) . We defined rhinitis current symptoms as the presence of sneezing or a runny or blocked nose in the past 12 months without common cold or flu (48) . We defined Doctor diagnosed eczema as the presence of an itchy rash in the past 12 months that affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks or around the neck, ears or eyes (49).

3.6 Covariates

We examined the effect of potential confounding variables that have an established or potential association with rhinitis, eczema and asthma in the fourth and sixth year of age of the child, and MD in pregnancy. Potential confounders considered included a priori were: maternal age, maternal education (low level: ≤6 years of school, medium level: 6 and ≤12 years of school and high level: university of technical college degree), parity, maternal history of eczema (yes/no), maternal history of asthma (yes/no), maternal history of rhinitis (yes/no), season of birth, infant sex (male or female), child BMI at 4 years and 6 years of age and child age.

3.7 Statistical Analysis

Data analysis was performed using IBM SPSS statistics. The primary outcome variables of interest were eczema, allergic rhinitis, asthma and lung function in 4 and 6 years of life. The primary exposure of interest was adherence to Mediterranean diet during pregnancy and exposure to PM2.5 and PM10 .

Descriptive statistics were performed for all variables used. Multivariate logistic binomial regression models were further used to examine the association between exposure in PM2.5 and PM 10 during pregnancy and the occurrence of eczema, allergic rhinitis and asthma with the interaction term of MD in 4 and 6 years of age after adjusting for confounders variables that were associated with both outcome and exposure or that were considered *a priori* to be important confounders were included in the multivariate model: maternal age, maternal education, parity, maternal history of allergy, season of birth, infant sex, child MBI, at 4 years and 6 years of age and child age. Cohort-specific relative risks (RR) with 95% CI were computed to estimate the degree of association. Association testing was conducted assuming a 0.05 significance level.

Linear regression model was used to examine the association between exposure in PM2.5 and PM10 during pregnancy and the lung function of the child with the interaction term od MD in 4 years of age after adjusting for confounders variables that were associated with both outcome and exposure or that were considered *a priori* to be important confounders were included in the multivariate model: maternal age, maternal education, parity, maternal history of allergy, season of birth, infant sex, child MBI, at 4 years of age. Cohort-specific Beta with 95% CI were computed to estimate the degree of association. Association testing was conducted assuming a 0.05 significance level.

All data used for the present study, are collected from the Rhea Birth Cohort.

Results

Table 1 presents maternal and child characteristics of the study population. Participating mothers had a mean age of 29 years and 56.6% (n=678) of them were primiparous. The labours were equally distributed in all four seasons of the year. The great majority of the women did not mention any allergy history (70%). About half of the study population had medium educational level (50.7%). More than half mothers included in the study had a high adherence to Mediterranean Diet (n=504).

As presented in Table 1 in the study participated 774 children in the fourth year follow up and 540 children in the sixth year follow up. The sex of the children was almost equally distributed, 51, 5 % male and 48,9% female.

Figure 1. Shows the prevalence of eczema, allergic rhinitis and asthma in children, in 4 and 6 years of age.

Figure 2. and Figure 3. Show the distribution of the exposure in PM2.5 and PM10 during every trimester of pregnancy and during the whole pregnancy.

Table 1. Characteristics of study population

		N (%)
Maternal characteristics		
Maternal age (years)	**Mean (SD)**	29.47 (42.5)
Parity		

	No (0)	504 (42.5)
	Yes (1)	678 (56.6)
Education		
	Low	249 (20.8)
	Medium	607 (20.7)
	High	337 (28.2)
Smoking before pregnancy		
	No (0)	611 (51)
	Yes (1)	498 (41.6)
Pre-pregnancy BMI (kg/m^2)	**Mean (SD)**	24.43 (4.914)
Origin		
	Greek	1082 (90.4)
	Other	111 (9.3)
Adherence to Mediterranean Diet		
	Low	326 (27.3)
	High	504 (42)
Maternal history of allergy		
	No	838 (70)
	Yes	297 (24.8)
Child characteristics		
Gender		
	Male	612 (51.1)
	Female	585 (48.9)
Season of birth		
	Winter	366 (30.6)
	Spring	257 (21.7)
	Summer	213 (17.8)
	Autumn	361 (30.2)

[1] Data entered as count (%) or Mean (Standard Deviation)

[1]

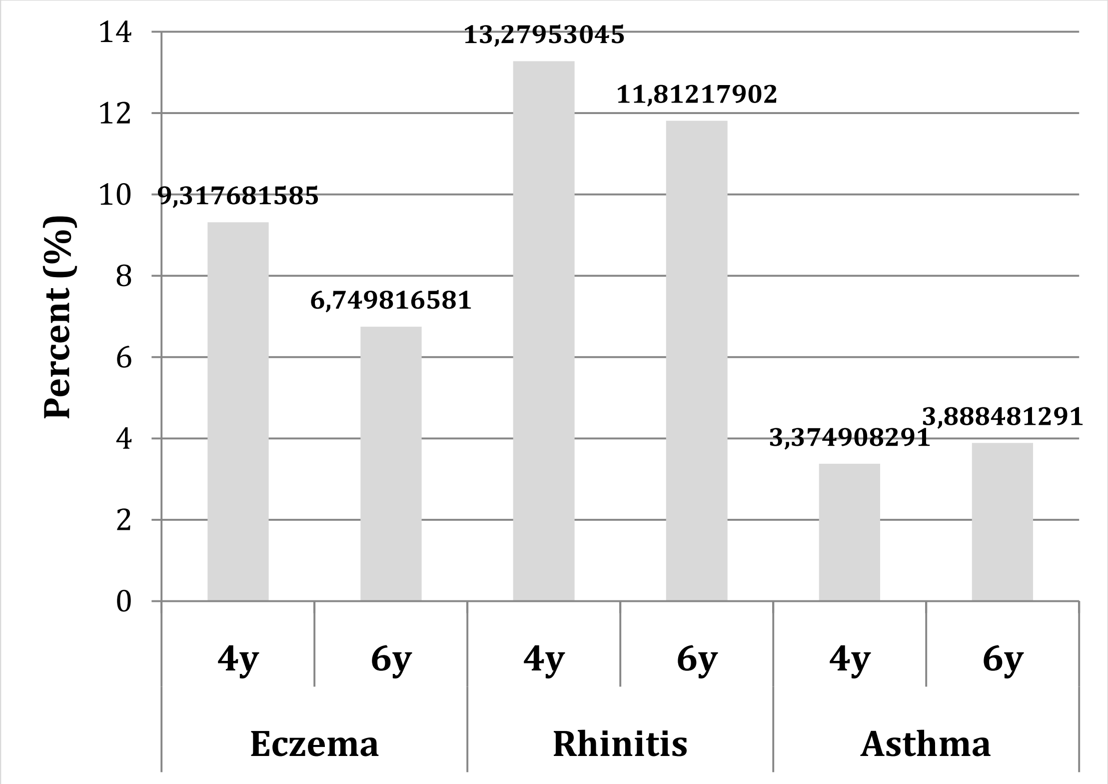

Figure 1. Prevalence of allergic disease in children in 4 and 6 years of age

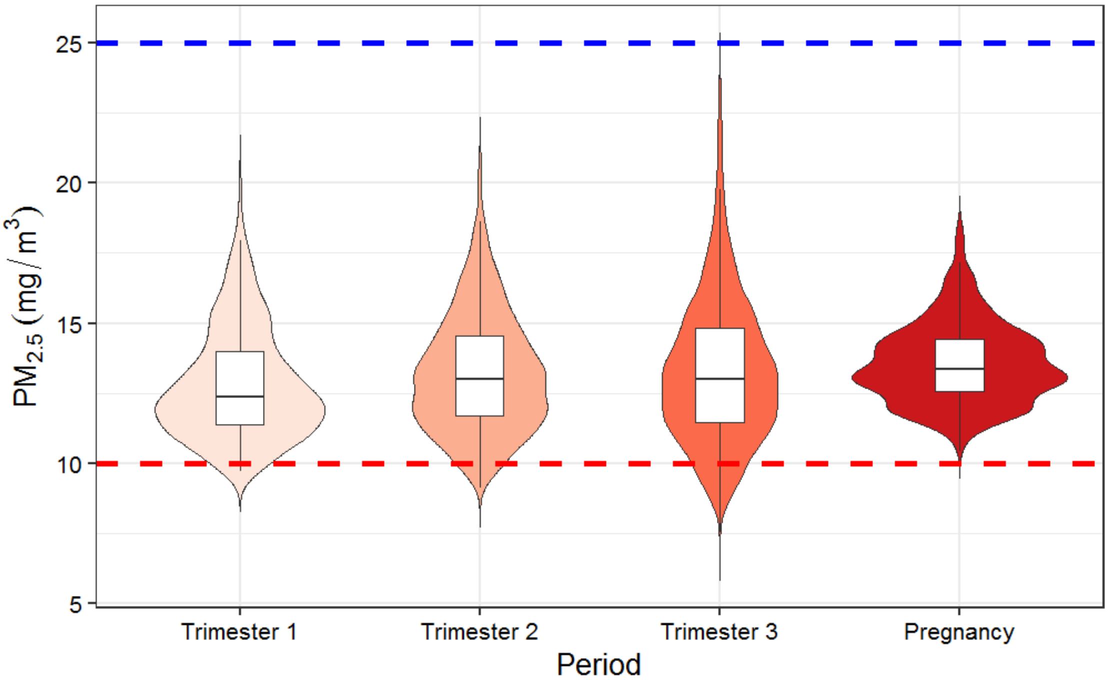

Figure 2. Distribution of PM2.5 (mg/m^3) during every trimester of pregnancy and during the whole period of pregnancy. Red dashed line represents the WHO average daily limits of PM2.5 exposure at 10(mg/m^3). Blue dashed line represents the EU average daily limits of PM2.5 exposure at 25(mg/m^3).

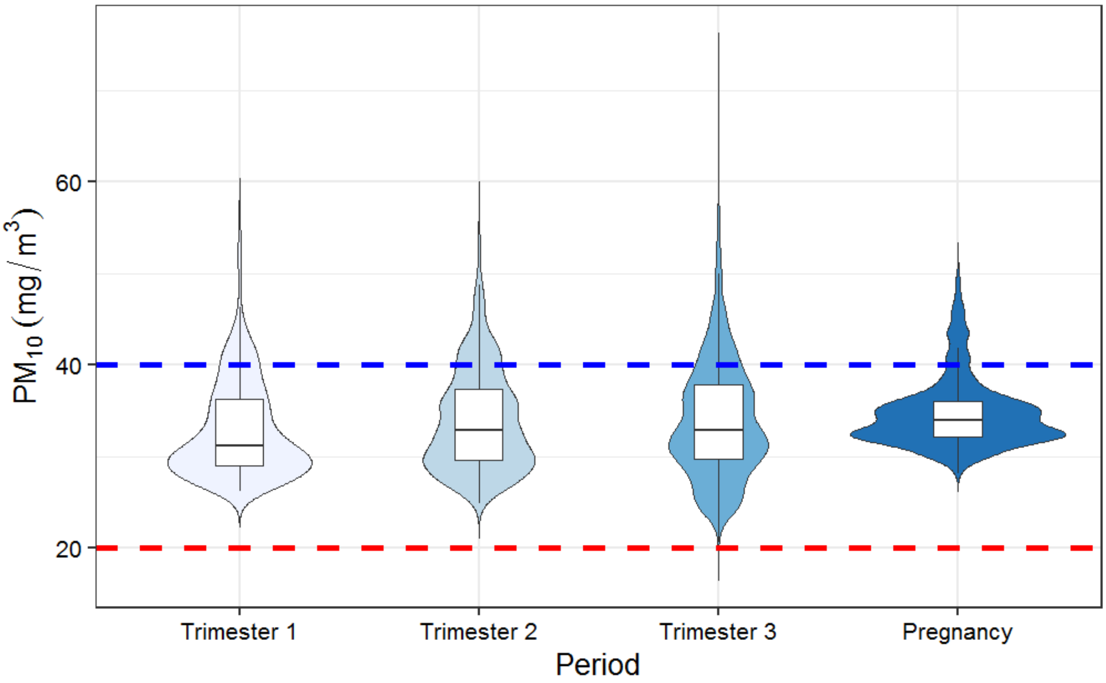

Figure 3. Distribution of PM10 (mg/m^3) during every trimester of pregnancy and during the whole period of pregnancy. Red dashed line represents the WHO average daily limits of PM10 exposure at 20(mg/m^3). Blue dashed line represents the EU average daily limits of PM10 exposure at 40(mg/m^3).

4.1 Associations of Prenatal Exposure to Particulate Matter with Outcomes and modification by Mediterranean Diet

Exposure to PM2.5 during the third trimester of pregnancy showed an association with the occurrence of doctor diagnosed eczema in the offspring at age 6 but not at age 4 (RR: 3.29 CI: (95%): 1.02,10.56). Exposures during the total pregnancy period or other trimesters showed no associations with eczema. When effect modification by MD was assessed, a significant association was observed during the second trimester of pregnancy (RR:28.86 CI: (95%): 2.94,283.1, p-value for interaction= 0.004 at 4 years and RR:36.01 CI: (95%): 2.47,524.19 p-value = 0.046 at 6 years, respectively), suggesting that maternal adherence to MD during the second trimester of pregnancy may be protective for eczema in the offspring (Table 2).

For allergic rhinitis current symptoms, exposure to PM during the whole pregnancy and the first trimester of pregnancy showed a significant association at age 4 (Whole Pregnancy RR:3.88 CI (95%): 1.05,14.34 and First Trimester RR:5.79 CI (95%): 1.49,22.57). A protective effect modification by MD was observed in 4 years with PM2.5 exposure during whole period of pregnancy (p-value for interaction: 0.023) and in the first (p-value for interaction: 0.021) and the second trimester (p-value for interaction: 0.001) (Table 3). No association of prenatal PM2.5 exposure were seen with AR at age 6.

For asthma no association was observed between the exposure and the outcome, and no effect modification by MD was observed, except from an interaction of MD with PM2.5 exposure in the third trimester and asthma at age 4 (p-value for interaction: 0.010) when adherence to MD seems NOT to have a protective role against the occurrence of asthma (Table 4).

As presented in Tables 5-7,maternal PM2.5 exposure during pregnancy does not seem to affect the lung function at age 4 except from the first Trimester of pregnancy when there is significance (First Trimester Beta:-7.97 CI (95%):-14.20,-1.74) and also, no effect modification by MD was observed.

Exposure to PM10 during the whole period of pregnancy showed an association with the occurrence of doctor diagnosed eczema in the offspring at age 6 but not at age 4 (RR (95%): 1.11, 11.80). Exposures during the total pregnancy period or other trimesters showed no associations with eczema. When effect modification by MD was assessed, a significant association was observed during the second trimester and the third trimester of pregnancy at age 6 (Second Trimester p-value for interaction: 0.028 and Third Trimester p-value for interaction:0.036) (Table 2).

For allergic rhinitis current symptoms, exposure to PM during the first trimester of pregnancy showed a significant association at age 4 (First Trimester RR: 2.05 CI (95%): 1.18,3.57). A protective effect modification by MD was observed in 4 years with PM10 exposure during the second trimester of pregnancy (p-value for interaction: 0.044). No effect modification by MD was observe in 6 year age (Table 3).

For asthma effect modification by MD was observed between the exposure in PM2.5 and the outcome, in the third trimester of pregnancy at 4 years of age.(Table 4).

As presented in Tables 5-7,maternal PM10 exposure during pregnancy does not seem to affect the lung function at age 4 and also, no effect modification by MD was observed.

Table 2. Effect of $PM_{2.5}$ and PM_{10} exposure during the whole pregnancy and every trimester of pregnancy specifically, on doctor diagnosed eczema in the offspring, in the fourth and sixth year's follow up of the Rhea Cohort and the effect modification by maternal Mediterranean diet during pregnancy.

		Doctor Diagnosed Eczema			
		4 years		6 years	
		Main effect	Interaction with MD	Main effect	Interaction with MD
Exposure		RR (95% CI)	p-value (direction)	RR (95% CI)	p-value (direction)
PM2.5					
Pregnancy	**M1***	2.66 (0.53, 13.29)	—	4.86 (0.64, 37.05)	—
	M2**	10.70 (0.54, 211.6)	0.320 (+)	8.27 (0.27, 254.1)	0.727(+)
T1	**M1**	6.81 (0.92, 50.13)	—	3.06 (0.30, 31.53)	—
	M2	25.91 (0.88, 764.5)	0.362(+)	46.02 (0.83, 2536.44)	0.126(+)
T2	**M1**	1.77 (0.44, 7.13)	—	3.98 (0.64, 24.67)	—
	M2	**28.86 (2.94, 283.1)**	**0.004(+)**	**36.01 (2.47, 524.19)**	**0.046(+)**
T3	**M1**	1.21 (0.47, 3.12)	—	**3.29 (1.02, 10.56)**	—

	M2	2.97 (0.49, 18.04)	0.329(+)	5.22 (0.64, 42.31)	0.610(+)
PM10					
Pregnancy	**M1**	0.93 (0.49, 1.75)	—	**3.61** **(1.11, 11.80)**	—
	M2	0.79 (0.20, 3.11)	0.823(-)	0.82 (0.62, 1.08)	0.127(-)
T1	**M1**	1.56 (0.76, 3.20)	—	1.09 (0.41, 2.89)	—
	M2	2.05 (0.53, 7.93)	0.668(+)	**4.91** **(1.06, 22.82)**	**0.028(+)**
T2	**M1**	0.87 (0.48, 1.58)	—	1.19 (0.57, 2.52)	—
	M2	1.88 (0.98, 5.20)	0.109(+)	**3.13** **(1.05, 9.31)**	**0.036(+)**
T3	**M1**	0.91 (0.61, 1.37)	—	1.54 (0.93, 2.56)	—
	M2	0.98 (0.42, 2.26)	0.869(-)	1.55 (0.62, 3.84)	0.984(+)

Abbreviations: PM: particulate matter, RR: Relative risk ,T1: First trimester of pregnancy (0-12 weeks), T2: Second trimester of pregnancy (13-24 week), T3: Third trimester of pregnancy (25-37 week).

* M1: Model 1, Log-binomial regression model for the effect PM2.5 and PM10 during pregnancy in the possible occurrence of eczema in the offspring, adjusted for: maternal age, parity, maternal education, maternal history of allergy, and adherence to Mediterranean Diet, season of birth, child age, child BMI and child gender.

** M2: Model 2, Log-binomial regression model for the effect PM2.5 and PM10 during pregnancy in the possible occurrence of eczema in the offspring, adjusted for: maternal age, parity, maternal education, maternal history of allergy, and adherence to Mediterranean Diet, season of birth, child age, child BMI and child gender, including the interaction term Mediterranean Diet.

(+) indicates a RR<1 for interactions and (-) indicates a RR>1 for interactions.

Table 3. Effect of $PM_{2.5}$ and PM_{10} exposure during the whole pregnancy and every trimester of pregnancy specifically, on allergic rhinitis current symptoms in the offspring, in the fourth and sixth year's follow up of the Rhea Cohort and the effect modification by maternal Mediterranean diet during pregnancy.

		Allergic Rhinitis Current Symptoms			
		4 years		6 years	
Exposure		**Main effect RR (95% CI)**	**Interaction with MD p-value (direction)**	**Main effect RR (95% CI)**	**Interaction with MD p-value (direction)**
PM2.5					
Pregnancy	**M1***	**3.88** **(1.05, 14.34)**	—	0.81 (0.15, 4.42)	—
	M2**	**28.93** **(3.17, 264.2)**	**0.023(+)**	2.62 (0.07, 96.74)	0.462(+)
T1	**M1**	**5.79** **(1.49, 22.57)**	—	0.13 (0.02, 0.91)	—
	M2	**43.09** **(4.87, 381.3)**	**0.021(+)**	0.71 (0.01, 78.66)	0.425(-)
T2	**M1**	1.87 (0.57, 6.11)	—	0.58 (0.17, 1.91)	—
	M2	**19.41** **(19.41, 107.13)**	**0.001(+)**	0.70 (0.06, 8.33)	0.870(-)
T3	**M1**	1.19	—	2.34	—

		(0.53, 2.66)		(1.06, 5.16)	
	M2	3.13 (0.67, 14.67)	0.225(+)	1.77 (0.28, 11.12)	0.762(+)
PM10					
Pregnancy	**M1**	1.57 (0.94, 2.62)	—	0.91 (0.45, 1.81)	—
	M2	2.32 (0.95, 5.69)	0.287 (+)	2.71 (0.68, 10.70)	0.094(+)
T1	**M1**	**2.05 (1.18, 3.57)**	—	0.37 (0.15, 0.90)	—
	M2	**3.11 (1.31, 7.43)**	0.231(+)	0.93 (0.15, 5.88)	0.240(-)
T2	**M1**	1.3 (0.78, 2.16)	—	0.70 (0.41,1.20)	—
	M2	**2.70 (1.17, 6.19)**	**0.044(+)**	0.81 (0.27, 2.41)	0.769(-)
T3	**M1**	1.13 (0.82, 1.57)	—	1.28 (0.33, 1.35)	—
	M2	1.41 (0.76, 2.63)	0.479(+)	1.18 (0.20, 3.96)	0.854(+)

Abbreviations: PM: particulate matter, RR: Relative risk, T1: First trimester of pregnancy (0-12 weeks), T2: Second trimester of pregnancy (13-24 week), T3: Third trimester of pregnancy (25-37 week).

* M1: Model 1, Log-binomial regression model for the effect PM2.5 and PM10 during pregnancy in the possible occurrence of allergic rhinitis in the offspring, adjusted for: maternal age, parity, maternal education, maternal history of allergy, and adherence to Mediterranean Diet, season of birth, child age, child BMI and child gender.

** M2: Model 2, Log-binomial regression model for the effect PM2.5 and PM10 during pregnancy in the possible occurrence of allergic rhinitis in the offspring, adjusted for: maternal age, parity, maternal education, maternal history of allergy, and adherence to Mediterranean Diet, season of birth, child age, child BMI and child gender, including the interaction term Mediterranean Diet.

(+) indicates a RR<1 for interactions and (-) indicates a RR>1 for interactions

Table 4. Effect of $PM_{2.5}$ and PM_{10} exposure during the whole pregnancy and every trimester of pregnancy specifically, on doctor diagnosed asthma in the offspring, in the fourth and sixth year's follow up of the Rhea Cohort and the effect modification by maternal Mediterranean diet during pregnancy.

		Doctor Diagnosed Asthma			
		4 years		6 years	
Exposure		**Main effect RR (95% CI)**	**Interaction with MD p-value (direction)**	**Main effect RR (95% CI)**	**Interaction with MD p-value (direction)**
PM2.5					
Pregnancy	**M1***	0.12 (0.01, 1.38)	—	6.66 (0.92, 48.28)	—
	M2**	0.01 (0.00, 1.46)	0.213 (-)	4.93 (0.10, 241.0)	0.844(+)
T1	**M1**	0,42 (0.04, 4.85)	—	2.52 (0.26, 24.32)	—
	M2	0.25 (0.00, 30.05)	0.787(-)	3.18 (0.05, 194.6)	0.882(+)
T2	**M1**	0.51 (0.08, 3.46)	—	1.02 (0.15, 7.01)	—
	M2	0.19 (0.00, 16.00)	0.603(-)	7.59 (0.20, 289.3)	0.185(+)
T3	**M1**	0.75	—	3.03	—

		(0.13, 4.29)		(0.91, 10.10)	
	M2	**0.02**	**0.010(-)**	1.12	0.448(+)
		(0.00, 0.55)		(0.07, 17.24)	
PM10					
Pregnancy	**M1**	0.53	—	0.73	—
		(0.14, 1.94)		(0.23, 2.35)	
	M2	2.06	0.216 (+)	0.82	0.911(-)
		(0.20, 21.47)		(0.13, 5.02)	
T1	**M1**	0.82	—	0.42	—
		(0.26, 2.54)		(0.13, 1.42)	
	M2	1.72	0.413(+)	0.42	0.953(-)
		(0.20, 14.68)		(0.06, 2.88)	
T2	**M1**	0.79	—	0.51	—
		(0.35, 1.77)		(0.25, 1.04)	
	M2	1.65	0.388(+)	1.08	0.260(+)
		(0.28, 9.70)		(0.26, 4.41)	
T3	**M1**	0.77	—	1.41	—
		(0.40, 1.50)		(0.77, 2.59)	
	M2	0.27	0.104(-)	0.72	0.299(-)
		(0.07, 1.01)		(0.17, 3.12)	

Abbreviations: PM: particulate matter, RR: Relative risk, T1: First trimester of pregnancy (0-12 weeks), T2: Second trimester of pregnancy (13-24 week), T3: Third trimester of pregnancy (25-37 week)

* M1: Model 1, Log-binomial regression model for the effect PM2.5 and PM10 during pregnancy in the possible occurrence of asthma in the offspring, adjusted for: maternal age, parity, maternal education, maternal history of allergy, and adherence to Mediterranean Diet, season of birth, child age, child BMI and child gender.

** M2: Model 2, Log-binomial regression model for the effect PM2.5 and PM10 during pregnancy in the possible occurrence of asthma in the offspring, adjusted for: maternal age, parity, maternal education, maternal history of allergy, and adherence to Mediterranean Diet, season of birth, child age, child BMI and child gender, including the interaction term Mediterranean Diet.

(+) indicates a RR<1 for interactions and (-) indicates a RR>1 for interactions

Table 5. Effect of $PM_{2.5}$ and PM_{10} exposure during the whole pregnancy and every trimester of pregnancy specifically, on FEV1 in the offspring, in the fourth year's follow up of the Rhea Cohort and the effect modification by maternal Mediterranean diet during pregnancy.

		FEV1 4 years	
		Main effect	**Interaction with MD**
Exposure		**Beta (95% CI)**	**p-value (direction)**
PM2.5			
Pregnancy	**M1** *	-2.84	—
		(-16.47, 10.79)	
	M2 **	-24.38	0.116 (-)
		(-55.25, 6.48)	
T1	**M1**	-2.05	—
		(-16.72, 12.62)	
	M2	-26.55	0.071(-)
		(-56.84, 3.74)	
T2	**M1**	-1.36	—
		(-13.30, 10.58)	
	M2	-13.41	0.199(-)
		(-35.21, 8.39)	

T3	M1	-7.62 (-16.25, 1.02)	—
	M2	-16.63 (-35.03, 1.76)	0.275(-)
PM10			
Pregnancy	M1	0.13 (-5.05, 5.31)	—
	M2	-7.38 (-19.16, 4.40)	0.155 (-)
T1	M1	0.52 (-5.17, 6.21)	—
	M2	-8.18 (-19.44, 3.09)	0.080(-)
T2	M1	2.25 (-2.25, 6.76)	—
	M2	-3.51 (-12.20, 5.19)	0.130(-)
T3	M1	-1.66 (-5.19, 1.87)	—
	M2	-5.87 (-13.68, 1.95)	0.237(-)

Abbreviations: PM: particulate matter, T1: First trimester of pregnancy (0-12 weeks), T2: Second trimester of pregnancy (13-24 week), T3: Third trimester of pregnancy (25-37 week)

* M1: Model 1, Linear regression model for the effect PM2.5 and PM10 during pregnancy in the possible affect of the FEV1 of the offspring, adjusted for: maternal age, parity, maternal education, maternal history of allergy, and adherence to Mediterranean Diet, season of birth, child age, child BMI and child gender.

** M2: Model 2, Linear regression model for the effect PM2.5 and PM10 during pregnancy in the possible affect of the FEV1 of the offspring, adjusted for: maternal age, parity, maternal education, maternal history of allergy, and adherence to Mediterranean Diet, season of birth, child age, child BMI and child gender, including the interaction term Mediterranean Diet.

(+) indicates a RR<1 for interactions and (-) indicates a RR>1 for interactions

Table 6. Effect of $PM_{2.5}$ and PM_{10} exposure during the whole pregnancy and every trimester of pregnancy specifically, on FVC in the offspring, in the fourth year's follow up of the Rhea Cohort and the effect modification by maternal Mediterranean diet during pregnancy.

		FVC 4 years	
Exposure		Main effect Beta (95% CI)	Interaction with MD p-value (direction)
PM2.5			
Pregnancy	M1*	3.28 (-10.53, 17.10)	—
	M2**	-10.09 (-41.49, 21.32)	0.339 (-)
T1	M1	6.51 (-8.43, 21.44)	—
	M2	-13.03 (-43.97, 17.91)	0.162(-)
T2	M1	2.88 (-9.23, 15.00)	—

	M2	-2.25 (-24.41, 19.91)	0.596(-)
T3	M1	-8.22 (-17.04, 0.60)	—
	M2	-17.97 (-36.76, 0.82)	0.248(-)
PM10			
Pregnancy	M1	0.70 (-4.56, 5.96)	—
	M2	-7.93 (-19.87, 4.01)	0.111 (-)
T1	M1	2.98 (-2.81, 8.77)	—
	M2	-6.72 (-18.16, 4.72)	0.055(-)
T2	M1	2.86 (-1.71, 7.43)	—
	M2	-1.84 (-10.67, 6.98)	0.225(-)
T3	M1	-8.22 (-17.04, 0.61)	—
	M2	-17.97 (-36.76, 0.82)	0.248(-)

Abbreviations: PM: particulate matter,T1: First trimester of pregnancy (0-12 weeks), T2: Second trimester of pregnancy (13-24 week), T3: Third trimester of pregnancy (25-37 week)

* M1: Model 1, Linear regression model for the effect PM2.5 and PM10 during pregnancy in the possible affect in the FVC of the offspring, adjusted for: maternal age, parity, maternal education, maternal history of allergy, and adherence to Mediterranean Diet, season of birth, child age, child BMI and child gender.

** M2: Model 2, Linear regression model for the effect PM2.5 and PM10 during pregnancy in the possible affect in the FVC of the offspring, adjusted for: maternal age, parity, maternal education, maternal history of allergy, and adherence to Mediterranean Diet, season of birth, child age, child BMI and child gender, including the interaction term Mediterranean Diet.

(+) indicates a RR<1 for interactions and (-) indicates a RR>1 for interactions

Table 7. Effect of $PM_{2.5}$ and PM_{10} exposure during the whole pregnancy and every trimester of pregnancy specifically, on FEV1- FVC ratio in the offspring, in the fourth year's follow up of the Rhea Cohort and the effect modification by maternal Mediterranean diet during pregnancy.

		Ratio FVC-FEV1 4 years	
		Main effect Beta (95% CI)	**Interaction with MD p-value (direction)**
Exposure			
PM2.5			
Pregnancy	M1*	-6.11 (-11.68, -0.53)	—
	M2**	-12.99 (-25.64, -0.34)	0.218 (-)
T1	M1	**-7.97 (-14.20, -1.74)**	—
	M2	-12.94 (-1.74, 0.00)	0.374(-)
T2	M1	-3.72	—

		(-8.09, 0.65)	
	M2	**-9.91**	0.067(+)
		(-17.71, -1.95)	
T3	**M1**	0.17	—
		(-2.89, 3.24)	
	M2	1.79	0.581(-)
		(-4.75, 8.33)	
PM10			
Pregnancy	**M1**	-0.59	—
		(-2.73, 1.54)	
	M2	0.42	0.678 (-)
		(-4.42, 5.29)	
T1	**M1**	-2.15	—
		(-4.59, 0.29)	
	M2	-1.63	0.820(-)
		(-6.49, 3.23)	
T2	**M1**	0.47	—
		(-2.12, 1.19)	
	M2	-1.49	0.461(+)
		(-4.70, 1.71)	
T3	**M1**	0.12	—
		(-1.13, 1.37)	
	M2	1.85	0.169(+)
		(-0.91, 4.61)	

Abbreviations: PM: particulate matter,T1: First trimester of pregnancy (0-12 weeks), T2: Second trimester of pregnancy (13-24 week), T3: Third trimester of pregnancy (25-37 week)

* M1: Model 1, Linear regression model for the effect PM2.5 and PM10 during pregnancy in the possible affect in the FEV1 –FVC ratio of the offspring, adjusted for: maternal age, parity, maternal education, maternal history of allergy, and adherence to Mediterranean Diet, season of birth, child age, child BMI and child gender.

** M2: Model 2, Linear regression model for the effect PM2.5 and PM10 during pregnancy in the possible affect in the FEV1 –FVC ratio of the offspring, adjusted for: maternal age, parity, maternal education, maternal history of allergy, and adherence to Mediterranean Diet, season of birth, child age, child BMI and child gender, including the interaction term Mediterranean Diet.

(+) indicates a RR<1 for interactions and (-) indicates a RR>1 for interactions

5. Discussion

5.1 Main findings

In this population-based birth cohort study, we found that there is a possible protective role of MD during pregnancy against the occurrence of eczema in the offspring at age 4 and 6 years associated with exposure to PM2,5 during pregnancy, and more specifically during the second trimester of pregnancy. A protective role of MD was also observed against the occurrence of allergic rhinitis at 4 years with exposure to PM2.5 during the whole pregnancy and particularly in the first and second trimester and against the onset of asthma at age 4 with exposure to PM2.5 during the third trimester of pregnancy. No effect modification by MD with lung function (FEV1, FVC, FEV1-FVC ratio) was found. Our results show that exposures to air pollution in specific time points during gestation and adherence in MD during pregnancy may affect the occurrence of eczema, allergic rhinitis and asthma.

5.2 Discussion under the light of literature

Exposure to air pollution during pregnancy may affect the occurrence of allergies and lung function (31). Previous studies have shown statistically significant associations between prenatal exposure to PM and the risk of allergy development of childhood (31). Additionally in other studies maternal exposure during pregnancy was associated with allergies in the offspring, which also supports our hypothesis that exposure in sensitive time points during pregnancy may affect the fetus allergy outcome (24,29,49).

To our knowledge up to date the are no other studies assessing the effect modification by Mediterranean diet during pregnancy on the association between prenatal exposure to air pollution and the risk for eczema, allergic rhinitis, asthma occurrence and lung function in the offspring. Existing studies assessed the effect of MD during pregnancy and the possible protective effect in allergic diseases, A prospective cohort study in six years old Menorcan children reported a reduced risk of asthma and atopy in children whose mothers had a high adherence to MD during pregnancy (43). The Avon Longitudinal Study of Parents and Children (ALSPAC) reported that adherence to MD during pregnancy may be associated with increased small airway function in childhood, but found no evidence for a reduced risk of asthma or other allergic outcomes (44). Data from meta-analyses suggest that high adherence to MD diet during pregnancy may have short term effects on allergic diseases in early childhood (50).

A possible explanation why maternal MD during pregnancy seems to have o protective role against allergies might be that MD is rich in antioxidants which reach the fetus during gestation and create a stronger immune system against possible factors that may promote and allergy or lung malfunction such as allergens. Those findings suggest that MD adherence may be a protective modifier against oxidative stress and inflammation caused by air pollution(51–53).

5.3 Impact of the study

The main strength of the present study is its novelty of assessing MD as a modification factor between exposure to air pollution during pregnancy and its possible protective role in the development of allergy-related outcomes in childhood. Furthermore, very few studies assessed pregnancy sensitivity windows to PM exposures so far. Moreover, another important part about the present research is that there is a follow up in the fourth and the sixth year of ages it may be possible to observe the evolution of allergic diseases during different time points of childhood.

5.4 *Limitations of the study*

The main limitations of the research are that the sample size decreases during time, so the results might be affected due to small population. Finally, as in all observational studies, residual confounding from unmeasured covariates is still possible.

6. Conclusion

Our findings suggest interplay between prenatal exposure to air pollution, adherence to MD and the development of allergy-related outcomes in the offspring during childhood. The data presented could support dietary interventions during gestation for mitigating offspring risk of allergies against prenatal exposure to air pollution.

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