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JOINT EFFECT OF PRENATAL EXPOSURE TO FINE PARTICULATE MATTER AND INTAKE OF PARACETAMOL (ACETAMINOPHEN) IN PREGNANCY ON ONSET OF ECZEMA IN EARLY CHILDHOOD. PROSPECTIVE BIRTH COHORT STUDY

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Abstract

Prenatal Paracetamol (Acetaminophen) has been associated with increased risk of allergic disease in early childhood, an association that could be due to increased altered susceptibility induced by air pollutants. The main goal of the study was to test the hypothesis that prenatal Paracetamol exposure increases the risk of developing eczema in early childhood and that this association is stronger for children who are exposed prenatally to higher concentrations of fine particulate matter (PM_{2.5}). The study sample consisted of 322 women recruited from January 2001 to February 2004 in the Krakow inner city area who gave birth to term babies and completed 5-year follow-up. Paracetamol use in pregnancy was collected by interviews and prenatal personal exposure to over 48 hours was measured in all recruited women in the second trimester of PM_{2.5} pregnancy. After delivery, every three months in the first 24 months of the newborn's life and every 6 months later, a detailed standardized face-to-face interview on the infant's health was administered to each mother by a trained interviewer. During the interviews at each of the study periods after birth, a history of eczema was recorded.

By Cox proportional hazard regression, prenatal exposure to Paracetamol increased the risk of eczema by 20% and PM_{2.5} by 6%, albeit non significantly. However, the the joint exposure to Paracetamol and higher prenatal PM_{2.5} was significant and doubled the risk of eczema symptoms (HR = 2.07, 95%CI: 1.01 – 4.34). The findings suggest that even very small doses of Paracetamol in pregnancy may affect the occurrence of allergy outcomes such as eczema in early childhood but only at the co-exposure to higher fine particulate matter.

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Keywords

birth cohort study; eczema; children; acetaminophen; pregnancy; prenatal fine particulate matter

Introduction

Eczema is the most common inflammatory skin disease in early childhood and is often the first manifestation for the so-called “atopic march” including food allergy, asthma and allergic rhinitis (1 – 5). Although genetic predisposition and allergic sensitization of infants to environmental factors are known to affect the onset and severity of eczema, a reported rise in allergy over the last several decades suggests an important role for the environment in the pathogenesis of infantile eczema (6 – 10). Environmental factors linked with industrialization and urbanization, higher allergen exposure in modern tight housing, an increase in variety of foods consumed, or use of certain pharmaceutical drugs may be involved in the rising trend in eczema prevalence (11 – 14).

A potential role in the pathogenesis of eczema for Paracetamol (Acetaminophen or Tylenol in the U.S.) has been suggested by recent studies linking Tylenol to asthma (15, 16). This drug has become the most common medication for pain and fever in adults and children and the increased use of Paracetamol over the past decades has occurred contemporaneously with the rise in prevalence of allergy-related diseases such as asthma or hay fever worldwide (17). The reason for this asthma epidemic may be an association of Paracetamol intake with an impaired endogenous antioxidant defenses, which play an important role in the pathogenesis of a number of inflammatory pulmonary diseases (18). It was shown in healthy volunteers, that ingestion of high therapeutic doses of Paracetamol reduced serum antioxidant capacity (19). In vitro studies on pulmonary cells demonstrated, that Paracetamol at subtoxic but clinically relevant concentrations decreased intracellular reduced glutathione (GSH) in pulmonary macrophages and type II pneumocytes (20 – 21).

The concentrations of Paracetamol that are reached in fetal tissue are not known, but the drug is rapidly and uniformly distributed in most tissues (22, 23). Paracetamol toxicity results from its bioactivation to a highly reactive metabolite, *N*-acetyl-*p*-benzoquinone imine (NAPQI), which is detoxified by (GSH) and subsequently may deplete glutathione cellular reserves (24, 25). Potential fetotoxicity from the Paracetamol toxic metabolite would depend on the efficiency of detoxication by glutathione conjugation, which may be reduced at fetal exposure to ambient hazards inducing oxidative stress responses (26 – 28). The main goal of this prospective birth cohort study was to assess the role of very low prenatal exposure to Paracetamol in the occurrence of eczema symptoms in early childhood and assess the possible interaction with prenatal exposure to particulate pollutants, which are potent inducers of oxidative stress and strong potential competitors for intracellular glutathione (29).

Material and methods

The study consisted of 322 women recruited from January 2001 to February 2004 in Krakow inner city area, who gave birth to term babies and completed 5-year follow-up. The women attending ambulatory prenatal clinics in the first and second trimesters of pregnancy were eligible for the study. The enrollment included only non-smoking women with singleton pregnancies ages 18–35 years, and who were free from chronic diseases such as diabetes and hypertension. Upon enrollment, a detailed questionnaire was administered to each subject to solicit information on demographic data, house characteristics, date of the last menstrual period (LMP), medical and reproductive history, occupational hazards,

alcohol consumption, nutritional habits, and smoking practices of others present in the home. Paracetamol use in pregnancy was collected by interviews and prenatal personal exposure to airborne over 48 hours was measured for all recruited PM_{2.5} women in the second trimester of pregnancy. After delivery, every three months in the first 24 months of the newborn's life and every 6 months later, a detailed standardized face-to-face interview on the infant's health was administered to each mother by a trained interviewer. During the interviews at each of the study periods at 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54 and 60 months of age after birth, a history of infantile eczema was recorded if the child experienced dry skin in combination with itchy rash and typical localization, which was confirmed by physician during the period from the last visit. In addition, the information about medication taken in each of the periods was gathered as well. Gestational age at birth denotes the interval between the last day of the mother's LMP and the date of birth. Maternal atopy was defined as reported medical diagnosis of eczema, asthma or hay fever. Prenatal and postnatal environmental tobacco smoke (ETS) was defined by the weighted average of the number of cigarettes smoked daily in the household in a given period. The definition of moldy/damp household was based on questions regarding noticeable moisture stains and visible mold growth on the walls within the household.

Measurement of prenatal personal exposure to fine particles

During the second trimester, a member of the air monitoring staff instructed the woman in the use of the personal monitor, which is lightweight, quiet and is worn in a backpack. The woman was asked to wear the monitor during the daytime hours for 2 consecutive days and to place the monitor near the bed at night. During the morning of the second day, the air monitoring staff-person and interviewer visited the woman's home to change the battery-pack and administer the full questionnaire. They also checked to see that the monitor had been running continuously and that there have been no technical or operating failures. A staff-member returned to the woman's home on the morning of the third day to pick up the equipment.

A Personal Environmental Monitoring Sampler (PEMS) was used to measure particle mass. The PEMS is designed to achieve the particle target size of 2.5 µm at a flow rate of 4.0 liters per minute (LPM) with an array of 10 impactor nozzles. Flow rates are calibrated (with filters in place) using a bubble meter prior to the monitoring, and are checked again with a change of the battery pack on the second day and at the conclusion of the monitoring. Pumps operated continuously at 2 LPM over the 48-hour period. To modify the sampler to achieve the 2.5 µm size cut at 2 LPM, 5 of the nozzles were blocked. Particles were collected on Teflon membrane filter (37 mm Teflo™, Gelman Sciences). The combination of low pressure drop (permitting use of a low power sampling pump), low hygroscopicity (minimizing bound water interference in mass measurements), and low trace element background (improving analytical sensitivity) of these filters make them highly appropriate for personal particle sampling.

Statistical methods

The purpose of the statistical analysis was to assess the relation of the prenatal use of Paracetamol and exposure to fine particles with the onset of eczema symptoms in the first five years of life. In the analysis, a set of covariates was considered which could have confounded the effect of the main exposure variables. The dependent variable was the onset of eczema symptoms in any of the subsequent periods of the follow-up. The overall effect of prenatal exposure on eczema events was assessed by the Hazard Ratio estimates from the Cox proportional hazards regression model. The hazard ratio (HR) is the ratio of the probability of the first eczema event occurring in the exposed group compared with the reference group, and the interpretation is similar to a relative risk. In the model, prenatal

PM_{2.5} was introduced as a dummy variable (below and above the 75th percentile value of 53 µg/m³). The Paracetamol variable was also dichotomized (0 – no intake of Paracetamol in pregnancy, 1 – intake of Paracetamol whenever in pregnancy irrespective of dose). In the statistical analysis we also considered a set of potential confounders or modifiers (maternal education, maternal atopy, gender of child, presence of older siblings, breastfeeding practice, prenatal and postnatal exposure to ETS, and the presence of molds in the household). All statistical analyses were performed with STATA 11 version software for Windows (30, 31).

Results

The characteristics of children grouped by the eczema onset over the 5-year follow-up did not differ across the groups (Table 1). Onset of eczema symptoms was highest in the first year of life and the rates substantially decreased at later age (Figure 1). Incidence rates were slightly higher in boys (43.4%, 95%CI: 35.6 – 51.2%) than in girls (36.2%, 95%CI: 28.7 – 43.7%), however the observed difference was statistically insignificant. As for the prevalence of potential hazards in the prenatal and postnatal periods, only living in a house with damp/mold was significantly higher in children with eczema symptoms.

Analysis of personal air samples collected from pregnant women in the second pregnancy trimester showed the median concentrations of prenatal PM_{2.5} of 34.8 µg/m³ with an interquartile range of 29.8 µg/m³. Most measurements (75%) were 53 µg/m³. While 24% of infants were exposed to prenatal ETS, 21% of them were exposed to postnatal passive smoke at home. There concentrations and reported weighted number was a significant correlation between prenatal PM_{2.5} of cigarettes smoked daily by household members during the pregnancy period (Spearman correlation = 0.212, p<0.0001) and cigarettes smoked daily postnatally (Spearman correlation = 0.199, p = 0.0003).

Paracetamol was used by 12.1% (95%CI: 8.5 – 15.7%) of women during the first trimester of pregnancy, 12.1% in the second trimester (95%CI: 4.3 – 10.0%), 7.1% (95%CI: 4.3 – 10.0%), in the third and 22.7% (95%CI: 17.6 – 26.8) ever during pregnancy. Users of Paracetamol in the first trimester of pregnancy declared an average intake of 2.2 g of Paracetamol (range 0.5 – 15 g), in the second trimester 1.6 g (range: 0.5 – 11g), in the third 2.2 (range 0.5 – 8 g) and 2.6 g (range 0.5 – 16 g) anytime in pregnancy. It was estimated that women used the drug mostly for pain problems (79.8%) and much less for fever or infection (20.8%). The minority of children (38.8%) was given Paracetamol, mainly at age of 4 and 5 years and the average cumulative dose of the drug was not different between the group of children with symptoms and without it. None of the demographic characteristics of women (age, educational level) was associated with the prenatal intake of Paracetamol. There was only a significant trend for the Paracetamol doses ever taken in pregnancy and the occurrence of eczema in children (nonparametric trend $z = 2.18$, $p = 0.029$).

Table 2 presents the Cox proportional hazard regression model for the effects of Paracetamol intake ever in pregnancy on the onset of eczema in the follow-up after adjusting for maternal characteristics (age, education, atopy), gender of child, older siblings, damp/mold house, and exposure to prenatal particulate matter. Although the adjusted HR estimates of the separate increased the risk of eczema by 6% (HR = 1.06, 95%CI: 0.72 – 1.57) and that of effect of PM_{2.5} Paracetamol by 20% (HR = 1.20; 95%CI: 0.81 – 1.77), they did not reach statistical significance. However, the interaction term for joint exposure to Paracetamol and higher was significant PM_{2.5} and doubled the risk of eczema symptoms (HR = 2.07, 95%CI: 1.01 – 4.34). Of potential confounders considered in the analysis only damp/mold in the home (HR = 1.22; 95%CI: 1.07 – 1.40) significantly increased the risk. In contrast, there was an inverse significant association between the presence of older siblings and incidence

of eczema symptoms (HR = 0.75; 95% CI: 0.58 – 0.98). None of the other covariates were associated with the onset of eczema. Adjusting the models for indication of prenatal Paracetamol use and the postnatal dose of the drug did not modify the risk estimates.

Discussion

In this study the joint impact of Paracetamol and PM_{2.5} was significant and doubled the risk of eczema. The estimated effect of both exposure variables was adjusted in the Cox proportional hazards regression models for a set of potential confounders. The association does not seem to be confounded by mothers' use or postnatal Paracetamol intake by children.

To our knowledge this is the first study showing an interaction between the prenatal exposure to fine particulate matter and Paracetamol intake in pregnancy on an allergic disease. We hypothesize that the manifestation of eczema symptoms in infants and young children associated with even low Paracetamol exposure may be a result of the competition of its metabolites for intracellular reduced glutathione with coexisting intrauterine exposure to particulate matter (29). Depletion of cellular glutathione resulting from the exposure to prenatal particulate matter may reduce the amount of glutathione available for the detoxification of Paracetamol toxic metabolite (NAPQI). This in turn may lead to an impaired antioxidant defences (20, 21, 25) and increased risk of allergic reaction since the depletion of glutathione in antigen-presenting cells can promote T-helper type 2 (TH2) cytokine responses (32). The recent evidence from a birth cohort study in NYC demonstrating that children with a common functional polymorphism in the glutathione S-transferase gene were more susceptible to the risk of asthma with reported prenatal Paracetamol intake, further strengthens the proposed link between the risk of allergic disease with Paracetamol and the glutathione pathway (15).

Over the last 10 years several cross-sectional and case controls studies have reported a positive relationship between postnatal Paracetamol use and asthma, hay fever and eczema (16, 33 – 35). Multicenter ISAAC international study (16) carried out in 31 countries has shown a significant association between Paracetamol use in infancy and childhood and risk of asthma and hay fever in children aged 6 – 7 years. Although similar increased risks were observed with eczema the association was found to be weaker. The effect of prenatal exposure to Paracetamol on allergic diseases has also been confirmed in a number of studies (15, 36 – 41). For example, the recently published Avon Longitudinal Study (37) found positive and significant associations of acetaminophen use in late pregnancy with asthma, wheezing and total IgE, but not hay fever, eczema or skin test positivity. The lack of a strong association between Paracetamol prenatal intake and eczema symptoms in our study might have resulted from the relatively low prevalence and small doses of Paracetamol taken during pregnancy in our population comparing with other data published (33 – 41).

The strength of our study is the careful prospective monitoring of eczema symptoms by regular interviews collected in 14 intervals over the 5-year follow-up, and the accurate personal prenatal exposure assessments of fine particulate matter and ETS exposure in the prenatal and postnatal periods, which were not taken into account in prior studies on eczema. Our assessment of total personal individual exposure to fine particulate pollutants included all potential sources of exposure during pregnancy, both indoors and outdoors. Another advantage of the study is the fact that the study sample belonged to a low-risk group recruited from a general urban community. However, the birth cohort differed from the broader population in several respects since we excluded women with conditions that could have affected health of the babies, such as maternal active cigarette smoking, multiple pregnancy or maternal pre-existing chronic diseases.

A limitation of the study is the lack of validation data regarding Paracetamol use. Our data on Paracetamol intake in pregnancy was based on interviews with mothers, which is useful for ranking individuals but does not necessarily permit confident assessments of absolute intake. Moreover, we were not able to measure IgE blood levels in mothers and children. Another potential limitation of our study comes from the fact that personal monitoring of exposure to fine particles among pregnant women was performed over a short period (48 hours) in the second trimester of pregnancy. To evaluate the correlation between the level of PM_{2.5} measured over 48 hours in the second trimester of pregnancy with those in the first and the third trimesters, a series of repeated measurements in each trimester was carried out in a subsample of 80 pregnant women who were recruited in the first trimester. The mean concentration of PM_{2.5} in the second trimester was 44.4 µg/m³ (SD: 46.5), not significantly different from the mean concentration in the first (46.2 µg/m³, SD: 34.0) and in the third trimester (35.9 µg/m³, SD: 35.3). This provides some confidence that the measurements of total personal level of exposure to fine particles taken in the second trimester may be representative of other pregnancy periods.

In conclusion, the findings of the study suggest that even very small doses of Paracetamol in pregnancy may contribute to the occurrence of allergy outcomes such as eczema in early childhood, if there is co-exposure to airborne particulate matter.

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Research highlights

1. Use paracetamol In pregnancy
2. Prenatal exposure to fine particulate matter
3. Joint effect of paracetamol and prenatal PM_{2.5} particulate matter on the risk of eczema in children

Figure 1.
Histograms of eczema onset by age and gender of children

Table 1
Characteristics of the study sample grouped by the presence of eczema symptoms during the 5-year follow-up

Variables	Eczema (-) N=123	Onset of eczema		Total N =322	P for difference
		1 st year N=128	2 nd year or later N=71		
Maternal age:					
	mean	27.96	27.73	27.82	0.8520
	SD	3.23	3.39	3.39	
Maternal education:					
elementary	n (%)	12 (9.8)	7 (5.5)	28 (8.7)	0.3804
medium	n (%)	26 (21.1)	35 (27.3)	77 (23.9)	
higher	n (%)	85 (69.1)	86 (67.2)	217 (67.4)	
Maternal atopy (+):	n (%)	25 (20.3)	34 (26.6)	78 (24.2)	0.4385
Parity:					
1	n (%)	67 (54.5)	88 (68.7)	204 (63.4)	0.0340
2	n (%)	56 (45.5)	40 (31.3)	118 (36.6)	
Gender:					
Boys	n (%)	62 (50.4)	69 (53.9)	159 (49.4)	0.1416
Girls	n (%)	61 (49.6)	59 (46.1)	163 (50.6)	
Gestational age:					
(weeks) > 36	mean	39.44	39.50	39.51	0.5192
	SD	1.216	1.115	1.142	
Birth weight (g):					
	mean	3425.4	3443.9	3430.4	0.8894
	SD	435.4	423.4	446.4	
Length at birth (cm):					
	mean	54.7	54.9	54.8	0.8159
	SD	2.70	2.35	2.73	
Head circumference (cm):					
	mean	33.9	34.1	33.9	0.1312
	SD	1.42	1.28	1.37	
Breastfeeding exclusive > 3 months					

Variables	Eczema (-) N=123	Onset of eczema		Total N=322	P for difference
		1 st year N=128	2 nd year or later N=71		
	n (%)	71 (55.9)	39 (54.9)	173 (53.7)	0.7755
Prenatal ETS (+)	n (%)	35 (27.3)	14 (19.7)	76 (23.6)	0.4120
Postnatal ETS (+) 1-5 yrs	n (%)	27 (21.1)	17 (23.9)	67 (20.8)	0.6832
Damp/mold house (+)	n (%)	42 (32.8)	26 (36.6)	95 (29.5)	0.0557
PM _{2.5} level > 53 µg/m ³	n (%)	36 (28.1)	15 (21.1)	77 (23.9)	0.3550

Cox proportional hazard regression model for the occurrence of eczema in the adjusted for potential follow-up and prenatal exposure to Paracetamol and PM_{2.5} confounders

Table 2

Predictors	Haz. Ratio	z	P>z	[95% Conf. Interval]	
Maternal age	1.03	1.05	0.294	0.98	1.08
Maternal atopy	1.22	1.21	0.228	0.88	1.70
Gender of child (girls)	0.88	-0.85	0.398	0.66	1.18
Older siblings	0.75	-2.12	0.034	0.58	0.98
Prenatal ETS	1.00	0.04	0.965	0.95	1.06
Postnatal ETS	1.02	0.37	0.710	0.94	1.10
Fish intake in pregnancy	0.98	-0.18	0.859	0.82	1.18
Damp/mold house	1.22	2.89	0.004	1.07	1.40
Prenatal PM _{2.5}	1.06	0.31	0.759	0.72	1.57
Prenatal Paracetamol	1.20	0.90	0.366	0.81	1.77
Interaction PM_{2.5} x Paracetamol	2.07	1.97	0.049	1.01	4.34