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Effect of prenatal exposure to fine particulate matter and intake of Paracetamol (Acetaminophen) in pregnancy on eczema occurrence in early childhood

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ABSTRACT

The 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 may be stronger in children who are exposed in fetal period 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 PM_{2.5} over 48 h was measured in recruited 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 trained interviewers. During the interviews at each of the study periods after birth, a history of eczema was recorded.

The incident rate ratio (IRR) for frequency of eczema events over the follow-up was estimated from the Poisson regression model and the overall effect of main exposure variables on eczema was assessed by odds ratios (ORs) by the logistic model. The estimated relative risk of eczema occurring whenever in the follow-up was related significantly neither with prenatal Paracetamol nor higher PM_{2.5} exposure, however, their joint effect was significant (OR interaction term = 6.04; 95%CI: 1.04–35.16). Of potential confounders considered in the analysis only damp/moldy home significantly increased the risk of eczema (OR = 1.53; 95%CI: 1.14–2.05). In contrast, there was an inverse significant association between the presence of older siblings and eczema (OR = 0.55; 95%CI: 0.35–0.84). The joint effect of the main exposure variables significantly increased frequency of eczema events (IRR = 1.78, 95%CI: 1.22–2.61).

In conclusion, the findings of the study suggest that Paracetamol use by mothers in pregnancy is not an independent risk factor for eczema in children, however, even very small doses of Paracetamol taken in pregnancy may contribute to the occurrence of allergic symptoms in early childhood if there is prenatal co-exposure to higher airborne fine particulate matter.

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1. 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 (Businco et al., 1997; Bergmann et al., 1998; Spergel and Paller, 2003; Illi et al.,

2004; van der Hulst et al., 2007). 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 (Kay et al., 1994; Strachan, 1995; Williams, 2000; Wadonda-Kabondo et al., 2003; Asher et al., 2006). 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 (Heinrich et al., 1999; Bisgaard et al., 2009; Krämer et al., 2009; Cohet et al., 2004).

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A potential role of Paracetamol (Acetaminophen or Tylenol in the U.S.) in the pathogenesis of eczema has been suggested by many studies linking prenatal (Shaheen et al., 2002, 2005; Garcia-Marcos et al., 2008; Persky et al., 2008; Rebordosa et al., 2008) or postnatal use of this drug (Shaheen et al., 2000; Barr et al., 2004; McKeever et al., 2005; Koniman et al., 2007; Beasley et al., 2008; Garcia-Marcos et al., 2010; Lowe et al., 2010; Belyhun et al., 2010; Beasley et al., 2011; Garcia-Marcos et al., 2011; Amberbir et al., 2011) to asthma and other allergic disorders. 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 (Newson et al., 2000). 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 (Morcillo et al., 1999). It was shown in healthy volunteers, that ingestion of high therapeutic doses of Paracetamol reduced serum antioxidant capacity (Nuttall et al., 2003). *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 (Dimova et al., 2000, 2005).

The concentrations of Paracetamol that reach fetal tissue are not known, but the drug is rapidly and uniformly distributed in most tissues (Forrest et al., 1982; Prescott, 1980). 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 (Chen et al., 1990; Micheli et al., 1994). 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 (Rusznjak et al., 1998; Devalia et al., 1996; Schwarze et al., 2006; Li et al., 2003; Heinrich and Slama, 2007; Mazzoli-Rocha et al., 2010; Peterson et al., 1998).

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.

2. 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 PM_{2.5} over 48 h was measured for all recruited 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 trained interviewers. 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 by children 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 damp/moldy household was based on questions regarding noticeable moisture stains and visible mold growth on the walls within the household. If mold patches on internal walls were present, the interviewer qualified the answer as positive only in the case the moldy area exceeded 1 m².

3. 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) developed by the Department of Environmental Health at Harvard University (Dr John D Spengler) was used to measure particle mass. The PEMS is designed to achieve the particle target size of $\leq 2.5 \mu\text{m}$ at a flow rate of 2.0 LPM (liters per minute). Flow rates were calibrated (with filters in place) using a bubble meter prior to the monitoring, and were 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. 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.

3.1. 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 occurrence of eczema symptoms in the first five years of life. First, the overall effect of main exposure variables on the frequency of eczema events in the follow-up was assessed by the Poisson regression model. The incident rate ratio (IRR) estimated from the Poisson model is the ratio of the probability of eczema frequency observed in the exposed group compared with the reference group. In addition, the multivariable logistic model was used to assess odd ratios (ORs) of eczema occurring whenever in the follow-up in relation to exposure variables in question. In the regression models, PM_{2.5} variable was introduced at two levels (below and above the 75th percentile value of 53 $\mu\text{g}/\text{m}^3$). 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 multivariable statistical analysis we considered a set of potential confounders or modifiers (maternal age and maternal atopy, gender of child, presence of older siblings, prenatal and postnatal exposure to ETS, and the presence of molds in the household). All statistical analyses were performed with STATA 12 version software for Windows.

4. 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. 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 (Fig. 1). As for the prevalence of potential hazards in the prenatal and postnatal periods, only living in a damp/moldy house was significantly higher in children with reported 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 was a significant correlation between prenatal PM_{2.5} concentrations and reported weighted number 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: 0.5–11 g), 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

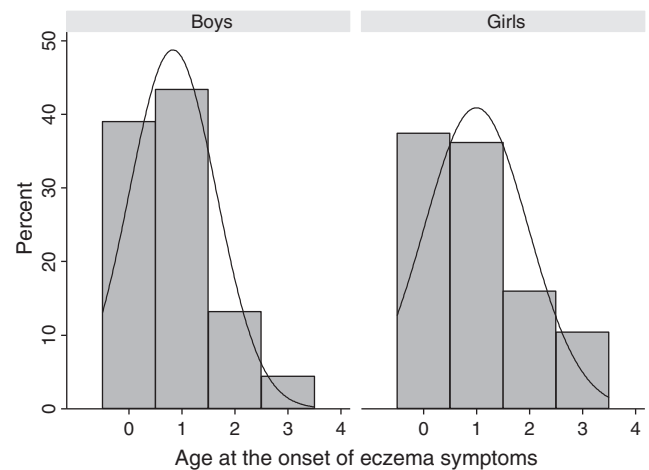


Fig. 1. Histograms of eczema occurrence by age and gender of children.

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. In the univariate analysis the association between Paracetamol use ever in pregnancy and the occurrence of eczema in children in the follow-up was at the border significance level ($\chi^2 = 2.947$, *p* = 0.086).

Table 2 presents the Poisson regression model for the effects of Paracetamol intake in pregnancy and prenatal exposure to fine particulate matter on the eczema frequency in the follow-up after adjusting for covariates. Neither the exposure to Paracetamol nor fine particulate matter affected independently the frequency of eczema events

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
		1st year N = 128	2nd year or later N = 71		
Maternal age					
Mean	27.96	27.73	27.75	27.82	0.8520
SD	3.23	3.39	3.71	3.39	
Maternal education					
Elementary n (%)	12 (9.8)	7 (5.5)	9 (12.7)	28 (8.7)	0.3804
Medium n (%)	26 (21.1)	35 (27.3)	16 (22.5)	77 (23.9)	
Higher n (%)	85 (69.1)	86 (67.2)	46 (64.8)	217 (67.4)	
Maternal atopy (+): n (%)	25 (20.3)	34 (26.6)	19 (26.8)	78 (24.2)	0.4385
Parity					
1 n (%)	67 (54.5)	88 (68.7)	49 (69.0)	204 (63.4)	0.0340
≥2 n (%)	56 (45.5)	40 (31.3)	22 (31.0)	118 (36.6)	
Gender					
Boys n (%)	62 (50.4)	69 (53.9)	28 (39.4)	159 (49.4)	0.1416
Girls n (%)	61 (49.6)	59 (46.1)	43 (60.6)	163 (50.6)	
Gestational age: (weeks) >36					
Mean	39.44	39.50	39.63	39.51	0.5192
SD	1.216	1.115	1.059	1.142	
Birth weight (g): (weeks) >36					
Mean	3425.4	3443.9	3414.6	3430.4	0.8894
SD	435.4	423.4	446.4	431.9	
Length at birth (cm)					
Mean	54.7	54.9	54.9	54.8	0.8159
SD	2.70	2.35	2.73	2.57	
Head circumference (cm)					
Mean	33.9	34.1	33.7	33.9	0.1312
SD	1.42	1.28	1.44	1.37	
Breastfeeding exclusive >3 months n (%)	63 (51.2)	71 (55.9)	39 (54.9)	173 (53.7)	0.7755
Prenatal ETS (+) n (%)	27 (22.0)	35 (27.3)	14 (19.7)	76 (23.6)	0.4120
Postnatal ETS (+) 1–5 yrs n (%)	23 (18.7)	27 (21.1)	17 (23.9)	67 (20.8)	0.6832
Damp/mold house (+) n (%)	27 (22.0)	42 (32.8)	26 (36.6)	95 (29.5)	0.0557
PM _{2.5} level>53 µg/m ³ n (%)	26 (21.1)	36 (28.1)	15 (21.1)	77 (23.9)	0.3550

Table 2

Poisson multivariable regression model (robust SE) for the occurrence of eczema in the follow-up and prenatal exposure to Paracetamol and PM_{2.5} adjusted for potential confounders.

Predictor variables	IRR	Robust Std. Err.	z	P>z	95% CI
Maternal age (continuous)	1.02	0.02	0.89	0.371	0.98 1.06
Maternal atopy (y/n)	1.49	0.21	2.80	0.005	1.13 1.97
Child's gender (girls)	0.87	0.11	−1.04	0.296	0.67 1.13
Older siblings (number)	0.75	0.09	−2.50	0.012	0.60 0.94
Damp/moldy house (y/n)	1.20	0.08	2.93	0.003	1.06 1.36
Prenatal ETS ^a	1.02	0.21	0.11	0.911	0.69 1.51
Postnatal ETS ^a	0.91	0.18	−0.49	0.621	0.62 1.34
Prenatal Paracetamol	1.00				
− +	1.23	0.22	1.20	0.231	0.87 1.74
+ −	1.27	0.22	1.37	0.170	0.90 1.77
+ +	1.78	0.35	2.98	0.003	1.22 2.61

^a Weighted number of cigarettes smoked daily at home.

in the follow-up, however their joint effect had a significant effect (IRR = 1.78, 95%CI: 1.22–2.61). Of potential confounders considered in the analysis only maternal atopy (IRR = 1.49; 95%CI: 1.13–1.97) and damp/moldy house significantly increased the risk (IRR = 1.20; 95%CI: 1.06–1.36). In contrast, there was an inverse significant association between the presence of older siblings and the frequency of eczema symptoms (IRR = 0.75; 95%CI: 0.60–0.94), but none of the other covariates was associated with eczema symptoms.

Table 3 shows that the estimated ORs for eczema occurring whenever in the follow-up were related significantly neither with Paracetamol nor PM_{2.5} exposure, however, the interaction term between both exposure variables was significant (OR = 6.04; 95%CI: 1.04–35.16). Of potential confounders considered in the analysis only damp/moldy house significantly increased the risk of eczema (OR = 1.53; 95%CI: 1.14–2.05). There was an inverse significant association between the presence of older siblings and eczema (OR = 0.55; 95%CI: 0.35–0.84), and none of the other covariates was significantly associated with the presence of symptoms.

5. Discussion

In this study the joint exposure to prenatal Paracetamol and PM_{2.5} was significantly associated with the occurrence of eczema in early childhood. Although independent effects of Paracetamol and PM_{2.5} were insignificant, their joint effect appeared to be significant (OR interaction term = 6.04; 95%CI: 1.04–35.16). It is important to mention that the joint effect of main exposure variables was adjusted in the regression models for a set of important potential confounders.

Table 3

Logistic multivariable regression model for the occurrence of eczema whenever in the follow-up and prenatal exposure to Paracetamol and PM_{2.5} adjusted for potential confounders.

Predictor variables	OR	Std. Err.	z	P>z	95% CI
Maternal age (continuous)	1.05	0.04	1.18	0.239	0.97 1.14
Maternal atopy (y/n)	1.67	0.49	1.77	0.077	0.95 2.96
Child's gender (girls)	1.01	0.25	0.06	0.955	0.63 1.63
Older siblings (number)	0.55	0.12	−2.74	0.006	0.35 0.84
Damp/moldy house (y/n)	1.53	0.23	2.85	0.004	1.14 2.05
Prenatal ETS ^a	1.27	0.47	0.63	0.530	0.61 2.64
Postnatal ETS ^a	0.96	0.37	−0.12	0.908	0.45 2.05
Prenatal Paracetamol	1.00				
− +	1.07	0.34	0.21	0.836	0.57 2.00
+ −	1.24	0.41	0.66	0.507	0.65 2.37
+ +	8.03	6.47	2.59	0.010	1.66 38.97

Interaction term (prenatal Paracetamol × Prenatal PM_{2.5}) = 6.04 (95%CI: 1.04–35.16).

^a Weighted number of cigarettes smoked daily at home.

To our knowledge this is the first study showing an interaction between a prenatal exposure to pollutants and Paracetamol on an allergic disease. The results of the study support our initial hypothesis that prenatal exposure to particulate pollutants may intensify the side effects of Paracetamol intake. We hypothesize that the manifestation of eczema symptoms in infants and young children associated with even low Paracetamol use in pregnancy may be a result of the competition of its metabolites for intracellular reduced glutathione with coexisting intrauterine exposure to particulate matter (Li et al., 2003). 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 defenses (Dimova et al., 2000, 2005; Micheli et al., 1994) and increased risk of allergic reaction since the depletion of glutathione in antigen-presenting cells can promote T-helper type 2 (TH2) cytokine responses (Peterson et al., 1998). The recent evidence from a birth cohort study in New York City 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 (Perzanowski et al., 2010).

Over the last 10 years several cross-sectional and case controls studies have reported an inconsistent findings on the association between postnatal Paracetamol use and eczema in children. For example, the multicenter ISAAC international study has shown a significant association between Paracetamol use in infancy and the risk of eczema in children aged 6–7 years (Beasley et al., 2008). Interestingly, the latter study surveying 13–14-year-old children provided evidence that the effect of Paracetamol was extended to adolescent children (Beasley et al., 2011). (Garcia-Marcos et al., 2010) in the large sample of Spanish schoolchildren have also shown that Paracetamol exposure in the first year of life in healthy children (without asthma and rhinoconjunctivitis) was associated with the eczema risk at the age of 6–7 (OR = 1.56; 95%CI: 1.36–1.80) as was antibiotic consumption (OR = 1.66; 95%CI: 1.43–1.92). The authors concluded that the Paracetamol use would be an independent risk factor for allergy since the association did not greatly change after additionally adjusting for the other drug and stratification by respiratory disease. However, (Lowe et al., 2010) in children with family history of allergic disease found no significant association between early Paracetamol use and risk of subsequent allergic disease (asthma, eczema, positive skin prick test) after adjustment for respiratory infections or drug use restricted to non-respiratory tract infections. Recently published cohort study in Ethiopia has shown that child's use of Acetaminophen was related significantly with wheezing but not with eczema in children between the age of 1 and 3 (Belyhun et al., 2010; Amberbir et al., 2011).

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 h) in the second trimester of pregnancy. To evaluate the correlation between the level of PM_{2.5} measured over 48 h 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 exposure to fine particles taken in the second trimester may be representative of other pregnancy periods.

In conclusion, the findings of our study suggest that Paracetamol use by mothers in pregnancy is not an independent risk factor for allergy outcomes such as eczema in children, however, even very small doses of Paracetamol taken in pregnancy may contribute to the occurrence of eczema in early childhood if there is prenatal co-exposure to higher airborne fine particulate matter.

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