Reviewer's report

Title: Prenatal exposure to perfluoroalkyl and polyfluoroalkyl substances and childhood atopic dermatitis: a prospective birth cohort study

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Prenatal exposure to perfluoroalkyl and polyfluoroalkyl substances and childhood atopic dermatitis: a prospective birth cohort study

The authors examine the association between prenatal exposure to PFASs and childhood atopic dermatitis (AD) in offspring up to 2 years of age. This prospective cohort study was conducted in two hospitals in Shanghai between 2012 and 2015 and 10 types of PFASs were measured in cord blood samples (n = 687). The authors looked at atopic dermatitis as outcome in offspring at 6, 12, and 24 months after birth using ISAAC, and diagnosis of AD was confirmed by two dermatologists. In female infants, but not male infants, the highest quartile of PFOA, PFNA, PFDA and PFHxS were associated with increased risk of AD compared with the lowest quartile.

The study is well designed, and several PFASs were examined in cord blood. Additionally, AD was assessed at 3 time points using ISAAC and diagnosis was confirmed by dermatologists. The paper is well-written; however, I see some weak points and have some comments and suggestions for improvements and clarifications.

Introduction:

1) Page 4, line 18: "toxicity, liver tumor, impaired thyroid function, and mammary glands"

Please clarify "mammary gland" here. Did you mean mammary gland development or differentiation?

2) Page 5, line 9-10, please modify the sentence as follows: Given that fetuses are more vulnerable to PFASs and they might impair functions of the immune system [21], we investigated the effect of prenatal exposure to PFASs on …
3) Page 9, about potential confounders; please mention how did you select these confounders? Previous studies, factors influencing exposure or outcome assessment in current data analysis, DAGitty etc?

Also, why did not the authors include breast-feeding history in adjusted model which is very important covariate?

Results;

1) Page 10, line 1-2: "A total of 811 children completed all the follow-up visits at 6 months, 12 months and 2 years."

For harmonization, please change 2 years to 24 months.

2) Page 10, line 4-5: "The majority of pregnant women had normal weight (BMI<24 kg/m2, 82.3%)…"

What is the reason to define BMI<24 kg/m2 as normal BMI (not BMI<25 kg/m2)?

3) Page 10, line 8: "29.7% of mothers were exposed to passive smoking during pregnancy."

Please define passive smoking clearly in Methods.

4) Page 10, line 9-10: "Among the newborns, 417 (51.6 %) were boys; 598 (73.9 %) were delivered by cesarean section."

It seems that number of deliveries with cesarean section is very high (73.9%), is it true? May cesarean section influence the outcome (AD)? In adjusted models, the authors included mode of delivery as a confounder, however if mode of delivery can influence risk of AD, the authors should discuss this point in Discussion.

5) Page 10, line 16-17: "The median (Q1-Q3) values of PFOA, PFOS, PFNA, PFDA, PFUA, PFDa, PFHxS and PFBS were 6.98 (4.94-9.55), 2.48 (1.82-3.24), …"

In the current study, exposure level of PFOA is significantly higher than PFOS, is it reported in China previously? Please explain your speculation about this point in
discussion. One possibility can be PFOS ban since 2009. Also, different transplacental passage efficiency.

6) Page 11, line 6-8: "In the first fully adjusted model, a log-unit increase in PFOA was associated with a 2.1-fold increase in AD risk (AOR 2.09, 95% CI 1.14-3.83). The corresponding number for PFNA was 2.17 (1.06-4.46). In the second fully adjusted model, …"

There is one crude and one adjusted model shown in Table 4 and 5. I do not see second fully adjusted model, please clarify it.

7) The authors present sex-stratified results, but there is no mention of testing the modifying effect of sex. The fact that the relationship is significant in girls but not in boys does not mean that the associations are different. An interaction test, or a difference test is mandatory to establish if the relationship really differs between girls and boys. If the authors find significant p-value for sex*PFASs (interaction), it is worthy to discuss sex differences. Please show it in Table 4 and 5.

8) Please show p-for trend when you applied quartile analysis (Table 4 and 5), it may provide better and more clear results.

Discussion:

1) Page 12, line 11: "infants conducted in Greenland and Ukraine, reported that PC5 score, dominated by …"

PC5? Principal component?

2) Page 12, line 12-15: "In contrast, a birth cohort study in Japan involving 2063 subjects found that prenatal exposure to perfluorotridecanoic acid (PFTrDA) was associated with a decreased risk of developing eczema in female infants at 24 months (OR= 0.39; 95% CI: 0.23, 0.64)[28]."

There is another study from Hokkaido birth cohort in Japan which found contrasting results with current manuscript. They followed up children in Okada et. al report (Ref.
28) and found that in utero exposure to long-chain PFASs, such as PFD0Da and PFTrDA, showed negative association with eczema in 4-year-old children (Goudarzi et al. Env. Int., 2016) suggesting that prenatal exposure to PFASs are immunotoxic and may suppress immune system. Please cite this paper and compare PFAS exposure level of these two studies from Hokkaido birth cohort with the current study. Also, writing few sentences regarding your speculation on longer follow up of children in your study would be interesting.

3) Page 12, line 21-23: "In addition, a case-control study with 231 asthmatic and 225 non-asthmatic children in Taiwan found that PFOA and PFOS were associated with asthma in a dose-response pattern [13]."

Please specify range of age in this study.

4) Page 14, second paragraph: With citing Ref. 38, and 40, the authors tried to explain mechanistic effects of PFASs on allergic diseases in humans through reproductive/steroid hormones. However, these studies have been conducted in adolescents and outcome is asthma.

A previous report showed that cortisol and cortisone (glucocorticoid hormones) concentrations were significantly lower in cord blood of infants with prenatal PFOS exposure in the fourth quartile compared with those in the first quartile. The highest quartile of prenatal PFOS exposure was positively associated with a significant higher DHEA (androgenic hormone and precursor of sex hormones) level compared with the lowest quartile, whereas PFOA showed a negative association with DHEA levels (Goudarzi et al. EHP, 2017). They concluded that prenatal exposure PFASs may disrupt glucocorticoid/androgenic ratio in fetus. Additionally, animal and human data suggest that perinatal glucocorticoid levels program the fetal hypothalamic-pituitary-adrenal (HPA) axis affecting its development, resulting in changes in HPA axis function that persist throughout life (Kapoor et al. 2008; Waffarn and Davis 2012).

Therefore, I suggest the authors to cite these references before references 38-40, explanation of influence of PFASs during pregnancy and early life can change hemostasis of steroid hormones which may result in hormone imbalance in later life. This approach is more clear, reasonable and understandable. Then, citing ref. 38 and 40 suggest that the influence of perinatal exposure to PFAS on allergic diseases may be still persistent in adolescents.
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