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Cord-serum per- and poly-fluoroalkyl substances (PFAS) and atopy and eczema at 12-months

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Statement of contribution

CJL and AJL conceived the study, and AJL obtained funding and wrote the first draft. SV undertook the assessment of PFAS under the supervision of JFM. All authors revised the manuscript and approved the final version.

Conflict of interest statement

Michael Abramson holds investigator initiated grants from Pfizer and Boehringer-Ingelheim for unrelated research. He has received assistance with conference attendance from and undertaken an unrelated consultancy for Sanofi. All other authors declare they have no conflicts of interest regarding this manuscript.

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To the editor,

The rapid rise in allergic disease prevalence associated with "Westernisation" indicates that environmental exposures are likely to be critical for the development of allergic diseases. As allergic diseases often occur very early in life, in utero and early life exposures while the immune system is still maturing are likely to be important. Exposures to per- and poly-fluoroalkyl substances (PFAS) have received increasing attention(1). PFAS were adopted into manufacturing processes in the 1950s due to their surfactant and surface chemical properties and were rapidly introduced into a wide range of products including food packaging. Concern about potential health impacts of these chemicals continues to increase as they have become ubiquitous in the environment. Some PFAS, such as perfluorooctane sulfonic acid (PFOS), bio-accumulate as they bind to lipoproteins in blood and are neither metabolised nor effectively excreted from the body as parent compounds. While a number of these chemicals have been phased out of manufacturing, other PFAS have been introduced to replace them.

Human exposure to PFAS is almost universal with global serum samples yielding measurable amounts, and there is evidence these compounds may induce immune suppression(2). Serum levels of PFAS in general population samples appear to have peaked during the 1990s, with levels of many PFAS having subsequently declined(3). However, most cord blood samples continue to contain detectable levels of PFAS(4), indicating ongoing maternal-infant exposure which may affect immune development during this critical time period. Very few studies have assessed the association between early life PFAS exposure and allergic disease outcomes(5-8), and these have shown mixed results.

To determine if PFAS in cord blood samples were associated with risks of eczema and allergic sensitisation, the earliest markers of allergic disease, we nested a case-control study within the Melbourne Atopy Cohort study(9). We selected 60 children with stored cord serum samples (see Table E1 for demographic details) based on their sensitisation and eczema status at 12 months of age: 15 each of: a) neither, b) atopy only (no eczema), c) non-

atopic-eczema, and d) atopic-eczema (both eczema and sensitisation). Individual sensitisation was assessed using skin prick tests to six allergens and atopy was defined as a 2mm or greater wheal to one or more allergens. Eczema was defined by either a parent report of a doctor diagnosis of "eczema" or use of topical steroids for a rash excluding the nappy area(9). A total of 23 PFAS were assessed using liquid chromatography coupled with tandem mass spectrometry (see online supplement for further details). Associations between levels of PFAS and the outcomes of eczema and atopy were assessed using multinomial logistic regression models. Adjustments were made for potential confounding factors, including sex and maternal education.

Of the assessed PFAS, 10 were detected in less than 5% of participants, and excluded from further analyses (Table E2). Values were dichotomized (detected vs not) for the six PFAS that were detectable in 10-95% of samples. The remaining seven PFAS were treated as continuous exposures with any non-detected samples allocated a value of zero. The level of each PFAS correlated at most moderately (highest correlation =0.53) with other measured PFAS (Table E3).

The majority of assessed PFAS tended to be associated with reduced risks of sensitisation or eczema (Table 1). These associations were significant for perfluoroundecanoic acid (PFUnDA) (all outcomes), and N-methyl perfluoro-1-octanesulfonamidoacetic acid (N-MeFOSAA) (non-atopic-eczema and atopic-eczema). Most of these associations were not materially changed when adjusted for parent characteristics and child sex (Table 2 and Figure E1). However, perfluorohexanoic acid (PFHxA) became significantly associated with atopy, and N-ethyl perfluoro-1-octanesulfonamidoacetic acid (NEtFOSAA) became associated with atopic-eczema (there was evidence of confounding by maternal age and education in both cases). When associations were further adjusted for the other significant PFAS, PFUnDA remained associated with all outcomes, NEtFOSAA was associated with atopic eczema, while associations were no longer detected for NMeFOSAA (data not shown).

Our results are consistent with the few studies that have been published in this area. Like

Wang et al.(8), who assessed associations in 244 children from Taiwan, we did not see associations between cord blood levels of PFOA, PFOS or perfluorononanoic acid (PFNA) and eczema. Unfortunately, Wang et al. did not measure the PFAS for which we observed associations.

A potential association between early life PFUnDA exposure and reduced risk of eczema was reported by Okada et al.(6), who examined associations between late pregnancy maternal plasma PFAS levels and allergic disease outcomes up to 2 years in ~2000 mother/infant pairs from Japan. They observed that among girls, when compared with infants of mothers in the lowest quartile of PFUnDA concentration, infants of mothers in the highest quartile had a reduced risk of eczema. This association was not seen in boys. In our own study, we also observed a somewhat stronger association between PFUnDA and eczema in girls (OR=0.18, 0.04-0.73) than boys (p-interaction=0.14). Okada et al. (6)also observed associations between perfluoro-n-tridecanoic acid (PFTriDA) and eczema, but no participant in our cohort had detectable levels of this PFAS.

The only other study published to date on this topic examined maternal serum during pregnancy in children from Ukraine and Greenland (n=1024) and found no association between PFUnDA and ever-eczema (0.95, 0.79-1.15) in 5-9-year-olds, which is much older than the present study(5). Associations between early life NEtFOSAA and NMeFOSAA exposure and allergic disease outcomes have not been previously reported.

At this time, we are not able to exclude the possibility of unmeasured confounding or ongoing exposure beyond the intrauterine period. We were also not able to examine associations with long term and other allergic diseases outcomes. We are currently seeking to measure these PFAS in all our stored samples.

The results of this small nested case-control study of children born between 1990 and 1994 suggest that early life PFAS exposure may impact on eczema and sensitisation. Interestingly, a protective effect was observed for PFUnDA, a result mirrored in a Japanese cohort(6),

possibly suggesting that it may be causing immune suppression. Furthermore, there is a growing body of evidence of possible immune suppression caused by PFAS in early life(2), making this an area requiring urgent investigation in larger studies. However, given the multiple comparisons made in this study, the result should be interpreted with caution at this time.

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Table 1. Unadjusted associations between PFAS and eczema and atopy outcomes at 1 year of age.

PFAS	Acronym	Atopy (no eczema)* mOR (95%CI)	Non-atopic eczema* mOR (95%CI)	Atopic eczema* mOR (95%CI)
Linear effect (per 1 standard deviation increase)				
Perfluorooctane sulfonic acid	PFOS	0.56 (0.26-1.23)	0.78 (0.39-1.57)	0.72 (0.35-1.47)
Perfluorooctanoic acid	PFOA	1.05 (0.52-2.12)	1.08 (0.54-2.19)	0.66 (0.30-1.45)
Perfluorohexane sulfonic acid	PFHxS	0.66 (0.30-1.46)	0.76 (0.38-1.53)	0.80 (0.41-1.56)
Perfluoroundecanoic acid	PFUnDA**	**0.04 (0.01-0.20)**	**0.04 (0.01-0.22)**	**0.10 (0.02-0.46)**
Perfluorobutanesulfonic acid	PFBS	1.14 (0.55-2.38)	1.24 (0.60-2.54)	1.07 (0.50-2.25)
Perfluorononanoic acid	PFNA	0.72 (0.35-1.49)	0.68 (0.32-1.44)	0.42 (0.17-1.06)
N-ethyl perfluoro-1-octanesulfonamidoacetic acid	NEtFOSAA**	0.89 (0.47-1.69)	0.45 (0.19-1.10)	0.54 (0.24-1.21)
Any vs not detected				
N-methyl perfluoro-1-octanesulfonamidoacetic acid (40/60)	NMeFOSAA**	0.14 (0.01-1.42)	**0.08 (0.01-0.79)**	**0.08 (0.01-0.79)**
Perfluoroheptanoic acid (23/60)	PFHpA	4.00 (0.88-18.26)	0.50 (0.10-2.63)	1.00 (0.22-4.56)
Perfluorodecanoic acid (21/60)	PFDA	0.42 (0.09-1.92)	0.57 (0.13-2.50)	0.57 (0.13-2.50)
N-ethyl perfluoro-1octanesulfonamido-ethanol (14/60)	NEtFOSE	0.55 (0.12-2.55)	0.23 (0.04-1.41)	0.11 (0.01-1.04)
Perfluorohexanoic acid (9/60)	PFHxA	0.42 (0.06-2.77)	0.69 (0.12-3.79)	†NE
Perfluorooctanesulfonamide (7/60)	FOSA	0.29 (0.03-3.12)	†NE	1.00 (0.17-5.99)

† Not estimable. No child with atopic eczema had detectable levels of PFHxA (exact p=0.10). No child with non-atopic eczema had detectable levels of FOSA (exact p=0.22).

* Reference category was children without eczema or atopy. Associations expressed as multinomial odds ratios (mOR) with their 95% confidence intervals (95%CI). Associations with p<0.05 are in bold.

**Second transitions for a subset of samples could not be confirmed as levels were close to the limit of quantification.

Table 2. Adjusted[†] associations between PFAS and eczema and atopy outcomes at 1 year of age.

PFAS	Acronym	Atopy (no eczema)* mOR (95%CI)	Non-atopic eczema* mOR (95%CI)	Atopic eczema* mOR (95%CI)
Linear effect (per 1 standard deviation increase)				
Perfluorooctane sulfonic acid	PFOS	0.38 (0.13-1.16)	0.68 (0.30-1.52)	0.64 (0.28-1.46)
Perfluorooctanoic acid	PFOA	0.69 (0.25-1.89)	0.67 (0.26-1.69)	0.29 (0.09-1.01)
Perfluorohexane sulfonic acid	PFHxS	0.81 (0.29-2.29)	0.79 (0.36-1.73)	0.88 (0.40-1.93)
Perfluoroundecanoic acid	PFUnDA**	**0.01 (<0.01-0.15)**	**0.01 (<0.01-0.18)**	**0.03 (<0.01-0.52)**
Perfluorobutanesulfonic acid	PFBS	1.56 (0.57-4.29)	1.53 (0.68-3.46)	0.93 (0.35-2.46)
Perfluorononanoic acid	PFNA	0.66 (0.26-1.72)	0.64 (0.29-1.44)	0.33 (0.09-1.17)
N-ethyl perfluoro-1-octanesulfonamidoacetic acid	NEtFOSAA**	0.87 (0.31-2.47)	0.29 (0.07-1.12)	**0.11 (0.02-0.60)**
Any vs not detected				
N-methyl perfluoro-1-octanesulfonamidoacetic acid (40/60)	NMeFOSAA**	0.13 (0.01-2.05)	**0.05 (<0.01-0.61)**	**0.06 (0.01-0.76)**
Perfluoroheptanoic acid (23/60)	PFHpA	4.37 (0.61-31.05)	0.30 (0.04-2.51)	0.68 (0.10-4.71)
Perfluorodecanoic acid (21/60)	PFDA	0.59 (0.09-3.80)	0.69 (0.13-3.70)	0.41 (0.07-2.29)
N-ethylperfluoro-1-octanesulfonamido-ethanol (14/60)	NEt FOSE	0.46 (0.06-3.80)	0.09 (0.01-1.01)	0.09 (0.01-1.36)
Perfluorohexanoic acid (9/60)	PFHxA	**0.01 (<0.01-0.52)**	0.48 (0.05-4.78)	††NE
Perfluorooctanesulfonamide (7/60)	FOSA	0.59 (0.04-9.55)	††NE	0.44 (0.05-4.07)

* Reference category was children without eczema or atopy. Associations expressed as multinomial odds ratios (mOR) with their 95% confidence intervals (95%CI). Associations with $p<0.05$ are in bold.

** Second transitions for a subset of samples could not be confirmed as levels were close to the limit of quantification

†All associations adjusted for sex, parity (first versus subsequent born infant), parental age, history of eczema and smoking, and mother's education.

††NE- not estimable. No child with atopic eczema had detectable levels of PFHxA. No child with non-atopic eczema had detectable levels of FOSA.