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Polybrominated biphenyls (PBBs) and prevalence of autoimmune disorders among members of the Michigan PBB registry

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Abstract

Background: Polybrominated biphenyls (PBBs), a class of endocrine disrupting chemicals, were the main chemicals present in one of the largest industrial accidents in the United States. We investigated the association between serum PBB-153 levels and autoimmune disorders among members of the Michigan PBB Registry.

Methods: Eight hundred and ninety-five members of the registry had both a serum PBB-153 measurement and had completed one or more questionnaires about autoimmune disorders. Autoimmune disorders were examined collectively and within specific organ systems. Sex-stratified unadjusted and adjusted log-binomial models were used to examine the association between tertiles of serum PBB-153 levels and autoimmune disorders. Models were adjusted by

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AUTHOR CONTRIBUTIONS

RBH: Formal analysis, Methodology, Writing-original draft, Writing-review & editing; **MLT:** Data curation, Methodology, Supervision, Writing-review & editing; **SM:** Methodology, Writing-review & editing; **ECS:** Methodology, Writing-review & editing; **MP:** Project administration, Supervision, Writing-review & editing; **HB:** Project administration, Writing-review & editing; **MST:** Project administration; Writing-review & editing; **MEM:** Resources, Writing-review & editing; **DBB:** Funding acquisition; Resources; Writing-review & editing; **MM:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing-review & editing.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

lifestage at exposure (*in utero*, childhood, adulthood), smoking history (never, past, current), and total serum lipid levels (continuous). We utilized cubic spline models to investigate non-linearity between serum PBB-153 levels and the prevalence of autoimmune disorders.

Results: Approximately 12.9% and 20.7% of male and female participants reported having one or more autoimmune disorders, respectively. After adjustment for potential confounders, we observed no association between PBB-153 tertiles and the composite classification of 'any autoimmune disorder' in either sex. We observed some evidence for an association between serum PBB-153 levels and rheumatoid arthritis in males and females; however, this was not statistically significant in females. We also observed some evidence for an association between serum PBB-153 levels and neurological- and thyroid-related autoimmune disorders in females, but again this was not statistically significant. Additionally, we identified dose-response curves for serum PBB-153 levels and the prevalence of autoimmune disorders that differed by lifestage of exposure and sex.

Conclusions: We observed some evidence that increasing serum PBB-153 levels were associated with three specified autoimmune disorders. Studies focusing on these three autoimmune disorders and the potential non-linear trend differences by lifestage of exposure warrant further investigation.

Keywords

Polybrominated biphenyls; Autoimmune disorders; Rheumatoid arthritis; Digestive autoimmune disorders; Thyroid autoimmune disorders; Michigan

INTRODUCTION

Over the past several decades, the prevalence of autoimmune disorders has increased in the United States (US),[1] with collective prevalence estimated as 7–9%.[2–5] Autoimmune disorders affect a wide range of cell types and organs in the body but the defining characteristic of these disorders is the immune system targeting and damaging the body.[2,3] In general, the immune system is tightly controlled and when this regulation is disrupted it can result in an autoimmune disorder.[6] Currently, the causes of many autoimmune disorders are not known. However, it is widely accepted that both genetics, the environment, and their interactions play a role in the process of developing an autoimmune disorder.[6,7]

A growing body of evidence suggests that exposure to environmental pollutants may increase the risk or severity of autoimmune disorders. In particular, exposure to endocrine disrupting chemicals (EDCs), may be associated with autoimmune disorders.[8,9] EDCs can mimic and interfere with naturally occurring hormones and may even directly interfere with their biosynthesis.[9] In the human body, estrogen has an important role in the normal function of the immune system.[10] It is possible that EDCs that mimic estrogen or interfere with its production or metabolism could increase the risk of autoimmunity.

EDCs are now ubiquitous and found in a variety of consumer products. In recent years, EDCs such as bisphenol A (BPA), phthalates, and polychlorinated biphenyls (PCBs), have been tentatively linked to alterations in immune system function.[11–14] One EDC group that has garnered little attention in this area is polybrominated biphenyls (PBBs). PBBs were

utilized as flame retardants in many commercial products until production was discontinued in 1976. However, one of the largest exposure events in the US happened when a flame retardant containing PBBs was mistakenly shipped as a nutritional supplement in 1973 and added to animal feed in Michigan.[15–17] The resulting industrial accident led to mass culling of farm animals, the quarantine and closure of many farms, and statewide exposure of Michiganders who came into contact with PBBs as chemical workers or farmers, or who unknowingly ingested food contaminated with PBBs.[18,19] In order to study the long-term and potential intergenerational health effects of PBB exposure, the Michigan PBB Registry was created.

Early studies among farmers and chemical workers exposed to PBBs through the Michigan environmental contamination episode found alterations in the immune system compared to unexposed farmers.[20–23] Specifically, those exposed to PBBs had higher number of lymphocytes with no surface markers compared to unexposed individuals.[23] Furthermore, results from a contemporary epigenetic study indicated that serum PBB-153 levels were associated with methylation differences in CpG sites enriched for estrogen-regulation pathways and several immune functions, as well as endocrine-related autoimmune disease.[24] At multiple community meetings across the state, members of the Michigan PBB Registry have expressed concern that exposure to PBBs may be associated with autoimmune disorders and in response, the Michigan PBB Registry research team added related questions to recent questionnaires. We thus examined the association between serum PBB-153 levels and autoimmune disorders among members of the Michigan PBB Registry. Understanding if PBBs are associated with autoimmune disorders will provide insight into the relationship between EDCs and autoimmune disorders.

METHODS

Sample.

Following the accidental introduction of PBBs into the food supply, the Michigan Department of Health and Human Services (MDHHS), in conjunction with the Centers for Disease Control and Prevention (CDC) and NIH set up the Michigan PBB Long-term Health Study (now called the Michigan PBB Registry) in 1976 to study the effects of PBB exposure on human health. In 2011, Emory University took over the management of the registry. The Michigan PBB Registry is now co-led by Emory University and our community partners (PBB Citizens Advisory Board and Pine River Superfund Citizen Task Force). Participants were recruited via several methods which have been described elsewhere.[25] Briefly, community meetings were held throughout the state between 2012 and 2020. From these meetings, individuals who were a part of the original registry and those who lived in Michigan during the time of the disaster (1973–1974), as well as their descendants were invited to participate. To address community concerns about PBBs exposure and several health conditions, including autoimmune disorders, a series of self-administered questionnaires and blood samples were collected. Three questionnaires, a general health questionnaire (GHQ: 2012–2015), an in-depth health questionnaire (IDQ: 2012–2015), and a comprehensive health questionnaire (CHQ: 2017–2020), were given to individuals in the PBB registry. Generally, one blood sample was collected per questionnaire completed

to measure PBBs and other chemicals in participants' blood. The GHQ and CHQ were completed by participants 18 years or older while the IDQ was completed by individuals between 18 and 60 years who participated in a reproductive study. Each questionnaire asked about various health conditions and demographic characteristics. The study was approved by the Emory University Institutional Review Board. All participants provided informed written consent prior to completing any study activities.

PBB measurements.

We utilized non-fasting venous blood samples collected from 2012 to 2020. We utilized recent samples collected rather than historic serum levels because recent research indicates that serum PBB levels remain high in this population[26] and PBBs have a long half-life (~12 years).[27] Samples were sent to Emory University for laboratory analysis.[28] Samples were centrifuged for 30 mins at 3,000 rpm, and the serum was removed and stored at −20°C until analysis. Samples were treated with formic acid to denature serum proteins and extracted using liquid-liquid and solid-phase extractions. Samples were analyzed for PBB-153 using gas chromatography-tandem mass spectrometry. For each run, one laboratory blank and two matrix-based samples were included as quality controls. Serum PBB-153 concentrations were reported in nanograms per milliliter (ng/mL). Among the 209 PBB congeners we selected PBB-153 because the original contaminant (FireMaster) was a combination of several PBB congeners with the most common and biologically persistent being PBB-153.[16,17,29] For individuals who provided more than one blood sample, we averaged their serum PBB-153 levels. Individuals with serum PBB-153 levels below the limit of detection (LOD) were assigned the LOD value divided by the square root of two. The LOD values ranged from 0.001 ng/mL to 0.05 ng/mL. Among the participants, 7.4% had levels below the LOD (n=66).

Autoimmune outcomes.

The presence of an autoimmune disorder was assessed via self-report for all three questionnaires in slightly different ways. In the GHQ, participants reported ever being diagnosed by a doctor with an autoimmune disorder. If a participant responded "yes", they were asked to specify the disorder via an open text field (Supplemental Table 1). We examined the open text field, and if the listed disorder was not an autoimmune disorder, we changed their response to no autoimmune disorder. In the IDQ, participants were presented with specific autoimmune disorders and asked if they were diagnosed by a doctor with the condition. Participants could also indicate that they suspected they had the disease or condition but had not yet been diagnosed by a doctor. We treated individuals without a doctor's diagnosis as not having an autoimmune disorder. In the CHQ, participants were again given a list of specific autoimmune disorders and asked to indicate if a doctor had diagnosed them with any of the conditions. In the CHQ, participants were not given the option to indicate if they suspected they had a specific disease or condition. For the GHQ, IDQ, and CHQ, we derived a composite variable for "any autoimmune disorder" if they indicated that they had been diagnosed by a doctor with at least one autoimmune disorder. We used this composite variable as our main outcome variable. For individuals who completed more than one questionnaire, we used data from the CHQ if it was available, since it was the most detailed questionnaire, then the IDQ, and then the GHQ.

In addition to the presence or absence of any autoimmune disorders, we considered autoimmune disorders by the following categories, (1) skin/joint system (alopecia, connective tissue disease, juvenile dermatomyositis, lupus, psoriasis, psoriatic arthritis, rheumatoid arthritis, scleroderma, Sjogren's syndrome, systemic sclerosis, and vitiligo); (2) Digestive system (celiac disease, Crohn's disease, and ulcerative colitis); (3) Neurological system (multiple sclerosis); (4) Thyroid (Grave's disease and Hashimoto's disease).

Covariates.

We selected potential confounding variables by identifying the minimal adjustment set from a directed acyclic graph. Covariates included lifestage at exposure, smoking status, and total serum lipid levels. Lifestage at exposure was calculated by subtracting the date of birth from the estimated date that the contaminated farm products were first ingested (July 1st, 1973). Anyone with a negative value was categorized as exposed *in utero* (i.e. born after exposure began). Smoking status was combined across the questionnaires, and individuals were classified as never smokers if they never reported smoking (both past or present), former smokers if they reported smoking in any questionnaire but did not report smoking in their most recent questionnaire and current smokers were classified as such if they reported being a smoker in their most recent questionnaire. Total serum lipid levels were measured by two laboratories, Emory University lab (2012–2015) and Quest laboratories (2017–2020). The Emory laboratory utilized the Abnova Triglyceride Quantification Assay Kit (Abnova Corporation) to measure triglycerides and Cayman Cholesterol Assay Kit (Cayman Chemical Company) to measure cholesterol. For this analysis total lipid level was included as a continuous variable. In addition to these covariates, we briefly considered inclusion of age at blood draw; however, we observed that age at blood draw and lifestage at exposure were highly correlated (r=0.99) and therefore, opted to only include lifestage at exposure.

Statistical Analysis.

To describe the cohort, we utilized frequency distributions for categorical variables and median and interquartile ranges (IQR) for continuous variables. Demographic characteristics were described for the entire sample and by self-reported sex assigned at birth (male n=387 and female n=508).

Due to the highly skewed nature of serum PBB-153 levels in this cohort, we examined sex-specific tertiles of serum PBB-153 levels. For males, tertile cutoffs were: <0.22 ng/mL (first tertile), 0.22-<0.76 ng/mL (second tertile), and ≥0.76 ng/mL (third tertile). For females, tertile cutoffs were <0.11 ng/mL (first tertile), 0.11-<0.37 ng/mL (second tertile), and ≥0.37 ng/mL (third tertile). In both instances, the first tertile (lowest serum PBB-153 levels) was used as the referent category. We utilized log-binomial models to assess the association between tertile of serum PBB-153 levels and prevalence of autoimmune disorders. Because of known sex-specific differences in autoimmune disorders, we stratified all regression models by sex and reported sex-specific prevalence ratios with p-values for the trend of increasing serum PBB-153 levels.

Next, we examined serum PBB-153 levels as a continuous variable to examine non-linearity. To allow for the non-linearity of the prevalence of autoimmune disorders by serum PBB-153 levels, we conducted restricted cubic spline models with 3 knots selected by automatic stepwise regression stratified by sex. The spline was restricted to participants (male n=314; female n=407) with serum PBB-153 levels between the 10th (male: 0.021 ng/mL; female: 0.012 ng/mL) and 90th percentiles (male: 4.051 ng/mL; female: 1.273 ng/mL) to reduce the influence of and the clustering of individuals at or below the LOD imputation and individuals with extreme values.

Additionally, we tested a possible multiplicative interaction by lifestage at exposure. Specifically, we included multiplicative terms between the natural log of serum PBB-153 level and lifestage at exposure. To further investigate this interaction, we stratified the models by lifestage at exposure. The stratified models were unadjusted due to sample size constraints. Lastly, when sample size permitted, we examined the association between serum PBB-153 levels as tertiles and specific autoimmune diseases or autoimmune diseases for a specific organ system.

Secondary Analysis.

To test the robustness of our results, we conducted several secondary analyses. First, for individuals who were exposed *in utero*, we ran an additional model with different serum PBB-153 level tertile cutoffs specific to this lifestage group (Male [n=91]: <0.015 ng/mL, 0.015-<0.046 ng/mL, ≥0.046 ng/mL; Female [n=130]: <0.011 ng/mL, 0.011-<0.03 ng/mL, ≥0.03 ng/mL). Very few individuals who were born after the exposure event were in the highest exposure category for the overall population tertiles. Second, because previous studies indicated potential differences in health outcomes depending on the lifestage exposure window for PBBs; we conducted a restricted cubic spline model with 3 knots automatically selected and stratified by lifestage exposure window and sex (male: *in utero* n=82, childhood n=121, and adulthood n=144; female: *in utero* n=117, childhood n=215, and adulthood, n=126). The 90th percentile was used as the cutoff in males and was 0.12 ng/mL, 2.44 ng/mL, and 10.23 ng/mL for the *in utero*, childhood, and adulthood models, respectively. The 90th percentile was used as the cutoff in females and was 0.09 ng/mL, 1.32 ng/mL, and 2.39 ng/mL for *in utero*, childhood, and adulthood models, respectively. Due to sample size the stratified models were not restricted by a lower bound serum level. Finally, among a subset of participants, body mass index (BMI; kg/m^2) data were available based on self-reported height and weight and averaged across questionnaires (male n=246; female n=375). We included BMI in our combined model and examined it as a potential effect modifier using a multiplicative term and stratification at the median value (median BMI: 28.6 kg/m^2). The stratified model was unadjusted due to sample size constraints.

RESULTS

Sample.

In total 1,088 individuals completed at least one of these questionnaires. From the sample, we excluded 193 participants who had missing data either for their serum PBB-153 levels, outcome, or covariates, giving a final analytical sample size of 895 participants (Figure

1). For each questionnaire, 609 completed the GHQ, 403 completed the IDQ, and 241 completed the CHQ. Many participants completed more than one questionnaire.

Sample Characteristics.

The final analytical sample included 895 participants, the majority of whom were White (n=840; 93.9%) and were assigned female at birth (n=508; 56.8%) (Table 1; Supplemental Table 2). The median BMI was 29.3 (Interquartile range [IQR]: 7.2) and 28.2 (IQR: 9.4) for males and females, respectively. Slightly more females had never smoked (n=328; 64.6%) compared to males (n=208; 53.7%). More males were exposed in adulthood (n=161; 41.6%) compared to females (n=140; 27.6%). Serum PBB-153 levels (including LOD imputed values) ranged from 0.0007 ng/mL to 221.42 ng/mL in males and 0.0007 ng/mL to 245.90 ng/mL in females. The median serum PBB-153 value was slightly higher in males (0.41 ng/mL) compared to females (0.23 ng/mL). More females (n=105; n=20.7%) had at least one autoimmune disorder compared to males (n=50; n=12.9%).

Main Effects.

After adjustment, males in the highest serum PBB-153 level category were more likely to have an autoimmune disorder (PR: 1.14; 95% CI: 0.50, 2.57) compared to males with the lowest levels (1st tertile) (lowest exposed) (Table 2). However, males in the 2nd tertile of serum PBB-153 levels were somewhat less likely to have an autoimmune disorder (prevalence ratio [PR]: 0.77; 95% confidence interval [CI]: 0.33, 1.81) compared to males in the 1st tertile of serum PBB-153 levels. In both cases, these associations were not statistically significant. By contrast, females in both the 2nd tertile (PR: 0.86; 95% CI: 0.50 1.48) and 3rd tertile (PR: 0.86; 95% CI: 0.50, 1.49) were less likely to have an autoimmune disorder compared to females in the 1st tertile (lowest levels).

When serum PBB-153 levels were examined as a continuous variable in males, we observed a non-linear trend that was not statistically significant (p-value: 0.26; Figure 2). The trend indicated that among those with low serum PBB-153 levels there was a lower prevalence of autoimmune disorders. As serum PBB-153 levels increased, the prevalence of autoimmune disorders also increased until the prevalence ratio again declined after about 1.5 ng/mL. By contrast, when serum PBB-153 levels were examined as a continuous variable in females, we observed a u-shaped non-linear trend that was statistically significant (p-value: 0.04; Figure 2). The non-linear trend indicated that the prevalence ratio for autoimmune disorders among females declined sharply for serum PBB-153 levels between the LOD and 0.42 ng/ml but then increased sharply with increasing serum PBB-153 levels.

Potential Interactions.

We observed limited evidence to support an interaction between serum PBB-153 levels and lifestage at exposure in males (p-value: 0.42) or in females (p-value: 0.67) (Table 3). In males exposed during adulthood, those with highest serum PPB levels (3rd tertile) had an elevated prevalence of autoimmune disorders (PR: 3.05; 95% CI: 1.09, 8.56) compared to those with lowest levels (1st tertile). By contrast, males exposed in childhood consistently had lower prevalence of autoimmune disorders compared to the individuals with lowest PPB levels; although these associations were not statistically significant. Among females,

serum PBB-153 levels during any lifestage at exposure consistently were associated with a lower prevalence of autoimmune disorders with the exception of females exposed during adulthood with the highest levels (PR: 1.17; 95% CI: 0.65, 2.11). Again, this association was not statistically significant.

Specific Autoimmune Disorders.

Among males, those in the highest serum PBB-153 level group had a higher unadjusted prevalence of skin and joint autoimmune disorders (PR: 2.13; 95% CI: 1.05, 4.32) compared to males in the lowest PPB-153 level group (Table 4). Additionally, males with highest PPB-153 levels had a higher unadjusted prevalence of rheumatoid arthritis (PR: 4.60; 95% CI: 1.61, 13.2) compared to those males with the lowest PPB-153 levels.

Among females, those in the highest PBB-153 level group had a higher unadjusted prevalence of rheumatoid arthritis (PR: 1.70; 95% CI: 0.73, 3.94) compared to the lowest serum PBB-153 level group; however, this association was not statistically significant (Table 4). Additionally, females with the highest PPB-153 levels also had elevated unadjusted prevalence of multiple sclerosis (PR: 1.94; 95% CI: 0.36, 10.5) and thyroid autoimmune disorders (PR: 1.94; 95% CI: 0.36, 10.5) compared to the lowest serum PBB-153 level group. Again, these associations were not statistically significant. Finally, females with the highest PBB-153 levels had a lower unadjusted prevalence of psoriasis (PR: 0.28; 95% CI: 0.09, 0.83) compared to the lowest serum PBB-153 level group.

Secondary Analyses.

When using tertiles specific to males exposed *in utero*, those in the highest serum PBB-153 level group (3rd tertile) were somewhat more likely to have an autoimmune disorder compared to the lowest serum PBB-153 level group (PR: 1.11; 95% CI: 0.51, 2.40) but the association was not statistically significant (Supplemental Table 3). Similarly, in females exposed *in utero*, those in the highest PPB level group had a higher prevalence of autoimmune disorders compared to the lowest serum PBB-153 level group (PR: 1.17; 95% CI: 0.51, 2.67) (Supplemental Table 3). Again, this association was not statistically significant.

When cubic splines were stratified by exposure window and sex, a linear trend was observed among those exposed *in utero* (male p-value: 0.74; female p-value: 0.25) with increasing serum PBB-153 levels associated with higher prevalence of autoimmune disorders in both males and females (Supplemental Figure 1). For males exposed in childhood, the test of non-linearity was not significant (p-value: 0.94). By contrast, for females exposed in childhood, the test of non-linearity was significant (p-value: 0.04). The observed dose-response curve among females demonstrated a u-shaped response. We did not observe a non-linear trend for those who were exposed in adulthood in either sex (male p-value: 0.59; female p-value: 0.68).

Among male participants who had BMI values, we observed attenuated adjusted prevalence ratio estimates compared to the main analysis (Supplemental Table 4). By contrast, among female participants who had BMI values, we observed similar, but slightly higher, adjusted prevalence ratio estimates compared to the main analysis (Supplemental Table 4).

Additionally, we did not observe evidence to suggest an interaction between serum PBB-153 levels and BMI (male p-value: 0.52; female p-value: 0.58; Supplemental Table 5).

DISCUSSION

We did not observe an association between serum PBB-153 levels and the overall prevalence of all autoimmune disorders in either sex. Observing only limited evidence for an association between serum PBB-153 levels and autoimmune disorders was unexpected for several reasons. First, we observed a higher prevalence of autoimmune disorders (17.3%) compared to the general population estimates (7.9%).[2–5] Next, it has been hypothesized, for several decades, that environmental exposures can trigger autoimmune diseases, especially among those genetically predisposed.[30] Although the evidence is inconsistent,[31–36] it is generally thought that EDCs could increase the risk for and severity of autoimmune disorders. A third reason these results are unexpected is because of results from previous immunological and epigenetic studies related to serum PBB levels. Generally, in studies directly following the industrial accident, individuals who were exposed to PBBs had a notable dysfunction in immune function compared to individuals who were not exposed.[20–23] The dysfunction in immune function was found in studies with smaller sample sizes which observed an increase in ‘null’ cells and a decrease in T and B-lymphocytes. However, two studies, one in humans and one in cattle exposed to PBBs did not observe any differences in immune function.[37,38] In a recent epigenetic study of exposed individuals, serum PBB-153 levels were associated with methylation changes at CpG sites enriched in genes that regulate the immune system and autoimmune disorders.[24]

Given these findings, we hypothesized that we would detect an association between serum PBB-153 levels and autoimmune disorders. While we cannot rule out the possibility that PBB is associated with autoimmunity in our data, the difference between the expected and observed results could be due to a few factors. First, it may be possible that PBB exposure does not stimulate the immune system but rather depresses it, lowering the risk of autoimmune disorders. Some evidence exists to support this hypothesis from early immunological studies[20,22,23] that demonstrated a decline in immune function. However, whether this decline persists is unknown. Further evidence to support this idea comes from a study of another EDC, hexachlorobenzene (HCB). In 146 patients HCB levels were significantly associated with lower levels of interferon gamma.[39] Given this hypothesis, we would expect that if the immune system was depressed in individuals exposed to PBBs, these individuals would be at risk for more infections. The Michigan PBB Registry does not currently collect these data but it is worth investigating in the future. Another reason for the discrepancy between the expected and observed results could be the way autoimmune disorders were assessed. In the current study, autoimmune disorders were grouped together and assessed using a single indicator variable for the composite disease outcome which makes sense given the underlying pathology (i.e., immune cells attacking self). Further, various combinations of autoimmune diseases co-occur at rates greater than expected by chance, within individuals and families, supporting the concept that shared genetic and environmental factors contribute to various autoimmune diseases.[1,5,40,41] However, specific environmental exposures may have more targeted effects on particular autoimmune phenotypes. We observed some evidence to support this idea in that there was a suggestion

that serum PBB-153 levels were associated with some individual autoimmune disorders but not others. Additionally, it is possible there is a threshold effect for PBBs exposure and autoimmune disorders. To support this idea, we observed a non-linear trend between serum PBB-153 levels and the prevalence of autoimmune disorders. EDCs are generally thought to have non-linear dose-response trends,[42] which is in line with our results. Furthermore, it is possible that a potential threshold effect may differ by exposure timing (i.e., *in utero*, childhood, adulthood). We observed some further evidence for this idea when we examined the dose-response relationship by exposure timing. We observed a clear linear trend among both sexes exposed *in utero* while females exposed in childhood had a u-shaped dose-response. Finally, it is possible our sample, which took place approximately 40 years after the accident suffers from survivor bias. Autoimmune disorders are associated with significant mortality; therefore, it is possible that individuals with autoimmune disorders that resulted from the PBB accident died prior to completing one of these questionnaires.[43,44] In general, PBB exposure and autoimmune disorders may require additional studies to confirm the null findings.

Interestingly, the observed relationships between serum PBB-153 levels and the prevalence of autoimmune disorders differed by exposure window. *In utero* represents a critical time for development and it is possible that humans are more susceptible to EDC exposure during this time period[45] which would explain the positive linear trend we observed in our study sample. Females exposed in childhood had a significant u-shaped trend that generally demonstrated an increased prevalence of autoimmune disorders with increasing serum PBB-153 levels. Again, childhood, and especially puberty, represent a critical time window[45] and PBB may be mimicking estrogen which is known to change during this time period. The linear trend for serum PBB-153 levels and the prevalence of autoimmune disorders during adulthood is interesting and warrants further study. One potential biological mechanism for this association may be due to the estrogenic properties of PBBs. Estrogen is known to affect the immune system and may be associated with autoimmunity.[10] PBBs could be binding to estrogen receptors and interfering with normal immune function. It is clear that the exposure timing of PBBs and other EDCs should be taken into consideration and needs to be investigated further.

We did observe some evidence for a potential relationship between serum PBB-153 levels and specific autoimmune disorders, including rheumatoid arthritis (both sexes but not statistically significant in females), multiple sclerosis (only females, not statistically significant) and thyroid-related autoimmune disorders (only females, not statistically significant). Notably, rheumatoid arthritis and autoimmune thyroid diseases are among the most common autoimmune disorders, especially among women, thus statistical power to detect associations with these conditions would be higher than for most other autoimmune diseases. An association between serum PBB-153 levels and rheumatoid arthritis is consistent with previous literature investigating exposure to EDCs and this autoimmune disorder. Among 1,721 adult participants of the National Health and Nutrition Examination Study (NHANES) from 1999 to 2002, polychlorinated biphenyls (PCB) levels were associated with an increased risk of rheumatoid arthritis among women but not men.[32] In a meta-analysis of pesticide exposure, exposure to insecticides, known EDCs, was associated with an increased risk for rheumatoid arthritis.[31] These studies taken together

with our findings, indicate that exposure to EDCs may increase the risk for developing rheumatoid arthritis. In the case of PBBs, these have mild estrogenic properties and may act on the immune system leading to the inappropriate inflammatory responses characteristic of rheumatoid arthritis. However, caution is warranted for this association given we were unable to adjust for confounding variables due to small sample size and additional studies are needed to confirm and understand the potential mechanisms for this association.

In addition to rheumatoid arthritis, we observed limited evidence for an unadjusted association between serum PBB-153 levels and multiple sclerosis and thyroid-related autoimmune disorders in females. However, these associations were not statistically significant. Currently, there is a dearth of knowledge regarding the role of EDCs in multiple sclerosis. However, many EDCs are known to negatively impact the neurological system, so it is plausible that PBB could increase the risk for neurological autoimmune disorders; although, further study is warranted. Given the previous PBB-related studies of thyroid function, it was unsurprising to observe a potential association between serum PBB-153 levels and thyroid-related autoimmune disorders. PBB levels have previously been associated with altered thyroid hormone levels among those exposed as children.[46] In addition, two studies specifically examining thyroid disease observed limited evidence for an association between PBB levels and thyroid disease.[25,47] However, studies investigating PCB, a similar EDC, have observed differing associations between PCB levels and the impact on thyroid-specific autoantibodies.[35,36] In a study of those living in proximity to an industrial accident that released PCB into the air, researchers found no association between PCB levels in the serum and thyroid autoantibody levels.[36] However, among 115 young adults of the Akwesasne Mohawk Nation, individuals who were breastfed had higher levels of PCB and this was correlated with higher levels of thyroid autoantibodies.[35] EDCs have demonstrated the ability to interrupt thyroid hormone function but whether this extends to thyroid-related autoimmune disease is still unclear and warrants further investigation.

Interestingly, we observed a negative association between serum PBB-153 levels and psoriasis in females. It is not entirely clear why PBB-153 may be inversely associated with psoriasis but one possible explanation stems from the estrogen like properties of PBB-153.[24] Studies have demonstrated that males have more severe psoriasis than females and it is believed that estrogen plays a role in this sex difference.[48] Therefore, it is possible that the added estrogenic properties of PBB-153 are acting in a similar protective manner for psoriasis in females. However, these results should be cautiously interpreted and require additional studies to confirm these findings and identify the potential biological mechanism underpinning such an association.

When we investigated potential interactions via stratification, we observed limited evidence for interactions between serum PBB-153 levels and exposure timing. From a previous study of other EDCs,[35] we would have expected to observe a potential interaction with exposure timing; however, in the main stratified model, we observed limited evidence for such an interaction. When we examined individuals exposed *in utero* using tertiles specific to them, we observed a non-significant trend with those in the highest serum PBB-153 level group being more likely to have an autoimmune disorder compared to the lowest group in both sexes. In general, it is possible that *in utero* exposure to PBBs has a greater

impact on the immune system compared to exposure during childhood or adulthood. In the current study, it may be possible that those in the *in utero* exposed group, have not reached the age where many autoimmune disorders are diagnosed, thus limiting our ability to detect a significant interaction. One interaction we could not account for was a potential gene-environment interaction. Reviews of autoimmune disorders routinely point to these interactions as potential combined triggers for autoimmune disorders.[6] In general, we did observe some evidence for a difference in the prevalence of autoimmune disorders by sex. A difference by sex is unsurprising given of the strong female preponderance for the majority of autoimmune disorders.[2–5] In our study, women did have a higher prevalence of autoimmune disorders, similar to the general population. Based on a previous epigenetic study examining sex differences,[49] we expected to observe some differences by sex for serum PBB-153 levels. Further study of potential sex differences between EDCs and autoimmunity is clearly warranted.

Based on these findings as well as several other studies, exposure to EDCs may influence the immune system. The extent to which PBBs and other EDCs induce and influence the severity of autoimmune disorders is currently unclear. In addition, in our sample ~3% of participants reported having more than one autoimmune disorder; the extent to which PBB and other EDCs can cause multiple autoimmune disorders in a single person is currently unknown. Research is needed to address important questions surrounding EDCs and the immune system including but not limited to: the extent to which EDCs depress or stimulate the immune system, the underlying mechanism between EDCs and their impact on the immune system, and any potential interactions that may occur between EDCs and their combined influence on the immune system. These questions are of the utmost importance to answer given the extent to which individuals are exposed to EDCs during their daily life and throughout their lifetime. Additionally, answering these questions would help inform evidence-based regulations as well as potential methods to prevent immune dysfunction triggered by EDCs.

Our study does have several limitations. First, our study is a cross-sectional design, thus the serum PBB-153 levels were measured at the same time of autoimmune disorder ascertainment; so, temporality cannot be established. However, PBBs have a slow elimination rate from the body,[27] so it is likely that individuals, especially those exposed *in utero* and childhood, were exposed to PBBs prior to the development of an autoimmune disorder. Second, the autoimmune disorders measurement is based on self-report of specific conditions and may miss other autoimmune disorders that were not included on the questionnaires, such as pernicious anemia. Therefore, it is possible that autoimmune disorders are underreported which could bias the findings. However, given we observed a similar sex-ratio between males and females that is observed in the general population, our measure may be fairly salient. Third, we do not know about the timing of the development of autoimmune disorders which means temporality between the exposure and outcome may be imprecise. However, many individuals in the study were exposed as children prior to the onset of many autoimmune disorders and we observed similar findings among these groups so this bias may be limited. Future studies should consider more robust measures of autoimmune disorders and include measures of timing as well as a longitudinal design. Fourth, it is possible that PBBs exposure could influence the severity of autoimmune

disorders. Our study did not ascertain disease severity but this should be included in future research. Fifth, we lacked some key covariate data on BMI, alcohol consumption, and family history. Without these covariates, residual confounding is possible. However, when we included BMI for a subset of the sample, we observed similar findings. Sixth, our study took place several decades after the exposure event, it is possible survivor bias altered the results of our study as previously noted. In addition, because the study relied on individuals who could complete a computer assisted questionnaire and attend an in-person blood draw, we may be missing individuals with severe mobility issues and comorbidities that preclude them from participating in the study. Seventh, it is possible that individuals were exposed to other EDCs, which could have influenced our findings. However, questions regarding interactions between EDCs is beyond the scope of this current study and should be addressed in future research. Eighth, due to the small sample size, we were unable to fully investigate the potential interaction by lifestage at exposure. Future studies should seek to enroll a larger sample size and fully investigate *in utero* exposures and sex-specific associations between EDCs and autoimmune disorders. Finally, the sample was a majority White and from a rural area, which is not representative of all those exposed.

Our study also has several strengths. First, the measurement of serum PBB-153 level has been rigorously validated. Second, many autoimmune disorders represent significant diagnoses that require ongoing monitoring and treatment, therefore, the recall of the specific autoimmune disorders we inquired about was likely high. Finally, our results were robust even after conducting several secondary analyses.

CONCLUSION

Serum PBB-153 levels may not be associated with autoimmune disorders overall but may be associated with some specific autoimmune disorders. Future studies should specifically be designed to account for disease timing and severity and should have an adequate sample size to understand the association, if any, between EDCs and autoimmune disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- Serum PBB-153 levels were not associated with the prevalence of autoimmune disorders as a composite outcome
- Serum PBB-153 levels may be associated with rheumatoid arthritis in males and females.
- Serum PBB-153 levels may be associated with neurological and thyroid autoimmune disorders in females.
- The dose-response curve between serum PBB-153 levels and autoimmune disorders may differ by lifestage exposure window (*in utero*, childhood, adulthood).

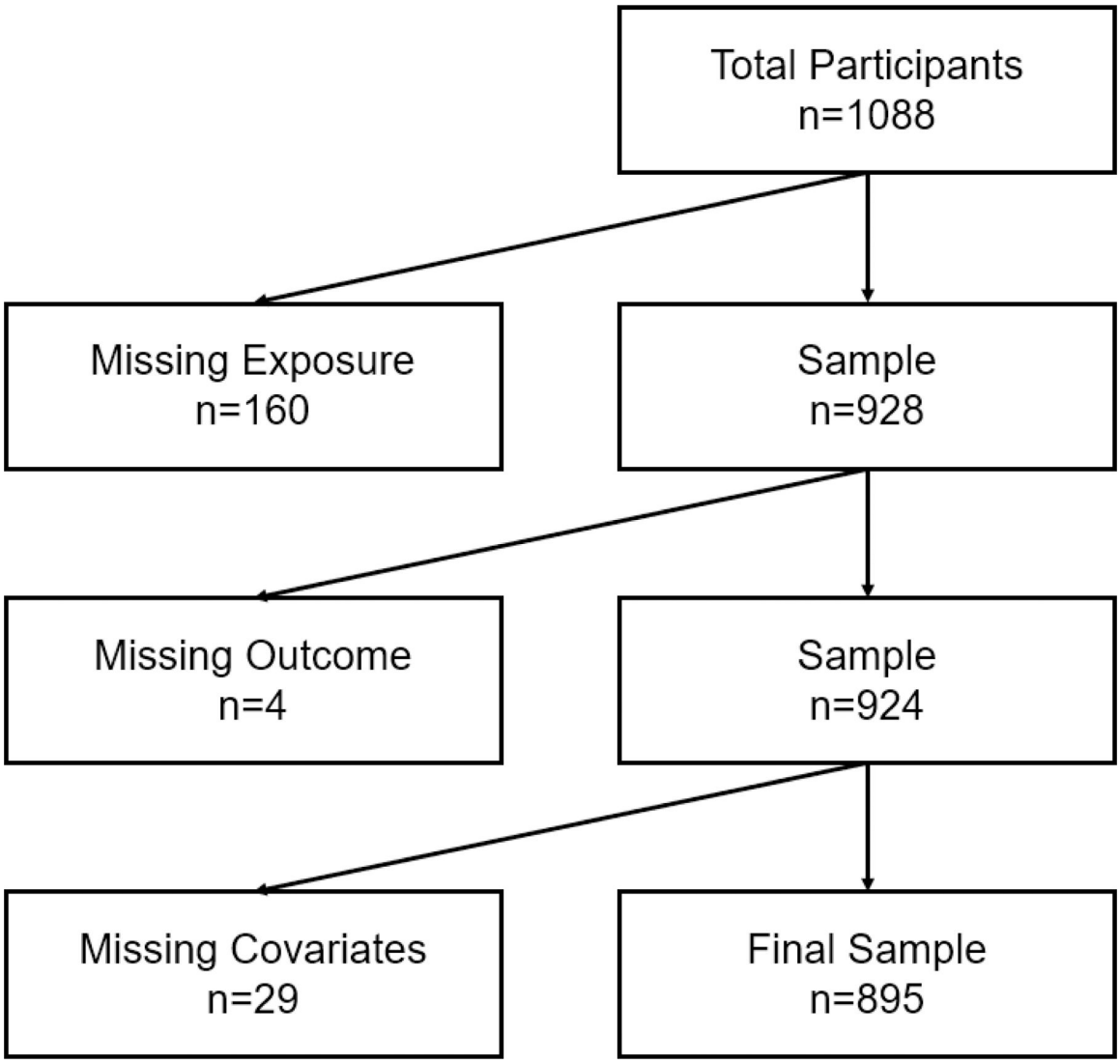

Figure 1.
Flowchart of participants of the Michigan PBB Registry who completed at least one questionnaire that included data on autoimmune disorders from 2012 to 2020 (n=1088)

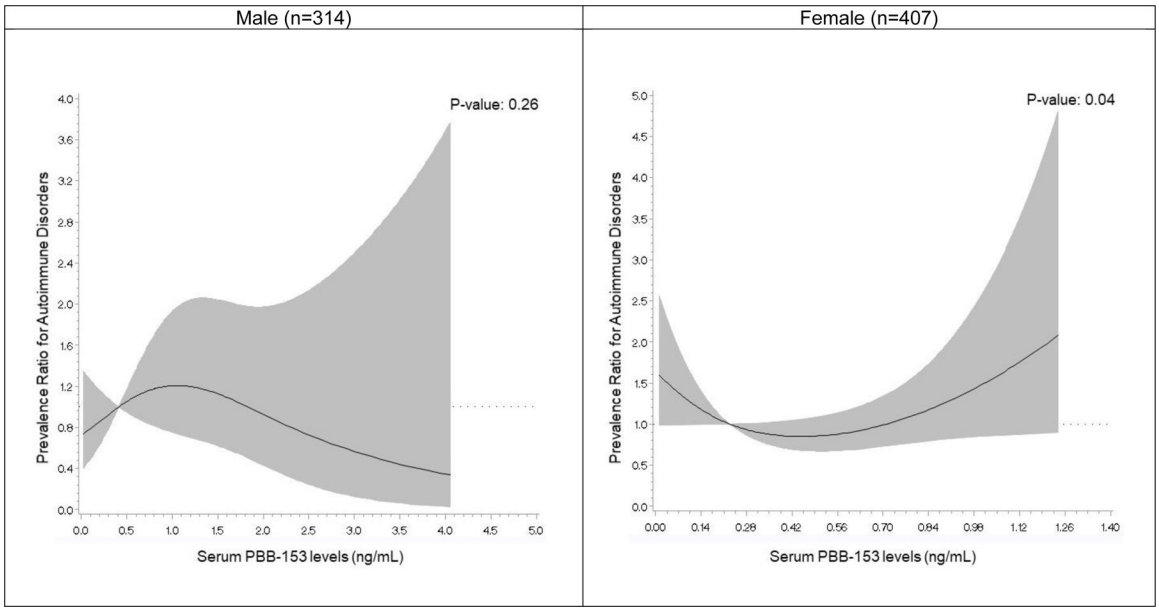

Figure 2.

Sex-specific non-linear association between serum PBB-153 level (x-axis) and autoimmune disorders (y-axis -prevalence ratio) among Michigan PBB Registry participants from 2012 to 2020 using adjusted restricted cubic spline modeling with 3 knots selected automatically

A cubic spline modeling testing for a non-linear relationship between serum PBB-153 levels and the prevalence of autoimmune disorders. The p-value from the test for curvature indicates a non-linear relationship between serum PBB-153 levels and the prevalence of autoimmune disorders. Splines were restricted to values between the 10^{th} and 90^{th} percentiles of serum PBB-153 level. The 10^{th} and 90^{th} percentiles were 0.021 and 4.051 ng/mL for males and 0.012 and 1.273 ng/mL for females.

Table 1.

Demographic characteristics of Michigan PBB Registry participants who completed at least one questionnaire that included data on autoimmune disorders from 2012 to 2020 (n=895)

Demographic characteristics, n (%)		All n=895	Sex	
			Male n=387	Female n=508
Serum PBB-153 Levels (ng/mL), range		0.0007, 245.90	0.0007, 221.42	0.0007, 245.90
Sex				
	Male	387 (43.2%)	387 (100%)	---
	Female	508 (56.8%)	---	508 (100%)
BMI, median (IQR)		28.6 (8.4)	29.3 (7.2)	28.2 (9.4)
	Missing	274	141	133
Smoking status				
	Current	135 (15.1%)	63 (16.3%)	72 (14.2%)
	Former	224 (25.0%)	116 (30.0%)	108 (21.2%)
	Never	536 (59.9%)	208 (53.7%)	328 (64.6%)
Race				
	White	840 (93.9%)	360 (93.0%)	480 (94.5%)
	Other	42 (4.7%)	21 (5.4%)	21 (4.1%)
	Missing	13 (1.4%)	6 (1.6%)	7 (1.4%)
Lifestage at exposure				
	In utero	221 (24.7%)	91 (23.5%)	130 (25.6%)
	<18 years	373 (41.7%)	135 (34.9%)	238 (46.8%)
	≥18 years	301 (33.6%)	161 (41.6%)	140 (27.6%)
Age at blood draw, median (IQR)		53.0 (22.0)	57.0 (23.0)	51.0 (21.0)
Age by Lifestage at exposure				
	In utero	31.0 (12.0)	32.0 (12.0)	30.0 (12.0)
	<18 years	51.0 (9.0)	51.0 (10.0)	51.0 (8.0)
	≥18 years	67.0 (10.0)	67.0 (10.0)	67.0 (9.0)
Total Lipid level (mg/dL), median (IQR)		676.3 (237.4)	638.9 (215.0)	718.0 (255.3)
Serum PBB-153 Levels (ng/mL), median (IQR)		0.28 (0.65)	0.41 (1.03)	0.23 (0.44)
Lipid-Adjusted Serum PBB-153 Levels (ng/g lipid),[1] median (IQR)		$4.1x10^{-4}$ ($9.6x10^{-4}$)	$6.3x10^{-4}$ ($1.6x10^{-4}$)	$3.1x10^{-4}$ ($6.0x10^{-4}$)
Autoimmune disorders				
	Yes	155 (17.3%)	50 (12.9%)	105 (20.7%)
	No	740 (82.7%)	337 (87.1%)	403 (79.3%)

[1] Lipid-adjusted serum PBB-153 levels are equal to the serum PBB-153 level divided by the total lipid level.

Table 2.

Sex-specific association between tertiles of serum PBB-153 levels and prevalence of autoimmune disorders among Michigan PBB Registry participants from 2012 to 2020 (n=895)

Serum PBB-153 Level		Unadjusted PR (95% CI) [1]	Adjusted PR (95% CI) [1,2]	P-trend [3]
Male[4] (n=387)				
	1st tertile	Ref.	Ref.	0.31
	2nd tertile	1.23 (0.60, 2.52)	0.77 (0.33, 1.81)	
	3rd tertile	1.86 (0.97, 3.57)	1.14 (0.50, 2.57)	
Female[5] (n=508)				
	1st tertile	Ref.	Ref.	0.75
	2nd tertile	1.08 (0.71, 1.64)	0.86 (0.50, 1.48)	
	3rd tertile	1.06 (0.69, 1.61)	0.86 (0.50, 1.49)	

[1] Prevalence ratio (PR); 95% Confidence Interval (CI)

[2] Model was adjusted for lifestage at exposure and smoking history.

[3] P-value for the trend of autoimmune disorder prevalence by increasing serum PBB-153 level adjusted for age at exposure and smoking history

[4] PBB tertiles for males were: <0.22 ng/mL (first tertile), 0.22-<0.76 ng/mL (second tertile), and ≥0.76 ng/mL (third tertile).

[5] Serum PBB-153 tertiles for females were: <0.11 ng/mL (first tertile), 0.11-<0.37 ng/mL (second tertile), and ≥0.37 ng/mL (third tertile).

Table 3.

Sex-specific associations between tertiles of serum PBB-153 levels and prevalence of autoimmune disorders among Michigan PBB Registry participants from 2012 to 2020 by lifestage at exposure (n=895)

		Unadjusted PR (95% CI) [2,3]			
	P-Interaction [1]	1st Tertile	2nd Tertile	3rd Tertile	P-trend[4]
Male (n=387)[5]					
Lifestage at Exposure[5]	0.42				
In utero (n=91) [7]		Ref.	1.59 (0.61, 4.14)	---	---
<18 years (n=135)		Ref.	0.88 (0.33, 2.33)	0.52 (0.15, 1.77)	0.27
≥18 years (n=161)		Ref.	2.95 (0.74, 11.79)	3.05 (1.09, 8.56)	0.08
Female (n=508)[6]					
Lifestage at Exposure	0.67				
In utero (n=130) [7]		Ref.	0.67 (0.10, 4.36)	---	---
<18 years (n=238)		Ref.	0.92 (0.46, 1.82)	0.74 (0.36, 1.53)	0.38
≥18 years (n=140)		Ref.	0.94 (0.25, 3.45)	1.17 (0.65, 2.11)	0.56

[1] P-value for the interaction between natural log of serum PBB-153 level (continuous) and lifestage at exposure

[2] Prevalence ratio (PR); 95% Confidence Interval (CI).

[3] Due to sample size constraints, these models were unadjusted.

[4] P-value for the trend of autoimmune disorder prevalence by increasing serum PBB-153 level

[5] Serum PBB-153 tertiles for males were: <0.22 ng/mL (first tertile), 0.22-<0.76 ng/mL (second tertile), and ≥0.76 ng/mL (third tertile).

[6] Serum PBB-153 tertiles for females were: <0.11 ng/mL (first tertile), 0.11-<0.37 ng/mL (second tertile), and ≥0.37 ng/mL (third tertile).

[7] *In utero* estimates for the third tertile could not be obtained due to small sample size.

Table 4.

Sex-specific association between tertiles of serum PBB-153 levels and prevalence of specific autoimmune disorders or groups of autoimmune disorders among Michigan PBB Registry participants from 2012 to 2020 (n=895)

Male [1] n=387					Female [2] n=508				
	Unadjusted PR (95% CI) [5]					Unadjusted PR (95% CI) [5]			
Target organ system / Specific condition [3,4]	**1st tertile**	**2nd tertile**	**3rd tertile**	**P-trend**	**Target organ system / Specific condition [1,2]**	**1st tertile**	**2nd tertile**	**3rd tertile**	**P-trend**
Skin/Joint system (n=50; 12.9%)	Ref.	1.77 (0.85, 3.69)	2.13 (1.05, 4.32)	0.06	Skin/Joint system (n=87; 17.1%)	Ref.	1.05 (0.67, 1.65)	0.81 (0.50, 1.32)	0.32
Psoriasis (n=12; 3.1%)	Ref.	1.97 (0.50, 7.70)	0.97 (0.20, 4.71)	0.65	Psoriasis (n=24; 4.7%)	Ref.	0.42 (0.17, 1.08)	0.28 (0.09, 0.83)	0.03
Rheumatoid arthritis (n=29; 7.5%)	Ref.	1.48 (0.43, 5.11)	4.60 (1.61, 13.2)	<0.001	Rheumatoid arthritis (n=37; 7.3%)	Ref.	1.85 (0.81, 4.25)	1.70 (0.73, 3.94)	0.38
Digestive system (n=5; 1.3%)	Ref.	0.98 (0.14, 6.88)	0.48 (0.04, 5.28)	0.52	Digestive system (n=19; 3.7%)	Ref.	0.71 (0.23, 2.18)	0.97 (0.35, 2.71)	0.91
Neurological system (n=1; 0.3%) [6]	Ref.	---	---	---	Neurological system (n=8; 1.6%)	Ref.	0.99 (0.14, 6.93)	1.94 (0.36, 10.5)	0.36
Thyroid system (n=1; 0.3%) [6]	Ref.	---	---	---	Thyroid system (n=10; 2.0%)	Ref.	1.98 (0.37, 10.6)	1.94 (0.36, 10.5)	0.55

[1] Serum PBB-153 tertiles for males were: <0.22 ng/mL (first tertile), 0.22-<0.76 ng/mL (second tertile), and ≥0.76 ng/mL (third tertile).

[2] Serum PBB-153 tertiles for females were: <0.11 ng/mL (first tertile), 0.11-<0.37 ng/mL (second tertile), and ≥0.37 ng/mL (third tertile).

[3] Skin/Joint conditions included: alopecia, connective tissue disease, juvenile dermatomyositis, lupus, psoriasis, psoriatic arthritis, rheumatoid arthritis, scleroderma, Sjogren's syndrome, systemic sclerosis, and vitiligo. Digestive conditions included: celiac disease, Crohn's disease, and ulcerative colitis. Neurological conditions included: multiple sclerosis. Thyroid conditions included: Grave's disease and Hashimoto's disease.

[4] Number and percentage of individuals with specific autoimmune conditions.

[5] Prevalence ratio (PR); 95% Confidence Interval (CI).

[6] Estimates could not be obtained due to sample size.