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Comment on “The influence of age at exposure to PCBs on birth outcomes”

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To the Editor:

We would like to comment on the article entitled “The influence of age at exposure to PBBs on birth outcomes” (Sweeney and Symanski, 2007, doi:10.1016/j.envres.2007.03.006). We have analyzed a mostly overlapping dataset described in our recently published article, “Maternal exposure to polybrominated and polychlorinated biphenyls: Infant birth weight and gestational age” (Givens et al., 2007). In brief, our sample included 899 infant birth records from 1975–1997 from women in the Michigan Long–Term Polybrominated Biphenyl (PBB) Study who also participated in the 1997–1998 Michigan Female Health Study telephone interview. The study population in Sweeney and Symanski (2007) included a total of 1,111 infant birth records from 1975–1994 from the Michigan Long–Term PBB Study cohort and a smaller cohort, the PCB Silo Cohort. Birth weight and gestational age were analyzed as separate outcomes in mixed–effects models in both articles; however, we found results that differed from Sweeney and Symanski (2007).

Our birth weight model (Givens et al., Table 2, 2007) included similar covariates to Sweeney and Symanski’s (2007) model presented in Table 4 (gestational age, maternal age at infant’s birth, PBB, PCB, parity, and infant gender) and a few additional covariates (maternal smoking status and decade of infant’s birth). In comparison to Sweeney and Symanski’s (2007) model, we did not include maternal age at enrollment, interval between blood test (taken at enrollment) and date of infant’s birth, maternal BMI at enrollment, prenatal care and paternal education.

Because our published results were contrary to Sweeney and Symanski’s (2007) results, we have attempted to replicate Sweeney and Symanski’s (2007) findings by including the additional variables of interval and maternal age at enrollment. Although our sample and methodological approaches are somewhat different, we were successfully able to reproduce

similar parameter estimates as those presented in Sweeney and Symanski's (2007) Table 4 (Table 1). Specifically, we were able to reproduce the association of maternal age at enrollment ≤ 10 years with approximately a 200 g heavier birth weight. However, we would like to raise several concerns with the interpretation of this result. The overall conclusion of a "maternal age at exposure" effect does not appear to be substantiated from the data for the following reasons: 1) "maternal age at enrollment" was used as a proxy for "maternal age at exposure," without considering the potential error introduced by this proxy, 2) a substantial proportion of the population did not have detectable serum PBB in the blood, but Sweeney and Symanski's (2007) models did not account for this, and 3) there are methodological issues that appear to be the source of the "maternal age at exposure" effect.

Concern 1: "Maternal age at enrollment" appears to have been considered as a proxy for "maternal age at exposure"

"Maternal age at enrollment" and "maternal age at exposure" are used interchangeably. In the introduction of Sweeney and Symanski (2007) age at exposure is defined as "the maternal age at onset of PBB exposure" and under 2.3 *The Study Population*, it is stated that "individual exposure is estimated by the participant's date of enrollment into the cohort." The tables in the article interchange these terms. Table 1 has in its title "...exposure levels of the PBB cohort at enrollment." The heading within Table 1 has "age at exposure," and the footnote at the bottom of Table 1 has "...age at entry into study." Similarly, the titles of Table 3 and Table 4 have "PBB levels at exposure" but "PBB level at enrollment" is used to represent this variable in the tables themselves. While the two variables are related, the time interval from the onset of the PBB exposure incident to an individual's enrollment into the PBB cohort can vary by years. The PBB contamination began in the summer or fall of 1973 and the earliest date of enrollment occurred in July 1976. The latest enrollment date reported in the Sweeney and Symanski (2007) study population was December 1980. This indicates that the interval between the PBB exposure incident and enrollment into the cohort was at least 3 years, at most nearly 7 years and varies among participants.

Concern 2: To evaluate whether maternal age at PBB exposure is associated with birth weight requires an interaction term

Sweeney and Symanski's (2007) conclusion that "these results provide support for the hypothesis that early age at exposure may be an important determinant in subsequent health effects due to environmental chemical exposures" was not strictly tested in their analyses. This conclusion implies that there is an effect of exposure that is modified by maternal age at that exposure. Measurable exposure to PBB varies in this cohort with approximately 20% having no detectable PBB in their blood. Individuals were originally recruited into the cohort if they lived on a farm that had been quarantined because of PBB exposure, had obtained products (meat, milk, poultry, and eggs) from a contaminated farm or wanted to have their blood tested to determine if they had been exposed. Presumably some (or many) of the infants born to mothers enrolled before the age of 10 (the "early exposure" group) were in fact, unexposed or had very low levels of exposure (PBB limit of detection (LOD) = 1.0 ppb). In order to conclude that an early maternal age at exposure affects birth weight, an interaction term between maternal age at exposure and PBB exposure is needed. From Sweeney and Symanski's (2007) analyses, we can only conclude that maternal age at enrollment into the cohort is somehow associated with birth weight, but this may be entirely unrelated to PBB exposure.

Concern 3: The “maternal age at exposure” effect appears to be an artifact of methodological issues

Table 1 shows a comparison of the estimates from the birth weight model in Sweeney and Symanski's (2007) Table 4 compared to the same model when evaluated in our dataset. All of the parameter estimates are in the same direction, and despite our differences in sample size and cohort inclusions, the parameter estimates are remarkably similar. The coefficient for maternal age at exposure ≤ 10 years, which we will refer to as “maternal age at enrollment” is 232 g in Sweeney and Symanski (2007) and 200 g in our dataset.

What poses a concern in these models is the inclusion of three related variables: 1) maternal age at enrollment, 2) interval between mother's blood draw (at enrollment) and date of infant's birth, and 3) maternal age at infant's birth. When modeled together these three variables are highly collinear. As supporting evidence, we present the results from two sets of analyses: 1) collinearity diagnostics and 2) an examination of the association between maternal age at enrollment and birth weight with and without adjustments for the other two variables. The results follow:

1) Collinearity diagnostics

Any one of these three variables can be determined from the other two variables. Maternal age at the time of infant's birth is the sum of the maternal age at enrollment and the interval between enrollment and infant date of birth (maternal age at enrollment + interval $\approx$ maternal age at infant's birth). At an intuitive level, these variables appear collinear. Most of the participants in the cohort had their initial blood test for PBB collected when they were enrolled into the study. The “interval” which is defined as the “interval between date of blood test and date of birth” is actually the time from entry into the study to infant date of birth. Thus, if you add interval to maternal age at enrollment, you will approximate maternal age at the time of infant's birth. Because one of the variables, maternal age at enrollment, was categorized in the Sweeney and Symanski's (2007) models, while interval and maternal age at infant's birth were continuous, the magnitude of the collinearity was diminished.

To more formally assess the collinearity between these variables, we evaluated the two-way correlations among these three variables. The Spearman's rank correlation coefficient between maternal age at enrollment and maternal age at infant's birth was 0.33. The highest correlation coefficient was between maternal age at enrollment (treated continuously) and interval ($R_s = -0.74$, $p < 0.0001$). When maternal age at enrollment was treated categorically, the correlation coefficient between maternal age at enrollment and interval was slightly smaller ($R_s = -0.64$, $p < 0.0001$), but still notable.

We also computed eigenvalues and condition indices using a Principal Components Analysis to determine which variables were collinear (Belsley, 2005). We built several models to determine the extent of collinearity under different conditions (Table 2). We used a cut-off for condition indices > 30 and variance decomposition proportions (VDP) > 0.5 to indicate multicollinearity. In Model 2.1, besides the intercept, the predictors with the highest VDPs were maternal age at infant's birth and maternal age at enrollment (the ≤ 10 years category). The VDP in the 11–16 years maternal age at enrollment category and the interval were only slightly below 0.5. When several insignificant variables were removed (Model 2.2), the multicollinearity remained. In model 2.3, when maternal age at enrollment was considered as a continuous variable instead of a categorical variable, all three variables in question had very high VDPs. Only when one of the three variables was eliminated does the collinearity disappear (Models 2.4 and 2.5).

2) Modeling the association of maternal age at enrollment with birth weight (unadjusted and adjusted)

Table 3 gives the results of unadjusted and adjusted models of maternal age at enrollment (both continuous and categorical), maternal age at infant's birth and interval between date of blood test and infant's birth with the outcome birth weight. The first model in Table 3 suggests an increase in birth weight with older maternal age at enrollment when categorized similarly to the maternal age at enrollment variable in Sweeney and Symanski's (2007) models. However, the direction of the association for maternal age at enrollment is opposite to what is reported in Table 4 of Sweeney and Symanski (2007). When maternal age at enrollment is modeled as a continuous variable, the direction of the association remains the same (Model 3.2). Adjusting maternal age at enrollment for interval (Model 3.3) or maternal age at infant's birth (Model 3.4) alters the estimates slightly, but does not change the direction of the association. Thus, modeling maternal age at enrollment, by itself or adjusted for interval or maternal age at infant's birth (but not both), indicates that younger age at enrollment is associated with lower birth weight. These results are quite different than Sweeney and Symanski's (2007) conclusions.

Finally, we included all three variables together in a model with birth weight as the outcome. In Model 3.5, when maternal age at enrollment was categorized, the results were similar and in the same direction as results presented in Sweeney and Symanski's (2007) Table 4. Alternatively, in Model 3.6, when maternal age at enrollment was continuous, none of the three variables had significant associations with birth weight; possibly because of the multicollinearity that exists in the data. Including all three variables in our model (Model 3.5) causes the maternal age at enrollment estimate to change directions from what is seen when maternal age at enrollment is modeled by itself with birth weight (Models 3.1 and 3.2). Instead of a decrease in birth weight with younger maternal age at enrollment, when all three variables are in the model we see an increase in birth weight with younger maternal age at enrollment (Model 3.5), as was indicated by Sweeney and Symanski (2007). Thus, it is only when maternal age at enrollment is a categorical variable and is adjusted for both maternal age at infant's birth and for interval between enrollment and infant's birth does the association change direction.

A primary focus of both articles was to determine the effect of maternal serum PBB on infant's birth weight. The suggestion of a non-monotonic relationship between maternal serum PBB and birth weight is consistent in both papers. Sweeney and Symanski (2007) found a significant quadratic PBB effect in their model in Table 3; however, their abstract describes only a linear relationship of 16 g heavier birth weight for every 10 ppb increase in PBB levels. When PBB levels were categorized, a similar positive association with birth weight is seen for the highly exposed. Sweeney and Symanski (2007) reported a 105 g higher birth weight when maternal PBB levels were ≥ 14 ppb (Table 4, $p = 0.0834$) compared to the referent group (< 14 ppb). Our PBB estimate was in the same direction, although slightly attenuated for maternal PBB levels ≥ 14 ppb (PBB estimate = 116 g, $p = 0.1278$, Givens et al., 2007). However, when we split PBB levels at the median value above the LOD, we found an inverse association with lower birth weight for maternal PBB levels > 3 ppb (Table 2, PBB estimate = -99 g, $p = 0.0484$, Givens et al., 2007). The relationship between maternal serum PBB and infant's birth weight is difficult to explain, given the change in direction for the PBB estimates when categorized at various levels. Hence, we can only conclude there was no dose-response relationship between maternal serum PBB levels and infant's birth weight.

In summary, we believe that the effect of "maternal age at exposure" reported in Sweeney and Symanski (2007) is an artifact of a collinearity problem between maternal age at exposure, enrollment, interval between enrollment and date of infant's birth and maternal age at infant's birth. In addition, the conclusion that maternal age at exposure is related to birth weight implies that there is an association of exposure with birth weight that is different for mothers exposed at different ages. This was not directly tested in the analyses presented in Sweeney and

Symanski's (2007) article. Finally, we note that maternal age at enrollment is not equivalent to maternal age at exposure to PBB.

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Table 1

Mixed Models for Infant Birth Weight

Variable	Sweeney and Symanski, 2007 (Table 4)			Givens et al., 2007 Dataset		
	Est. Coefficient	SE	p-value	Est. Coefficient	SE	p-value
Intercept [^]	—	—	—	2723.71	177.24	<0.0001
Gestational age (weeks)	59.72	5.97	<0.0001	68.91	7.53	<0.0001
Age at enrollment	232.35	89.18	0.0094	200.09	92.95	0.0319
≤ 10 years	89.92	57.77	0.1202	117.96	65.56	0.0727
11–16 years	ref	—	—	ref	—	—
≥ 17 years	15.71	4.96	0.0016	14.75	5.70	0.0101
Age of the mother (years)	12.76	5.24	0.0152	15.94	5.94	0.0076
BMI at enrollment (kg/m ²)	104.79	60.41	0.0834	164.40	69.99	0.0193
PBB	ref	—	—	ref	—	—
≥ 14.00 ppb	—45.71	54.24	0.3997	—47.44	62.26	0.4465
PCB	*	*	*	—56.72	68.84	0.4104
≥ 9.0 ppb	ref	—	—	ref	—	—
missing	ref	—	—	ref	—	—
< 9.0 ppb	112.62	30.68	0.0003	88.08	49.40	0.08
Parity	ref	—	—	ref	—	—
>2	22.08	9.26	0.0174	*	*	*
Paternal education (years)	198.93	24.09	<0.0001	198.22	28.18	<0.0001
Infant gender	ref	—	—	ref	—	—
Male	—10.45	5.06	0.0393	—8.30	5.33	0.1206
Female	—30.71	34.22	0.3700	—53.10	40.90	0.1974
Interval (years) [°]	—49.37	84.99	0.5616	—222.49	140.30	0.1162
Prenatal Care	ref	—	—	19.97	121.09	0.8694
2 nd Trimester	ref	—	—	ref	—	—
3 rd Trimester	ref	—	—	ref	—	—
None/missing	ref	—	—	ref	—	—
1 st Trimester	ref	—	—	ref	—	—

[^] The value for the intercept was not included in Sweeney and Symanski (2007)

* Indicates the data was not available or not included in the model

[°] Interval between date of blood test (enrollment) and date of birth

Table 2

Collinearity Diagnostics - Principal Components Analysis[^]

Condition Indices	Model 2.1 (Table 1)	Model 2.2 (Table 1 Without PCB & Prenatal Variables)	Model 2.3 (Model 2.2 with maternal age at enrollment continuous)	Model 2.4 (Model 2.2 without maternal age at infant's birth)	Model 2.5 (Model 2.2 without interval)
	36.669	34.132	42.569	21.774	25.772
Variance Decomposition Proportions					
Intercept	0.922	0.928	0.008	0.989	0.994
PBB (≥ 14 ppb)	0.001	0.000	0.002	0.001	0.000
PCB (≥ 9 ppb)	0.008	—	—	—	—
PCB (missing)	0.001	—	—	—	—
Parity (> 2)	0.184	0.175	0.007	0.028	0.120
Maternal age at infant's birth	0.782	0.779	0.982	—	0.359
Male infant	0.007	0.008	0.001	0.000	0.005
Gestational age	0.005	0.004	0.014	0.001	0.000
Interval	0.477	0.485	0.904	0.016	—
Age at enrollment (continuous)	—	—	0.847	—	—
Age at enrollment (≤ 10 years)	0.590	0.608	—	0.200	0.323
Age at enrollment (11–16 years)	0.448	0.461	—	0.110	0.152
BMI at enrollment	0.110	0.122	0.047	0.982	0.673
Prenatal care (2nd trimester)	0.014	—	—	—	—
Prenatal care (3rd trimester)	0.013	—	—	—	—
Prenatal care (none/missing)	0.015	—	—	—	—

[^] Condition Indices > 30 and Variance Decomposition Proportions > 0.5 as an indicator of multicollinearity; reference categories for each variable are not shown

Table 3
Mixed Models with the outcome Birth Weight adjusted for three explanatory variables: maternal age at enrollment, maternal age at infant's birth, and interval between date of blood test and infant's birth

Model variables	Estimate	S.E.	CI	p-value
Model 3.1:				
Intercept	3564.19	29.70	(3505.82, 3622.57)	<.0001
Maternal age at enrollment (categorical)				
≤ 10 years	-71.86	63.97	(-197.58, 53.87)	0.26
11–16 years	-18.59	51.99	(-120.78, 83.60)	0.72
≥ 17 years (ref)	—	—	—	—
Model 3.2:				
Intercept	3398.16	58.33	(3283.52, 3512.80)	<.0001
Maternal age at enrollment (continuous)	8.43	3.04	(2.46, 14.40)	0.006
Model 3.3:				
Intercept	3551.40	33.95	(3484.68, 3618.13)	<.0001
Maternal age at enrollment (categorical)				
≤ 10 years	-102.82	75.20	(-250.61, 44.97)	0.17
11–16 years	-38.75	58.03	(-152.80, 75.29)	0.50
≥ 17 years (ref)	—	—	—	—
Interval in years	2.94	3.72	(-4.36, 10.24)	0.429
Model 3.4:				
Intercept	3224.30	107.93	(3012.18, 3436.43)	<.0001
Maternal age at enrollment (categorical)				
≤ 10 years	-21.81	65.98	(-151.48, 107.87)	0.74
11–16 years	9.78	52.94	(-94.27, 113.84)	0.85
≥ 17 years (ref)	—	—	—	—
Maternal age at infant's birth	12.36	3.77	(4.95, 19.78)	0.001
Model 3.5:				
Intercept	3005.50	140.82	(2728.74, 3282.26)	<.0001
Maternal age at enrollment (categorical)				
≤ 10 years	160.19	99.47	(-35.31, 355.68)	0.11
11–16 years	124.63	70.59	(-14.10, 263.37)	0.08
≥ 17 years (ref)	—	—	—	—
Maternal age at infant's birth	22.45	5.62	(11.40, 33.50)	<.0001
Interval in years	-13.42	5.51	(-24.24, -2.59)	0.015
Model 3.6:				
Intercept	3186.31	100.52	(2988.75, 3383.87)	<.0001
Maternal age at enrollment (continuous)	0.08	13.80	(-27.04, 27.20)	1.00
Maternal age at infant's birth	15.35	14.28	(-12.71, 43.42)	0.28
Interval in years	-5.40	14.15	(-33.20, 22.41)	0.70

^a Interval between date of blood test (enrollment) and date of birth