Prenatal and early-life polychlorinated biphenyl (PCB) levels and behavior in Inuit preschoolers

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ABSTRACT

Background: Whereas it is well established that prenatal exposure to polychlorinated biphenyls (PCBs) can disrupt children's behavior, early postnatal exposure has received relatively little attention in environmental epidemiology.
Objectives: To evaluate prenatal and postnatal exposures to PCB-153, a proxy of total PCB exposure, and their relation to inattention and activity in 5-year-old Inuits from the Cord Blood Monitoring Program.
Methods: Prenatal exposure to PCBs was informed by cord plasma PCB-153 levels. We used a validated pharmacokinetic model to estimate monthly infants' levels across the first year of life. Inattention and activity were assessed by coding of video recordings of children undergoing fine motor testing. We used multivariable linear regression to evaluate the association between prenatal and postnatal PCB-153 levels and inattention (n = 97) and activity (n = 98) at 5 years of age.
Results: Cord plasma PCB-153 was not associated with inattention and activity. Each interquartile range (IQR) increase in estimated infant PCB-153 levels at 2 months was associated with a 1.02% increase in the duration of inattention (95% CI: 0.04, 2.00). Statistical adjustment for the duration of breastfeeding slightly increased regression coefficients for postnatal level estimates, some of which became statistically significant for inattention (months: 2–4) and activity (months: 2–5).
Conclusions: Our study adds to the growing evidence of postnatal windows of development during which children are more susceptible to neurotoxicants like PCBs.

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1. Introduction

The human brain undergoes multiple developmental processes starting shortly after fertilization and extending well beyond birth (Rice and Barone, 2000). Numerous environmental contaminants, including polychlorinated biphenyls (PCBs), can affect these developmental processes in both in vitro and in vivo models, and lead to altered behavior in laboratory animals exposed prenatally and/or postnatally to mixtures or individual congeners of polychlorinated biphenyls (PCBs) (reviewed by Eubig et al., 2010). Several epidemiologic studies support the contention that low-level prenatal exposure to PCBs can impair neurobehavior in infancy and childhood, including attention and activity (Jacobson and Jacobson, 2003; Plusquellec et al., 2007, 2010; Sagiv et al., 2008, 2010). Although exposure to PCBs through lactation can lead to levels in children several fold higher than prenatal levels

(Lackmann, 2006) during a period of brain maturation (Dubois et al., 2014; Rice and Barone, 2000), the association between postnatal exposure to PCBs and behavior has received relatively little attention (Polanska et al., 2013).

Because cost and ethical considerations preclude collecting blood samples in nursing infants, we developed pharmacokinetic models to estimate complete time-courses of levels of persistent organic pollutants, including PCBs (Verner et al., 2009, 2013). These pharmacokinetic models, which can generate individual-specific exposure estimates based on maternal/cord blood levels, information on children and maternal physiology, and duration of breast-feeding, were shown to accurately predict Inuit infants' blood levels: 2,2′,4,4′,5,5′-hexachlorobiphenyl (PCB-153) levels estimated using the pharmacokinetic model presented in Verner et al. (2013) and cord blood levels explained 74% of the variability in levels measured in 6-month-olds' blood. In a previous study of 11-month-old Inuits, we used monthly estimates of infants' PCB-153 levels from birth until behavioral assessment to evaluate potential windows of vulnerability across early development that could be related to impairments in attention and activity. We found that infant inattention was mostly related to prenatal exposure whereas the activity level was best predicted by postnatal exposure, with the strongest association obtained with estimated PCB-153 levels during the 4th month of life (Verner et al., 2010).

In this study, we used a pharmacokinetic model to reconstruct early postnatal PCB levels in a sample of Inuit preschoolers from Nunavik (Quebec, Canada) and examined the time window-specific associations between estimated PCB levels and indicators of inattention and activity assessed when children were 5 years of age. We used PCB-153 as a surrogate for the environmental mixture of PCBs found in biological specimens of the Inuit because this compound is resistant to degradation and was highly correlated to other frequently detected PCB congeners in plasma and breast milk in this population (Ayotte et al., 2003; Muckle et al., 2001a).

2. Methods

2.1. Study design and population

This study was a follow-up of the Cord Blood Monitoring Program, aimed to document prenatal exposure to environmental contaminants, which took place between 1993 and 1996. Observations when subjects were 5 years old took place in Nunavik, between January 2000 and October 2002. The following inclusion criteria were used for entry into the follow-up: children between 4 and 6 years of age, biological mother as primary caretaker, duration of pregnancy $\geq$ 35 weeks, birth weight $\geq$ 2500 g, no diagnosed neurological condition, developmental disorder or severe chronic disease. Eligibility was first determined through the database of the Cord Blood Monitoring Program. The eligible mothers were then contacted by phone and met for an interview. From the 228 eligible participants, 32% could not be reached by our research assistants and 25.7% refused to participate. The main reason for refusal to participate was the obligation to travel by plane to another community to meet our research staff. Study participants were not statistically different from excluded subjects and eligible non-participants on the following variables: age of the mother at delivery and 5-year testing, parity, smoking during pregnancy, birth weight, gestational age at birth and cord plasma levels of PCBs, mercury and lead (Despres et al., 2005). A total of 110 children from 14 villages were tested. The research procedures were approved by the Laval University ethics committee and an informed consent was obtained from a parent of each participant.

2.2. Behavioral measurements

Children underwent fine motor testing between the ages of 4 and 6 (detailed in Despres et al., 2005). Briefly, fine motor function was assessed using quantitative measures of postural hand tremor, reaction time, sway oscillations, and alternating and pointing movements. The testing session was videotaped to allow documenting visual inattention, activity, and emotional reactivity. Child behavior was coded on a second-by-second basis from video recordings by two Ph.D. students in psychology who were blinded with respect to the exposure to contaminants and confounders (Plusquellec et al., 2010) using the software The Observer® 5.0 (Noldus Information Technology, Wageningen, Netherlands). The average duration of the video recordings coded for behavioral function was 12.7 min per child. Inattention was defined as the proportion of the time (%) the child looked away from the test material or tester during the fine motor tasks. Activity duration was defined as the proportion of the time (%) the child was moving erratically, rocking backward and forward or swinging right and left during the fine motor tasks. Of note, these observational measures of activity and attention are not clinical assessments of hyperactivity or deficits in attention. Inter-observer reliability was evaluated using videos that were coded by both research assistants. Agreement between observers was defined as both research assistants coding the same behavior at the same time, with a tolerance window of 2 s. Levels of inter-observer agreement reached kappa values of 0.94 for inattention and 0.70 for activity. Some videos could not be coded due to poor quality or bad framing: activity and inattention could be evaluated in 103 and 102 children, respectively. Inattention and activity levels measured using this approach were significantly correlated ($p < 0.05$) with attention (r = 0.21) and activity (r = 0.21) scores from the Infant Behavioral Rating Scales, a component of the Bayley Scales of Infant Development II (Plusquellec et al., 2010).

2.3. Exposure assessment

Prenatal exposure was informed by cord plasma PCB-153 levels measured as described in Rhainds et al. (1999) and Muckle et al. (2001b) and expressed on a lipid basis. We estimated monthly infants' PCB-153 levels using a validated pharmacokinetic model presented in Verner et al. (2013). This model simulates lifetime exposure to persistent organic pollutants in women, placental diffusion to the fetus during pregnancy and lactational transfer to the nursing infant. Based on maternal age at delivery, pre-pregnancy body weight, gestational weight gain, child weight profile, child's sex, duration of total breast-feeding and cord blood PCB-153 level (ng/g lipids), we generated individual-specific PCB-153 profiles from birth until 12 months of age. The simulations were performed using the acslX software (Aegis Technologies Group, Inc., Huntsville, AL, USA).

2.4. Data analysis

Behavioral measures were examined for outliers. Two extreme activity values (4 and 8 SDs from the mean) were winsorized to the highest value contained within the range of the mean $\pm$ 3 standard deviations. Associations between each exposure estimate and 5-year-olds' inattention and activity were assessed by multivariable linear regression models. Activity was $\log_{10}$-transformed to satisfy regression model assumption of homoscedasticity.

Data on covariates came from medical records, biomarker levels and questionnaires administered to mothers at delivery and at 5-year assessments. We identified potential confounders using a directed acyclic graph (Shrier and Platt, 2008): maternal age at delivery, pre-pregnancy body weight, gestational weight gain, parity, socioeconomic status measured using the Hollingshead Four Factor Index (Hollingshead, 1975), duration of breastfeeding, and cord blood mercury and omega-3 levels. Variables associated with any of the two behavioral measures at $p < 0.20$ in bivariate analyses were included in the statistical models. Missing covariate values were imputed using regression models where model R^2s were >0.05; the median of observed values was used elsewhere. Because plasma PCB-153 levels are highly correlated with other

organochlorine compounds like p,p′-DDE (r = 0.88) and HCB (r = 0.79) in this population, they were not considered for inclusion in regression models to avoid multicollinearity. Final models included maternal pre-pregnancy body weight, gestational weight gain, socioeconomic status and parity. We performed additional analyses to evaluate whether results were sensitive to adjustment for the duration of breastfeeding and adjustment for lead levels in cord or child blood Statistical analyses were performed using SPSS for Windows (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Population characteristics

Characteristics of mothers and children are presented in Table 1. Child age at testing time ranged from 4.8 to 6.1 years of age. Mean breastfeeding duration was 57.1 weeks and ranged from 0 to 258. All included mothers reported smoking and more than a third reported drinking alcoholic beverages during pregnancy. Cord plasma PCB-153 levels had a median value of 99 ng/g lipids (range = 22–490). Median estimated children's PCB-153 levels were 120 ng/g lipids (range = 18–783) at 2 months, 100 ng/g lipids (range = 10–780) at 6 months and 109 ng/g lipids (range = 8–1268) at 12 months.

3.2. Association between PCB-153 levels and behavioral indicators

Information necessary for pharmacokinetic modeling was available for 97 children with a measure of inattention and 98 children with activity assessment. Cord plasma PCB-153 levels were not associated significantly with inattention or activity in regression models (Fig. 1A). Each IQR increase in estimated children's PCB-153 levels at 2 months was associated with a 1.02% increase in the duration of inattention (95% CI: 0.04, 2.00), and this association was attenuated and not significant for subsequent months (Fig. 1A). Including the duration of breastfeeding as a covariate in regression models increased the strength of the association between postnatal estimates of PCB-153 levels and both inattention and activity; significant associations were observed with

Table 1
Characteristics of study participants (n = 98).

	N (%)	Mean	SD	Range
Maternal characteristics				
Maternal age at delivery (years)		25	5	15–39
Pre-pregnancy body weight (kg)		61	12	40–95
Gestational weight gain (kg)		10	6	0–37
Socioeconomic status (Hollingshead index)		28	12	9–55
Parity		4	2	1–8
Smoking during pregnancy				
Yes	75 (100%)			
No	0 (0%)			
Alcohol use during pregnancy				
Yes	37 (38%)			
No	61 (62%)			
Child characteristics				
Sex				
Female	52 (53%)			
Male	46 (47%)			
Age at behavioral assessment (years)		5.4	0.4	4.8–6.1
Duration of breastfeeding (weeks)		57	71	0–258
Exposure to environmental contaminants				
Cord blood lead (ug/dL)		5	4	1–27
Cord blood mercury (ug/L)		23	19	2–104
Cord plasma PCB-153 (ng/g lipids)		122	83	22–490
Child blood lead (ug/dL)		5	5	1–37
Child blood mercury (ug/L)		9	9	0–38
Child plasma PCB-153 (ng/g lipids)		153	208	10–1467
Behavioral indicators				
Inattention (% of examination time)		10	5	0–25
Activity (% of examination time)		5	12	0–100

inattention (estimated PCB-153 levels for months 2, 3 and 4) and activity (estimated PCB-153 levels for months 2, 3, 4 and 5) (Fig. 1B). The size of the associations, in models adjusted and unadjusted for breastfeeding duration, decreased after the first few months of life. Results were similar after adjustment for cord or child blood lead levels. In the regression model of inattention, including both estimated children's PCB-153 at 2 months and 5-year blood lead concentration, both PCB-153 and lead levels were significant predictors of inattention. Adjustment for sex, age at assessment, crowding and alcohol consumption during pregnancy did not change the results materially.

4. Discussion

In this study, we evaluated the association between measured cord plasma and monthly estimated levels of PCB-153 during the first year of life, and inattention and activity in Inuit preschoolers. Results from main analyses were suggestive of a small association between estimated children's PCB-153 levels at 2 months and increased preschooler inattention, although the effect estimate was approximately the same as that observed with cord plasma levels. Activity was not associated with any exposure estimate in main analyses.
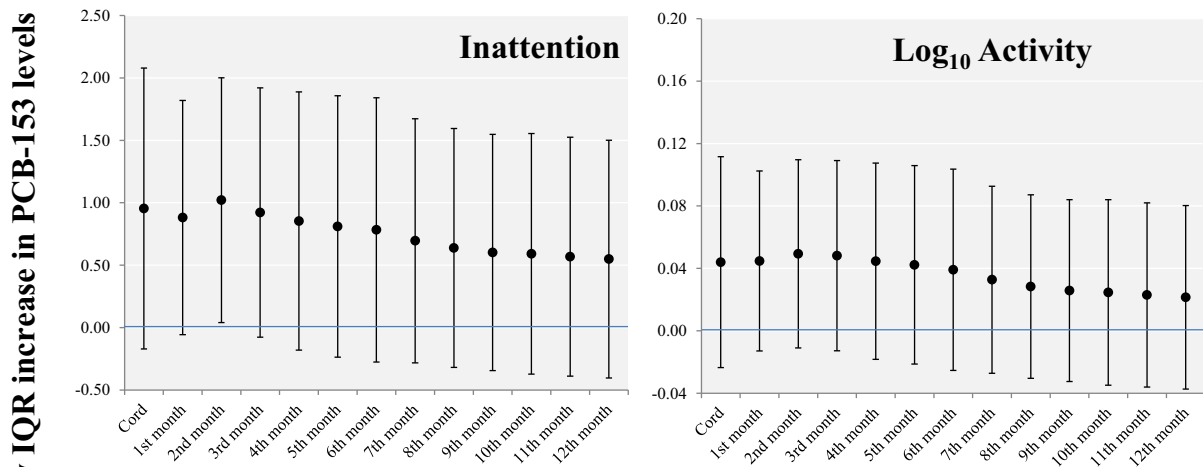
Statistical adjustment for the duration of breastfeeding in regression models slightly increased regression coefficients for postnatal level estimates, some of which became statistically significant for inattention (months: 2–4) and activity (months: 2–5). Whether to control for breastfeeding duration in regression models is an important question in studies of lactational exposures. This question becomes even more pivotal when breastfeeding duration is used to estimate children's levels, which is the case in our study. On the one hand, the duration of breastfeeding is correlated with estimated children's levels and may introduce collinearity (Lackmann, 2006; Ayotte et al., 2003). On the other hand, the fact that the duration of breastfeeding was also reported to have beneficial effects on children's behavior makes it a potential confounder (Groen-Blokhuis et al., 2013; Julvez et al., 2007). Although the duration of breastfeeding was not associated with the outcomes at p < 0.2 in our study, our findings suggest that breastfeeding may negatively confound the association between postnatal PCB-153 and behavioral outcomes. Hence, it may be necessary to systematically evaluate the impact of confounding by breastfeeding in studies of postnatal exposure to lipophilic persistent organic pollutants like PCBs.

In our study, where children were inattentive for an average of 10% of fine motor testing time, each IQR increase in estimated PCB-153 levels at 2 months of age was associated with an additional 1.02% of inattention time. The effect size decreased for subsequent months, suggesting that neurodevelopmental processes related to attention may be more vulnerable to PCBs during the first months of life than during later months. Whereas multiple studies have observed an association between prenatal exposure to PCBs and deficits in children's attention (Jacobson and Jacobson, 2003; Sagiv et al., 2010; Stewart et al., 2003, 2005), few studies assessed the effects of postnatal exposure on this outcome. Based on measured plasma PCB levels at 4 years of age, Jacobson and Jacobson (2003) found no association between postnatal exposure and attention at 4 and 11 years. Similarly, no association was observed between plasma PCB-153 levels measured at 5 years of age and attention assessed concurrently in a previous analysis of the cohort presented in our study (Plusquellec et al., 2010). In a previous study where a pharmacokinetic model was used to estimate postnatal PCB-153 levels, prenatal, but not postnatal, PCB-153 levels were associated with inattention at 11 months of age (Verner et al., 2010). The strength of the association with estimated PCB-153 levels at 2 months of age in our study (1.02% increase per IQR) was only marginally greater than that obtained with cord blood levels (0.95% increase per IQR). Overall, children's attention seems to be particularly affected by PCB exposure during the prenatal period, but our results suggest that early postnatal period may also play a role.

A) Models adjusted for parity, socioeconomic status, pre-pregnancy body weight and gestational weight gain

B) Models adjusted for parity, socioeconomic status, pre-pregnancy body weight, gestational weight gain <u>and duration of breastfeeding</u>
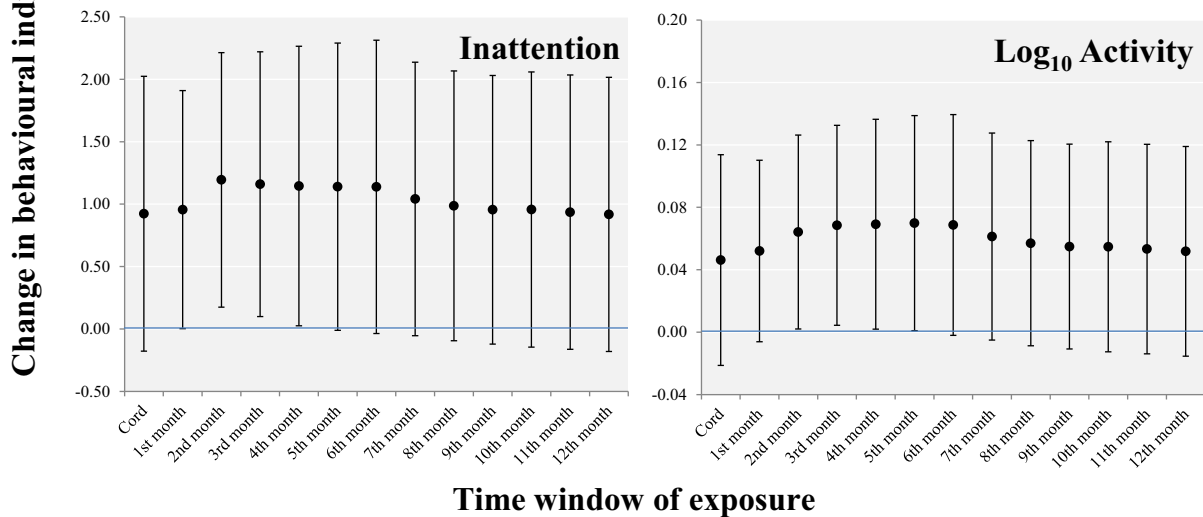

Fig. 1. Changes in inattention and activity (% of examination time) per 1 IQR increase in measured cord plasma and estimated children's PCB-153 levels. Note: activity was $\log_{10}$-transformed prior to regression analyses. Error bars represent 95% confidence intervals. A) Models adjusted for parity, socioeconomic status, pre-pregnancy body weight and gestational weight gain. B) Models adjusted for parity, socioeconomic status, pre-pregnancy body weight, gestational weight gain and duration of breastfeeding.

Statistically significant associations between postnatal PCB-153 levels and increased activity were observed after statistical adjustment for breastfeeding duration. In the same cohort, PCB-153 levels measured at the time of behavioral assessment were previously associated with a shorter latency to initiate activity (Plusquellec et al., 2010). An association between estimated early PCB-153 levels and increased activity was also observed in our previous study of 11-month-old Inuits (Verner et al., 2010). In contrast, increases in serum PCB levels at 4 years of age were associated with decreased activity in the Michigan study (Jacobson et al., 1990). In a recent study of our group, we did not find any association between concurrent PCB levels and teacher's report of hyperactivity and inattention in Inuit children at age 11 (Boucher et al., 2012). Taken together, these studies suggest that postnatal exposure to PCBs may have an impact on children's activity level, although the direction of the association is still unclear. Whether early postnatal exposure to PCBs is associated with diagnosis of hyperactivity and inattention or greater behavioral problems in school as yet to be assessed.

The effect estimates in this study, although statistically significant in certain cases, were relatively small. The clinical significance of observed associations, namely in terms of school achievement, has yet to be evaluated. Our approach to assess behavior through coding of video recordings, although extensively used to assess behavior in other fields (e.g., Courage et al., 2006; Graziano et al., 2011; Lewis et al., 2006; Manfra et al., 2014; Miller et al., 2014), is still in its early days in environmental epidemiology. In this context, the behavioral outcomes used in our study must be considered as a tool to detect subtle associations between low levels of PCBs exposure and behavioral development. Thus, the associations observed in our study must be interpreted as subclinical.

Limitations to this study include the small sample size, which may have prevented the detection of certain associations. Although participants included in this study do not differ significantly from those who were excluded, results obtained in this subset may not be generalizable to the population. In addition, error in estimated infants' PCB-153 levels

may have introduced noise in our analyses and biased effect estimates towards the null: in a previous validation study of 150 Inuit children, levels estimated using the pharmacokinetic model explained 74% of the variability in measured PCB-153 levels at ~6 months (range 3–14 months), leaving 26% of the variability unaccounted for (Verner et al., 2013). Another limitation, which applies any study of postnatal exposure, is that PCB levels across development are correlated. This correlation likely hampered our ability to clearly identify a critical window of vulnerability. Because measured PCB-153 levels are highly correlated with the levels of other persistent compounds like p,p'-dichlorodiphenyldichloroethylene (p,p'-DDE) measured in cord plasma, we cannot rule out the possibility that reported associations are attributable to a mixture of chemicals rather than PCBs exclusively.

5. Conclusion

Overall, our study was suggestive of a small association between estimated early postnatal PCB-153 levels and behavior in Inuit preschoolers. These results add to the growing evidence of postnatal windows of development during which children are susceptible to neurotoxic insults (Braun et al., 2012; Verner et al., 2010). Along with other early life environmental factors such as maternal smoking during pregnancy (Latimer et al., 2012) and exposure to lead (Plusquellec et al., 2007), lactational exposure to PCBs may increase the risk of behavioral problems in infancy and childhood. This route of exposure should therefore be taken into consideration when evaluating the risk of environmental contaminants. Nevertheless, these findings should not discourage mothers from nursing their infants as the numerous health benefits associated with breastfeeding likely outweigh the risk from contaminants at current environmental levels.

References

Ayotte, P., Muckle, G., Jacobson, J.L., Jacobson, S.W., Dewailly, E., 2003. Assessment of pre- and postnatal exposure to polychlorinated biphenyls: lessons from the Inuit cohort study. Environ. Health Perspect. 111 (9), 1253–1258.

Boucher, O., Jacobson, S.W., Plusquellec, P., Dewailly, E., Ayotte, P., Forget-Dubois, N., et al., 2012. Prenatal methylmercury, postnatal lead exposure, and evidence of attention deficit hyperactivity disorder among Inuit children in Arctic Quebec. Environ. Health Perspect. 120 (10), 1456–1461.

Braun, J.M., Hoffman, E., Schwartz, J., Sanchez, B., Schnaas, L., Mercado-Garcia, A., et al., 2012. Assessing windows of susceptibility to lead-induced cognitive deficits in Mexican children. Neurotoxicology 33 (5), 1040–1047.

Courage, M.L., Reynolds, G.D., Richards, J.E., 2006. Infants' attention to patterned stimuli: developmental change from 3 to 12 months of age. Child Dev. 77 (3), 680–695.

Despres, C., Beuter, A., Richer, F., Poitras, K., Veilleux, A., Ayotte, P., et al., 2005. Neuromotor functions in Inuit preschool children exposed to Pb, PCBs, and Hg. Neurotoxicol. Teratol. 27 (2), 245–257.

Dubois, J., Dehaene-Lambertz, G., Kulikova, S., Poupon, C., Huppi, P.S., Hertz-Pannier, L., 2014. The early development of brain white matter: a review of imaging studies in fetuses, newborns and infants. Neuroscience 276, 48–71.

Eubig, P.A., Aguiar, A., Schantz, S.L., 2010. Lead and PCBs as risk factors for attention deficit/hyperactivity disorder. Environ. Health Perspect. 118 (12), 1654–1667.

Graziano, P.A., Calkins, S.D., Keane, S.P., 2011. Sustained attention development during the toddlerhood to preschool period: associations with toddlers' emotion regulation strategies and maternal behavior. Infant Child Dev. 20 (6), 389–408.

Groen-Blokhuis, M.M., Franic, S., van Beijsterveldt, C.E., de Geus, E., Bartels, M., Davies, G.E., et al., 2013. A prospective study of the effects of breastfeeding and FADS2 polymorphisms on cognition and hyperactivity/attention problems. Am. J. Med. Genet. B Neuropsychiatr. Genet. 162B (5), 457–465.

Hollingshead, A.B., 1975. Four Factor Index of Social Status. Unpublished manuscript.

Jacobson, J.L., Jacobson, S.W., 2003. Prenatal exposure to polychlorinated biphenyls and attention at school age. J. Pediatr. 143 (6), 780–788.

Jacobson, J.L., Jacobson, S.W., Humphrey, H.E.B., 1990. Effects of exposure to Pcbs and related-compounds on growth and activity in children. Neurotoxicol. Teratol. 12 (4), 319–326.

Julvez, J., Ribas-Fito, N., Forns, M., Garcia-Esteban, R., Torrent, M., Sunyer, J., 2007. Attention behaviour and hyperactivity at age 4 and duration of breast-feeding. Acta Paediatr. 96 (6), 842–847.

Lackmann, G.M., 2006. Human milk, environmental toxins and pollution of our infants: disturbing findings during the first six months of life. Int. J. Biomed. Sci. 2 (2), 178–183.

Latimer, K., Wilson, P., Kemp, J., Thompson, L., Sim, F., Gillberg, C., et al., 2012. Disruptive behaviour disorders: a systematic review of environmental antenatal and early years risk factors. Child Care Health Dev. 38 (5), 611–628.

Lewis, M.D., Granic, I., Lamm, C., 2006. Behavioral differences in aggressive children linked with neural mechanisms of emotion regulation. Ann. N. Y. Acad. Sci. 1094, 164–177.

Manfra, L., Davis, K.D., Ducenne, L., Winsler, A., 2014. Preschoolers' motor and verbal self-control strategies during a resistance-to-temptation task. J. Genet. Psychol. 175 (3–4), 332–345.

Miller, A.L., Seifer, R., Crossin, R., Lebourgeois, M.K., 2014. Toddler's self-regulation strategies in a challenge context are nap-dependent. J. Sleep Res. http://dx.doi.org/10.1111/jsr.12260.

Muckle, G., Ayotte, P., Dewailly, E., Jacobson, S.W., Jacobson, J.L., 2001a. Determinants of polychlorinated biphenyls and methylmercury exposure in Inuit women of child-bearing age. Environ. Health Perspect. 109 (9).

Muckle, G., Ayotte, P., Dewailly, E.E., Jacobson, S.W., Jacobson, J.L., 2001b. Prenatal exposure of the northern Quebec Inuit infants to environmental contaminants. Environ. Health Perspect. 109 (12), 1291–1299.

Plusquellec, P., Muckle, G., Dewailly, E., Ayotte, P., Jacobson, S.W., Jacobson, J.L., 2007. The relation of low-level prenatal lead exposure to behavioral indicators of attention in Inuit infants in Arctic Quebec. Neurotoxicol. Teratol. 29 (5), 527–537.

Plusquellec, P., Muckle, G., Dewailly, E., Ayotte, P., Begin, G., Desrosiers, C., et al., 2010. The relation of environmental contaminants exposure to behavioral indicators in Inuit preschoolers in Arctic Quebec. Neurotoxicology 31 (1), 17–25.

Polanska, K., Jurewicz, J., Hanke, W., 2013. Review of current evidence on the impact of pesticides, polychlorinated biphenyls and selected metals on attention deficit/hyperactivity disorder in children. Int. J. Occup. Med. Environ. Health 26 (1), 16–38.

Rhainds, M., Levallois, P., Dewailly, E., Ayotte, P., 1999. Lead, mercury, and organochlorine compound levels in cord blood in Quebec, Canada. Arch. Environ. Health 54 (1), 40–47.

Rice, D., Barone, S., 2000. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. Environ. Health Perspect. 108, 511–533.

Sagiv, S.K., Nugent, J.K., Brazelton, T.B., Choi, A.L., Tolbert, P.E., Altshul, L.M., Korrick, S.A., 2008. Prenatal organochlorine exposure and measures of behavior in infancy using the Neonatal Behavioral Assessment Scale (NBAS). Environ. Health Perspect. 116 (5), 666–673.

Sagiv, S.K., Thurston, S.W., Bellinger, D.C., Tolbert, P.E., Altshul, L.M., Korrick, S.A., 2010. Prenatal organochlorine exposure and behaviors associated with attention deficit hyperactivity disorder in school-aged children. Am. J. Epidemiol. 171 (5), 593–601.

Shrier, I., Platt, R.W., 2008. Reducing bias through directed acyclic graphs. BMC Med. Res. Methodol. 8, 70.

Stewart, P., Fitzgerald, S., Reihman, J., Gump, B., Lonky, E., Darvill, T., et al., 2003. Prenatal PCB exposure, the corpus callosum, and response inhibition. Environ. Health Perspect. 111 (13), 1670–1677.

Stewart, P., Reihman, J., Gump, B., Lonky, E., Darvill, T., Pagano, J., 2005. Response inhibition at 8 and 9 1/2 years of age in children prenatally exposed to PCBs. Neurotoxicol. Teratol. 27 (6), 771–780.

Verner, M.A., Ayotte, P., Muckle, G., Charbonneau, M., Haddad, S., 2009. A physiologically based pharmacokinetic model for the assessment of infant exposure to persistent organic pollutants in epidemiologic studies. Environ. Health Perspect. 117 (3), 481–487.

Verner, M.A., Plusquellec, P., Muckle, G., Ayotte, P., Dewailly, E., Jacobson, S.W., et al., 2010. Alteration of infant attention and activity by polychlorinated biphenyls: unravelling critical windows of susceptibility using physiologically based pharmacokinetic modeling. Neurotoxicology 31 (5), 424–431.

Verner, M.A., Sonneborn, D., Lancz, K., Muckle, G., Ayotte, P., Dewailly, E., et al., 2013. Toxicokinetic modeling of persistent organic pollutant levels in blood from birth to 45 months of age in longitudinal birth cohort studies. Environ. Health Perspect. 121 (1), 131–137.