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Impact of fetal and childhood mercury exposure on immune status in children

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ABSTRACT

Background: Mercury exposure have been shown to affect immune status in animals as reflected by cytokine expression. It is unclear whether low levels of exposure during fetal and/or childhood periods could impact on immune status in humans.
Objectives: To test the hypothesis that fetal and childhood mercury exposure is associated with childhood cytokine profiles and to investigate whether childhood selenium levels interact with any of the associations found.
Methods: Children were recruited from a previously established birth cohort between the ages of 6–9 years for assessment and measurement of blood mercury, selenium and cytokine profile (interleukin (IL)-4, IL-6, IL-8, IL-10, IL-13 and TNF-alpha). Multivariable linear regression models were used to assess the adjusted association of cord blood mercury concentration and current mercury concentrations with levels of the cytokine levels. We tested whether the association with current mercury level varied by current selenium level and cord blood mercury level.
Results: IL-10 was negatively associated with current blood mercury concentration. The effect was greatest in cases with low cord blood mercury and low current selenium concentrations. None of the other cytokine levels were associated with either cord blood or current blood mercury concentrations, except that cord blood mercury was negatively associated with IL-6.
Conclusions: Childhood mercury exposure was negatively associated with childhood IL-10 levels. It is postulated that while selenium is protective, low levels of fetal mercury exposure may increase the degree of this negative association during childhood. Further studies into the clinical significance of these findings are required.

1. Introduction

In utero exposure to environmental pollutants may exert long-term effects on health and development. Growing fetuses are usually more susceptible to the harmful effects of pollutants compared to adults partly due to plasticity in the developing fetuses (Horton, 2005) and the immature metabolic system (Qanungo and Mukherjea, 2000; Ginsberg et al., 2004). Several birth cohort studies have documented the association of altered neurocognitive functions in individuals with higher *in utero* exposure to various environmental pollutants including heavy metals (Debes et al., 2006; Kim et al., 2013; Grandjean et al., 1997; Lam et al., 2013) and persistent organic pollutants (Gladen and Rogan, 1991; Huisman et al., 1995), even when the maternal body load is within acceptable levels (Harada, 1995). Studies have suggested changes in reproductive (Gladen et al., 2000; Mocarelli et al., 2011), metabolic (Verhulst et al., 2009) and immune systems (Weisglas-Kuperus et al., 1995; Glynn et al., 2008) as a result of *in utero* exposure to environmental pollutants, implying that low level environmental pollutants to the developing fetus may incur subtle impact to the developmental trajectory and function of various systems and is therefore of particular concern.

Mercury, in its organic form, passes through the placenta efficiently (Kajiwara et al., 1996). Thus, cord blood mercury concentrations are higher than the maternal mercury concentrations, and developing fetuses are exposed to higher mercury concentrations than even their mothers (Fok et al., 2007). Subtle impacts of *in utero* low-dose mercury exposure on neurocognitive

Abbreviations: CI, Confidence Interval; IL, Interleukin

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Table 1
Comparison of maternal mercury (blood/hair) and cord blood mercury level in different countries/regions.

Publication	Country/region	Study year	Sample size	Hg level		
				Maternal blood	Maternal hair	Cord blood
Fok et al. (2007)	Hong Kong	2000–2001	1057	Median (Total Hg): 24.6 nmol/L (4.94 ug/L) Interquartile range: 18.2–34.3 nmol/L (3.66–6.89 ug/L)	Median (Total Hg): 1.7 ppm Interquartile range: 1.4–2.4 ppm	Median (Total Hg): 44.0 nmol/L (8.84 ug/L) Interquartile range: 31.6–61.6 nmol/L (6.35–12.38 ug/L)
Grandjean et al. (1997)	Faroe Islands	1986–1987	914		Mean (Total Hg): 4.27 ug/g Interquartile range: 2.6–7.7 ug/g	Mean (Total Hg): 115 nmol/L (22.9 ug/L) Interquartile range: 66.9–206.1 nmol/L (13.4–41.3 ug/L)
Gundacker et al. (2010)	Austria	2005	53	Median (Total Hg): 3.5 nmol/L (0.7 ug/L)	–	Median (Total Hg): 5.5 nmol/L (1.1 ug/L)
Ashley-Martin et al. (2015)	Canada	2008–2011	1260	Mean (MeHg): 4.3 nmol/L (0.86 ug/L) SD: 14.2 nmol/L (2.84 ug/L)	–	–
Evans et al. (2014)	NHANES, USA	2003–2004	1250[a]	Median (MeHg): 4.0 nmol/L (0.8 ug/L) SD: 5.0 nmol/L (1.0 ug/L)	–	–
Bjornberg et al. (2003)	Sweden	1996–1999	123	–	Mean (Total Hg): 0.35 ug/g Range: 0.07–1.5 ug/g	Median (MeHg): 6.5 nmol/L (1.3 ug/L) Range: 0.50–28.4 nmol/L (0.10–5.7 ug/L)
Davidson et al. (1995)	Seychelles Islands	1989	738	–	Mean (Total Hg): 5.9 ppm Range: 0.5–26.7 ppm	–
Tatsuta et al. (2014)	Japan	2001–2003	387	–	Mean (Total Hg): 2.0 ug/g 5th–95th percentile: 1.0–4.2 ug/g	Mean (Total Hg): 10.1 ng/g 5th–95th percentile: 4.3–22.2 ng/g
Sato et al. (2006)	Hawaii, USA	2004–2005	212	–	–	Mean: 24.1 nmol/L (4.82 ug/L) SD: 17.0 nmol/L (3.4 ug/L)
Ramon et al. (2009)	Spain	2004–2006	554	–	–	Mean (Total Hg): 47 nmol/L (9.4 ug/L) Range: 43.9–50.9 nmol/L (8.8–10.2 ug/L)

Hg: mercury; IQR: interquartile range; MeHg: methylmercury.
[a] Women of reproductive age instead of pregnant women.

(Orenstein et al., 2014; Grandjean et al., 1999; Myers et al., 2003; Lam et al., 2013) and cardiovascular function (Thurston et al., 2007; Valera et al., 2012; Grandjean et al., 2004) have been reported in studies of populations with high fish consumption. However little is known about the impact of *in utero* exposure to mercury on immune function. Immunotoxicity of mercury in its various forms has been well demonstrated both in animal models (Faustman et al., 2002) and *in vitro* models (Gardner et al., 2009), indicating that mercury may have a role to play in Th1/Th2 imbalance and susceptibility to autoimmune diseases and dysregulated immune response to infections.

So far human studies on immunotoxicity of mercury are mainly cross-sectional in design with lack of longitudinal studies to investigate the potential impact of *in utero* mercury exposure on the immune system and its function. The effect of current mercury exposure on immune function in humans is equally unclear from the few observational studies which reported mixed findings. Furthermore, many of these studies investigated the impact of inorganic mercury rather than methylmercury. Methylmercury, which is the species of mercury that general populations are more commonly exposed to, was associated with increased pro-inflammatory cytokines, antinuclear and antinucleolar autoantibodies and decreased anti-inflammatory cytokines in one study (Nyland et al., 2011a), but not in a smaller study of 61 mother-infant pairs (Nyland et al., 2011b). A few studies reported the level of mercury body load was positively associated with pro-inflammatory cytokines (Nyland et al., 2011a; Gardner et al., 2009; Gardner et al., 2010b), however they reported positive (Nyland et al., 2011a), negative (Gardner et al., 2009) and no association (Gardner et al., 2010b) of blood mercury exposure with anti-inflammatory cytokines, respectively. It should be noted however, that the studies by Gardner et al. investigated inorganic mercury exposure (Gardner et al., 2009; Gardner et al., 2010b) which is more common in situations related to occupational exposure, in contrast to the situation with many general populations, where methylmercury via fish consumption is the main risk (Lam et al., 2013). The majority of previous studies on the association between mercury exposure and immune function were conducted in adults with only one study in children, reporting a negative, rather than positive, association between mercury exposure (in this study likely to be mainly methylmercury) and a pro-inflammatory cytokine, TNF-alpha (Gump et al., 2012). The mixed findings may be due to the interacting effects by factors that may have impact on the action of mercury and/or the cytokine profile, such as selenium body load, mercury species and pattern of exposure, and individual susceptibility to disturbances in immunological response (Nyland et al., 2011a). Selenium mitigates methylmercury toxicity (Tatsuta et al., 2014) and independently affects immune response (Kiremidjian-Schumacher and Stotzky, 1987), however only one study has considered, but did not find such interacting effect (Nyland et al., 2011a). This study reported negative association of mercury exposure and some pro-inflammatory and anti-inflammatory cytokines amongst individuals with elevated antinuclear autoantibodies, indicating higher susceptibility to immune dysfunction. However, no studies have been able to evaluate whether mercury exposure during critical periods of development, such as the prenatal period, could alter the long term immune response to mercury.