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Effect of hemoglobin adjustment on the precision of mercury concentrations in maternal and cord blood

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ABSTRACT

The cord-blood mercury concentration is usually considered the best biomarker in regard to developmental methylmercury neurotoxicity. However, the mercury concentration may be affected by the binding of methylmercury to hemoglobin and perhaps also selenium. As cord-blood mercury analyses appear to be less precise than suggested by laboratory quality data, we studied the interrelationships of mercury concentrations with hemoglobin in paired maternal and cord blood samples from a Faroese birth cohort ($N=514$) and the Mothers and Children's Environmental Health study in Korea ($n=797$). Linear regression and structural equation model (SEM) analyses were used to ascertain interrelationships between the exposure biomarkers and the possible impact of hemoglobin as well as selenium. Both methods showed a significant dependence of the cord-blood concentration on hemoglobin, also after adjustment for other exposure biomarkers. In the SEM, the cord blood measurement was a less imprecise indicator of the latent methylmercury exposure variable than other exposure biomarkers available, and the maternal hair concentration had the largest imprecision. Adjustment of mercury concentrations both in maternal and cord blood for hemoglobin improved their precision, while no significant effect of the selenium concentration in maternal blood was found. Adjustment of blood–mercury concentrations for hemoglobin is therefore recommended.

1. Introduction

The cord-blood mercury (Hg) concentration has been suggested as the best risk indicator in regard to methylmercury-associated developmental neurotoxicity (Grandjean and Budtz-Jørgensen, 2007). However, as a biomarker of prenatal methylmercury exposure, the total Hg concentration in cord blood is associated with imprecision that exceeds the level suggested by laboratory quality assurance data (Grandjean et al., 2005; Grandjean and Budtz-Jørgensen, 2007). Some of this imprecision may be due to variable binding of methylmercury (MeHg) to erythrocytes, in which mercury binds to hemoglobin (Sakamoto et al., 2004). Previous studies have documented that Hg concentrations are higher in cord blood than in the corresponding maternal blood, likely due to the easy transfer of MeHg through the placenta (Kajiwara et al., 1996; Morrissette et al., 2004; Sakamoto et al., 2012), the greater affinity of MeHg to fetal hemoglobin (Hsu et al., 2007; Iyengar and Rapp, 2001), and the higher hematocrit in newborns compared to their mothers (Stern and Smith, 2003). For this reason, standardization of the blood–Hg

Abbreviations: AAS, atomic absorption spectrometry; AGFI, adjusted goodness of fit index; AIC, Akaike information criterion; CB-Hb, hemoglobin in cord blood; CB-Hg, Hg in cord blood; CFI, comparative fit index; CV, coefficient of variation; GFI, goodness of fit index; GM, geometric means; Hg, mercury; IQR, interquartile range; MB-Hb, hemoglobin in maternal blood; MB-Hg, Hg in maternal blood; MB-Se, selenium in maternal blood; MeHg, methylmercury; MH-Hg, Hg in maternal hair; MOCEH, Mothers and Children's Environmental Health; Se, selenium; SEM, structural equation model; SLS, sodium lauryl sulfate; TLI, Tucker–Lewis index.

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concentration to the one in erythrocytes has been recommended (Sakamoto et al., 2004). Adjustment for the hemoglobin concentration would likely be even better, although the impact on the imprecision has not been determined so far.

Another factor of possible relevance is that selenium (Se) is thought to bind to MeHg (Harris et al., 2003), thus possibly affecting the toxicokinetics of the latter. Hence, Se status could conceivably interfere with the transplacental transfer of MeHg and thus the partition between mother and fetus. However, previous studies of Se–MeHg interactions have mainly focused on impacts on MeHg toxicity under particular exposure regimens that may not reflect human exposures. The earliest experimental studies showed that Se reduced the acute toxicity of MeHg injected into rats, thus suggesting the notion that Se may form complexes with MeHg in the blood, thereby decreasing the bioavailability of both elements (Ganther et al., 1972). More recent research in rodents supports that antioxidant nutrients, including Se, in the diet may alter the reproductive and developmental toxicity associated with MeHg exposure (Beyrouty and Chan, 2006). As Se is known to co-exist with MeHg in fish and sea mammals (Burger and Gochfeld, 2007; Burger et al., 2007; Cabanero et al., 2005; Kaneko and Ralston, 2007), a potential toxicokinetic interaction may occur in regard to transplacental transfer of MeHg from maternal seafood diets. Although human evidence on this possibility is not available, we considered Se as a covariate.

Imprecision of the exposure parameter is a crucial concern, because the exposure parameter in routine statistical calculations is usually treated as an independent variable without error (Grandjean and Budtz-Jørgensen, 2007). However, all biomarkers are subject to imprecision, and non-differential errors tend to bias the dose–response relationship toward the null (Fuller, 1987). To take into account the imprecision, a useful approach is to employ a structural equation model, where confounders and effect variables are included (Budtz-Jørgensen et al., 2002; Grandjean and Budtz-Jørgensen, 2007). In a Faroese birth cohort, the average total imprecision (expressed as the coefficient of variation) for the cord-blood Hg concentration was found to be about 25% (Grandjean et al., 2005; Grandjean and Budtz-Jørgensen, 2007), a magnitude large enough to bias apparent dose–response relationships. The imprecision for hair Hg measurements is much greater. As only a very small part of such imprecision can be ascribed to laboratory variability, identification of other error sources is important.

Therefore, we assessed exposure biomarker imprecision and the impact of adjustment for hemoglobin and Se. We utilized data from birth cohort studies in the Faroe Islands and in Korea (Mothers and Children's Environmental Health, MOCEH).

2. Materials and methods

2.1. Subjects

A cohort of 514 singleton births was assembled at the National Hospital in the Faroe Islands during a 20-month period in 2007–2009. This North Atlantic population is of mainly Scandinavian origin, relatively uniform, and is covered by a modern health care service. The Faroese are of particular interest in environmental epidemiology, as pilot whale is among the traditional food items eaten as part of their marine diet. Pods of this small whale species are occasionally caught and the meat and blubber are shared locally. Because of the high MeHg concentration in the meat (Julshamn et al., 1987), the Faroese have a high average exposure to this contaminant and a wide range of exposure levels that depend on whale availability (Budtz-Jørgensen et al., 2004; Grandjean et al., 1992). At parturition, we obtained whole blood from the cord immediately after clamping. Maternal blood and hair was obtained approximately two weeks after parturition, when the mother brought the infant in for a scheduled health check-up. Cord blood and maternal blood were analyzed for total Hg and hemoglobin, while the maternal blood was also analyzed for Se. Complete samples sets were available from 514 subjects.

The MOCEH study was carried out in Korea to determine the effects of maternal environmental exposure on fetal and postnatal growth and development. All pregnant women living in the targeted study site (i.e., Seoul, Cheonan, and Ulsan), who were in their first trimester of pregnancy at the time of screening, were eligible. The maternal blood samples were obtained during late pregnancy (28–42 gestational weeks). The recruitment period in the MOCEH study was from 2006 to 2008 for the hospitals and clinics. A total of 921 women were eligible, and 124

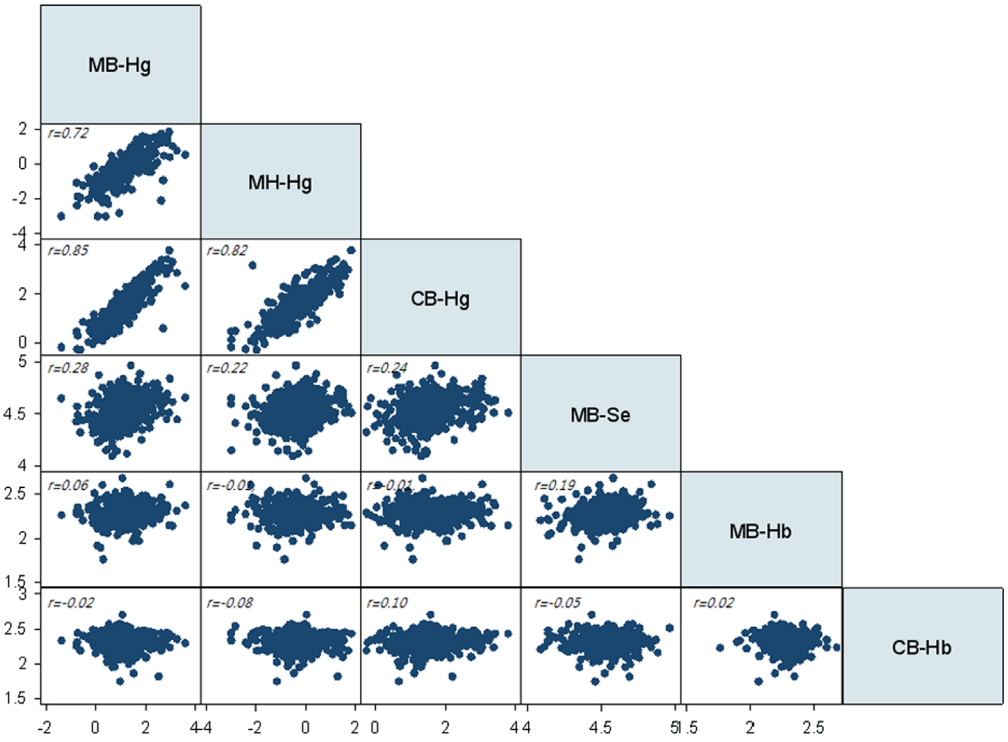

Fig. 1. Correlations between logarithmic transformations of biomarkers in the Faroese birth cohort. [a] MB-Hg, Hg in maternal blood; MH-Hg, Hg in maternal hair; Hg, latent variable; CB-Hg, MB-Se, Selenium in maternal blood; MB-Hb, Hemoglobin in maternal blood; Hg in cord blood; CB-Hb, hemoglobin in cord blood.