

Mercury and Prenatal Growth

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The intrauterine environment is critical for healthy prenatal growth and affects neonatal survival and later health. Mercury is a toxic metal which can freely cross the placenta and disrupt a wide range of cellular processes. Many observational studies have investigated mercury exposure and prenatal growth, but no prior review has synthesised this evidence. Four relevant publication databases (Embase, MEDLINE/PubMed, PsycINFO, and Scopus) were systematically searched to identify studies of prenatal mercury exposure and birth weight, birth length, or head circumference. Study quality was assessed using the NIH Quality Assessment Tool, and results synthesised in a narrative review. Twenty-seven studies met the review criteria, these were in 17 countries and used 8 types of mercury biomarker. Studies of birth weight (total = 27) involving populations with high levels of mercury exposure, non-linear methods, or identified as high quality were more likely to report an association with mercury, but overall results were inconsistent. Most studies reported no strong evidence of association between mercury and birth length (n = 14) or head circumference (n = 14).

systematic review

pregnancy

childhood

mercury

toxic metal

birth weight

birth length

head circumference

prenatal growth

1. Introduction

Prenatal development involves the growth and development of foetal internal systems and is implicated in a range of later health outcomes. Overall prenatal growth and intrauterine health are commonly benchmarked after birth using neonatal birth weight, birth length (crown to heel), head circumference, and other anthropometric measures [1]. The prevalence of births classed as low birth weight (<2500 g) globally in 2015 was 14.6% [2] and the rate of decline is not on course to meet WHO targets [3]. Growth measures at birth are predictive of infant mortality [4], risk of childhood illness and impaired development [5], and may even be associated with long-term adult health [6]. The most up to date (2015) report on childhood mortality estimated that 45% of deaths (2.6 million) below the age of 5 years were neonates, most linked to prenatal or intrapartum conditions [7].

Prenatal development is dependent upon an optimal intrauterine environment and foetal responses to this environment, which are mediated by mechanisms such as the production of foetal and placental hormones, modified blood flow, and metabolic changes [8]. The developmental environment is also linked to maternal reproductive health and is sensitive to maternal nutrition and contact with harmful environmental agents [8]. Identifying hazardous substances and reducing exposure to them may be an effective way of improving overall neonatal health and survival [9].

The toxic metal mercury (Hg) is one such substance of concern and is frequently flagged in antenatal care guidance usually in the context of advice on fish consumption [10]. Mercury is abundant in the earth's crust and is mobilised into the environment through human industrial activity and natural events such as volcanic activity [11][12][13]. Routes to human contact are well documented [13][14][15], and include the food chain, soil, water contamination, and mercury-containing cosmetics and other goods [16].

The human toxicity of mercury varies depending on the duration of exposure, dosage, and the specific compound of mercury. Elemental mercury when ingested is relatively benign due to low gastrointestinal absorption, but when inhaled can enter the blood stream where it can cross both the placenta and blood–brain barrier. In contrast, inorganic mercury when ingested tends to accumulate within the kidneys and can also be formed within the body from oxidised elemental mercury. Both forms are highly reactive with sulphur-containing proteins and can deactivate enzymes, inhibit DNA methylation and cell division, and lead to oxidative stress and cell death [14][17]. Methylmercury (MeHg)—an organic compound bound with carbon—is the most bioavailable form of mercury and can easily enter the body through the digestion of contaminated foods [14]. MeHg is lipid soluble and can be distributed throughout the body with a high reactivity with sulphhydryl groups, leading to disruption of a wide range of basic cellular functions [18].

Mercury may be a threat to the developing foetus because both elemental and organic forms of mercury can cross the placenta during gestation [11][18], where it may accumulate in a far higher dose-to-weight ratio than is possible in an adult. The removal and excretion of mercury is relatively slow: in adults elemental mercury has a biological half-life of 35–90 days, inorganic mercury approximately 40 days, and methylmercury approximately 65 days [18]. Therefore, prolonged exposure may lead to the accumulation of harmful quantities. However, whether low level mercury exposure during pregnancy harms foetal growth to any measurable degree is unclear. There have been many observational studies investigating this question, but no prior meta-analyses or systematic reviews have been published.

Governmental and non-governmental organisation guidelines for fish consumption as a source of mercury exposure vary, in terms of quantity and species to avoid [10]. This is in part due to uncertainty about the cost/benefits of associated nutrients and elements in fish, including mercury. Much of the focus of previous research has been on the neurodevelopmental impact of mercury exposure. However, the widespread reactivity of mercury makes it possible that exposure interferes with overall foetal growth and not only the brain. The aim of this study is to review the evidence on mercury exposure during pregnancy and prenatal growth. Specific objectives are: (1) to systematically search for studies of prenatal mercury exposure and perinatal growth outcomes; (2) to evaluate the quality of the existing evidence; (3) to synthesise the evidence and compare for differences based on quality and other methodological dimensions.

2. Current Insights

Currently, identified a diverse range of studies including populations including populations together encompassing a wide range of Hg concentrations. Biomarkers were used that correspond with mercury exposure during

preconception, early, late, and the full term of pregnancy.

When considering only studies that adjusted for key confounders and were considered high quality, a greater proportion of results reported strong evidence of a negative association of mercury concentrations with birthweight. Overall, most model estimates were negative, and a minority of analyses found stronger evidence of a negative association. However, taken together most analyses from these studies did not indicate strong evidence of an association between maternal mercury concentrations and birth weight. Confidence intervals which did not overlap with the null were reported in 16 estimates from 11 studies, out of a total of 49 estimates from 27 studies. These analyses tended to use subgroups by Hg levels or use cohorts with relatively higher mean mercury concentrations than other studies of the same tissue, but this pattern was inconsistent.

A clearer pattern was seen with birth length and head circumference. Almost all studies reported no strong evidence that prenatal mercury exposure is associated with birth length (10 of 14 studies), or head circumference (13 of 14 studies). While there were a few studies of these two outcomes that reported a negative association, it may be that unidentified confounding or other methodological challenges have influenced their results. The lack of strong evidence was similar when considering only high quality studies, although studies tended to show negative associations which overlapped with the null particularly results from high quality studies of head circumference. It is therefore not possible to rule out a small negative effect which studies were underpowered to detect.

The prevalence of mercury in the environment and well publicised dangers from contamination events has led to chronic mercury exposure at lower levels being a concern for both health professionals and pregnant women. Both NHS (National Health Service, in England) and CDC (Centers for Disease Control and Prevention, in the USA) guidelines, among others, identify mercury as a danger during pregnancy and recommend avoiding excessive consumption of mercury-containing foods [19][20]. This review does not find strong evidence that lower levels of exposure common to most countries is associated with prenatal growth. If this is accurate, it is possible that guidance to avoid dietary mercury may be unnecessary or overly complicated for any marginal gain in birth outcomes. Such guidance is not without potential harms, including the loss of the many beneficial nutrients contained in fish [21].

Two major events have informed much of our awareness of acute mercury toxicity: seed grain contamination in Basra, Iraq, and coastal pollution in Minamata, Japan [13]. Both resulted in detrimental effects on foetal growth and infant mortality. However, in both cases the exposure was qualitatively different from that of chronic exposure from diet. In Basra, grain stores were treated with a fungicide containing organic mercury species, which led to mass poisoning in the following months [22]. In Minamata, an industrial plant contaminated the bay and marine life within it with organic mercury compounds [23]. In contrast, chronic dietary exposure as studied in this review frequently involves bio-methylation of elemental or inorganic species into methylmercury. Secondly, both contamination events involved far higher levels of mercury accumulation than any study in this review reported: hair mercury concentrations peaked in Basra at 120 to 600 µg/g [24] and in Minamata a maximum of 705 µg/g was reported [25]. It may be that the harms seen from acute poisoning are not generalisable to chronic exposure.

The strengths of the study are firstly that it is the first systematic review of the large number of studies which were conducted on prenatal mercury exposure and foetal growth. Secondly, a wide variety of populations were involved and study authors reported the predominant modes of exposure to include cooking with liquefied natural gas [26], rice consumption [27], local fish consumption in areas contaminated with small scale gold or tin mining [28][29], and seafood consumption ([e.g., [30]). It also includes populations with Western diets that have relatively low levels of mercury exposure (e.g., [31][32][33]). Thirdly, we were able to identify studies which used a variety of types of tissue to measure prenatal mercury exposure. These can contain different forms of mercury and are sensitive to different durations of mercury exposure. Finally, we followed methods pre-specified by a protocol and used tools such as albatross plots to review the evidence in a systematic manner. By doing so, we have avoided focusing solely on the positive or most interesting results from each study.

There are several possible limitations to this review. First, the heterogeneity of biomarkers used to measure mercury made it difficult to compare results between all studies. We identified two comprehensive reviews of mercury biomarkers which informed our comparisons [34][35], but there is a degree of uncertainty in our current knowledge of how mercury accumulates and is distributed across tissues. Consequently, it was not possible to compare mean mercury concentrations between biomarkers, and we were unable to identify with confidence which study populations experienced the highest levels of prenatal mercury exposure. This impaired our ability to make judgements of potential non-linear effects at higher levels of mercury exposure.

References

1. Camerota, M.; Bollen, K.A. Birth Weight, Birth Length, and Gestational Age as Indicators of Favorable Fetal Growth Conditions in a US Sample. *PLoS ONE* 2016, 11, e0153800.
2. Blencowe, H.; Krusevec, J.; de Onis, M.; Black, R.E.; An, X.; Stevens, G.A.; Borghi, E.; Hayashi, C.; Estevez, D.; Cegolon, L.; et al. National, regional, and worldwide estimates of low birthweight in 2015, with trends from 2000: A systematic analysis. *Lancet Glob. Health* 2019, 7, e849–e860.
3. World Health Organization. Comprehensive Implementation Plan on Maternal, Infant and Young Child Nutrition. Available online: (accessed on 20 March 2021).
4. Katz, J.; Lee, A.C.; Kozuki, N.; Lawn, J.E.; Cousens, S.; Blencowe, H.; Ezzati, M.; Bhutta, Z.A.; Marchant, T.; Willey, B.A.; et al. Mortality risk in preterm and small-for-gestational-age infants in low-income and middle-income countries: A pooled country analysis. *Lancet* 2013, 382, 417–425.
5. Hack, M.; Klein, N.K.; Taylor, H.G. Long-term developmental outcomes of low birth weight infants. *Future Child.* 1995, 5, 176–196.
6. Negrato, C.A.; Gomes, M.B. Low birth weight: Causes and consequences. *Diabetol. Metab. Syndr.* 2013, 5, 49.
7. Wang, H.; Bhutta, Z.A.; Coates, M.M.; Coggleshall, M.; Dandona, L.; Diallo, K.; Franca, E.B.; Fraser, M.; Fullman, N.; Gething, P.W.; et al. Global, regional, national, and selected subnational

levels of stillbirths, neonatal, infant, and under-5 mortality, 1980–2015: A systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016, 388, 1725–1774.

8. Kwon, E.J.; Kim, Y.J. What is fetal programming? A lifetime health is under the control of in utero health. *Obstet. Gynecol. Sci.* 2017, 60, 506–519.

9. Shapira, N. Prenatal Nutrition: A Critical Window of Opportunity for Mother and Child. *Women's Health* 2008, 4, 639–656.

10. Taylor, C.M.; Emmett, P.M.; Emond, A.M.; Golding, J. A review of guidance on fish consumption in pregnancy: Is it fit for purpose? *Public Health Nutr.* 2018, 21, 2149–2159.

11. Bose-O'Reilly, S.; McCarty, K.M.; Steckling, N.; Lettmeier, B. Mercury exposure and children's health. *Curr. Probl. Pediatr. Adolesc. Health Care* 2010, 40, 186–215.

12. World Health Organization. Elemental Mercury and Inorganic Mercury Compounds: Human Health Aspects. Available online: (accessed on 20 March 2021).

13. Driscoll, C.T.; Mason, R.P.; Chan, H.M.; Jacob, D.J.; Pirrone, N. Mercury as a Global Pollutant: Sources, Pathways, and Effects. *Environ. Sci. Technol.* 2013, 47, 4967–4983.

14. Oliveira, C.S.; Nogara, P.A.; Ardisson-Araújo, D.M.P.; Aschner, M.; Rocha, J.B.T.; Dórea, J.G. Neurodevelopmental Effects of Mercury. *Advances in Neurotoxicology* 2018, 2, 27–86.

15. Lehnherr, I.; St. Louis, V.L.; Hintelmann, H.; Kirk, J.L. Methylation of inorganic mercury in polar marine waters. *Nat. Geosci.* 2011, 4, 298–302.

16. Environmental Protection Agency. Mercury in Consumer Products. Available online: (accessed on 20 March 2021).

17. Bernhoft, R.A. Mercury toxicity and treatment: A review of the literature. *J. Environ. Public Health* 2012, 2012, 460508.

18. Broussard, L.; Hammett-Stabler, C.; Winecker, R.; Ropero-Miller, J. The Toxicology of Mercury. *Lab. Med.* 2002, 33, 614–625.

19. CDC. Environmental Exposures: Mercury. Available online: (accessed on 28 March 2021).

20. NHS. Foods to Avoid in Pregnancy. Available online: (accessed on 28 March 2021).

21. Oken, E.; Kleinman, K.P.; Berland, W.E.; Simon, S.R.; Rich-Edwards, J.W.; Gillman, M.W. Decline in fish consumption among pregnant women after a national mercury advisory. *Obstet. Gynecol.* 2003, 102, 346–351.

22. Al-Tikriti, K.; Al-Mufti, A.W. An outbreak of organomercury poisoning among Iraqi farmers. *Bull. World Health Organ.* 1976, 53, 15–21.

23. James, A.K.; Nehzati, S.; Dolgova, N.V.; Sokaras, D.; Kroll, T.; Eto, K.; O'Donoghue, J.L.; Watson, G.E.; Myers, G.J.; Krone, P.H.; et al. Rethinking the Minamata Tragedy: What Mercury Species

Was Really Responsible? *Environ. Sci. Technol.* 2020, 54, 2726–2733.

24. Skerfving, S.B.; Copplestone, J.F. Poisoning caused by the consumption of organomercury-dressed seed in Iraq. *Bull. World Health Organ.* 1976, 54, 101–112.

25. Harada, M. Minamata Disease: Methylmercury Poisoning in Japan Caused by Environmental Pollution. *Crit. Rev. Toxicol.* 1995, 25, 1–24.

26. Arinola, G.O.; Dutta, A.; Oluwole, O.; Olopade, C.O. Household Air Pollution, Levels of Micronutrients and Heavy Metals in Cord and Maternal Blood, and Pregnancy Outcomes. *Int. J. Environ. Res. Public Health* 2018, 15, 2891.

27. Hong, C. Prenatal Methylmercury Exposure through Rice Consumption in Rural China. (Doctoral Dissertation, 2017). Available online: (accessed on 10 March 2021).

28. Baldewsingh, G.; Wickliffe, J.; van Eer, E.; Shankar, A.; Hindori-Mohangoo, A.; Harville, E.; Covert, H.; Shi, L.; Lichtveld, M.; Zijlmans, W. Prenatal Mercury Exposure in Pregnant Women from Suriname's Interior and Its Effects on Birth Outcomes. *Int. J. Environ. Res. Public Health* 2020, 17, 4032.

29. Marques, R.C.; Bernardi, J.V.E.; Dórea, J.G.; Brandão, K.G.; Bueno, L.; Leão, R.S.; Malm, O. Fish consumption during pregnancy, mercury transfer, and birth weight along the Madeira River Basin in Amazonia. *Int. J. Environ. Res. Public Health* 2013, 10, 2150–2163.

30. Foldspang, A.; Hansen, J.C. Dietary intake of methylmercury as a correlate of gestational length and birth weight among newborns in Greenland. *Am. J. Epidemiol.* 1990, 132, 310–317.

31. Govarts, E.; Remy, S.; Bruckers, L.; Den Hond, E.; Sioen, I.; Nelen, V.; Baeyens, W.; Nawrot, T.S.; Loots, I.; Van Larebeke, N.; et al. Combined Effects of Prenatal Exposures to Environmental Chemicals on Birth Weight. *Int. J. Environ. Res. Public Health* 2016, 13, 495.

32. Bloom, M.S.; Buck Louis, G.M.; Sundaram, R.; Maisog, J.M.; Steuerwald, A.J.; Parsons, P.J. Birth outcomes and background exposures to select elements, the Longitudinal Investigation of Fertility and the Environment (LIFE). *Environ. Res.* 2015, 138, 118–129.

33. Taylor, C.M.; Golding, J.; Emond, A.M. Blood mercury levels and fish consumption in pregnancy: Risks and benefits for birth outcomes in a prospective observational birth cohort. *Int. J. Hyg. Environ. Health* 2016, 219, 513–520.

34. Branco, V.; Caito, S.; Farina, M.; Teixeira da Rocha, J.; Aschner, M.; Carvalho, C. Biomarkers of mercury toxicity: Past, present, and future trends. *J. Toxicol. Environ. Health B Crit. Rev.* 2017, 20, 119–154.

35. Castro, N.S.S.; Lima, M.O. Hair as a Biomarker of Long Term Mercury Exposure in Brazilian Amazon: A Systematic Review. *Int. J. Environ. Res. Public Health* 2018, 15, 500.

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