Published in final edited form as:

Curr Environ Health Rep. 2016 December ; 3(4): 392–404. doi:10.1007/s40572-016-0108-x.

Manganese Exposure and Cognition Across the Lifespan: Contemporary Review and Argument for Biphasic Dose-Response Health Effects

Kaitlin Vollet, MPH,

Division of Epidemiology, Department of Environmental Health, College of Medicine, University of Cincinnati, Cincinnati, OH 45267-0056

Erin N. Haynes, DrPH, MS, and

Division of Epidemiology, Department of Environmental Health, College of Medicine, University of Cincinnati, Cincinnati, OH 45267-0056

Kim N. Dietrich, PhD, MA

Division of Epidemiology, Department of Environmental Health, College of Medicine, University of Cincinnati, Cincinnati, OH 45267-0056

Abstract

Manganese (Mn) is both an essential micronutrient and potential neurotoxicant. This dual role underlies a growing body of literature demonstrating that Mn exhibits a biphasic dose-response relationship with neurocognitive outcomes. We reviewed recent epidemiologic studies from 2007–2016 that investigated the relationship between Mn exposure and cognitive outcomes across the lifespan: early life, school-aged children, and adulthood. In total, 27 research articles were included in this review: 12 pediatric and 15 adult studies (10 occupational and five environmental exposures). The majority of these studies provided evidence of the negative effects of Mn exposure on cognition. The pediatric literature provides evidence that both high and low levels of Mn are negatively associated with intellectual development. Future Mn research should include examination of non-linear relationships and multiple neurotoxicants across the lifespan, and particularly during critical developmental windows.

Keywords

pediatric; manganese; dose-response; literature review; occupational; cognition

Correspondence to: Erin N. Haynes.

Compliance and Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors in the conduct of this literature review.

Conflict of Interest

Kaitlin Vollet, Erin N. Haynes, and Kim N. Dietrich declare that they have no conflict of interest.

Introduction

Manganese (Mn), an essential micronutrient, is required for the normal development of many organ systems and is crucial to brain growth and development [1, 2]. It is ubiquitous in the environment, naturally occurring in air, water, soil, and food [3]. Excess environmental exposure may arise from contaminated drinking water [4–6], air pollution [7–10], gasoline enhanced with methylcyclopentadienyl manganese tricarbonyl (MMT) [11], agricultural fungicides [12, 13], infant formulas [14], parenteral nutrition [15, 16], and illicit intravenous drug use [17]. Abundant in the diet, nutritional intake is the most common source for those who are not occupationally exposed [18]. Tight homeostatic mechanisms maintain adequate levels within the body through regulated gastrointestinal absorption and excretion [2]. To our knowledge, naturally occurring Mn deficiency has never been reported in humans; however, through experimentation in animal models and humans, inadequate Mn consumption has been associated with reproductive defects, weight loss, impaired growth, dermatological conditions, and altered mood [19, 20]. While Mn deficiency is a potential concern, overexposure may result in accumulation in the basal ganglia within the brain and thus, has been associated with adverse neurotoxic effects [21].

Many of the initial epidemiologic studies of Mn and health outcomes examined occupational inhalation exposures within industries such as ferromanganese welding, mining, and refining. In 1837, Couper was the first to document a Parkinson's Disease-like syndrome in Mn poisoned Scottish Mn ore crushers [22] followed by Rodier in 1955 who further described Mn poisoning in Moroccan miners [23]. Elevated acute exposures to Mn have resulted in *manganism*, a condition characterized by Parkinsonian symptoms such as tremor, dystonia, and weakness [24]. Roels (1987) and Iregren (1990) were among the first to evaluate low-level Mn exposures among workers and describe subclinical effects such as memory and reaction time deficits [25, 26], whereas Mergler (1999) conducted one of the earliest community level studies to investigate the impact of low-level environmental Mn exposures on neurological function [27].

Numerous biomarkers have been used to characterize internal dose measures of Mn. Given the essentiality of Mn for normal physiological function, it is understandable that each of these internal dose measures describe a unique aspect of Mn homeostasis. While blood Mn is the most commonly used biological indicator of Mn exposure, it may be more indicative of recent exposures rather than total body burden due to its short half-life and rapid hepatic clearance [28, 29]. Blood Mn may be best suited to characterize variability between subjects as opposed to within subjects [30]; therefore, blood Mn may be the most appropriate measure when comparing between exposed and unexposed populations. Hair Mn has been the most widely used biomarker of exposure with cognitive associations found for children [7–9, 31–33], and it may adequately characterize chronic low-level exposures [34]. Mn levels in the dentin of shed deciduous teeth have been used to provide semi-cumulative measurements for both prenatal and postnatal Mn concentrations [12, 13, 37]. Although urine Mn has been proposed as an exposure biomarker [38–40], due to primary homeostatic biliary excretion of Mn and the short half-life, only slight levels of Mn are eliminated in the urine; thus, use of urine as a biomarker is not recommended [29, 41, 42]. Saliva level remains a relatively understudied marker for Mn exposure; however, the limited research

available does not provide evidence of its potential utility [41, 43]. Fingernails and toenails are non-invasive biological indicators of internal dose that have the potential to quantify longer-term exposure, ranging from seven to twelve months [39, 42, 43].

It is well recognized that environmental exposures do not occur in isolation and that the toxicity of an individual chemical can be modified by co-exposure to other toxicants [44, 45]. Thus, it is important to consider other toxicant exposures, particularly those with similar health outcomes, although in research studies associating Mn exposure with neurocognition, this has not been extensively done. Environmental tobacco smoke (ETS) is an example of one co-exposure that should be adjusted for in studies of Mn. Exposure to ETS has been recognized as a potential threat to children's health for almost two decades [49, 50]. During childhood ETS can impact cognition and intelligence [51–53], and there is evidence linking ETS exposure to behavioral disorders [54–56]. The toxicity of Pb has been studied for decades, and associations with decrements in intelligence and neuromotor function, as well as increases in behavior problems in childhood, delinquency in adolescence, and criminality in adulthood are well established [47]. Federal bans on Pb in paint and gasoline have resulted in dramatic reductions in childhood blood Pb concentrations; however, no threshold for the effects of Pb exposure on children's cognition and behavior has been identified [48].

Children may be particularly susceptible to the neurotoxic effects of environmental Mn exposure, as their brains are undergoing a dynamic developmental process involving complex pathways of growth, differentiation, pathway direction, and apoptosis, all of which can be influenced by environmental factors [57, 58]. Adolescence is another critical time point to consider as the brain is undergoing transformative changes that may influence intellectual function as myelination continues in that period [59, 60]. During adolescence, the prefrontal cortex undergoes substantial structural and functional developmental changes [61–63]. Additionally, elderly populations are more vulnerable to many environmental contaminants due to pre-existing conditions, lifelong exposures, and changes in absorption, metabolism, and excretion, among other factors [64]. Therefore, this review evaluates the recent literature that assesses the impact of Mn exposure on cognitive abilities across the lifespan: early life, school-aged children, adulthood, and occupational exposure.

Methods

A systematic search of the scientific literature was conducted to identify epidemiologic studies that explored the relationship between Mn exposure and cognitive outcomes. Studies of an ecological, meta-analysis or case study design were excluded. The current review encompasses studies examining in utero and pediatric Mn exposures published between January 2013 and March 2016. Two recent literature reviews have been published; one examining pediatric exposure to metals, including Mn, in relation to cognitive and behavioral effects, and another regarding manganese and childhood behavior, cognition, and motor functions [65, 66]. We used PubMed and Medline along with the following search terms to identify relevant studies: (manganese) AND (child* OR fetal OR infan* OR prenatal OR postnatal) AND (cognit* OR intelligen* OR neurodevelopment* OR memory) ("2013/01/01"[Date - Publication]: "2016/03/01"[Date - Publication]).

In 2007, a review was published including adult Mn exposures and neurological symptoms [24]. Therefore, studies that evaluated environmental and occupational exposures among adults and were published between November 2007 and December 2015 were included in the synthesis. The studies were obtained using both PubMed and Medline and the following search terms: (manganese) AND (cognit* OR memory OR intelligence OR neurotoxicity) AND (welders OR occupational OR occupational OR environ*) AND ("2007/07/01"[Date - Publication]: "2016/01/01"[Date - Publication]). Studies were excluded if a neurocognitive outcome was not assessed.

Early Life Exposure to Manganese and Cognitive Outcomes

Early life is a critical window of exposure. In utero, Mn circulates through maternal blood and serves a vital role in fetal growth [67]. Maternal blood Mn concentrations increase as the gestational trimesters progress potentially due to maternal changes in Mn metabolism [67] and shifts in Mn mobilization in tissue due to elevated concentrations of estrogen and progesterone throughout pregnancy [68]. Animal models have demonstrated that Mn crosses both blood-brain barrier and placenta[3], providing opportunity for Mn to act as essential nutrient for growth and potential neurotoxicant, if there is an excess of exposure. Within this review, we identified five studies that examined the impact of Mn on cognition from birth to four years (Table 1).

A South Korean prospective cohort of 232 mother-child pairs collected maternal blood Mn concentrations upon arrival to the hospital for delivery, with a mean concentration of 22.5 µg/L [69]. No specific source of exposure was identified. An inverted U-shaped association between maternal blood Mn concentrations and infant Mental Development Index (MDI) scores at six months of age was observed. As the mothers' blood Mn concentrations reached 24–28 µg/L, the positive association of Mn on cognition transitioned into a negative effect. Using umbilical cord blood, a study was conducted in Taiwan among 230 participants to assess in utero low dose exposures to neurotoxic metals, Mn, Pb, mercury (Hg), and arsenic (As) [70]. Statistically significant inverse associations were observed between elevated co-exposures to Mn and Pb and Comprehensive Developmental Inventory for Infants and Toddlers (CDIIT) scores at two years of age, suggesting an interactive effect. Elevated cord blood Mn concentrations have been associated with decreased psychomotor scores in previous research [71].

Tooth dentin was used as a novel cumulative biomarker for prenatal and early postnatal Mn exposure [13, 37, 72] in a California birth cohort of 204 Mexican-American maternal-child pairs exposed to maneb and mancozeb fungicides containing Mn. The neonatal line, a formation at the time of birth due to changes in dental mineralization, was used to differentiate prenatal and postnatal exposures in the children's deciduous teeth. In females whose mothers had hemoglobin levels below the normal reference range of 11.6 g/dL, prenatal Mn levels were inversely related to six month MDI scores. Similarly, a statistically significant inverse relationship between postnatal Mn exposure and MDI scores at six months was established for females only. Hemoglobin measurements were obtained as a surrogate marker to assess maternal iron (Fe) deficiency which is hypothesized to increase Mn uptake. Conversely, among males, postnatal Mn levels were positively associated with

MDI scores at 24 months [13]. A study of 60 Uruguayan children aged 14–45 months demonstrated an inverse relationship between hair Mn and BSID scores for females only, in unadjusted models [31]. When models were adjusted for covariates, sex-stratified analysis showed a statistically significant positive relationship between hair Mn and receptive language scores among males. In Bangladesh, a study examined water Mn concentrations and BSID scores among 524 20–40 month old children [73]. No statistically significant association was observed with cognition in models that also included other neurotoxicants, such as Pb and As. Due to the lack of a biomarker for Mn, exposures from other sources may not have been accurately represented in the study. These three studies are among the first to explore the relationship between Mn and cognitive skills in pre-school aged children, a developmental stage where substantial neurological changes are readily visible [74].

Exposure to Manganese in School-Aged Children and Cognitive Outcomes

While greater amounts of Mn are crucial for normal brain development during infancy [1], young children may also be more vulnerable to Mn insufficiency or over exposure due to differences in homeostatic control and greater absorption and retention rates [2]. Seven of the identified studies have explored the relationship between Mn exposure and cognition among school-aged children, ranging from five to twelve years old (Table 1).

Recent studies have reported negative associations with cognitive outcomes at both low and high levels of Mn exposure, supporting a biphasic dose-response relationship. A study of children between the ages of seven and nine living near a ferromanganese refinery in Ohio was the first to establish a non-linear U-shaped relationship between both hair and blood Mn concentrations with pediatric IQ scores [7]. Lower IQ scores were statistically significantly associated with blood Mn concentrations greater than 11.2 µg/L or lower than 8.2 µg/L and hair Mn levels greater than 747 ng/g. Decreased IQ scores were also found at hair Mn concentrations lower than 207.2 ng/g; however, this finding was not statistically significant. Likewise, a South Korean study described cognitive deficits among school-aged children and an association with both low and elevated blood Mn levels [75]. Those with Mn concentrations greater than 21.453 µg/L had statistically significantly lower scores on the Learning Disability Evaluation Scale (LDES) with respect to learning quotient, thinking, reading, and calculation. Conversely, those with Mn levels below 8.154 µg/L had lower scores on the Stroop Color-Word Test, indicating decreased cognitive inhibition. Both studies indicate adverse cognitive associations at similar blood Mn concentrations; lower than approximately 8.2 µg/L [7, 75].

A Brazilian study of 70 children reported a statistically significant negative relationship between hair Mn concentrations and IQ as well as digit span scores in seven to twelve year olds living near a ferromanganese alloy plant [9]. A 1 µg/g increase in hair Mn was associated with an approximate one point decrease in IQ when including maternal education as a covariate. In Ecuador, researchers found a relationship between hair Mn concentrations and reduced intelligence scores, measured on the Raven's Colored Progressive Matrix (RCPM) scale, in a group of 93 five to eleven year old children [33]. Those with hair Mn concentrations higher than 2 µg/g had the lowest scores. The observed elevated levels of Mn are associated with the contamination of the Puyango River which stems from mining

activities. Another study explored the relationship between exposure from Mn-mining activities and learning as well as memory in Mexican children between the ages of seven and eleven years [8]. Greater hair Mn levels were associated with lower Children's Auditory Verbal Learning Test (CALVT) scores. An association between hair Mn and long term memory scores was observed, with females having a stronger association than males. No statistically significant relationships were established between blood Mn concentrations and cognition.

A study of 69 Brazilian children aged six to twelve years assessed exposures to multiple metals and cognitive outcomes, indicated by the Raven's Colored Progressive Matrix (RCPM) [32]. Measured in serum, whole blood, hair, and water, statistically significant inverse relationships were established between both hair Mn and water Mn with IQ. Mn exposure in the area was tied to the natural presence of Mn in groundwater as well as maneb and mancozeb use in the tobacco fields. Mn exposure from the same fungicides was quantified in tooth dentin from 248 seven to ten year old children in the previously described California cohort [12, 13]. When considering children with prenatal blood Pb levels $0.8 \mu\text{g/dL}$, statistically significant inverse associations were established between prenatal Mn and Full Scale IQ. However, when stratified by sex, higher prenatal and postnatal dentin Mn levels were positively associated with IQ scores in males. This finding is inconsistent with the current literature but demonstrates an area where further research is warranted.

Non-Occupational Exposure to Manganese and Cognition in Adulthood

The vast majority of epidemiologic studies of mature individuals have examined occupational Mn exposures. The limited prior research on non-occupational exposure suggests potential cognitive deficits related to Mn among those environmentally exposed [27, 76]. While adults are estimated to only absorb 1–5% of ingested Mn [2], inhaled Mn can directly enter the body and cross the blood-brain barrier by circumventing the hepatic removal system and may also be transported through olfactory neurons and directly deposited within the brain [77]. Therefore, Mn inhalation is of greater concern for adults in general community studies [78]. In this review, five of the identified studies examined the relationship between environmental Mn exposure and cognition in adult populations (Table 2).

Two studies assessed exposures from ferromanganese refineries in Brazilian communities and found inverse relationships between hair Mn concentrations and intelligence [43, 79]. A study of 89 Brazilian men and women assessed Mn exposure in scalp hair, axillary hair, fingernails, and saliva [43]. In addition to the relationships described in hair, elevated fingernail Mn levels were found to be associated with lower scores in visual working memory. No associations were detected with Mn in saliva. Another Brazilian cross-sectional study of 82 mothers found an association among hair Mn concentrations and lower Raven's Standard Progressive Matrix (RSPM) scores after adjusting for age, education and income [79].

Air measurements were frequently used in the studies included in this review to estimate Mn exposure [10, 38, 80]. In a Central Mexican mining district, air Mn levels $0.1 \mu\text{g/m}^3$ and

greater were associated with lower scores on the Digit Span Forward and Backward Tasks among 288 men and women [10]. Measured blood Mn concentrations were not significantly related to any outcome. A pilot study conducted in the same area found a correlation between blood Mn and poorer intelligence scores on the Mini-Mental State Examination (MMSE) [76]. Using the US EPA's AERMOD dispersion model, a study of 186 adult participants living in rural Ohio determined personal estimates for chronic exposure to Mn in air [80]. Scores in working and visuospatial memory were inversely correlated with levels of Mn in air.

An Italian study included elderly residents living near former ferromanganese plants in a region previously described as having an increased prevalence of Parkinsonian disorders [81]. Elevated levels of Mn in the soil were associated with poorer RCPM when comparing the residents and an unexposed reference group [38]. The study of 82 participants also found an inverse correlation between urinary Mn concentrations and TMT scores. Limited research exists on the impact of Mn on cognitive functions in elderly populations. However, this investigation contributes to the existing literature, suggesting negative cognitive impacts of Mn exposure may occur across the lifespan.

Occupational Exposure to Manganese and Cognitive Deficits

One of the earliest descriptions of Mn overexposure was in an occupational study of Chilean miners who presented with the condition referred to as “locura manganica” meaning Mn madness [82]. In the mid-1900s, overexposure among Moroccan miners was deemed as one of the most critical occupational threats due to the potential of serious motor and mental disabilities [23]. As technological advancements and exposure control measures were implemented, intense acute exposures decreased and the focus of research shifted to chronic lower level exposures and the corresponding health implications. Seven of the ten included studies were cross-sectional [39, 40, 42, 83–87] and three were follow-up studies with prospective longitudinal designs [5, 88] (Table 2).

In 1990, a study was conducted among Mn-alloy workers and referents in Canada with statistically significant cognitive deficits described among the exposed workers [5]. Neurological functions were again assessed among the cohort 14 years after the closure of the study. When compared with referents, Mn exposure was associated with lower cognitive flexibility scores, captured on the Trail Making Test (TMT) and Symbol Digit Modalities Test, in those workers who were 45 years or older when exposure had ceased. A follow-up study of similar design recruited 26 participants from a previous cohort of Bay Bridge welders to assess the permanency of Mn-related health outcomes 3.5 years after reducing or eliminating Mn exposures [88]. Improvements in Verbal IQ (WAIS-III), cognitive flexibility (Stroop Color/Word), visuospatial memory (Rey-Osterrieth), visuomotor tracking speed (WAIS-III), and verbal skills (WAIS-III) were seen at follow up when compared to the baseline scores. A third prospective study was conducted among 53 steel workers in Denmark. Slight visuomotor deficits were associated with the steel workers; however, no statistically significant relationships were observed with respect to a measure of psychometric intelligence [89].

A study in Russia estimated that welders had on average 5.1 µg/L greater blood Mn concentrations than the referents [40]. Additionally, Mn concentrations were measured in urine and air. Both blood and air Mn concentrations were inversely related to scores on the Digit Symbol test. Another study noted a negative relationship between blood Mn and Korean Complex Figure Test (K-CFT) scores among 43 welders and 29 controls in Korea [40, 85]. PI (Pallidal Index) was associated with cognitive impairments, suggesting that the PI may be a better marker of cognitive ability than blood [85]. Supporting the aforementioned conclusions, a study conducted by the same research group within the same study population described decreased memory functions among welders when compared with a control group. Functional MRI results suggest that compared to healthy controls, Mn exposed welders have increased brain activation in networks of working memory [86]. A study in Iran assessed 90 welders, smelters, and controls for neuropsychological outcomes on the Cambridge Neuropsychological Test Automated Battery (CANTAB) and found that biomarkers of Mn exposure in urine, blood, toenails, and air were statistically significantly higher among the workers [39]. All three biomarkers demonstrated negative correlations with many of the measured neurocognitive outcomes.

A recent occupational study of Mn-exposed workers was the first to evaluate the correlation between Mn exposure and cognition via the Montreal Cognitive Assessment (MoCA) [84]. Cumulative exposure index (CEI) values were calculated based on an eight-hour time-weighted average of Mn air exposure from within the specific factory department and the number of Mn exposure-years. Higher Mn CEI values were inversely related to cognitive function and levels of plasma brain-derived neurotrophic factor (BDNF), a protein important in learning and cognition. The data suggest that plasma BDNF levels may be of potential use as an indicator of Mn related cognitive impairment [84]. In a study of 46 apprentice welders, CEI was statistically significantly associated with CPT score deficits, suggesting Mn impacts at low levels. In this study, total CEI was calculated based on the worker's past exposure, including the time spent on specific tasks, average Mn concentrations, and the percentage of time using a respirator [42, 87]. Using CEIs, calculated based on employment records and personal air sampling, to represent inhalable and respirable Mn exposure, an Australian study among 143 smelters found statistically significant associations with lower Digit Symbol, Stroop Color-Word task, and TMT scores [83]. The authors note that age, education, and estimated IQ are more indicative of neuropsychological performance than the calculated Mn exposure.

Discussion

This review supports the existing premise that Mn is both an essential micronutrient and potential neurotoxicant. Mn exhibits a non-linear or hormetic dose-response [90] as illustrated in Figure 1. Throughout childhood, both high and low levels of Mn have been negatively associated with intellectual development [7, 46, 69, 75]. To our knowledge, no studies among adult populations have examined a potential non-linear association between Mn and neurocognition. Inclusion of multiple neurotoxicants within statistical models is critical when considering the potential neurotoxicant role of Mn on neurocognition. Exposure to ETS, even at very low levels, is associated with decreased cognitive outcomes among adolescents [53]. A biomarker of ETS exposure, serum cotinine was included as a

potential confounder in several studies [7, 75] reducing recall bias and strengthening the analyses by quantifying exposure to this known neurotoxicant thereby better avoiding confounding by ETS. While the majority of the pediatric studies in this review do not include an indicator of ETS exposure in the statistical analysis, three studies captured self-reported smoking during pregnancy [12, 13, 70]. The correlation between Pb and cognition has been well-established with no known safe level of exposure [91]. Several epidemiologic studies have observed interactive effects between the two metals on intelligence during early life [70, 92] as well as adolescence [12, 93]; however, this is not true for all studies [13, 73, 94]. The majority of the pediatric studies included in this review did consider Pb as a potential confounder. Although independent exposures to As and Mn have been associated with cognitive decrements, Mn and As interactions have not consistently been proven significant [4, 95, 96]. In a study near a hazardous waste site, statistically significant interactions were observed between the elements [97]; however, several studies did not detect significance among As and Mn interactions and cognition [32,70,73, 95].

Stronger associations between Mn exposures and cognitive deficits among females have been suggested by several studies [8, 12, 13, 31, 98, 99]. These differences may be due to fluctuations in Fe and hormone levels as females are more likely to be deficient in Fe due to menstruation, limited bioavailability of dietary Fe, and pregnancy [100, 101]. Several previous epidemiologic studies have suggested a correlation between Fe deficiency and elevated Mn concentrations in blood during infancy [102], early childhood [103], and adulthood [100], highlighting hemoglobin and ferritin as an important potential covariates. In two of the child studies, there were no sex differences in mean hair Mn concentrations [8, 98] and in the third study, boys had statistically significantly higher levels of hair Mn [31]. Therefore, it is hypothesized that the gender differences demonstrated in younger children are not in the uptake of Mn but rather in Mn neuropathology. Among school aged children, higher prenatal and postnatal Mn levels were positively associated with IQ scores in males [12]. In contrast, Mergler et al. discovered gender differences in a community level study of adults, suggesting that males are at greater risk of impact from Mn exposure [27]. These observations regarding sex differences support previous studies which have shown that estrogen plays a neuroprotective role against toxic exposures [104]. Younger girls with lower estrogen levels may be more vulnerable to the cognitive impacts of Mn overexposure, while mature women with higher levels of estrogen may experience its neuroprotective effects. Studies regarding male exposures are more abundant in the literature due to the saturation of occupational studies, predominantly conducted among male participants. Thus, future studies should consider sex differences and include measures of Fe status.

The persistence of Mn induced cognitive effects remains an important factor with regards to remedial efforts. Bouchard et al. [5] and Bowler et al. [88] observed restoration in certain cognitive areas after the termination of occupational Mn exposures for many years. In Italy, Lucchini et al. did not find any statistically significant associations among low-level Mn and cognition in adolescents [94]. This may be attributed to the historical cessation of high levels of Mn in the area when the children were in their first years of life, suggesting the potential reversibility of Mn induced cognitive impairment [94].

A case study involving two siblings, both receiving parenteral nutrition, found decreases in blood Mn concentrations and Mn deposition in the basal ganglia, revealed by MRI, following a reduction in Mn supplementation [105]. Neither child had clinical symptoms of Mn overexposure; therefore, the data suggest that overtime Mn can be cleared from the brain in circumstances when sub-clinical exposure has ceased.

Future Directions

There are several key areas that need further exploration related to Mn exposure and neurocognition, including 1) identification of a biomarker or a combination of biomarkers that could be used to indicate levels at which there would be cause of concern; 2) examination of potential covariates, including Fe, and other metals that may influence cognition in conjunction with Mn; 3) examination of the non-linear relationship between Mn and neurocognition in adult populations; and 4) basic science research to explore the role of hormones in both males and females in the redistributing Mn from tissue stores and its impact on neurocognition and the interplay between Ca and Mn in bone health.

Other sources of Mn exposure including soy-based formulas and parenteral nutrition need further exploration on their potential neurocognitive impacts. In this review, only one of the identified studies examining fetal Mn exposure included breastfeeding status as a covariate [69]. Another study captured breastfeeding duration; however, the variable was not statistically significant within the model [13]. Due to the lack of epidemiologic data, future studies should both evaluate breast feeding status, and in cases where the child is formula fed, consider the specific formula compositions. In addition, epidemiologic research regarding cognition and Mn supplementation in parenteral nutrition is necessary to form safe healthcare policies and practices.

Conclusion

In recent years, epidemiologic studies have explored the vulnerability of whole life Mn exposures, ranging from in utero to 75 years. The evaluation of covariates known to play a role in neurotoxicity, such as ETS, Pb, and As, should be included in statistical models, along with a measure of Fe status. Moreover, the role of Mn as both essential micronutrient and neurotoxicant warrants inclusion in statistical models examining the relationship between Mn exposure and neurocognition across the lifespan.

Abbreviations

BSID	Bayley Scales of Infant Development
CANTAB	Cambridge Neuropsychological Test Automated Battery
CAVLT	Children's Auditory Verbal Learning Test
CCTT	Children's Color Trails Test
CDIIT	Comprehensive Developmental Inventory for Infants and Toddlers
CFS	Cognitive Function Scanner

CPT	Continuous Performance Test
ETS	Environmental Tobacco Smoke
IQ	Intelligence Quotient
K-AVLT	Korean Auditory Verbal Learning Test
K-CFT	Korean Complex Figure Test
LDES	Learning Disability Evaluation Scale
MDI	Mental Development Index
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MR	Matrix Reasoning
NAB	Neuropsychological Assessment Battery
PI	Pallidal Index
RAVLT	Rey Auditory Verbal Learning Test
RCPM	Raven's Colored Progressive Matrix
RSPM	Raven's Standard Progressive Matrix
TAVIS	The Brazilian Attention Test
TMT	Trailing Making Test
WAIS	Wechsler Adult Intelligence Scale
WCST	Wisconsin Card Sorting Test
WISC	Wechsler Intelligence Scale for Children

References

Papers of particular interest, published recently, have been highlighted as:

•Of importance

••Of outstanding importance

1. Takeda A, Ishiwatari S, Okada S. Manganese uptake into rat brain during development and aging. *J Neurosci Res.* 1999; 56(1):93–98. [PubMed: 10213480]
2. Aschner JL, Aschner M. Nutritional aspects of manganese homeostasis. *Mol Aspects Med.* 2005; 26(4–5):353–362. [PubMed: 16099026]
3. ATSDR. Toxicological Profile for Manganese. 2012
4. Wasserman GA, et al. Water manganese exposure and children's intellectual function in Araihaazar, Bangladesh. *Environ Health Perspect.* 2006; 114(1):124–129. [PubMed: 16393669]

5. Bouchard M, et al. Neurobehavioral functioning after cessation of manganese exposure: a follow-up after 14 years. *Am J Ind Med.* 2007; 50(11):831–840. [PubMed: 17096374]
6. Khan K, et al. Manganese exposure from drinking water and children's academic achievement. *Neurotoxicology.* 2012; 33(1):91–97. [PubMed: 22182530]
7. Haynes EN, et al. Manganese Exposure and Neurocognitive Outcomes in Rural School-Age Children: The Communities Actively Researching Exposure Study (Ohio, USA). *Environ Health Perspect.* 2015; 123(10):1066–1071. [PubMed: 25902278] This study established an inverse U-shaped relationship between Mn concentrations measured in both hair and blood and IQ among environmentally exposed school-aged children.
8. Torres-Agustin R, et al. Effect of environmental manganese exposure on verbal learning and memory in Mexican children. *Environ Res.* 2013; 121:39–44. [PubMed: 23141434]
9. Carvalho CF, et al. Elevated airborne manganese and low executive function in school-aged children in Brazil. *Neurotoxicology.* 2014; 45:301–308. [PubMed: 24308913]
10. Solís-Vivanco R, et al. Cognitive impairment in an adult Mexican population non-occupationally exposed to manganese. *Environ Toxicol Pharmacol.* 2009; 28(2):172–178. [PubMed: 21784000]
11. Gulson B, et al. Changes in manganese and lead in the environment and young children associated with the introduction of methylcyclopentadienyl manganese tricarbonyl in gasoline--preliminary results. *Environ Res.* 2006; 100(1):100–114. [PubMed: 16337847]
12. Mora AM, et al. Prenatal and postnatal manganese teeth levels and neurodevelopment at 7, 9, and 10.5 years in the CHAMACOS cohort. *Environ Int.* 2015; 84:39–54. [PubMed: 26209874] This study found an association between postnatal dentin levels of Mn and positive cognitive outcomes in males. Exposure to both high levels of Mn and Pb was inversely associated with IQ.
13. Gunier RB, et al. Manganese in teeth and neurodevelopment in young Mexican-American children. *Environ Res.* 2015; 142:688–695. [PubMed: 26381693] This study identified an association between elevated postnatal Mn levels measured in dentin and lower MDI scores among females aged 6–24 months. Interactions with prenatal hemoglobin levels were detected.
14. Collipp PJ, Chen SY, Maitinsky S. Manganese in infant formulas and learning disability. *Ann Nutr Metab.* 1983; 27(6):488–494. [PubMed: 6651226]
15. Reynolds AP, Kiely E, Meadows N. Manganese in long term paediatric parenteral nutrition. *Arch Dis Child.* 1994; 71(6):527–528. [PubMed: 7726613]
16. Ono J, et al. Manganese deposition in the brain during long-term total parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 1995; 19(4):310–312. [PubMed: 8523631]
17. Koksai A, et al. Chronic manganese toxicity due to substance abuse in Turkish patients. *Neurol India.* 2012; 60(2):224–227. [PubMed: 22626708]
18. Aschner M. Manganese: brain transport and emerging research needs. *Environ Health Perspect.* 2000; 108(Suppl 3):429–432. [PubMed: 10852840]
19. Friedman BJ, et al. Manganese balance and clinical observations in young men fed a manganese-deficient diet. *J Nutr.* 1987; 117(1):133–143. [PubMed: 3819860]
20. Penland JG, Johnson PE. Dietary calcium and manganese effects on menstrual cycle symptoms. *Am J Obstet Gynecol.* 1993; 168(5):1417–1423. [PubMed: 8498421]
21. Slood WN, Gramsbergen JB. Axonal transport of manganese and its relevance to selective neurotoxicity in the rat basal ganglia. *Brain Res.* 1994; 657(1–2):124–132. [PubMed: 7820609]
22. Couper J. On the effects of black oxide of manganese when inhaled into the lungs. 1837: *Br Ann Med Pharm Vit Stat Gen Sci.* 1:41–42.
23. Rodier J. Manganese poisoning in Moroccan miners. *Br J Ind Med.* 1955; 12(1):21–35. [PubMed: 14351643]
24. Zoni S, Albini E, Lucchini R. Neuropsychological testing for the assessment of manganese neurotoxicity: a review and a proposal. *Am J Ind Med.* 2007; 50(11):812–830. [PubMed: 17918193]
25. Roels H, et al. Epidemiological survey among workers exposed to manganese: effects on lung, central nervous system, and some biological indices. *Am J Ind Med.* 1987; 11(3):307–327. [PubMed: 3578289]
26. Iregren A. Psychological test performance in foundry workers exposed to low levels of manganese. *Neurotoxicol Teratol.* 1990; 12(6):673–675. [PubMed: 2255315]

27. Mergler D, et al. Manganese neurotoxicity, a continuum of dysfunction: results from a community based study. *Neurotoxicology*. 1999; 20(2–3):327–342. [PubMed: 10385894]
28. O'Neal SL, Zheng W. Manganese Toxicity Upon Overexposure: a Decade in Review. *Curr Environ Health Rep*. 2015; 2(3):315–328. [PubMed: 26231508]
29. Smith D, et al. Biomarkers of Mn exposure in humans. *Am J Ind Med*. 2007; 50(11):801–811. [PubMed: 17924418]
30. Baker MG, et al. Variance components of short-term biomarkers of manganese exposure in an inception cohort of welding trainees. *J Trace Elem Med Biol*. 2015; 29:123–129. [PubMed: 24916793]
31. Rink SM, et al. Associations between hair manganese levels and cognitive, language, and motor development in preschool children from Montevideo, Uruguay. *Arch Environ Occup Health*. 2014; 69(1):46–54. [PubMed: 23930796]
32. do Nascimento SN, et al. Cognitive deficits and ALA-D-inhibition in children exposed to multiple metals. *Environ Res*. 2015; 136:387–395. [PubMed: 25460660] This study described negative associations among Mn levels measured in both hair and water and child IQ scores.
33. Betancourt Ó, Tapia M, Méndez I. Decline of General Intelligence in Children Exposed to Manganese from Mining Contamination in Puyango River Basin, Southern Ecuador. *Ecohealth*. 2015; 12(3):453–460. [PubMed: 25851196]
34. Liang G, et al. Manganese accumulation in hair and teeth as a biomarker of manganese exposure and neurotoxicity in rats. *Environ Sci Pollut Res Int*. 2016
35. Chojnacka K, Gorecka H, Gorecki H. The effect of age, sex, smoking habit and hair color on the composition of hair. *Environ Toxicol Pharmacol*. 2006; 22(1):52–57. [PubMed: 21783686]
36. Eastman RR, et al. Hair as a biomarker of environmental manganese exposure. *Environ Sci Technol*. 2013; 47(3):1629–1637. [PubMed: 23259818]
37. Gunier RB, et al. Biomarkers of manganese exposure in pregnant women and children living in an agricultural community in California. *Environ Sci Technol*. 2014; 48(24):14695–14702. [PubMed: 25390650]
38. Lucchini RG, et al. Neurofunctional dopaminergic impairment in elderly after lifetime exposure to manganese. *Neurotoxicology*. 2014; 45:309–317. [PubMed: 24881811] This Italian study investigated the impact of lifelong Mn exposure and established a significant relationship between elevated Mn concentrations and cognitive decline among elderly participants.
39. Hassani H, et al. Relations of biomarkers of manganese exposure and neuropsychological effects among welders and ferroalloy smelters. *Ind Health*. 2016; 54(1):79–86. [PubMed: 26423330]
40. Ellingsen DG, et al. A neurobehavioral study of current and former welders exposed to manganese. *Neurotoxicology*. 2008; 29(1):48–59. [PubMed: 17942157]
41. Zheng W, et al. Biomarkers of manganese intoxication. *Neurotoxicology*. 2011; 32(1):1–8. [PubMed: 20946915]
42. Laohaudomchok W, et al. Toenail, blood, and urine as biomarkers of manganese exposure. *J Occup Environ Med*. 2011; 53(5):506–510. [PubMed: 21494156]
43. Viana GF, et al. Noninvasive biomarkers of manganese exposure and neuropsychological effects in environmentally exposed adults in Brazil. *Toxicol Lett*. 2014; 231(2):169–178. [PubMed: 24992226] This study concluded that Mn concentrations measured in hair and fingernails were inversely associated with neurocognitive outcomes in environmentally exposed adults.
44. Weiss B, Bellinger DC. Social ecology of children's vulnerability to environmental pollutants. *Environ Health Perspect*. 2006; 114(10):1479–1485. [PubMed: 17035129]
45. Bellinger DC. A strategy for comparing the contributions of environmental chemicals and other risk factors to neurodevelopment of children. *Environ Health Perspect*. 2012; 120(4):501–507. [PubMed: 22182676]
46. Claus Henn B, et al. Early postnatal blood manganese levels and children's neurodevelopment. *Epidemiology*. 2010; 21(4):433–439. [PubMed: 20549838]
47. Dietrich, KN. Environmental toxicants. In: Yeats, KO., editor. *Pediatric Neuropsychology*. New York: Guilford; 2010. p. 211–264.
48. Bellinger DC. Very low lead exposures and children's neurodevelopment. *Current Opinion in Pediatrics*. 2008; 20(2):172–177. [PubMed: 18332714]

49. Baghurst PA, et al. Effects of maternal smoking upon neuropsychological development in early childhood: importance of taking account of social and environmental factors. *Paediatr Perinat Epidemiol.* 1992; 6(4):403–415. [PubMed: 1282258]
50. Olds DL, Henderson CR Jr, Tatelbaum R. Prevention of intellectual impairment in children of women who smoke cigarettes during pregnancy. *Pediatrics.* 1994; 93(2):228–233. [PubMed: 7510063]
51. Eskenazi B, Bergmann JJ. Passive and active maternal smoking during pregnancy, as measured by serum cotinine, and postnatal smoke exposure. I. Effects on physical growth at age 5 years. *Am J Epidemiol.* 1995; 142(9 Suppl):S10–S18. [PubMed: 7572982]
52. Joad JP. Smoking and pediatric respiratory health. *Clin Chest Med.* 2000; 21(1):37–46. vii–viii. [PubMed: 10763088]
53. Yolton K, et al. Exposure to environmental tobacco smoke and cognitive abilities among U.S. children and adolescents. *Environ Health Perspect.* 2005; 113(1):98–103. [PubMed: 15626655]
54. Brook JS, Brook DW, Whiteman M. The influence of maternal smoking during pregnancy on the toddler's negativity. *Arch Pediatr Adolesc Med.* 2000; 154(4):381–385. [PubMed: 10768677]
55. Orlebeke JF, Knol DL, Verhulst FC. Child behavior problems increased by maternal smoking during pregnancy. *Arch Environ Health.* 1999; 54(1):15–19. [PubMed: 10025411]
56. Yolton K, et al. Environmental tobacco smoke exposure and child behaviors. *J Dev Behav Pediatr.* 2008; 29(6):450–457. [PubMed: 19093323]
57. Dietrich KN. *Environmental Toxicants. Pediatric Neuropsychology.* ed.
58. Landrigan, PJaAM. *Children's health and the environment: an overview.* Mt. Sinai: 2011. p. 1-10.
59. Frangou S, Chitins X, Williams SC. Mapping IQ and gray matter density in healthy young people. *Neuroimage.* 2004; 23(3):800–805. [PubMed: 15528081]
60. Shaw P, et al. Intellectual ability and cortical development in children and adolescents. *Nature.* 2006; 440(7084):676–679. [PubMed: 16572172]
61. Blumberg HP. Significance of adolescent neurodevelopment for the neural circuitry of bipolar disorder. *Ann N Y Acad Sci.* 2004; 1021:376–383. [PubMed: 15251913]
62. Lewis DA. Development of the prefrontal cortex during adolescence: insights into vulnerable neural circuits in schizophrenia. *Neuropsychopharmacology.* 1997; 16(6):385–398. [PubMed: 9165494]
63. Bourgeois JP, Goldman-Rakic PS, Rakic P. Synaptogenesis in the prefrontal cortex of rhesus monkeys. *Cereb Cortex.* 1994; 4(1):78–96. [PubMed: 8180493]
64. Geller AM, Zenick H. Aging and the environment: a research framework. *Environ Health Perspect.* 2005; 113(9):1257–1262. [PubMed: 16140638]
65. Sanders AP, Claus Henn B, Wright RO. Perinatal and Childhood Exposure to Cadmium, Manganese, and Metal Mixtures and Effects on Cognition and Behavior: A Review of Recent Literature. *Curr Environ Health Rep.* 2015; 2(3):284–294. [PubMed: 26231505]
66. Zoni S, Lucchini RG. Manganese exposure: cognitive, motor and behavioral effects on children: a review of recent findings. *Curr Opin Pediatr.* 2013; 25(2):255–260. [PubMed: 23486422]
67. Tholin K, et al. Changes in blood manganese levels during pregnancy in iron supplemented and non supplemented women. *J Trace Elem Med Biol.* 1995; 9(1):13–17. [PubMed: 8846152]
68. Das K, Chowdhury AR. Metallic ion concentration during menstrual cycle in normally menstruating women. *Indian J Med Sci.* 1997; 51(2):52–44. [PubMed: 9355709]
69. Chung SE, et al. Maternal Blood Manganese and Early Neurodevelopment: The Mothers and Children's Environmental Health (MOCEH) Study. *Environ Health Perspect.* 2015; 123(7):717–722. [PubMed: 25734517] This study described a correlation between both high and low maternal blood Mn levels at the time of delivery and subsequent cognitive deficits in the children at 6 months of age.
70. Lin CC, et al. In utero exposure to environmental lead and manganese and neurodevelopment at 2 years of age. *Environ Res.* 2013; 123:52–57. [PubMed: 23578827]
71. Takser L, et al. Manganese, monoamine metabolite levels at birth, and child psychomotor development. *Neurotoxicology.* 2003; 24(4–5):667–674. [PubMed: 12900080]

72. Arora M, et al. Determining fetal manganese exposure from mantle dentine of deciduous teeth. *Environ Sci Technol*. 2012; 46(9):5118–5125. [PubMed: 22455722]
73. Rodrigues EG, et al. Neurodevelopmental outcomes among 2- to 3-year-old children in Bangladesh with elevated blood lead and exposure to arsenic and manganese in drinking water. *Environ Health*. 2016; 15(1):44. [PubMed: 26968381]
74. Hadders-Algra M. The neuromotor examination of the preschool child and its prognostic significance. *Ment Retard Dev Disabil Res Rev*. 2005; 11(3):180–188. [PubMed: 16161096]
75. Bhang SY, et al. Relationship between blood manganese levels and children's attention, cognition, behavior, and academic performance--a nationwide cross-sectional study. *Environ Res*. 2013; 126:9–16. [PubMed: 23790803]
76. Santos-Burgoa C, et al. Exposure to manganese: health effects on the general population, a pilot study in central Mexico. *Environ Res*. 2001; 85(2):90–104. [PubMed: 11161659]
77. Dorman DC, et al. Olfactory transport: a direct route of delivery of inhaled manganese phosphate to the rat brain. *J Toxicol Environ Health A*. 2002; 65(20):1493–1511. [PubMed: 12396865]
78. Keen CL, Bell JG, Lonnerdal B. The effect of age on manganese uptake and retention from milk and infant formulas in rats. *J Nutr*. 1986; 116(3):395–402. [PubMed: 3950766]
79. Menezes-Filho JA, et al. Elevated manganese and cognitive performance in school-aged children and their mothers. *Environ Res*. 2011; 111(1):156–163. [PubMed: 20943219]
80. Bowler RM, et al. Environmental exposure to manganese in air: Associations with cognitive functions. *Neurotoxicology*. 2015; 49:139–148. [PubMed: 26096496]
81. Lucchini RG, et al. High prevalence of Parkinsonian disorders associated to manganese exposure in the vicinities of ferroalloy industries. *Am J Ind Med*. 2007; 50(11):788–800. [PubMed: 17918215]
82. Mena I, et al. Chronic manganese poisoning. Clinical picture and manganese turnover. *Neurology*. 1967; 17(2):128–136. [PubMed: 6066873]
83. Summers MJ, et al. The effect of occupational exposure to manganese dust and fume on neuropsychological functioning in Australian smelter workers. *J Clin Exp Neuropsychol*. 2011; 33(6):692–703. [PubMed: 21416424]
84. Zou Y, et al. Cognitive function and plasma BDNF levels among manganese-exposed smelters. *Occup Environ Med*. 2014; 71(3):189–194. [PubMed: 24415644] This study found associations between occupational exposure to elevated Mn levels and lower cognitive function in the workers. Additionally, the study described a negative relationship between plasma BDNF levels and Mn concentrations.
85. Chang Y, et al. High signal intensity on magnetic resonance imaging is a better predictor of neurobehavioral performances than blood manganese in asymptomatic welders. *Neurotoxicology*. 2009; 30(4):555–563. [PubMed: 19376157]
86. Chang Y, et al. Altered working memory process in the manganese-exposed brain. *Neuroimage*. 2010; 53(4):1279–1285. [PubMed: 20620213]
87. Laohaudomchok W, et al. Neuropsychological effects of low-level manganese exposure in welders. *Neurotoxicology*. 2011; 32(2):171–179. [PubMed: 21192973]
88. Bowler RM. Prospective study on neurotoxic effects in manganese-exposed bridge construction welders. *Neurotoxicology*. 2011; 32(5):596–605. [PubMed: 21762725]
89. Blond M, Netterstrom B, Laursen P. Cognitive function in a cohort of Danish steel workers. *Neurotoxicology*. 2007; 28(2):328–335. [PubMed: 17335905]
90. Hayes DP. Nutritional hormesis. *Eur J Clin Nutr*. 2007; 61(2):147–159. [PubMed: 16885926]
91. Bellinger DC. Very low lead exposures and children's neurodevelopment. *Curr Opin Pediatr*. 2008; 20(2):172–177. [PubMed: 18332714]
92. Claus Henn B, et al. Associations of early childhood manganese and lead coexposure with neurodevelopment. *Environ Health Perspect*. 2012; 120(1):126–131. [PubMed: 21885384]
93. Kim Y, et al. Co-exposure to environmental lead and manganese affects the intelligence of school-aged children. *Neurotoxicology*. 2009; 30(4):564–571. [PubMed: 19635390]
94. Lucchini RG, et al. Inverse association of intellectual function with very low blood lead but not with manganese exposure in Italian adolescents. *Environ Res*. 2012; 118:65–71. [PubMed: 22925625]

95. Wasserman GA, et al. Arsenic and manganese exposure and children's intellectual function. *Neurotoxicology*. 2011; 32(4):450–457. [PubMed: 21453724]
96. Wasserman GA, et al. Water arsenic exposure and children's intellectual function in Araihaaz, Bangladesh. *Environ Health Perspect*. 2004; 112(13):1329–1333. [PubMed: 15345348]
97. Wright RO. Neuropsychological correlates of hair arsenic, manganese, and cadmium levels in school-age children residing near a hazardous waste site. *Neurotoxicology*. 2006; 27(2):210–216. [PubMed: 16310252]
98. Riojas-Rodriguez H, et al. Intellectual function in Mexican children living in a mining area and environmentally exposed to manganese. *Environ Health Perspect*. 2010; 118(10):1465–1470. [PubMed: 20936744]
99. Bouchard MF, et al. Intellectual impairment in school-age children exposed to manganese from drinking water. *Environ Health Perspect*. 2011; 119(1):138–143. [PubMed: 20855239]
100. Finley JW, Johnson PE, Johnson LK. Sex affects manganese absorption and retention by humans from a diet adequate in manganese. *Am J Clin Nutr*. 1994; 60(6):949–955. [PubMed: 7985639]
101. Coad J, Conlon C. Iron deficiency in women: assessment, causes and consequences. *Curr Opin Clin Nutr Metab Care*. 2011; 14(6):625–634. [PubMed: 21934611]
102. Park S, et al. Blood manganese concentration is elevated in infants with iron deficiency. *Biol Trace Elem Res*. 2013; 155(2):184–189. [PubMed: 23955423]
103. Smith EA, et al. Increased whole blood manganese concentrations observed in children with iron deficiency anaemia. *J Trace Elem Med Biol*. 2013; 27(1):65–69. [PubMed: 22940083]
104. Green PS, Simpkins JW. Neuroprotective effects of estrogens: potential mechanisms of action. *Int J Dev Neurosci*. 2000; 18(4–5):347–358. [PubMed: 10817919]
105. Kafritsa Y, et al. Long-term outcome of brain manganese deposition in patients on home parenteral nutrition. *Arch Dis Child*. 1998; 79(3):263–265. [PubMed: 9875025]

Figure 1. Observed inverted U-shaped association between manganese exposure and neurocognition in pediatric populations.

Table 1

Pediatric studies assessing manganese exposure and cognition

Author, Year	Country	Study Design	Exposure	Participants	Age at Cognitive Assessment	Biomarkers/Environmental Measures, n	Outcome Measure/s	Covariates	Association	Conclusions
Early Life										
Rodriguez, 2016 [73]	Bangladesh	Prospective Cohort	Drinking water	524	20–40 months	Water (µg/L), n = 525	BSID	Gender, maternal age, maternal education, maternal Raven score, ETS exposure, HOME score, hematocrit levels	None	No association between Mn exposure and cognitive outcomes.
Chung, 2015 [69]	South Korea	Prospective Cohort	No specific source of exposure	232	6 months	Maternal Blood at delivery (µg/L), n = 352	BSID	Gender, birth weight, birth order, maternal age, gestation period, income, breastfeeding status, maternal nutritional status, residence	Inverse U-shaped	Significant inverse U-shaped association with MDI scores.

Author , Year	Count ry	Study Design	Exposur e	Partici pants	Age at Cognit ive Asses sment	Biomar kers/ Environ mental Measur es, n	Outc ome Meas ure/s	Covariat es	Associ ation	Conclu sions
Gunier, 2015 [13]	USA, Califor nia	Prospe ctive Cohort	Fungicid es	204	6–24 month s	Dentin (⁵⁵ Mn) ⁴³ Ca AUC × 10 ⁴), prenata l n = 197, postnat al n = 193	BSID	Gender, age, maternal educatio n & intelligen ce, psychom etrician, location of assessm ent, income, HOME score, prenatal dentin.	Linear	Higher postna tal Mn levels were associ ated with lower MDI scores . Femal es had strong er associ ations. Interac tions with prenat al hemog lobin levels.
Rink, 2014 [31]	Urugu ay	Cross- Section al	Environ mental low-level	60	14–45 month s	Hair (µg/g)	BSID	No covariate s were included in the model.	Linear	Signifi cant invers e correla tion betwe en MnH and BSID scores among female s. A positiv e associ ation was observ ed for males.

Author , Year	Count ry	Study Design	Exposur e	Partici pants	Age at Cognit ive Asses sment	Biomar kers/ Environ mental Measur es, n	Outc ome Meas ure/s	Covariat es	Associ ation	Conclu sions
Lin, 2013 [70]	Taiwa n	Prospe ctive Cohort	Gasoline and vehicle exhaust	230	2 years	Cord blood (µg/L), n = 230	CDII T	Gender, maternal age & educatio n, ETS during pregnan cy and after delivery, HOME score, fish intake, As (Mn × Pb model), Hg (Mn × Pb model)	Linear	Invers e associ ation betwe en Mn in cord blood and cogniti ve and langua ge DQs. Elevat ed Mn and Pb are associ ated with lower cogniti ve and langua ge DQs.
School-Aged Children										
Betan court, 2015 [33]	Ecuado r	Cross - Sectio nal	Mining Contami nation of the Puyango River	93	5–11 years	Hair (µg/g), n = 93	RCP M	Age, educatio nal level	Lin ear	Significant positive correlatio n with RCPM scores (indicates lower levels of general intelligence e).
Hayne s, 2015 [7]	USA	Cross - Sectio nal	Ferroma nganese refinery air pollution	404	7–9 years	Hair (ng/g), n = 370 Blood (µg/L), n = 327	WIS C-IV	Gender, parental IQ & educatio n, parental Confiden	Inv ers e U- sha ped	Both high and low blood and hair Mn concentra tions are associate

Author , Year	Count ry	Study Design	Exposur e	Partici pants	Age at Cognit ive Asses sment	Biomar kers/ Environ mental Measur es, n	Outc ome Meas ure/s	Covariat es	Associ ation	Conclu sions
								ce t score, creatinin e, serum cotinine, blood Pb, communi ty		d with lower child IQ scores.
Mora, 2015 [12]	USA, Califor nia	Prosp ective Cohor t	Fungicid es	248	7–10 years	Dentin (⁵⁵ Mn) ⁴³ Ca AUC × 10 ⁴), prenata l n = 248, postnat al n = 244	WIS C-IV	Gender, age, maternal educatio n, & intelligen ce, maternal years in the US, number of children in the home, psychom etrician, income, HOME score	Lin ear	Postnatal levels of Mn were positively associate d with IQ scores in males only. Exposure to high Pb and high Mn levels are inversely related to IQ.
do Nasci mento, 2015 [32]	Brazil	Cross - Sectio nal	Water and fungicide s	69	6–12 years	Serum (µg/L ⁻¹), n = 53 Whole Blood (µg/L ⁻¹), n = 66 Hair (µg/g ⁻¹), n = 50 Water (mg/L ⁻¹), n = 64	RCP M	Gender, age, and parental educatio n	Lin ear	Mn in hair and water are both inversely related with lower IQ scores.

Author , Year	Count ry	Study Design	Exposur e	Partici pants	Age at Cogni tive Asses sment	Biomar kers/ Environ mental Measur es, n	Outc ome Meas ure/s	Covariat es	Associ ation	Conclu sions
Carvalho, 2014 [9]	Brazil	Cross - Sectio nal	Ferroman ganese alloy plant	70	7–12 years	Hair (µg/g), n = 70	WISC-III, Corsi Block - Tapping Test, TAVI S-III & WCS T	Maternal educatio n	Linear	Significant inverse relationshi p with lower IQ and digit span scores.
Bhang , 2013 [75]	South Korea	Cross - Sectio nal	Low- Level Environ mental Exposur e	1089	8–11 years	Blood (µg/L), n = 1001	KEDI - WISC, CCT & T, LDE S & Stroop Color - Word Test	Gender, region, IQ, maternal educatio n & age at pregnan cy, urine cotinine, blood Pb	Invers e U- shaped	Mn is inversely associate d with scores in thinking, reading, calculatio n and LQ. Mn was positively associate d with scores on the Stroop Color- Word Test.
Torres - Agustín, 2012 [8]	Mexico	Cross - Sectio nal	Mn Mining contamin ation	174 (79 expos ed, 95 unexp osed)	7–11 years	Hair (µg/g), n = 174 & Blood (µg/L), n = 174	CAV LT	Gender, blood Pb, age, hemoglo bin, & maternal educatio n	Linear	Mn in hair is associate d with lower long-term memory and learning scores.

Table 2

Adult studies assessing manganese exposure and cognition

Author, Year	Country	Study Design	Exposure	Participants	Age at Cognitive Assessment	Biomarkers/Environmental Measures, n	Outcome Measures	Covariates	Association	Conclusions
Adult Environmental Exposures										
Bowler, 2015 [80]	USA, OH	Cross-Sectional	Ferromanganese smelter	186	35–75 yrs.	Air ($\mu\text{g}/\text{m}^3$), n = 186	Stroop Color/Word, Rey-Osterrieth, Trails A, Trails B, NAB, WAIS-III, Auditory Consonant Trigrams	Education, town of residence	Linear	Mn in air is inversely associated with cognitive function.
Lucchini, 2014 [38]	Italy	Cross-Sectional	Ferromanganese plants	255	65–75 yrs.	Soil (ppm), n = 255 Air (ng/m^3), n = 254 Blood ($\mu\text{g}/\text{L}$), n = 238 Urine ($\mu\text{g}/\text{L}$), n = 239	MMSE, Story Recall Test, RCPM, TMT, WAIS	Age, distance from the nearest ferromanganese plant (TMT model)	Linear	Mn in soil is inversely associated with RCPM scores. Urinary Mn concentrations are associated with lower TMT scores.

Author, Year	Country	Study Design	Exposure	Participants	Age at Cognitive Assessment	Biomarkers/Environmental Measurements, n	Outcome Measures	Covariates	Association	Conclusions
Viana, 2014 [43]	Brazil	Cross-Sectional	Ferromanganese refinery	89	15–55 yrs.	Scalp Hair ($\mu\text{g/g}$), $n = 79$ Axillary Hair ($\mu\text{g/g}$), $n = 17$ Fingernails ($\mu\text{g/g}$), $n = 72$ Saliva ($\mu\text{g/g}$), $n = 80$	WASI-III, RAVLT, TAVIS-3, TMT	Years of schooling (for all models), gender (for IQ and visual working memory), area of residence (IQ only)	Linear	Hair Mn concentrations are inversely associated with IQ. Mn in fingernails is associated with lower visual working memory scores and cognitive flexibility.
Menezes-Filho, 2011 [79]	Brazil	Cross-Sectional	Ferromanganese alloy plant	82	14–46 yrs.	Hair ($\mu\text{g/g}$), $n = 77$	RCPM	Age, education years, family income	Linear	Higher hair Mn levels were associated with worse performance on the RCPM.
Solís-Vivanco, 2009 [10]	Mexico	Cross-Sectional	Mn mining	288	20–87 yrs.	Blood ($\mu\text{g/L}$), $n = 288$ Air ($\mu\text{g/m}^3$), $n = 288$	MMSE, Digit Span (WAIS), Word Association, Clock, Word List, Semantic example Design	Age, education, gender	Linear	Higher air levels of Mn are associated with poorer Digit Span Recall scores.

Author, Year	Country	Study Design	Exposure	Participants	Age at Cognitive Assessment	Biomarkers/Environmental Measures, n	Outcome Measures	Covariates	Association	Conclusions
Occupational Exposures										
Hassani, 2015 [39]	Iran	Cross-Sectional	Air	29 Welders 31 Ferro alloy smelters 35 smelters 30 Controls	Mean Ages Welders = 31 yrs. Smelters = 35 yrs. Controls = 34 yrs.	Air (mg/m ³), n = 58 Blood (µg/L), n = 88 Urine (µg/L), n = 88 Toenails (µg/g), n = 83	CANTAB	Age, work history, smoking	Between group	Mn exposure, measured by the 3 biomarkers, was significantly higher among workers.
Zou, 2014 [84]	China	Cross-Sectional	Air	293 Controls 819 Exposed	Mean controls = 36 yrs. Mean exposed = 40 yrs.	CEI (mg/m ³ × year), n = 96 & 96	MoCA	Gender, education, smoking, alcohol consumption	Linear	Higher CEIs are associated with lower scores on the MoCA and decreased plasma BDNF levels.
Bowler, 2011 [88]	USA, CA	Prospective Cohort	Air	26 Welders	32–65 yrs.	Blood (µg/L), n = 24	WAIS-III, Stroop Tests, Rey-Osterrieth	Age	Between group	Cognitive improvements at follow up compared to the baseline scores.

Author, Year	Country	Study Design	Exposure	Participants	Age at Cognitive Assessment	Biomarkers/Environmental Measurements, n	Outcome Measures	Covariates	Association	Conclusions
Laohaudomchok, 2011 [87]	USA, MA	Cross-sectional	Air	46 Welders	Mean = 37.4 yrs.	CEI (mg/m ³ × hr), n = 46	CPT and NES3	Age	Linear	Total CEI is associated with lower CPT scores.
Summers, 2011 [83]	Australia	Cross-sectional	Air	143 Workers	Mean = 38 yrs.	Mn CEI inhalable (mg-years/m ³), n = 143 Mn CEI respirable (mg-years/m ³), n = 143	Digit Symbol, Controlled Oral Association Test, TMT, MR, Stroop Tests	Age, education, and estimated IQ	Linear	Inhalable Mn was associated with deficits on the Digit Symbol and Stroop Tests. Respirable Mn was associated with better performance on the Digit Symbol and lower scores on TMT, A, MR, and Stroop Test.

Author, Year	Country	Study Design	Exposure	Participants	Age at Cognitive Assessment	Biomarkers/Environmental Measures, n	Outcome Measures	Covariates	Association	Conclusions
Chang, 2010 [86]	Korea	Cross-Sectional	Air	21 Controls 23 Welders	42–58 yrs.	Air (mg/m ³), n = 21 & 23 Blood (µg/dL), n = 21 & 23	K-AVLT, K-CFT, Digit Span Test (WAIS), and the Stroop Test	Age, gender, educational level	Between group	Welders had decreased memory function compared to controls.
Chang, 2009 [85]	Korea	Cross-Sectional	Air	29 Controls 43 Welders	40–57 yrs.	Air (mg/m ³), n = 29 & 43 Blood (µg/dL), n = 29 & 43 PI (Pallidol index), n = 29 & 43	K-AVLT, K-CFT, Digit Span Test, Digit Symbol Test, Stroop Test	Age, gender, educational level, smoking, alcohol consumption	Linear	Blood Mn is inversely associated with K-CFT. PI is inversely associated with Digit Symbol, Digit Span Backward, and positively associated with the Stroop tests.
Ellingsen, 2008 [40]	Russia	Cross-Sectional	Air	96 Referents 96 Welders	18–66 yrs.	Blood (µg/L), n = 96 & 96 Urine (µg/g cr), n = 96 & 96 Air	Q 16, Digit Symbol 1 & Digit Span (WAIS)	Age, education, facility of work,	Linear	Blood and air Mn concentrations are inversely associated with

Author, Year	Country	Study Design	Exposure	Participants	Age at Cognitive Assessment	Biomarkers/Environmental Measures, n	Outcome Measures	Covariates	Association	Conclusions
						($\mu\text{g}/\text{m}^3$), n = 96 & 96				performance on the Digit Symbol test.
Blond, 2007 [89]	Denmark	Prospective Cohort	Air	97–106 Referents 51–53 Exposed	35–68 yrs.	Blood (nmol/l), n = 53	CFS	Age, gender, social status	Between group	Association between workers and visuomotor impairments.
Bouchard, 2007 [5]	Canada	Prospective Cohort	Air	68 Referents 69 Exposed	43–74 yrs.	CEI (mg Mn/m ³), n = 68 & 69	Cancellation, Digit Span, Delayed Word Recall, Trail Making A, Trail Making B, Stroop Tests, Symbol Digit Modalities Test	Age, education, alcohol consumption, smoking	Linear	Mn exposure is associated with cognitive flexibility deficits. Those who were 45 years + when exposed ceased to have persistent cognitive flexibility deficits compared to non-welders 14 years

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Author, Year	Country	Study Design	Exposure	Participants	Age at Cognitive Assessment	Biomarkers/ Environmental Measures, n	Outcome Measures/s	Covariates	Association	Conclusions
										later.