Neurotoxicology 73 (2019) 1–7

Contents lists available at ScienceDirect

Neurotoxicology

journal homepage: www.elsevier.com/locate/neuro

The effects of manganese exposure from drinking water on school-age children: A systematic review

P.U. Iyare

Water and Environmental Engineering, University of Surrey, United Kingdom

ARTICLE INFO

Keywords:
Manganese
Drinking water
Children
Intelligence
Neurobehavioural

ABSTRACT

The aim of this study was to analyse the published literature on the potential effects of manganese exposure from drinking water on school-age children, with emphasis on cognitive, and neurodevelopment and behavioural effects. A systematic review of up-to-date scientific evidence published from 2006 to 2017 was conducted using Science Direct. A further search was carried out using PubMed and Web of Science. A total of 21 studies were reviewed and categorised into 12 cognitive and 9 neurodevelopment and behavioural effects. The most utilised cognitive test was the Wechsler Intelligence Scale for Children (WISC) or some subtests from it. 10 of the 12 studies on cognitive effects reported an adverse effect of manganese exposure from drinking water on children. 3 out of the 9 studies on neurodevelopment and behavioural effects reported that manganese exposure from drinking water was associated with poorer neurobehavioural performances in school children. 4 others implied the presence of some sex-specific associations with manganese exposure. 1 study suggested that children suffering from attention deficit hyperactivity disorder (ADHD) may be more susceptible to manganese exposure. Another study suggested that manganese was a beneficial nutrient as well as a neurotoxicant. Regardless of the limitations of the studies analysed, the adverse effects of manganese exposure from drinking water on school-aged children is sufficiently demonstrated. Further investigation into the subject to address inconsistencies in existing studies is recommended.

1. Introduction

Manganese is a commonly occurring metal in groundwater, and high concentrations have been recorded in countries where groundwater is used as the source of drinking water Frisbie et al. (2012). Although essential for human nutrition, extreme exposure has been correlated with harmful health impacts, since such concentrations exceed the human homeostatic range. Compared to adults, children have a higher tendency of being affected by environmental toxic exposure because of their immature manganese homeostatic mechanisms (Landrigan et al., 2004). 50 μg/L has been recommended as the safe level for manganese in drinking water in the European Union (The Council of the European Union, 1998) and developed countries such as United States (U.S. EPA, 2004), United Kingdom (Drinking Water Inspectorate, 2014), Canada (Health Canada, 2017), and Japan (Wakayama, 2003). In 2011, the health-based standard set by the World Health Organisation (WHO) for manganese in water (400 μg/L) was discontinued (Frisbie et al., 2012) – since the concentrations usually recorded in drinking water was well below the health-based value – notwithstanding, there has been an increasing interest in researching into the exposure of manganese in children, with recent studies suggesting that high concentrations of the metal may adversely affect brain developmental functions. Progress in this field of research has been impeded by the lack of a strong consensus among researchers on the perfect biomarker of exposure; different studies have used hair, blood and/or water manganese to represent exposure in children (Bellinger, 2013). Some of these surveys have recorded relationships between neurological development problems and manganese exposure, and the effects of the exposure in water has been reported by only a few investigations.

Thus, this report reviews the works published on the effects of manganese in drinking water on children and highlights the existing knowledge gaps.

2. Methods

A literature search on the subject was conducted using the online Science Direct database for publications released between 2006 and 2017. Other search engines considered included PubMed and Web of Science. Basic search on Science Direct using the topic yielded 207 results; the Boolean search method was used for different combinations of key words, and the results are shown in Table 1. The technique was adopted to select the most relevant papers and reduce bias. After reviewing the abstracts and scanning through each publication, 14 publications were chosen. Articles based on case studies or reviews of publications on the subject were excluded. Also, a basic search on

https://doi.org/10.1016/j.neuro.2019.02.013
Received 24 October 2018; Received in revised form 17 February 2019; Accepted 19 February 2019
Available online 21 February 2019
0161-813X/

Table 1
Combination of Terms and Results.

Terms Used	Results (2006 – 2017)
Manganese AND "drinking Water" AND children	1268
Refine filter: Drinking water	44
Manganese AND "drinking Water" AND "school-age" AND children	36

PubMed using the topic yielded 6 results. All 6 studies were relevant to this review, with 3 studies occurring in the previous search with Science Direct. Furthermore, another search was undertaken on the Web of Science database, which generated 15 results. 4 were included in this study, 3 occurred in the previous searches with Science Direct (2) and PubMed (1). Whereas, 8 were not relevant to the objective of this study. The criteria for the inclusion of studies in this review paper included publications in peer-reviewed scientific journals, cognitive functions as well as neurodevelopment and behavioural disorder.

3. Results

The 21 studies retrieved included a mix of cross-sectional studies (13), cohort studies (4), and epidemiological studies (4). The studies reviewed have been summarised under two categories: cognitive effects (12) and neurodevelopment and behavioural effects (9). The characteristics of the reviewed studies have been condensed in Table 2.

3.1. Cognitive effects

Wasserman et al. (2006) investigated intellectual function in 142 children, all 10-year old's, in a rural community in Bangladesh, who had been drinking water from a tube well with an average manganese and arsenic concentration of $793\,\mu g/L$ and $3\,\mu g/L$ respectively. The height, head circumference, weight and blood manganese of the children were measured, and their intellectual functions were evaluated on tests based on the Wechsler Intelligence Scale for Children – III (WISC III). Inferences about IQ (Intelligence Quotient) points lost at given levels of exposure could not be made, because the U.S. standardisation norms could not be applied to generate IQ scores in the study population. Although, sound procedures were used for adapting a widely used instrument to the Bangladeshi cultural setting. This was achieved by applying six subtests that seemed the most culturally adaptable to the cultural context. They included Similarities, Digit Span, Picture Completion, Coding, Block Design, and Mazes. After adjustments for sociodemographic variables, with arsenic having no effect, manganese was found to be associated with neurotoxic effects, which included reduced perceptual reasoning and working memory, in children. However, the study examined only 10-year-old children, making it difficult to ascertain whether the behaviour-related problem could be detected at younger ages or intensified at older ages.

Wright et al. (2006) undertook a study to assess the potential association between hair metal levels and the neuropsychological function and behaviour of school-aged children. A psychological test was conducted on 32 children between the ages of 11 and 13. Higher hair manganese and arsenic concentrations, especially in combination, were found to be inversely associated with children's neuropsychological function i.e. significantly lower scores on an IQ test, as well as on tests of verbal learning and memory. A major limitation of this pilot study was the limited sample size and weak statistical power, which may have reduced the probability of detecting true associations between hair metal levels and children's outcome scores. It also limited the ability to distinguish true from artifactual associations.

Bouchard et al. (2011) examined the relationship between manganese exposure from drinking water and children's IQ. The study also assessed the relationship between hair manganese and estimated manganese intakes from water consumption and from the diet. This cross-sectional study involved 362 children 6–13 years of age living in communities supplied by groundwater. Manganese concentration was measured in home tap water and children's hair. Manganese intake from water ingestion and the diet was estimated using a food frequency questionnaire and IQ was assessed with the Wechsler Abbreviated Scale of Intelligence (WASI). This study demonstrated that children exposed to higher concentration of manganese in tap water had lower IQ scores. Thus, suggesting that exposure to manganese at levels common in groundwater is associated with intellectual impairment in children. Also, manganese intake from water ingestion, but not from the diet, was significantly associated with elevated hair manganese, suggesting that manganese exposure from drinking water was metabolised differently than that from the diet and could lead to overload and subsequent neurotoxic effects expressed by intellectual impairments in children. Compared to previous studies, this study included a larger sample size, and manganese exposure by ingestion, including from dietary sources was thoroughly assessed. Repeated water sampling in the same house showed little variation in manganese concentration over the year, suggesting that one measure is representative of long-term exposure. The other metals present in tap water did not affect the association between manganese and IQ. However, associations could be attributable to unmeasured confounders, but manganese concentration in tap water was completely dissociated from socioeconomic status, which diminishes the potential for confounding. Some level of exposure misclassification was to be expected, because only manganese exposure from water consumed at home was considered. Despite measures taken to wash hair samples, residual external contamination cannot be ruled out completely.

Khan et al. (2011) also investigated the effects of manganese and arsenic on children's academic performance in the same community, and 840 school-aged children between the ages of 8 and 11 were considered in this survey. Water samples from each pupil's home were collected and scores in three subjects (English, Mathematics and Bangla) were obtained from their respective schools. A significant inverse association was recorded between water manganese and mathematics, but not between manganese and language scores, suggesting that many of the Bangladeshi children may experience inferior performance in Mathematics as a result of high levels of manganese in drinking water. Positive and significant relationships between water manganese and both externalising and internalising behaviour scores were observed, thus suggesting more problematic behaviour as exposure increased. This study is unique because it uses a well-standardised measure of child behaviour problems, which assesses both externalising and internalising behaviour. It also examines specificity in the exposure/behavior problems association. However, unmeasured teachers' biases might have evolved from teacher–child interactions at the family level in rural Bangladesh sociocultural context.

Menezes-Filho et al. (2011) undertook an investigation on the relationship between manganese in hair and blood, as well as, lead in blood of school-aged children. 83 children (6–12 years of age) living close to a ferromanganese alloy plant in Brazil were examined using the WISC–III. Whereas, the Raven Progressive Matrix was administered to the primary caregivers (94% of the mothers), who responded to a questionnaire on socio demographics and birth history. The findings of this study confirmed the suggestion that high manganese in hair (but not blood) is associated with poor cognitive performance, particularly in verbal and total IQ. Additionally, cognitive performance of the mothers was also inversely associated with manganese exposure, suggesting that in the surrounding area of the alloy plant, manganese exposure was impacting both children (directly and indirectly) and adults. This is the first study to demonstrate not only that children's intellectual impairment, but also mothers' cognition can be affected by manganese exposure.

Whereas, Roels et al. (2012) comprised of five presentations involving a number of studies, with six studies examined on cognitive

Table 2
Characteristics of Studies.

Location	First author & Year	Age (Years)	Sample Size	Study Design	Exposure Measure	Psychological Test	Observed Effect
Cognitive Effects							
Bangladesh	Wasserman et al. (2006)	10	142	Cross-sectional in a follow-up cohort	Water, blood	WISC-III	MnW ↓ Full scale verbal & performance IQ
USA	Wright et al. (2006)	11 - 13	32	Cross-sectional	Hair	WASI CVLT-C WRAML	MnH ↓ Full scale verbal IQ & memory test
Canada	Bouchard et al. (2011)	6 - 13	362	Cross-sectional	Water, Hair	WASI	MnW ↓ Full scale, verbal & performance IQ MnH ↓ Full scale IQ
Bangladesh	Khan et al. (2011)	8 - 11	201	Cross-sectional	Water, blood	CBCL	MnW ↑ Total internalising & externalising behaviour scores
Brazil	Menezes-Filho et al. (2011)	6 - 12	83	Cross-sectional	Hair, blood	WISC III	MnH↓ Full scale & Verbal IQ
Mexico	Hernández-Bonilla et al. (2016)	7 - 11	267	Cross-sectional	Hair	ROCF	MnH ↓ Visuoperception and visual memory
Bangladesh	Wasserman et al. (2016)	8 - 11	303	Cohort	Blood	WISC-IV	MnB ↓ Full scale IQ, verbal, reasoning & memory test
Canada	Bouchard et al. (2017)	5.9-13.7	259	Cohort	Hair, nail, and saliva	WISC-IV	Non-significant effect
Canada	Dion et al. (2017)	10.5 - 18	287	Cross-sectional in a follow-up cohort	Water, Hair	WISC	MnH ↓ Full scale, verbal & performance IQ
Canada	Lao et al. (2017)	9 - 15	23	Epidemiological	Basal ganglia	Santa Ana	MnBG ↓ Motor performance
Canada	Ntihabose et al. (2017)	6 - 13	274	Epidemiological	Hair, nail, saliva	—	Non-significant effect
Neurodevelopment and Behavioural Effects							
Canada	Bouchard et al. (2007)	6 - 15	46	Cross-sectional	Hair	CTRS-R	MnH ↑ Oppositional & hyperactivity subscales
South Korea	Hong et al. (2014)	8 - 11	1,001	Cross-sectional	Blood	WISC	MnB ↓ Full-Scale IQ
Canada	Oulhote et al. (2014)	6 - 13	375	Cross-sectional	Water, hair	CVLT-C	MnH MnW ↓ verbal & performance IQ
USA	Mora et al. (2015)	7, 9, 10	248	Cross-sectional	Teeth	WISC-IV	MnT, Sex-specific association
Bangladesh	Rodrigues et al. (2016)	1.7 - 3.3	524	Cohort	Water	BSID-III	Non-significant effect; MnW inverse-U ∝ fine motor scores
Italy	Bauer et al. (2017)	10 - 14	142	Epidemiological	Tooth	VRAM	MnT, Sex-specific association
Italy	Chiu et al. (2017)	11–14	195	Cross-sectional	Teeth	CATSYS	MnT, Sex-specific association
Bangladesh	Rahman et al. (2017)	10	1265	Cross-sectional	Water	WISC-IV	MnW, Sex-specific association
Brazil	Rodrigues et al. (2018)	7 - 12	225	Cross-sectional	Blood, hair, nail	CBCL	MnN ↑ Externalizing behaviour, thought & social problems

IQ: intelligence quotient; ADHD: attention deficit and hyperactivity disorder; MnB: manganese in blood; MnW: manganese in drinking water; MnH: manganese in hair; MnT: manganese in tooth; MnN: manganese in nail; WISC: Wechsler Intelligence Scale for Children; CATSYS: Computerized Adaptive Testing System; CVLT-C: California Verbal Learning Test; CTRS-R: Conners' Teacher Rating Scales: Revised; BSID-III: Bayley Scales of Infant and Toddler Development, Third Edition; VRAM: Virtual Radial Arm Maze; ROCF: Rey-Osterrieth Complex Figure.

function in school-age children. The studies used different biomarkers (hair, blood and plasma) to assess the relationship between manganese exposure and cognitive deficits in children and adults. The results of all six studies indicated a negative impact of excess environmental manganese exposure from air and drinking water on children's cognitive performance, with special attention to hair manganese as a potential biomarker of exposure. Although all of these studies demonstrated an inverse relationship between manganese exposure and cognitive performance, they did not use the same tests, nor did they use the same biomarkers of exposure.

Hernández-Bonilla et al. (2016) assessed the association between manganese environmental exposure, and effects on visuoperception and visual memory in school children. 267 children (7 to 11 years old) from the mining district of Molango and a non-mining area, Agua Blanca, in Hidalgo state, Mexico were evaluated. The Rey-Osterrieth Complex Figure (ROCF) test was used to assess visuoperception and short-term visual memory, with hair as a biomarker of exposure. Linear regression models were constructed to estimate the associations between hair manganese and ROCF scores, adjusted for potential confounders. Manganese exposure levels were associated with increased distortion, angle, overtracing and size errors as well as omission of perceptual units in visuoperceptual assessment. Manganese exposure was also associated with an increased number of overtracings and omissions errors, and a decreased number of perceptual units drawn, total score and percentage immediate recall in the short-term visual memory assessment. According to the author, this was the first study to use ROCF to assess the effects on visuoperceptual abilities and visual memory associated with Mn exposure in school children. The main limitation of this study is the epidemiological design since cross-sectional studies do not address temporality and causality to identify early neurological and cognitive susceptibility windows.

Wasserman et al. (2016) carried out a 2-year follow-up study to ascertain if reduction in manganese and arsenic exposure is related to better intellectual results. 303 children – 8–11 years old – were recruited within a year at baseline. Over 12 months after the baseline assessment, 58 community wells were installed, averaging 225 m in depth and supplying groundwater with average arsenic and manganese content of 2.9 μg/L and 0.45 mg/L, respectively. Of the 303 children examined at baseline, 296 were seen at follow-up, nearly 3 years later. Over the period, the reduction in exposure was not correlated with significant improvement in total IQ scores, except for limited developments in working memory. Although, it was impossible to reliably identify which well each child used at each point across follow-up.

Bouchard et al. (2017) examined the relationship between manganese exposure and cognition in school-aged children drinking well water in Canada. 259 children (5.9–13.7 years of age) were included in the survey, with WISC–IV to assess their cognition. Compared to previous studies, the manganese concentration in drinking water was lower, and no significant association between manganese exposure and cognition was found, but the result suggested sex-specific relationships and possible beneficial effects in boys. A strength of this study was the long duration of residency in the current homes of most study participants. This is because the health effects of manganese exposure in drinking water, if any, would most likely result from long term exposure. The greatest drawback of this study was the limited range of manganese concentrations in drinking water and a small sample size leading to wide confidence intervals, especially for sex stratified associations.

Dion et al. (2017) also reassessed the relationship between drinking water manganese exposure and IQ in a follow-up study. 287 out of the initial 380 children participated in the follow-up examination. The age range at follow-up was 10.5 to 18 years. Higher manganese concentration in drinking water measured at follow-up was associated with higher IQ in boys, whereas the reverse was recorded in girls. The results of the study suggested that prolonged exposure to manganese was related differently with cognition in girls and boys. IQ scores were not significantly associated with the concentration of the metal in hair, although similar trends for concentration in water were observed. Performance IQ scores decreased significantly for children whose manganese concentration in water increased between baseline and follow-up. According to the author, this was the first study to follow a cohort from childhood to adolescence to investigate possible neurotoxic effects arising from manganese exposure from drinking water. Although it was subject to several limitations, its longitudinal design made it possible to follow changes done to water treatment systems in participating households. Some of the limitations included the lack of data on maternal and early life manganese exposure. This impeded the investigation to determine whether exposure during critical development periods, such as the prenatal period or early childhood, contributed to cognitive performance at adolescence. Additionally, confounders or mediators that were not taken into account could have potentially impacted the results. For example, metabolic disorders or genetics could alter manganese absorption and elimination in the body. Also, the concentration of the metal in drinking water increased or decreased significantly at follow-up for only a small number of participants, limiting the statistical power to investigate changes in level of exposure.

Based on brain MRI, Lao et al. (2017) applied a 3D surface-based morphometry method on 3 bilateral basal ganglia structures in school-age children chronically exposed to manganese through drinking water to investigate the effect of manganese exposure on brain anatomy. 23 children aged 9–15 were grouped into 10 high manganese exposure and 13 age matched low exposure participants, according to the manganese concentration in their drinking water, to examine the differences associated with exposure through drinking water. The outcome of this study demonstrated significant enlargement of many areas of the basal ganglia structures, preferentially affecting the putamen. Furthermore, these areas showed significant correlations with fine motor performance, indicating a possible link between altered basal ganglia neurodevelopment and declined motor performance in high manganese exposed children. Collectively, these results suggest that neuro-circuits within the motor loop are at risk in children with manganese exposure through drinking water. The limitations of this study include the reliance on manganese concentration in drinking water to define exposure groups. This is because air and food could also be potential sources of manganese exposure. Also, the possible influence of other contaminants present in water was not explored. Thirdly, ages 9–15 represents a period at which the brain is still rapidly developing. To avoid the over-fitting problem of using nonlinear regression with a limited sample size, a simple linear regression was adopted to factor out or control the effect of age. This is recognized as one of the caveats of this study.

Ntihabose et al. (2017) assessed hair, saliva and toenails as biomarkers of low-level manganese exposure from drinking water in school-aged children. This is the first study to test toenails as a biomarker of exposure to manganese from drinking water. 274 children, aged 6 to 13, were involved in the study. Compared to other studies, the levels of manganese in drinking water and biomarkers were significantly lower. Only hair and toenails exhibited some degree of correlation with manganese exposure from drinking water. No significant difference was detected in exposure or biomarker manganese concentrations between sex. Nevertheless, variations in hair manganese were higher in girls than boys. This result demonstrated that sex can potentially affect manganese levels in biomarkers.

3.2. Neurodevelopment and behavioural effects

Bouchard et al. (2007) measured manganese concentration in the hair of 46 children (6–11 years old) in Canada. This pilot study demonstrates that children living in houses linked to wells with higher manganese levels displayed higher concentrations of the metal in hair, indicating tap water use as a source of the exposure in this community. The results of the study showed that exposures to high level of manganese in tap water was associated with elevated levels of manganese in hair and that manganese in hair showed significant association with heightened degrees of hyperactive and oppositional behaviours in the classroom. These associations remained significant after adjustment for income, age, and sex. The findings of this study suggest a continuum in the relationship between hair manganese and hyperactive behaviors in the classroom, with all children presenting elevated levels on certain scales having hair manganese levels above the normal range. Some limitations of this study include: the small sample size usually results in small statistical power, which nonetheless was sufficient to detect significant relationships. Also, the participants were self-selected, and it is probable that parents who thought that their child had behavioural challenges were more interested in volunteering. Furthermore, a series of confounders were not evaluated—for example, maternal education, familial stress, and perinatal stress.

Hong et al. (2014) investigated the potential impact of manganese on children with Attention Deficit Hyperactivity Disorder (ADHD). A total of 890 children, ages 8–11 were assessed. Using the Child Behavior Checklist (CBCL) it was discovered that children living with ADHD may be more susceptible to manganese neurotoxicity exposure than the average school-aged population, which leads to increased possibility of developing comorbid mental illness. The absence of information on other potential confounders or possible sources of exposure, such as iron status or diet was a limitation of this study. Also, symptoms scores on the CBCL were used rather than actual diagnosis of conduct or depressive disorders. The past or current treatment history of ADHD children was not assessed. In addition, other candidate biomarkers of manganese exposure such as hair manganese level were not measured.

Oulhote et al. (2014) examined the relationship between neurobehavioural functions, and manganese in drinking water and hair in Canada, using 375 children (6–13 years old) as volunteers. The exposure-response association was evaluated using generalised additive models. Higher levels of exposure to manganese were associated with poorer performance of memory, attention, and motor functions, but not hyperactivity, in children. The results of this study suggested that, even at low levels, a significant relationship existed between intake of manganese in water and poor neurobehavioural performance in children. The strengths of this study included the thorough assessment of potential confounders, adjusting for several socioeconomic status indicators, as well as maternal intelligence and depression symptoms, and water lead concentrations. Also, the Structural equation modeling (SEM) approach was employed, which addresses issues arising from multiple testing and missing data that may not be adequately considered by standard regression analyses. The SEM findings were compared with the more traditional approach of analyzing each test score separately, and the findings were consistent. Whereas, a limitation of this study was that the reported associations could be attributable to unmeasured confounders, but water manganese did not vary with socioeconomic factors, thus reducing the potential for confounding.

Mora et al. (2015) carried out a similar neurodevelopmental study in 248 children (7–10.5 years old) residing near farmlands treated with manganese-containing fungicides in California. A higher prenatal and postnatal manganese levels in dentine of deciduous teeth, a novel biomarker, were associated with poor behavioural outcomes, such as maternal-reported internalising, externalising, and hyperactivity problems, in school-aged girls and boys, but better cognitive, visuospatial and verbal memory, and motor function in boys. Some of the strengths of this study include its longitudinal design, use of comprehensive neurodevelopmental assessments at different ages, information on a wide variety of potential confounders, and use of a novel matrix for manganese measurements. Whereas, some limitations included the limited statistical power as a result of the relatively small sample size, which was further reduced in the stratified analyses (i.e., child sex and prenatal lead exposure). Also, multiple comparisons were conducted, making it difficult to rule out the probability that some associations were due to chance.

Rodrigues et al. (2016) investigated the associations between environmental exposure to arsenic, manganese, and lead and neurodevelopmental outcomes at age 20 to 40 months in Bangladeshi children and the potential interactions of the same metals on these outcomes. Data from 524 children was evaluated, and water was collected from each family's primary drinking source during the first trimester of pregnancy and at ages 1, 12 and 20–40 months. At age 20–40 months, blood lead was measured, and neurodevelopmental outcomes were assessed using a translated, culturally-adapted version of the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III). Where blood lead levels were high, lead was associated with decreased cognitive scores on the BSID-III, and effects of other metals were not detected. In the setting of lower lead levels, the adverse effects of arsenic and manganese on neurodevelopment were observed. Water manganese was associated with fine motor scores in an inverse-U relationship, indicating a beneficial effect of increased manganese at lower concentrations and the negative effects at higher concentrations. A major strength of this study was the ability to study children in two different regions of Bangladesh with different exposure and demographic profiles. Also, the effects of combinations of both low and high environmental exposures on neurodevelopmental outcomes were investigated. A limitation of this study was the lack of a biomarker of exposure for arsenic and manganese. Furthermore, there was a potential for exposure misclassification since other sources of exposure such as food were not considered.

Bauer et al. (2017) examined whether prenatal or postnatal manganese measured in deciduous teeth was associated with scores on a test of visuospatial learning and memory. Deciduous teeth were collected from 142 participants (ages 10–14 years) residing near varied ferromanganese industries in Italy. Manganese concentrations were measured in prenatal and postnatal tooth regions by laser ablation inductively coupled plasma mass spectrometry (ICP-MS). The Virtual Radial Arm Maze (VRAM), an animal-human analogue task, was used to assess visuospatial learning and memory. A "U" shaped association was observed between prenatal manganese and VRAM performance measures among girls only, suggesting that both low and high prenatal manganese may adversely affect visuospatial learning and working memory. This "U" shaped association was not observed among boys, and was not observed for exposure in the postnatal period in either sex. Instead, associations of postnatal manganese with VRAM performance during adolescence did not vary by sex and were null. The results of this study suggest that the prenatal period may be a critical window for the impact of environmental manganese on visuospatial ability and executive function, especially for females. The strengths of this study include the use of dentine as an exposure biomarker. Thus, enhancing retrospective and objective evaluation of exposure during multiple developmental stages (prenatal and early postnatal) and identifying which stages, if any, were critical windows for manganese-associated neurodevelopment. Also, neurobehavioural testing at a sensitive time point (late childhood and adolescence) was performed. This has not yet been frequently studied in the context of fetal manganese exposure. This study was the first to use VRAM, a sensitive and novel outcome, to assess manganese neurotoxicity in humans. Using the VRAM provides an animal-human analogue to bridge the gap between animal and human endpoints of manganese neurotoxicity, and supports interpretation of results from epidemiologic and toxicological studies. Although, the small sample size limited statistical power to detect associations, particularly in stratified models. In addition, there may have been unmeasured confounding or effect modification from maternal iron status, in which low maternal iron increased manganese absorption and negatively impacts neurodevelopment.

Chiu et al. (2017) measured manganese concentrations in the dentine of shed teeth from 195 children, 11 to 14 years of age to assess sex-specific differences in sensitivity to prenatal and childhood manganese exposure on neuromotor function. Differences were observed in the link between manganese and entire body stability, as boys recorded better body stability, as opposed to girls with heightened instability at higher prenatal manganese concentrations. The association may not be as strong when considering early postnatal or childhood cumulative Mn exposures. These findings suggested that there may be time-dependent and sex-specific associations. The limitations of this study were similar to those listed in Mora et al. (2015).

Rahman et al. (2017) prospectively assessed the effects of water manganese, from fetal life to school age, on children's cognitive abilities and behaviour. 1265 10-year-old children in rural Bangladesh were evaluated using the WISC-IV and the Strengths and Difficulties Questionnaire (SDQ), respectively. Manganese in drinking water used during pregnancy and by the children at 5 years and 10 years was measured using inductively coupled plasma mass spectrometry. Elevated prenatal and early childhood exposure to water manganese (mainly from medium-deep wells) appeared to increase the risk of children's behaviour problems at 10 years of age. However, no positive associations of prenatal water manganese and cognitive abilities in girls were found. The major strengths of this study include the large sample size and the population-based prospective design with manganese measured in all water sources used by the children and in all those used by their mothers during pregnancy. However, a limitation of the study was the lack of water samples from the children's schools, which might have caused nondifferential misclassification of the children's exposure, particularly at 10 years. At 5 years, only 30% of the children attended school, and then only for a short time each day. Also, cognitive assessments were expressed as raw scores because the WISC-IV was not yet standardised for Bangladeshi children.

Rodrigues et al. (2018) evaluated behavioural effects in school-aged children living near a ferro-manganese alloy plant and examined their association with Mn exposure. Occipital hair, toenails and blood samples were collected from 225 children (7–12 years old) enrolled in four elementary schools with different levels of exposure to manganese, based on dust manganese deposition rates. Manganese in the three biomarkers of exposure were determined by graphite furnace atomic absorption spectrometry. The CBCL reported by parents was used to assess children's behaviour. Hair and blood manganese were not associated with any scale of the CBCL behaviour scores. Non-linear associations between toenail manganese and externalising behaviour were observed, as well as with aggressive and rule-breaking behaviour. Further positive associations were observed between toenail manganese and thought and social problems. The results suggested that excessive exposure to manganese may be associated with behavioural disorders in children. The strengths of this study include the use of different biomarkers, the application of a validated neuropsychological instrument in Brazil, the control by sociodemographic variables, the use of robust statistical models to test the associations, and the use of linear and non-linear modelling. However, the study was limited by the analytical technique for quantification of manganese in hair, which made impossible a reliable comparison with a previous study carried out in two communities close to the study region. Additionally, there were difficulties in accessing the parents.

4. Discussion

Out of the twelve studies on cognitive effects, nine (Wasserman et al., 2006; Wright et al., 2006; Bouchard et al., 2011; Khan et al., 2011; Menezes-Filho et al., 2011; Roels et al., 2012; Hernández-Bonilla et al., 2016; Dion et al., 2017; Ntihabose et al., 2017) reported that exposure to manganese from drinking water has adverse effects on children's cognitive functions. Lao et al. (2017) indicated that neurocircuits within the motor loop were at risk in children with manganese exposure through drinking water. Whereas, Wasserman et al. (2016) only reported a limited development in the working memory of the children considered in their 2-year follow up study, and Bouchard et al. (2017) only suggested that sex-specific relationships may exist in boys, with possible beneficial effects. Both studies recorded no significant correlation between manganese exposure and cognitive functions.

Of the nine studies on neurodevelopment and behavioural effects, three (Mora et al., 2015; Bauer et al., 2017; Chiu et al., 2017) measured the manganese concentration in the dentine of shed teeth, a novel biomarker for manganese exposure. Both Mora et al. (2015) and Chiu et al. (2017) recorded poor behavioural performances and body instability in girls, with boys having better body stability, cognitive and motor functions. Rahman et al. (2017) reported an increased risk of parent-reported conduct problems (frequent temper tantrums or hot tempers, disobedience, fighting with other children, etc.) particularly in boys, and low scores for prosocial behaviour in girls. This implies that there may be some sex-specific associations with manganese exposure. Bauer et al. (2017) recorded a correlation between prenatal manganese and VRAM performance measures among girls but not boys. Thus, suggesting that girls may be specifically susceptible to prenatal manganese overexposure in relation to visuospatial development. Three other surveys (Bouchard et al., 2007; Oulhote et al., 2014; Rodrigues et al., 2018) reported that manganese exposure from drinking water was associated with poorer neurobehavioural performance in school children. While, Hong et al. (2014) suggested that children suffering from ADHD may be more susceptible to manganese neurotoxicity compared to the average school-age children, Rodrigues et al. (2016) proposed a beneficial effect of increased manganese at lower concentrations and adverse effects at higher concentrations.

The studies reviewed propose that manganese exposure from drinking water is associated with cognitive, and neurodevelopment and behavioural effects. Although the differences in the analytical methods and tests administered on the children makes comparison quite problematic, some helpful indications can be obtained from the studies published to date. There was no consistency in the results of the 21 studies considered. The reason for this disparity can be associated with many variables, such as the valence state of the metal, bioavailability and chemical form of the element, the efficiency of the exposure metrics, the biomarkers used – which could be subject to exogeneous contamination (Zheng et al., 2011), – and the use of neuropsychological tests. Also, the cross-sectional nature of some of the studies hampered cause–effect inferences. Other limitations presented while writing this review include: the lack of a validated and standardised measure of intelligence, also the lack of an authenticated biomarker for measuring exposure, as some of the studies focused on one agent of exposure and did not adjust or measure the possible effects of other agents. Finally, "geographic generalisability" presented a limitation because comparing children living in Bangladesh with those from countries like Canada was difficult due to possible differences in socio-economic, other demographic factors.

5. Conclusion

Regardless of these limitations, the studies considered have sufficiently demonstrated adverse effects of exposure to manganese from drinking water on school-aged children. Similarly, a previous systematic review by Zoni and Lucchini (2013), which considered 10 publications from five countries, further supports the evidence that manganese exposure adversely affects cognitive, and neurodevelopment and behavioural functions in children. Only 3 out of the 10 papers reviewed by Zoni and Lucchini (2013) were reviewed in this study (Bouchard et al., 2011; Khan et al., 2011; Menezes-Filho et al., 2011). Based on this finding, preventive measures to decrease manganese exposure from drinking water, especially with respect to children, should be promoted. Further research is required to better understand and address the inconsistencies of these findings such as the sex-specific effects, the role of genetic factors and the most suitable biomarker of exposure. It is also needful to research into the indicators of cumulative exposure since manganese toxicity could be the result of bioaccumulation. Lastly, more investigations are required into understanding the potential for harm or benefits of manganese exposure on body stability in children. This is because increased exposure to neurotoxicants could be creating a global pandemic resulting in poor academic performance and behavioural performance among children in the society.

Conflict of interest

This study was funded by the Niger Delta Development Commission of Nigeria.

Acknowledgment

I am grateful to Dr Steve Pedley for encouraging and motivating me to publish what began as a coursework.

I would like to thank the Niger Delta Development Commission (NDDC) of Nigeria (Grant ID: NDDC/DEHSS/2016PGFS/EDS/MSC/012) for funding my graduate degree programme.

I would also like to express my profound gratitude to my wife, Diana for her continued support, advice and assistance, especially in proof reading this review paper.

I am grateful for the love and support of all my extended family members, especially my mum and late dad who believed in me and invested so much into my academic pursuit.

References

Bauer, J.A., Henn, B.C., Austin, C., Zoni, S., Fedrighi, C., Cagna, G., Placidi, D., White, R.F., Yang, Q., Coull, B.A., 2017. Manganese in teeth and neurobehavior: sex-specific windows of susceptibility. Environ. Int. 108, 299–308.

Bellinger, D.C., 2013. Prenatal exposures to environmental chemicals and children's neurodevelopment: an update. Safety Health Work 4, 1–11.

Bouchard, M., Laforest, F., Vandelac, L., Bellinger, D., Mergler, D., 2007. Hair manganese and hyperactive behaviors: pilot study of school-age children exposed through tap water. Environ. Health Perspect. 115, 122.

Bouchard, M.F., Sauvé, S., Barbeau, B., Legrand, M., Brodeur, M.-È., Bouffard, T., Limoges, E., Bellinger, D.C., Mergler, D., 2011. Intellectual impairment in school-age children exposed to manganese from drinking Water. Environ. Health Perspect. 119, 138–143.

Bouchard, M.F., Surette, C., Cormier, P., Foucher, D., 2017. Low level exposure to manganese from drinking water and cognition in school-age children. NeuroToxicology.

Chiu, Y.-H.M., Claus Henn, B., Hsu, H.-H.L., Pendo, M.P., Coull, B.A., Austin, C., Cagna, G., Fedrighi, C., Placidi, D., Smith, D.R., Wright, R.O., Lucchini, R.G., Arora, M., 2017. Sex differences in sensitivity to prenatal and early childhood manganese exposure on neuromotor function in adolescents. Environ. Res. 159, 458–465.

Dion, L.-A., Saint-Amour, D., Sauvé, S., Barbeau, B., Mergler, D., Bouchard, M.F., 2017. Changes in Water manganese levels and longitudinal assessment of intellectual function in children exposed through drinking Water. NeuroToxicology.

Drinking Water Inspectorate, 2014. Speciation of Manganese in Drinking Water [Online]. United Kingom: WRc Ref: UC9780/15749-0. Available: http://dwi.defra.gov.uk/research/completed-research/reports/DWI70-2-276.pdf [Accessed 31 January 2019]. .

Frisbie, S.H., Mitchell, E.J., Dustin, H., Maynard, D.M., Sarkar, B., 2012. World Health Organization discontinues its drinking-water guideline for manganese. Environ. Health Perspect. 120, 775–778.

Health Canada, 2017. Guidelines for Canadian Drinking Water Quality—Summary Table. Water and Air Quality Bureau. Healthy Environments and Consumer Safety Branch, Health Canada, Ottawa, Ontario.

Hernández-Bonilla, D., Escamilla-Núñez, C., Mergler, D., Rodríguez-Dozal, S., Cortez-Lugo, M., Montes, S., Tristán-López, L., Catalán-Vázquez, M., Schilmann, A., Riojas-Rodriguez, H., 2016. Effects of manganese exposure on visuoperception and visual memory in schoolchildren. Neurotoxicology 57, 230–240.

Hong, S.-B., Kim, J.-W., Choi, B.-S., Hong, Y.-C., Park, E.-J., Shin, M.-S., Kim, B.-N., Yoo, H.-J., Cho, I.-H., Bhang, S.-Y., Cho, S.-C., 2014. Blood manganese levels in relation to comorbid behavioral and emotional problems in children with attention-Deficit/Hyperactivity disorder. Psychiatry Res. 220, 418–425.

Khan, K., Factor-Litvak, P., Wasserman, G.A., Liu, X., Ahmed, E., Parvez, F., Slavkovich, V., Levy, D., Mey, J., van Geen, A., 2011. Manganese exposure from drinking water and children's classroom behavior in Bangladesh. Environ. Health Perspect. 119, 1501.

Landrigan, P.J., Kimmel, C.A., Correa, A., Eskenazi, B., 2004. Children's health and the environment: public health issues and challenges for risk assessment. Environ. Health Perspect. 112, 257.

Lao, Y., Dion, L.-A., Gilbert, G., Bouchard, M.F., Rocha, G., Wang, Y., Leporé, N., Saint-Amour, D., 2017. Mapping the basal Ganglia alterations in children chronically exposed to manganese. Sci. Rep. 7, 41804.

Menezes-Filho, J.A., Novaes, Cd.O., Moreira, J.C., Sarcinelli, P.N., Mergler, D., 2011. Elevated manganese and cognitive performance in school-aged children and their mothers. Environ. Res. 111, 156–163.

Mora, A.M., Arora, M., Harley, K.G., Kogut, K., Parra, K., Hernández-Bonilla, D., Gunier, R.B., Bradman, A., Smith, D.R., Eskenazi, B., 2015. Prenatal and postnatal manganese teeth levels and neurodevelopment at 7, 9, and 10.5 years in the Chamacos cohort. Environ. Int. 84, 39–54.

Ntihabose, R., Surette, C., Foucher, D., Clarisse, O., Bouchard, M.F., 2017. Assessment of saliva, hair and toenails as biomarkers of low level exposure to manganese from drinking water in children. NeuroToxicology.

Oulhote, Y., Mergler, D., Barbeau, B., Bellinger, D.C., Bouffard, T., Brodeur, M.-È., Saint-Amour, D., Legrand, M., Sauvé, S., Bouchard, M.F., 2014. Neurobehavioral function in school-age children exposed to manganese in drinking Water. Environ. Health Perspect. 122, 1343.

Rahman, S.M., Kippler, M., Tofail, F., Bölte, S., Hamadani, J.D., Vahter, M., 2017. Manganese in drinking water and cognitive abilities and behavior at 10 years of age: a prospective cohort study. Environ. Health Perspect. 125.

Rodrigues, E.G., Bellinger, D.C., Valeri, L., Hasan, M.O.S.I., Quamruzzaman, Q., Golam, M., Kile, M.L., Christiani, D.C., Wright, R.O., Mazumdar, M., 2016. 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 15, 44.

Rodrigues, J.L.G., Araújo, C.F.S., dos Santos, N.R., Bandeira, M.J., Anjos, A.L.S., Carvalho, C.F., Lima, C.S., Abreu, J.N.S., Mergler, D., Menezes-Filho, J.A., 2018. Airborne manganese exposure and neurobehavior in school-aged children living near a Ferro-manganese alloy plant. Environ. Res. 167, 66–77.

Roels, H.A., Bowler, R.M., Kim, Y., Claus Henn, B., Mergler, D., Hoet, P., Gocheva, V.V., Bellinger, D.C., Wright, R.O., Harris, M.G., Chang, Y., Bouchard, M.F., Riojas-Rodriguez, H., Menezes-Filho, J.A., Téllez-Rojo, M.M., 2012. Manganese exposure and cognitive deficits: a growing concern for manganese neurotoxicity. NeuroToxicology 33, 872–880.

The Council of the European Union, 1998. Council Directive 98/83/Ec on the Quality of Water Intended for Human Consumption [Online]. Available: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:1998:330:0032:0054:EN:PDF [Accessed 31 January 2019]. .

U.S. EPA, 2004. Drinking Water Health Advisory for Manganese. EPA-822-R-04-003. Washington, DC, U.S. Environmental Protection Agency.

Wakayama, H., 2003. Revision of Drinking Water Quality in Japan. Ministry of Health, Labour and Welfare., Japan.

Wasserman, G.A., Liu, X., Parvez, F., Ahsan, H., Levy, D., Factor-Litvak, P., Kline, J., van Geen, A., Slavkovich, V., LoIacono, N.J., 2006. Water manganese exposure and children's intellectual function in Araihazar, Bangladesh. Environ. Health Perspect. 114, 124.

Wasserman, G.A., Liu, X., Parvez, F., Factor-Litvak, P., Kline, J., Siddique, A.B., Shahriar, H., Uddin, M.N., van Geen, A., Mey, J.L., 2016. Child intelligence and reductions in water arsenic and manganese: a Two-year follow-up study in Bangladesh. Environ. Health Perspect. 124, 1114.

Wright, R.O., Amarasiriwardena, C., Woolf, A.D., Jim, R., Bellinger, D.C., 2006. Neuropsychological correlates of hair arsenic, manganese, and cadmium levels in school-age children residing near a hazardous waste site. NeuroToxicology 27, 210–216.

Zheng, W., Fu, S.X., Dydak, U., Cowan, D.M., 2011. Biomarkers of manganese intoxication. Neurotoxicology 32, 1–8.

Zoni, S., Lucchini, R.G., 2013. Manganese exposure: cognitive, motor and behavioral effects on children: a review of recent findings. Curr. Opin. Pediatr. 25, 255.