HHS Public Access

Author manuscript

Int J Environ Health Res. Author manuscript; available in PMC 2017 September 05.

Published in final edited form as:

Int J Environ Health Res. 2016 ; 26(5-6): 483–496. doi:10.1080/09603123.2016.1194381.

Medication use associated with exposure to manganese in two Ohio towns

Rosemarie M. Bowler[a], **Shane W. Adams**[a], **Chris W. Wright**[a], **Yangho Kim**[b], **Andrew Booty**[c], **Michelle Colledge**[d], **Vihra V. Gocheva**[a], and **Danelle T. Lobdell**[e]

[a]Department of Psychology, San Francisco State University, San Francisco, CA, USA

[b]Department of Occupational and Environmental Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, South Korea

[c]Department of Psychiatry, University of California San Francisco, San Francisco, CA, USA

[d]ATSDR, Chicago, IL, USA

[e]National Health and Environmental Effects Research Laboratory, U.S. EPA, Research Triangle Park, NC, USA

Abstract

This report describes the use of medications as a proxy when medical record reviews are unavailable, to study the health effects of residents environmentally exposed to air-manganese (n = 185) compared to unexposed residents (n = 90). Participants' current medication lists and medication questionnaire responses were collected in clinical interviews and categorized into 13 domains. Exposed participants reported fewer hours of sleep than controls (6.6 vs. 7.0). The exposed used significantly more medications than unexposed participants (82.2 % vs. 67.8 %) and, when adjusting for age, education, and personal income, also for pain (aOR = 2.40) and hypothyroidism (aOR = 7.03). Exposed participants with higher air-Mn concentrations, monitored for 10 years by the U.S. Environmental Protection Agency, were 1.5 times more likely to take pain medications. The exposed participants take significantly more medications than unexposed participants in the categories of hypothyroidism, pain, supplements, and total medications.

Keywords

Air; heavy metals; illness; pollution; communities

Correspondence to: Rosemarie M. Bowler.

Disclaimer

The views expressed in this manuscript are those of the authors and do not necessarily reflect the views or policies of the U.S. EPA or ATSDR.

Disclosure statement

No potential conflict of interest was reported by the authors.

Introduction

Manganese (Mn) is an essential element with natural low levels ubiquitously found in water, food, and air. However, due to industrialized processes, both workplace and environmental exposures to Mn have increased (Mergler et al. 1999; Santos-Burgoa et al. 2001; Solís-Vivanco et al. 2009). In 2009, an estimated 928,727 pounds of Mn from over 1,900 different facilities were released into the air in the US, accounting for roughly 7 % of all facility released pollutants (Agency for Toxic Substances and Disease Registry [ATSDR] 2012). Occupational studies have reported health problems among workers, especially those working without adequate protection and ventilation, who manufacture steel, add Mn to paints and glazes, and weld (Roels et al. 1987). Additionally, residents who have been exposed to environmental Mn near industrial sources, such as smelters, have developed health consequences similar to those described in occupational settings (Feldman 1999). Residential and occupational studies have identified deficits in motor, tremor, and cognitive functions with inhalation exposure to Mn in the air (Mergler et al. 1999; Rodríguez-Agudelo et al. 2006; Solís-Vivanco et al. 2009; Kim et al. 2011; Bowler, Kornblith, et al. 2015). General environmental ambient air-Mn (Mn/A) exposures are typically significantly lower than in occupational study settings (Colledge et al. 2015).

The mood, cognitive, motor, and neurological impairments associated with elevated Mn exposure, described as Mn-induced parkinsonism, (Feldman 1999; Cersosimo & Koller 2006) differ slightly from Parkinson's disease but share similarities of psychomotor abnormalities, tremor, bradykinesia, and postural sway. This indicates that Mn-induced parkinsonism is not easily separable from idiopathic Parkinson's disease (Rutchik et al. 2012; Andruska & Racette 2015). Other medical conditions currently associated with Mn exposure include hypertension (Lee & Kim 2011), hypotension (Šarić & Hrustić 1975; Jiang & Zheng 2005), hypothyroidism (Soldin & Aschner 2008), and diabetes (Forte et al. 2013).

The association between blood pressure and Mn is controversial. Former studies (Šarić & Hrustić 1975; Jiang & Zheng 2005) of workers exposed to Mn/A found participants were more likely to have hypotension, however, most recently Lee and Kim (2011) found increased blood pressure was associated with increased blood Mn levels in a sample of adult men and women, even after controlling for other heavy metals (blood lead, mercury, and cadmium).

Very little is known about the effects of overexposure to Mn on thyroid homeostasis. In a review of the current literature, Soldin and Aschner (2008) reported that overexposure to Mn may directly or indirectly cause hypothyroidism through the dopaminergic dysregulation of the thyroid-stimulating hormone (TSH), resulting in decreased thyroid hormone synthesis. In an animal study, rats were given a Mn-rich diet for five weeks, after which decreased serum TSH concentrations were found as a result of Mn accumulation (Buthieau & Autissier 1983).

In addition to decreased blood pressure and thyroid hormone function, overexposure to Mn has been associated with complications in respiratory and cardiac function, pain with muscle cramps, headaches, and sleep disturbances (Crossgrove & Zheng 2004; Soldin & Aschner

2008). Contrastingly, previous studies have identified the prevalence of diabetes to be increased in those with low levels of blood Mn (Forte et al. 2013).

Self-report of medication use in epidemiologic studies

In recent decades, adult environmental studies of Mn exposure have reported physical (Santos-Burgoa et al. 2001; Haynes et al. 2010; Kim et al. 2015) and mental health problems identified through cognitive (Bowler, Kornblith, et al. 2015), mood (Bowler et al. 2012), motor, and neurological (Rodríguez-Agudelo et al. 2006; Kim et al. 2011; Bowler, Beseler, et al. 2015) testing of study subjects, but medical record reviews for exposed residents are rare in the literature. When medical records and clinical testing are unavailable, examination of residents' current prescribed medication use (Dayal et al. 1994; Zmirou et al. 1994; Bowler et al. 2002) has been used as a proxy of health effects associated with Mn or other neurotoxic chemical exposures. Bowler et al. (2002) reported increased medication use in a Northern California community in an accidental Catacarb chemical release from an adjacent oil refinery when residents were compared to a similar control town. Medication use after a spill of hydrofluoric acid in Texas was also described by Dayal et al. (1994). In a study by Kehoe et al. (1994), the authors compared 1,380 participants' self-reported medication use with physician-reported use and found very few differences, suggesting accurate recall of medication use, especially when concerning chronic conditions, see also (Harlow & Linet 1989; Kriegsman et al. 1996). Agreement between self-reported medication recall and pharmaceutical records ranges between 75 and 87 % (West et al. 1995). Participants were shown to under-report rather than over-report their medication use.

When self-reported questionnaire data on medication use is supplemented with personal interviews, the accuracy of recall is further increased (Bergmann et al. 2004). This methodology, which is used in the current study, helps to limit any recall biases on self-report questionnaires alone and improves the accuracy of medication history recall.

The objective of this present study was to evaluate currently prescribed medications, over-the-counter medications, and herbal supplements in residents of two towns with elevated Mn/A compared to residents in an unexposed comparison town.

This study is the first report of medication use as a potential indicator of human health effects in adult residents of the United States who have been exposed to elevated modeled Mn/A concentrations in the environment.

Methods

Study design and participant selection

A cross-sectional study design was used in this health study conducted in three Ohio towns (Bowler, Kornblith, et al. 2015), two with reported high levels of Mn/A (Marietta and East Liverpool) and one town which is demographically similar, but unexposed to Mn/A (Mount Vernon). East Liverpool was reported by the U.S. Environmental Protection Agency (EPA) to have the highest measured concentrations of respirable Mn/A in the U.S. (U.S. EPA 2012). Mn/A emissions in Marietta were also reported to be among the highest in the U.S. (U.S. EPA 2011).

Residents of Marietta, Ohio reside in close proximity to a ferromanganese smelter, whose operations began in the early 1950s (U.S. EPA 2010). Over 10 years of air-sampling, conducted by the Ohio EPA, found consistently elevated levels of Mn/A (ATSDR 2007) as a result of long-term emissions from Eramet Marietta, Inc. Residents from East Liverpool, Ohio were shown to have high Mn/A (ATSDR 2010) from an open-air Mn storage and packaging facility, which began operations in the late 1960s.

Mount Vernon, Ohio was chosen as the unexposed comparison town because it is demographically very similar (U.S. Census Bureau 2001a, 2001b) to both Marietta and East Liverpool, as well as the state of Ohio. Mount Vernon also has a low number of major industries (U.S. EPA 2011) and consequently, the Ohio EPA (2010) and U.S. EPA (2011) have reported no area air pollution control activities related to toxic metals and particulate emissions. In the Mount Vernon participant recruitment zone, Mn/A emissions were slightly above background levels from long-range transport, natural emissions, and other unknown sources (U.S. EPA 2009; U.S. EPA 2011).

Study participant recruitment

Recruitment of study participants has been described in more detail elsewhere (Kim et al. 2011; Bowler et al. 2012). In each of the three towns, recruitment letters were sent to selected residents, inviting them to participate in the study. The goal was to recruit 100 participants per town. Study participants in the exposed and unexposed towns were randomly selected (Marietta and Mt. Vernon only) using county parcel and water records within the local zip codes, purchased mailing lists, and reverse address lists. Residents of Marietta were selected within a 12 air-miles zone from the exposure source, which emitted fine Mn/A particulate during the high temperature industrial processes of a ferromanganese smelter. The particle sizes from the Mn storage and packaging facility in East Liverpool were slightly larger than those from the Marietta smelter. Larger airborne particles travel a shorter distance and, therefore required a smaller study area equal to or less than a 2 air-miles radius from the source (ATSDR 2010). Because of the small geographic study area for East Liverpool, all residents in the 2 air-miles radius were invited to participate.

In Marietta, 1,732 letters were sent to eligible residents, to which 187 responded with interest, 122 participants were eligible, and 100 were tested. In East Liverpool, 1,309 letters were sent, to which 192 responded with interest, 123 participants were eligible, and 86 were tested (14 residents did not attend their appointment). In Mount Vernon, 2,297 recruitment letters were sent and 245 individuals indicated interest by responding with provided postcards. Of those, 117 were eligible and 100 were recruited, with the remaining 17 being unable to attend due to personal scheduling conflicts. Ultimately, 90 participants were tested (9 residents did not attend their appointment and 1 participant was excluded post-testing).

Study inclusion and exclusion criteria

In all three towns, a maximum of two residents per household were included in the study, provided they had lived in their respective towns for a minimum of 10 years and were between the ages of 30–75 years. Interested residents were excluded if they did not meet the age and residence criteria or if they had met one of the exclusion criteria, described by

Bowler et al. (2012). These exclusion criteria consisted of having a diagnosed neurodegenerative disease (multiple sclerosis, Alzheimer's dementia, Huntington's chorea, and PD), brain ailments (meningitis, encephalitis, stroke with hospitalization for more than one day, brain surgery, prior head injury, and epilepsy), psychiatric conditions (schizophrenia, major psychiatric diagnosis, and bipolar disorder), receiving current medical treatment (anticonvulsive, alcohol/drug dependence, and hepatic condition), being pregnant or nursing, medically unable to participate in the study, having exposure to hazardous chemicals other than Mn (pesticides, fungicides, herbicides, carbon monoxide, and neurotoxic metals), including ever working at one of the Mn emission sources or having lived in the other exposed town. An a priori decision was made to recruit and test 100 participants from each town.

At the conclusion of the residents' participation in the health study, participants were each given a $50 gift certificate to a local retail store. The institutional review board of both San Francisco State University (SFSU) and the Ohio Department of Health (ODH) granted research approval. Written informed consent of residents was gathered prior to data collection. The ODH, US EPA, Ohio EPA, and the ATSDR provided technical assistance, study design input, and review of the SFSU protocol.

Data collection

All three towns had the same method of test administration using the same neurological and neuropsychological measures in addition to personal interviews with the clinical neuropsychologist (RB). This methodology is further described in previous manuscripts (Bowler, Kornblith, et al. 2015; Kim et al. 2015).

The neuropsychologist interviewed each participant regarding his or her health concerns and medication use. Prior to the interviews, the participants completed a self-reported health questionnaire, which included demographic information, lifestyle factors, work history data, and medical background information, including symptoms and medication use. The health questionnaire was developed with the input of neurologists, internal medicine specialists, neurotoxicologists, and neuropsychologists.

In addition to the medications reported by each participant in the health questionnaire, participants were asked to bring their prescription medications or a list of the names of their prescribed medications and supplements to their personal interview.

From the health questionnaires and lists of currently prescribed medications and supplements, the medical co-authors and specialists in occupational (YK) and psychiatric medicine (AB), independently derived 12 categories of medications with one additional category for over-the-counter supplements (see Table 1). The level of inter-rater agreement for the placement of medications into categories was 100 %.

Mn/A exposure estimates for the two exposed towns

Personal Mn/A exposure for each participating residential address was estimated using the U.S. EPA's AERMOD dispersion model data calibrated with Mn/A measurements of total suspended particulates (TSP), collected over a 10-year period from 2003 to 2013 for the two

exposed towns from monitors operated by Ohio EPA. This methodology is discussed in further detail by Colledge et al. (2015). Briefly, a generic area emissions rate of 1 gram per second was assumed over the entire surface area of the two source facilities, yielding off-site concentrations at all study subject receptor locations and area air monitoring sites. One air monitoring site was selected as the reference monitor in each community, and the concentrations modeled at the receptors were scaled to this reference location as a ratio. The air data collected at the reference monitor were multiplied by the modeled receptor ratio to yield an estimated long-term average exposure for each study subject. The air sampling method and Mn analyses were identical for both exposed towns. The ATSDR minimal risk level is 0.3 μg/m^3 (ATSDR 2012). The sampling and measurement methods for both exposed towns showed that the modeled mean average Mn/A exposure levels in Marietta ranged from 0.03 to 1.61 μg/m^3 with a mean of 0.21 mg/m^3, while Mn/A levels in East Liverpool ranged from 0.01 to 6.32 μg/m^3 with a mean of 0.88 mg/m^3. The respirable fraction of Mn/A was derived from multiplying the TSP values by the average fraction of respirable particulates to TSP as identified by collocated monitors and fingerprint morphology analysis. The estimated respirable Mn/A distribution was as follows: Marietta (PM10: 0.18 μg/m^3 [AM], range 0.03–1.33 μg/m^3; PM2.5: 0.05 μg/m^3 [AM], range 0.007–0.34 μg/m^3) and East Liverpool (PM10: 0.31 μg/m^3 [AM], range 0.005–2.21 μg/m^3; PM2.5: 0.03 μg/m^3 [AM], range 0.001–0.23 μg/m^3). Results indicate that even though the TSP air-Mn levels in East Liverpool were generally higher than in Marietta, the Marietta residents have a higher exposure to respirable Mn particulate matter.

Those participants who lived further away from the Mn point source had lower modeled mean average Mn/A levels. Participants from the two exposed towns had stable and long residential histories with ongoing exposure to Mn in air. The mean length of residence was 37 years in Marietta and 47 years in East Liverpool.

Statistical analyses

The participants from the Mn exposed towns of Marietta and East Liverpool were combined into one group for analyses to achieve sufficient power. This was acceptable because we used the same methods to estimate exposure within the two towns. For the purposes of this study, the participants from the two exposed towns will be referred to as the ‘exposed group,’ whereas the participants from the unexposed comparison town will be referred to as the ‘unexposed group.’ One participant from the exposed group was excluded from these analyses because no information on medication use was provided. Differences in demographic variables between exposed and unexposed groups were evaluated using chi-square tests. Preliminary analysis of data for the number of sick days reported over a two-year period revealed several outliers in the dataset who reported being sick every day. Therefore, all cases with extreme values, defined as a z-score of ±1.96, were excluded. This resulted in the removal of five cases solely for the comparison of reported sick days between the exposed and unexposed group.

The combined participants from the exposed group (n = 185) and unexposed (n = 90) group were compared on the established 12 medication and 1 supplement categories using independent samples t-tests and chi-square (χ^2) tests, as appropriate. Cramer’s V was used

to compute effect sizes. In order to control familywise error associated with conducting multiple statistical comparisons, the per-comparison significance level was adjusted using the false discovery rate procedure outlined by Benjamini and Hochberg (1995). International Classification of Diseases (ICD) codes were assigned by the senior physician co-author (YK) to determine if exposure groups differed regarding illnesses. Chi-square analyses between the exposed and unexposed groups regarding illnesses by ICD code (respiratory, thyroid, cardiac, digestive, arthritis/osteoporosis, diabetes, mental illness, and having had cancer) showed no differences.

The chi-square analyses were also used as preliminary analyses for hierarchical logistic regressions between medication category and exposure group. The significant medication categories from the chi-square analyses were further analyzed using hierarchical binomial logistic regression. Hierarchical binomial logistic regressions were performed to determine whether exposure predicted current medication use by category when controlling for the effects of age, education, and personal income. For the evaluation of hypothyroid medications, sex was added as a covariate to the model to control for hypothesized differences described by Aoki et al. (2007). Years of residence in the respective town was not included in the regression model because of the significant co-linearity and strong zero-order correlation between years of age and years of residence ($r = 0.460$, $p < 0.001$).

To further explore the relationship of medication use in the exposed group, estimated modeled concentrations of Mn (AERMOD) were analyzed with medication category, using binomial logistic regressions. No measurements of Mn/A concentrations for the unexposed group were available.

Results

Demographic, lifestyle factors, and health characteristics for participants from the exposed groups ($n = 185$) and unexposed group ($n = 90$) are shown in Table 2. The exposed group had significantly fewer years of education (13.8 vs. 15.2 years) and significantly more years of residence in their respective town (41.1 vs. 33.6 years). Additionally, the exposed group reported significantly fewer hours of sleep per night (6.6 vs. 7.0 h) than the unexposed group. They also reported significantly ($p = 0.007$) higher percentage of current medication use than the unexposed group (82.2 % vs. 67.8 %).

When asked about work status, 8.2 % of the exposed (*E*) group and 3.4 % of the unexposed (*U*) group reported being disabled. A review of the reasons for being disabled revealed that the disabilities were primarily for orthopedic injuries ($E = 3.8$ %, $U = 3.3$ %); and the remainder were from the exposed group within the following categories: cancer (2.2 %), respiratory (1.1 %), and cardiac (0.5 %). Examination of the differences in medication use by category of those disabled compared to the non-disabled indicated that they differed on depression and respiratory medication use, with disabled residents using more medications. Table 3 shows the association between exposure group and medication category using chi-square analyses. Exposure group was significantly associated with the use of gastrointestinal (GI) medication ($V = 0.15$, $p = 0.01$), pain medication ($V = 0.21$, $p < 0.001$), hypothyroid medication ($V = 0.16$, $p = 0.009$), supplements ($V = 0.23$, $p < 0.001$), and total medications

($V = 0.16$, $p = 0.007$). All significant associations showed small to moderate effect sizes according to the effect size conventions for Cramer's V.

Table 4 and Figure 1 show the hierarchical binomial logistic regression results and the estimated adjusted odd ratios of taking medication by category for both groups. Exposure group significantly predicted the use of hypothyroid medication, pain medication, supplements, and total prescribed medications above and beyond the control variables of age, education, and personal income. Exposure did not significantly predict medication use for other medication categories. Using Nagelkerke's R^2 as a description of variance, the model explained 25 % of the variance between groups for hypothyroid medication and 9 % of the variance for pain. Participants from the Mn-exposed towns were 8.07 times more likely to take hypothyroid medication (95 % CI [1.80, 36.16]) and 2.44 times more likely to take pain medication (95 % CI [1.27, 4.69]). Exposed participants were also 2.33 times more likely to take prescription medication in general (95 % CI [1.21, 4.48]) and 3.40 times more likely to take supplements (95 % CI [1.54, 7.49]). Using Nagelkerke's R^2 as a description of variance, the model explained 19 % of the variance between groups for using medications in general and 17 % of the variance between groups for supplement use. As illustrated in Table 4, increasing age was significantly associated with an increased likelihood of prescribed medication use; however, age was not associated with increased use of medications within specific categories.

Because 10 years of modeled Mn/A concentration data were available for the exposure zones, supplementary analyses were conducted to determine whether the level of exposure predicted medication use for Mn-exposed participants, while controlling for age, education, and personal income. Exposed participants were 1.55 times more likely to take pain medication (95 % CI [1.04, 2.30]) for every one unit increase in Mn/A concentration. Using Nagelkerke's R^2 as a description of variance, increased modeled Mn/A explained 9 % of the variance for the use of pain medications and 6 % for hypothyroid medications. Mn/A did not correlate with the total number of symptoms self-reported by exposed participants in a questionnaire ($r_s = 0.04$, $p = 0.645$).

Discussion

Medical record reviews of Mn-exposed persons are rare in the neurotoxicologic literature. This study examined Mn health consequences, using current medications as a proxy for medical record review in a Mn-exposed and unexposed group. Dayal et al. (1994) suggested that using prescribed medication data as a measurement of health may be a more reliable procedure than self-report of symptoms or illnesses. This study examined the health effects of Mn exposure by comparing demographically similar residents from two Mn-exposed towns of Marietta and East Liverpool, Ohio, with the unexposed town of Mount Vernon. Examination of medication lists brought by participants and endorsements of medication use in completed health questionnaires indicated that the Mn-exposed group used significantly more medications than the unexposed group.

Studies examining the adverse health effects of environmental Mn exposure have increased in the last decade internationally (Rodríguez-Agudelo et al. 2006; Solís-Vivanco et al. 2009;

Haynes et al. 2010). Parkinsonism, and with extremely high exposures, manganism, is associated with differentiating symptoms, signs, and other adverse health effects, as described by Feldman (1999), while others (as cited on the first page of our introduction) cite mood, motor, tremor, and cognitive functions. In this study, an increase in medication use was found for the categories of hypothyroidism and pain, as well as total medications, suggesting adverse physical health among participants from the Mn-exposed towns. Exposed participants also reported taking more supplements than the unexposed to prevent or ameliorate illness.

Prevalence rates of hypothyroidism in the United States' general population range from 3.7 to 4.6 % (Aoki et al. 2007; Golden et al. 2009). In the current study, 4.4 % of participants from the unexposed town used medication for hypothyroidism. When examining the Mn-exposed group, the use of hypothyroid medication was over three times more prevalent (15.1 %). Taking medication for hypothyroidism was not associated with taking medications from any of the other medication categories. Hypothyroidism, with exposure to Mn/A in residents, has not previously been reported.

Alterations in the levels of Mn in blood can result in metabolic dysfunction and is found in certain diseases. A significant increase in blood Mn has been described in people diagnosed with hypothyroidism (Soldin & Aschner 2008), which may be the result of an interaction between Mn and thyroid hormone homeostasis. The results of this study may support the Soldin and Aschner (2008) postulation of an interaction between higher concentrations of Mn and dysfunctional thyroid hormone homeostasis. A similar homeostatic relationship was found in persons with diabetes, however previous studies have found blood Mn levels are lower in those with diabetes (Forte et al. 2013).

Lee and Kim (2011) reported log blood Mn relationships for both systolic and diastolic blood pressure when controlling for sex, age, regional area, education, smoking/drinking status, hemoglobin, and serum creatinine, in a representative sample of the Korean National Health and Nutrition Examination Survey 2008 survey. The current study, however, found no association between the Mn/A-exposed participants and the unexposed group for hypotension or hypertension and diabetes.

The prevalence of GI disease in the U.S., particularly gastroesophageal reflux disease, is estimated at 20 % (Dent et al. 2005) with 16 % of symptomatic people taking medication (Isolauri & Laippala 1995). In this study, 22.7 % of Mn-exposed and 10 % of unexposed participants use GI medication. In the exposed group, GI medication use was significantly associated with pain medication use. Provided this relationship, it is likely that the exposed participants' GI medication use was for the purpose of treating the GI side effects, which are frequently associated with chronic pain medication use (Bhatt et al. 2008).

The prevalence of chronic pain – pain that is recurrent, lasting at least 6 months – in the U.S. is estimated at 30.7 % (95 % CI [29.8, 31.7]) (Johannes et al. 2010). In the current study, 16.6 % of unexposed participants used medication for pain management, while participants from the Mn-exposed towns used pain medications at a higher rate of 37.2 %, making the prevalence of pain in the exposed group higher than that reported in the U.S. general

population. As shown in Table 4, those residents with Mn exposure were more than twice as likely to use medication for pain. When examining Mn/A concentrations across the exposed group only, higher concentrations of Mn/A were also associated with more pain medication use. The majority of pain medications were used to treat headaches or migraines, but non-steroidal anti-inflammatory medicine and muscle relaxants were also used by Mn-exposed participants. Headaches and muscle cramps have been identified as early manifestations of Mn toxicity in humans (Jiang & Zheng 2005; Forte et al. 2013). It is hypothesized that muscle cramps could be the result of long-term Mn exposure and the development of dystonia, hypokinesia, or muscle rigidity, common in Mn-exposed populations (Pal et al. 1999). Further research is needed to develop a causal model between Mn/A and chronic pain. This is the first report of an association between Mn exposure as well as higher concentrations of Mn/A and the prevalence of chronic pain.

The occupational literature describes the onset of Parkinsonism from Mn overexposure as manganism. Symptoms at that point are similar to Parkinson's disease and include dystonia, gait abnormalities, bradykinesia, and rigidity (Guilarte 2010; Guilarte & Gonzales 2015). However, as the literature indicates, motor disturbances in Mn-exposed persons are resistant to levodopa medication (Guilarte et al. 2006) and Mn-affected persons may use more medications to ameliorate their health problems. Mn exposure and subsequent disturbances may worsen pre-existing medical conditions, resulting in increased medication use.

Limitations of the study

The principal investigator (PI) discussed the medication lists with each participant and verified the medications in the health questionnaire. However, the medication lists were more specific as to the name of each medication and more fully represent the current medication use of the participants. A limitation of the study is the self-reported nature of the medication and subsequent lack of independent validation of the participants' medications with their medical records. According to West et al. 1995, it is more likely that if inaccuracies exist, they are the result of *under-reporting* medications. For that reason, health conditions may be slightly under-reported. Although review of medical records is desirable, it may not be practical in large epidemiologic studies.

Although there are refined Mn/A measurements and exposure modeling for both East Liverpool and Marietta, OH, there are no Mn/A exposure data for Mount Vernon, OH. However, no significant industrial sources of manganese were identified in Mount Vernon when an unexposed population was in the process of being selected. Moreover, no personal air sampling was available in Mount Vernon, but the Toxic Release Inventory (TRI) data from 2010 (U.S. EPA 2010) indicated insignificant levels of Mn/A in Mount Vernon, the source of which was largely long-range transportation and other natural emissions.

A follow-up study is desirable to both evaluate more long-term medication use and determine the causal relationship between Mn exposure and adverse health. Not all residents studied may have received regular medical care and their adverse health effects are not known.

Strengths of the study

Although many occupational and some environmental studies of Mn exposure have shown adverse health function, this is the first environmental study of increased medication use in adult-exposed residents in the U.S. Reported use of a specific medication is likely more objective, avoids recall bias, and is likely less inflated than would be a review of self-reported symptoms alone (Dayal et al. 1994).

Power analysis confirmed that the number of residents in the combined exposed towns was sufficient to satisfy the study requirements. The methodology used in the three towns was identical. All three towns were similar in size as were most demographic characteristics according to the 2008–2012 U.S. Census Bureau (2014). A careful cross-sectional study design, recruitment, and final selection of residents using strict inclusion/exclusion criteria assured the elimination of other illnesses similar to those from Mn such as Parkinson's disease. The study also controlled for the potential of confounding illnesses. Interviews with each of the 275 residents, who brought their medication lists to the PI, assured an accurate review of medications as a surrogate of medical health and added strength to the study. Additionally, two co-author physicians, one in occupational medicine (YK) and one in psychiatry (AB) reviewed all of the individual medications and assisted in forming the medication categories.

Moreover, the 10-year monitoring of Mn/A in the exposure zones of East Liverpool and Marietta and air dispersion modeling permitted analyses of Mn concentration associations with medications used.

Use of the local unexposed town's medication data, in addition to prevalence data in the U.S., suggested that the greater use of current medication use for hypothyroidism and pain health problems may be an outcome of environmental Mn exposure. Moreover, in examining modeled concentrations of Mn/A exposure within the exposed towns only revealed higher modeled concentrations of Mn/A were associated with increased use of pain medications. Current medication use can be an informative surrogate for medication record review.

Conclusions

This first environmental study of Mn/A-exposed adults and medication use indicates a higher prevalence of medication use for hypothyroidism and pain health problems among the Mn/A-exposed group. Medication use may be a better method of classifying adverse health outcomes compared to using generalized self-reports of health complaints.

Acknowledgments

Funding

This work was supported by the US Environmental Protection Agency [cooperative agreement number 83416001] to San Francisco State University and US EPA Contracts [EP-11-D-000424] and [EP-13-D-000146].

References

Andruska KM, Racette BA. Neuromythology of manganism. Curr Epidemiol Rep. 2015; 2:143–148. [PubMed: 26046010]

Aoki Y, Belin RM, Clickner R, Jeffries R, Phillips L, Mahaffey KR. Serum TSH and total T4 in the United States population and their association with participant characteristics: National Health and Nutrition Examination Survey (NHANES 1999–2002). Thyroid. 2007; 17:1211–1223. [PubMed: 18177256]

[ATSDR] Agency for Toxic Substances and Disease Registry. Health consultation. Washington County Air Quality, Marietta; Washington County, Ohio: 2007.

[ATSDR] Agency for Toxic Substances and Disease Registry. Health consultation: East Liverpool Air Quality. 2010

[ATSDR] Agency for Toxic Substances and Disease Registry. Toxicological profile for manganese. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service; 2012.

Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J Roy Stat Soc. 1995; 57:289–300.

Bergmann MM, Jacobs EJ, Hoffman K, Boeing H. Agreement of self-reported medical history: comparison of an in-person interview with a self-administered questionnaire. Eur J Epidemiol. 2004; 19:411–416. [PubMed: 15233312]

Bhatt DL, Scheiman J, Abraham NS, Antman EM, Chan FKL, Furberg CD, Johnson DA, Mahaffey KW, Quigley EM, Harrington RA, et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. J of the Am College of Cardiology. 2008; 52:1502–1517.

Bowler RM, Beseler CL, Gocheva VV, Colledge M, Kornblith ES, Julian JR, Kim Y, Bollweg G, Lobdell DT. Environmental exposure to manganese in air: associations with tremor and motor function. Sci Total Environ. 2015; 541:646–654. [PubMed: 26437342]

Bowler RM, Gysens S, Hartney C, Ngo L, Rauch SS, Midtling J. Increased medication use in a community environmentally exposed to chemicals. Ind Health. 2002; 40:335–344. [PubMed: 12502236]

Bowler RM, Harris M, Gocheva V, Wilson K, Kim Y, Davis SI, Bollweg G, Lobdell DT, Ngo L, Roels HA. Anxiety affecting parkinsonian outcome and motor efficiency in adults of an Ohio community with environmental airborne manganese exposure. Int J Hyg Environ Health. 2012; 215:393–405. [PubMed: 22112744]

Bowler RM, Kornblith ES, Gocheva VV, Colledge MA, Bollweg G, Kim Y, Beseler CL, Wright CW, Adams SW, Lobdell DT. Environmental exposure to manganese in air: Associations with cognitive functions. Neurotoxicology. 2015; 49:139–148. [PubMed: 26096496]

Buthieau A, Autissier N. Effects of manganese ions on thyroid function in rat. Arch Toxicol. 1983; 54:243–246. [PubMed: 6661032]

Cersosimo MG, Koller WC. The diagnosis of manganese-induced parkinsonism. NeuroToxicology. 2006; 27:340–346. [PubMed: 16325915]

Colledge MA, Julian JR, Gocheva VV, Beseler CL, Roels HA, Lobdell DT, Bowler RM. Characterization of air manganese exposure estimates for residents in two Ohio towns. J Air Waste Manag Assoc. 2015; 65:948–957. [PubMed: 26211636]

Crossgrove J, Zheng W. Manganese toxicity upon overexposure. NMR Biomed. 2004; 17:544–553. [PubMed: 15617053]

Dayal H, Li Y-H, Dayal V, Mittal CK, Snodgrass W. Use of medication data to validate an association in community-based symptom prevalence studies. Arch Environ Health. 1994; 49:93–97. [PubMed: 8161247]

Dent J, El-Serag HB, Wallander M, Johansson S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut. 2005; 54:710–717. [PubMed: 15831922]

Feldman, RG. Occupational and environmental neurotoxicology. Philadelphia, PA: Lippincott-Raven; 1999.

Forte G, Bocca B, Peruzzu A, Tolu F, Asara Y, Farace C, Oggiano R, Madeddu R. Blood metals concentration in Type 1 and Type 2 diabeties. Biol Trace Elem Res. 2013; 156:79–90. [PubMed: 24222606]

Golden SH, Robinson KA, Saldanha I, Anton B, Ladenson PW. Prevalence and incidence of endocrine and metabolic disorders in the United States: a comprehensive review. J Clin Endocrinol Metabol. 2009; 94:1853–1878.

Guilarte T. Manganese and Parkinson's disease: a critical review and new findings. Environ Health Perspect. 2010; 118:1071–1080. [PubMed: 20403794]

Guilarte TR, Gonzales KK. Manganese-induced Parkinsonism is not idiopathic Parkinson's disease: environmental and genetic evidence. Toxicol Sci. 2015; 146:204–212. [PubMed: 26220508]

Guilarte T, McGlothan J, Degaonkar M, Chen M-K, Barker PB, Syversen T, Schneider JS. Evidence for cortical dysfunction and widespread manganese accumulation in the nonhuman primate brain following chronic manganese exposure: a 1H-MRS and MRI study. Toxicol Sci. 2006; 94:351–358. [PubMed: 16968886]

Harlow SD, Linet MS. Agreement between questionnaire data and medical records. Am J Epidemiol. 1989; 129:233–248. [PubMed: 2643301]

Haynes EN, Heckel P, Ryan P, Roda S, Leung YK, Sebastian K, Succop P. Environmental manganese exposure in residents living near a ferromanganese refinery in Southeast Ohio: a pilot study. Neurotoxicology. 2010; 31:469–474.

Isolauri J, Laippala P. Prevalence of symptoms suggestive of gastroesophageal reflux disease in an adult population. Ann Med. 1995; 27:67–70. [PubMed: 7742002]

Jiang Y, Zheng W. Cardiovascular toxicities upon manganese exposure. Cardiovasc Toxicol. 2005; 5:345–354. [PubMed: 16382172]

Johannes C, Le TK, Zhou X, Johnston JA, Dworkin RH. The prevalence of chronic pain in United States adults: results of an Internet-based survey. J Pain. 2010; 11:1230–1239. [PubMed: 20797916]

Kehoe R, Wu S-Y, Leske MC, Chylack LT. Comparing self-reported and physician-reported medical history. Am J Epidemiol. 1994; 139:813–818. [PubMed: 8178794]

Kim Y, Bowler RM, Abdelouahab N, Harris M, Gocheva V, Roels HA. Motor function in adults of an Ohio community with environmental manganese exposure. Neurotoxicology. 2011; 32:606–614. [PubMed: 21840336]

Kim Y, Lobdell DT, Wright CW, Gocheva VV, Hudgens E, Bowler RM. Blood metal concentrations of manganese, lead, and cadmium in relation to serum ferritin levels in Ohio residents. Biol Trace Elem Res. 2015; 165:1–9. [PubMed: 25578336]

Kriegsman DM, Penninx BW, Van Eijk JTM, Boeke AJP, Deeg DJ. Self-reports and general practitioner information on the presence of chronic diseases in community dwelling elderly: a study on the accuracy of patients' self-reports and on determinants of inaccuracy. J Clin Epidemiol. 1996; 49:1407–1417. [PubMed: 8970491]

Lee B-K, Kim Y. Relationship between blood manganese and blood pressure in the Korean general population according to KNHANES 2008. Environ Res. 2011; 111:797–803. [PubMed: 21601843]

Mergler D, Baldwin M, Belanger S, Larribe F, Beuter A, Bowler R, Panisset M, Edwards R, Geoffroy A, Sassine MP, Hudnell K. Manganese neurotoxicity, a continuum of dysfunction: results from a community based study. Neurotoxicology. 1999; 20:327–342. [PubMed: 10385894]

Ohio EPA. Ohio Environmental Protection Agency. 2010:2009–2010. Ohio Air Monitoring Site Report. In Prepared by Division of Air Pollution Control.

Pal PK, Samii A, Calne DB. Manganese neurotoxicity: a review of clinical features, imaging and pathology. Neurotoxicology. 1999; 20:227–238. [PubMed: 10385886]

Rea, L., Parker, R. Designing and constructing survey research. Vol. 296. San Francisco: Josey-Bass; 1992.

Rodriquez-Agudelo Y, Riojas-Rodriguez H, Rios C, Rosas I, Pedraza ES, Miranda J, Siebe C, Texcalac JL, Santos-Burgoa C. Motor alterations associated with exposure to manganese in the environment in Mexico. Sci Total Environ. 2006; 368:542–556. [PubMed: 16793118]

Roels H, Lauwerys R, Buchet JP, Genet P, Sarhan MJ, Hanotiau I, de Fays M, Bernard A, Stanescu D. Epidemiological survey among workers exposed to manganese: Effects on lung, central nervous system, and some biological indices. Am J Ind Med. 1987; 11:307–327. [PubMed: 3578289]

Rutchik JS, Zheng W, Jiang Y, Mo X. How Does an Occupational Neurologist Assess Welders and Steelworkers for a Manganese-Induced Movement Disorder? An International Team's Experiences in Guanxi, China Part I. J Occup Environ Med. 2012; 54:1432–1434. [PubMed: 23135302]

Santos-Burgoa C, Rios C, Mercado LA, Arechiga-Serrano R, Cano-Valle F, Eden-Wynter RA, Texcalac-Sangrador JL, Villa-Barragan JP, Rodriguez-Agudelo Y, Montes S. Exposure to manganese: health effects on the general population, a pilot study in central Mexico. Environ Res. 2001; 85:90–104. [PubMed: 11161659]

Šarić M, Hrustić O. Exposure to airborne manganese and arterial blood pressure. Environ Res. 1975; 10:314–318. [PubMed: 1193039]

Soldin OP, Aschner M. Effects of manganese on thyroid hormone homeostasis. Neurotoxicology. 2008; 28:951–956.

Solis-Vivanco R, Rodriguez-Agudelo Y, Riojas-Rodriguez H, Rios C, Rosas I, Montes S. Cognitive impairment in an adult Mexican population non-occupationally exposed to manganese. Environ Toxicol Pharmacol. 2009; 28:172–178. [PubMed: 21784000]

U.S. Census Bureau. Census 2000 summary file 1: state of Ohio/prepared by the US Census Bureau. 2001a

U.S. Census Bureau. Census 2000 summary file 3: state of Ohio/prepared by the US Census Bureau. 2001b

U.S. Census Bureau. Ohio QuickFacts. 2014

U.S. EPA. 2009. National-Scale Air Toxics Assessment (NATA). 2002

U.S. EPA. Toxic Release Inventory (TRI) program. TRI data and tools. 2010

U.S. EPA. National-Scale Air Toxics Assessment (NATA). 2011

U.S. EPA. Air quality system, query for national manganese data. U.S. Environmental Protection Agency; 2012.

West SL, Savitz DA, Koch G, Strom BL, Guess HA, Hartzema A. Recall accuracy for prescription medications: self-report compared with database information. Am J Epidemiol. 1995; 142:1103–1112. [PubMed: 7485055]

Zmirou D, Deloraine A, Saviuc P, Tillier C, Boucharlat A, Maury N. Short-term health effects of an industrial toxic waste landfill: a retrospective follow-up study in Montchanin. France. Arch Environ Health. 1994; 49:228–238. [PubMed: 8031177]

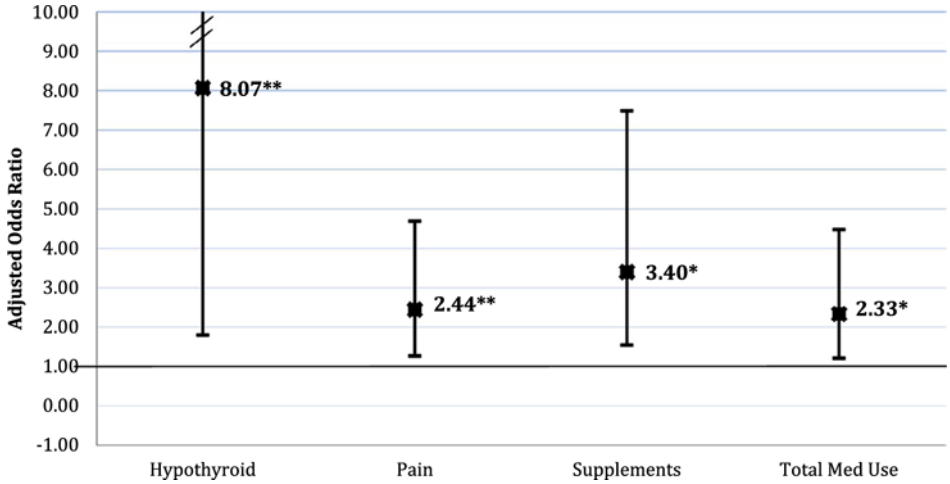

Figure 1.

Adjusted odds ratios for unexposed and exposed groups and medication use by category using binomial logistic regressions.

*Significant at $p \leq 0.05$;

**significant at $p \leq 0.01$.

Notes: Hypothyroid covariates: age, education, sex, and personal income. 95 % CI for Hypothyroid category is 1.80–36.16.

Table 1

Common medications listed by category with number used per category: exposed and unexposed participants.

Medication category	Medications used *n*	Common medications used
Anti-anxiety	13	Alprazolam (Xanax) Clonazepam (Klonopin) Lorazepam (Ativan)
Antidepressant	41	Fluoxetine (Prozac) Paroxetine (Paxil) Sertraline hydrochloride (Zoloft)
Arthritis/osteoporosis	15	Alendronate sodium (Fosamax) Celecoxib (Celebrex) Raloxifene hydrochloride (Evista)
Blood pressure	156	Atenolol (Tenormin) Hydrochlorthiazide Lisinopril (Zestril)
Cardiac	65	Aspirin (Baby aspirin – low dose) Clopidogrel (Plavix) Warfarin (Coumadin)
Cholesterol	66	Atorvastatin calcium trihydrate (Lipitor) Fenofibrate (Tricor) Simvastatin (Zocor)
Diabetes	67	Glyburide (Micronase) Metformin hydrochloride (Glucophage) Pioglitazone hydrochloride (Actos)
Gastrointestinal	56	Calcium carbonate (Tums) Esomeprazole (Nexium) Omeprazole (Prilosec)
Hypothyroid	32	Levothyroxine (Synthroid/Levoxyl)
Pain	109	Acetaminophen (Tylenol) Ibuprofen Meloxicam (Mobic)
Respiratory	60	Albuterol Montelukast (Singulair) Tiotropium bromide (Spiriva)
Sleep	9	Tylenol PM Doxylamine succinate (Unisom) Zolpidem tartrate (Ambien)

Int J Environ Health Res. Author manuscript; available in PMC 2017 September 05.

Table 2

Demographic, lifestyle factors, and exposure characteristics for unexposed and exposed groups with means, standard deviations, frequencies, and *t*-test/chi-square results.

	n	Unexposed *M* (SD)	*n*	Exposed *M* (SD)	χ^2/t (df)[a]	Effect size *V/d*	*P*
Age	90	55.3 (11.0)	186	55.2 (10.9)	$t = 0.3$ (274)	0.04	0.78
Sex							
Male (%)	40	44.4 %	76	40.9 %	0.3 (1)	0.03	0.57
Female (%)	50	55.6 %	110	59.1 %			
Ethnicity							
White (%)	87	96.7 %	176	94.6 %	0.6 (1)	0.05	0.45
Non-White (%)	3	3.3 %	10	5.4 %			
Years of education	90	15.2 (3.0)	186	13.8 (2.6)	$t = 3.8$ (274)	0.46	<0.001*
Personal income[b]							
$0–$19,999 (%)	23	25.6 %	61	32.8 %	3.63	0.12	0.46
$20,000–39,999 (%)	27	30.0 %	60	32.3 %			
$40,000–69,999 (%)	25	27.8 %	37	19.9 %			
$70,000+(%)	10	11.1 %	15	8.1 %			
Health insurance type							
Private/other (%)	61	67.8 %	121	65.1 %	1.7 (2)	0.16	0.43
Government (%)	9	10.0 %	29	15.6 %			
None (%)	20	22.2 %	36	19.4 %			
Years residence in town	90	33.6 (17.2)	186	41.1 (16.9)	$t = -3.4$ (274)	0.41	0.001*
Mn in blood (pg/F)	90	9.5 (3.2)	186	10.0 (3.5)	$t = -1.1$ (274)	0.13	0.26
Mn in diet (mg/week)	90	14.4 (12.2)	185	13.2 (13.2)	$t = 0.7$ (272)	0.08	0.48
Fe in diet (mg/week)	90	40.1 (26.9)	185	38.0 (29.3)	$t = 0.6$ (272)	0.07	0.57
Alcohol consumed (g/week)	90	29.2 (61.5)	126	22.5 (53.6)	$t = 0.9$ (243)	0.12	0.37
Drink alcohol (% Yes)	90	45.6 %	84	45.4 %	0.0 (1)	0.00	0.98
Cigarettes smoked/day	90	6.5 (10.2)	126	8.4 (11.8)	$t = -1.3$ (274)	0.16	0.20
Smoke cigarettes (% Yes)	90	20.0 %	45	24.3 %	0.6 (1)	0.05	0.42
Body mass index (BMI)	90	29.6 (6.3)	126	28.1 (6.1)	$t = 1.8$ (263)	0.22	0.07
People taking medications (% Yes)	61	67.8 %	152	82.2 %	7.2 (1)	0.16	0.007*

	n	Unexposed *M* (SD)	*n*	Exposed *M* (SD)	χ^2/t (df)[a]	Effect size *V/d*	*P*
Total medications/person	90	2.1 (2.5)	185	3.2 (3.4)	$t = -3.1$ (273)	0.38	0.002 *
Hospitalization in last 5 years (% Yes)	85	35.3 %	167	31.1 %	0.4 (1)	0.04	0.51
Number sick days in last 2 years[c]	82	3.46 (5.0)	153	4.07 (8.0)	$t = -0.6$ (232)	0.08	0.53
Avg. hours of sleep/night	89	7.0 (1.0)	182	6.6 (1.5)	$t = 2.4$ (269)	0.29	0.007 *
Number of doctor visits in past year	88	2.9 (2.7)	169	3.8 (5.1)	$t = -1.5$ (255)	0.19	0.12
Disabled (% Yes)	87	3.4 %	171	8.2 %	1.9 (1)	0.08	0.17
Sexual dysfunction (% Yes)	90	16.7 %	183	14.8 %	0.2 (1)	0.03	0.68

[a] χ^2 indicated as percentages (%); effect sizes – Cohen's *d* or Cramer's *V* (Rea & Parker 1992).

[b] Eleven personal income data categories were collapsed to four to generate an interpretable chi-square analysis.

[c] Five outliers were excluded from analyses for 'No. sick days in last 2 years' with ≥90 sick days.

* Significant at $p \leq 0.011$, corrected Benjamini–Hochberg significance level.

Int J Environ Health Res. Author manuscript; available in PMC 2017 September 05.

Table 3

Number of participants taking medications by category for all groups combined and unexposed vs. exposed groups.

	All groups (*N* = 275)	**Unexposed (*n* = 90)**		**Exposed (*n* = 185)**				
	Medication (Yes)	**Medication (Yes)**		**Medication (Yes)**				
Medication category	***n***	***n***	**%**	***n***	**%**	**χ^2 (df)**	***V***	***p***
Anti-anxiety	13	6	6.7	7	3.8	1.17 (1)	0.06	0.29
Antidepressant	38	15	16.7	23	12.4	0.91 (1)	0.06	0.34
Arthritis/osteoporosis	13	4	4.4	9	4.8	0.02 (1)	0.01	0.88
Blood pressure	101	31	34.4	70	37.8	0.30 (1)	0.03	0.58
Cardiac	58	21	23.3	37	20.0	0.40 (1)	0.04	0.53
Cholesterol	61	17	18.9	44	23.8	0.84 (1)	0.06	0.36
Diabetes	39	8	8.8	31	16.7	3.08 (1)	0.11	0.08
Gastrointestinal	51	9	10.0	42	22.7	6.47 (1)	0.15	0.01*
Hypothyroid	32	4	4.4	28	15.1	6.73 (1)	0.16	0.009*
Pain	84	15	16.6	69	37.2	12.15 (1)	0.21	<0.001*
Respiratory	23	9	10.0	14	7.6	0.47 (1)	0.04	0.49
Sleep	9	0	0	9	4.9	4.53 (1)	0.13	0.03*
Total medication	210	61	67.8	149	80.5	7.17 (1)	0.16	0.007*
Supplements	67	9	10.0	58	30.5	14.98 (1)	0.23	<0.001*

*Significant at $p \leq 0.02$, corrected Benjamini–Hochberg significance level.

Table 4

Binomial logistic regression results for participants taking medications by category for unexposed and exposed groups.

				95 % CI	
Medication category	**Step**	**Variable entered**	**Adjusted odds ratio**	**Lower**	**Upper**
Hypothyroid[a]	1	Age	1.06	1.01	1.11
		Education	0.99	0.83	1.19
		Personal Income	1.20	0.67	2.15
		Sex	0.12	0.03	0.42
	2	Exposure	8.07	1.80	36.16
Pain	1	Age	0.98	0.96	1.01
		Education	0.95	0.84	1.06
		Personal Income	0.81	0.59	1.12
	2	Exposure	2.44	1.27	4.69
Supplements	1	Age	1.05	1.02	1.08
		Education	0.85	0.75	0.98
		Personal Income	1.03	0.72	1.49
	2	Exposure	3.40	1.54	7.49
Total medication use	1	Age	1.08	1.05	1.11
		Education	0.96	0.85	1.09
		Personal Income	1.09	0.76	1.56
	2	Exposure	2.33	1.21	4.48

[a]Covariates for Hypothyroid category: age, education, personal income, and sex.