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Associations between former exposure to manganese and olfaction in an elderly population: Results from the Heinz Nixdorf Recall Study

Swaantje Casjens[a,*], Beate Pesch[a], Sibylle Robens[a], Benjamin Kendzia[a], Thomas Behrens[a], Tobias Weiss[a], Nadin Ulrich[a], Marina Arendt[b], Lewin Eisele[b], Noreen Pundt[b], Anja Marr[b], Christoph van Thriel[c], Rainer Van Gelder[d], Michael Aschner[e], Susanne Moebus[b], Nico Dragano[f], Karl-Heinz Jöckel[b], Thomas Brüning[a]

[a] *Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr-Universität Bochum (IPA), Bochum, Germany*
[b] *Institute for Medical Informatics, Biometry and Epidemiology (IMIBE), University of Duisburg-Essen, Essen, Germany*
[c] *Leibniz Research Centre for Working Environment and Human Factors (IfADo), Dortmund, Germany*
[d] *Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA), Sankt Augustin, Germany*
[e] *Department of Molecular Pharmacology, Albert Einstein College of Medicine, NY, USA*
[f] *Institute for Medical Sociology, Medical Faculty, University of Düsseldorf, Düsseldorf, Germany*

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ABSTRACT

Occupational exposure to manganese (Mn) has been associated with impairments in olfaction and motor functions, but it has yet to be determined if such effects persist upon cessation of exposure. The objective of this study was to evaluate the influence of former occupational Mn exposure on olfaction within the framework of a prospective cohort study among an elderly German population. Information on job tasks with recognized Mn exposure and data on odor identification assessed with Sniffin' sticks was collected during the second follow-up of the Heinz Nixdorf Recall Study. The study population consisted of 1385 men aged 55–86 years, 354 of whom ever worked in jobs with potential Mn exposure (median 58.3 $\mu g/m^3$ years, interquartile range 19.0–185 $\mu g/m^3$ years). Multiple exposure measures, including job tasks, cumulative Mn exposure, and Mn determined in blood samples (MnB) archived at baseline, were used to estimate effects of Mn on olfaction. Having ever worked as welder was associated with better olfaction compared to other blue-collar workers without Mn exposure. Blue-collar workers identified less odors in comparison to white-collar workers. Concentrations of previous Mn exposure >185 $\mu g/m^3$ years or MnB $\geq$15 $\mu g/L$ were not associated with impaired olfaction. In addition to a strong age effect, participants with lower occupational qualification identified less odors. We found no relevant association of former Mn exposure at relatively low levels with impaired olfaction. Possible neurotoxic Mn effects may not be persistent after cessation.

1. Introduction

Manganese (Mn) is an essential trace element naturally found in the environment. It is required for a variety of key physiological processes, including amongst others, antioxidant defense, energy metabolism, and immune function (Chen et al., 2015). Mn import, excretion and its concentration in blood (MnB) are tightly regulated. Control of Mn homeostasis involves a complex network of proteins, but none of these are specific for Mn. Particularly well studied is its interaction with iron (Fe), an important redox-active metal. Mn competes with Fe for protein binding, indicated by a negative association of MnB and serum ferritin (SF) (Aguirre and Culotta, 2012).

The tight homeostasis of Mn can be disturbed by occupational exposure, impaired hepatobiliary excretion and other circumstances (Perl and Olanow, 2007). Occupational settings with anticipated Mn exposure comprise the production and processing of steel, ferroalloys, and dry-cell batteries (ATSDR, 2008). A large

* Corresponding author at: Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr-Universität Bochum (IPA), Bürkle-de-la-Camp-Platz 1, 44789, Bochum, Germany.
E-mail address: casjens@ipa-dguv.de (S. Casjens).

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workforce of welders is exposed to inhalable Mn and Fe especially when welding steel with high-emission techniques (Pesch et al., 2012). Inhaled Mn can bypass the blood-brain barrier and reach structures deep within the brain by transport down the olfactory nerve to the olfactory bulb (Aschner and Dorman, 2006). Mn distributes non-uniformly in the brain accumulating in regions susceptible to oxidative injury, namely the globus pallidus, striatum, and substantia nigra (Bowman and Aschner, 2014).

Occupational exposure to Mn can result in various neurological dysfunctions. High exposures can cause neurotoxicity with the development of a movement disorder known as manganism which is distinct from idiopathic Parkinson's disease (Guilarte and Gonzales, 2015). There is clear evidence of neurologic effects from inhalation of high Mn concentrations, but results from studies at lower doses and on former exposure remain controversial. Several cross-sectional studies with small sample sizes in active workers or environmentally Mn-exposed persons found olfactory impairment (Antunes et al., 2007; Bowler et al., 2007; Guarneros et al., 2013; Lucchini et al., 2014). In large population-based studies focusing on occupations with Mn exposure olfaction is rarely considered. One such study examined the association of manufacturing occupation and olfaction and found no correlation (Schubert et al., 2011).

In addition to methodological shortcomings as possible reasons for inconsistent results, active and former workers with exposure to Mn may differ in the amount of accumulated Mn in the brain. Animal experiments showed that the Mn in the brain is eliminated after exposure (Aschner and Dorman, 2006). In humans the kinetics of Mn accumulation are less known. One study described no improvement in olfactory impairment in confined-space welders even after 3.5 years of exposure cessation (Bowler et al., 2011). Nevertheless, it is unclear whether Mn-induced neurotoxicity observed in active workers can persist as neurodegenerative effect after cessation of exposure.

Within the framework of the prospective Heinz Nixdorf Recall (Risk Factors, Evaluation of Coronary Calcium and Lifestyle) Study (HNRS) we investigated the association of exposure to Mn with olfactory dysfunction in elderly men. We evaluated multiple measures of exposure to Mn, including occupations with anticipated Mn exposure, cumulative inhalable exposure to Mn, and Mn in blood samples archived at baseline.

2. Materials and methods

2.1. Subjects

The study population of this analysis comprised 1474 men who underwent olfactory testing using Sniffin' sticks tests in the second follow-up survey of HNRS (2011–2014). HNRS is a prospective population-based cohort study in an industrial area in Germany. Its rationale, design, and conduct have been previously described (Schmermund et al., 2002). In brief, 4814 subjects (about 50% females) aged from 45 to 75 years were included. They were recruited from a random sample from the general population of the cities of Bochum, Essen, and Mülheim starting in December 2000. The overall recruitment efficacy proportion for the baseline recruitment (2000–2003) was 56% (Stang et al., 2005). This analysis was part of the project AeKo ("Arbeitsmedizinische Forschung in epidemiologischen Kohortenstudien"- Occupational medical research in epidemiological cohort studies), which aimed at investigating occupational risk factors within the HNRS. Approval for the study was obtained from the ethical commission of the Medical Faculty of the University Duisburg-Essen. All participants signed an informed consent.

From 1474 men enrolled for AeKo, we excluded 51 participants with missing olfactory testing, 26 participants with acute (e.g. a cold, a blocked nose or other sinonasal complaints) and six participants with sustained olfactory impairment (e.g. surgery), and six participants with conditions known to affect olfaction, such as Parkinson's disease. The dataset of the statistical analysis consisted of 1385 men with information on the occupational history and on job tasks with anticipated exposure to inhalable Mn as well as diverse blood parameters.

2.2. Odor identification test

Sniffin' sticks were applied to assess the identification of 12 odors (orange, leather, cinnamon, peppermint, banana, lemon, licorice, coffee, clove, pineapple, rose, and fish). Odors were presented in felt-tip pens. The individual pens were consecutively placed in front of both nostrils at a distance of approximately two cm. The participants could identify the odor as a multiple-choice task from a list of four potential answers resulting in a dichotomous variable of correct or false odor identification. The cumulative score of all 12 Sniffin' stick results yielded count data with values between 0 and 12. Subjects were classified as normosmic if ten or more odors were identified correctly, hyposmic if seven to nine odors were identified, and anosmic if less than seven odors were identified (Hummel et al., 2001).

2.3. Assessment of exposure to Mn

2.3.1. Job tasks with anticipated exposure to Mn

Exposure to Mn was initially assessed using a supplemental job-specific questionnaire for regular (N = 24), occasional welding (N = 187), and for other occupations with exposure to hot metal fumes (production of steel and alloys) or particulate matter that may contain Mn (battery production) (N = 99). In the main interview participants gave detailed information about their occupational history. Men who worked in their last job as blue-collar worker (N = 267) constituted the reference group. The remaining group comprised men with a white-collar job as last occupation (N = 618). Farmers were not among the participants from this industrial district.

2.3.2. Calculation of cumulative inhalable exposure to Mn

We established a job-exposure matrix (JEM) for occupations with Mn exposure using 4635 personal measurements of inhalable Mn compiled in the German exposure database MEGA from 1989 to 2015 (Gabriel et al., 2010). Mn was determined by inductively coupled plasma mass spectrometry (ICP-MS) in personal samples of inhalable particles. Multiple imputation was performed for 10% of all measurements that were below the limit of quantification (Lotz et al., 2013). Textual information about workplaces was assigned to the corresponding at-risk occupation assessed in the supplemental questionnaire of the HNRS. We classified welding measurements by major welding process and material. Mixed-effects models were applied to the natural log-transformed Mn concentrations with imputed non-detects to assess the geometric means of exposure to Mn in the various occupational settings according to a model developed in the WELDOX study (Pesch et al., 2012). In addition to the materials we implemented the median-centered year and sampling duration of measurement as covariate. Intensity scores were assigned for working as welder (=1) and for other occupations as welding frequently (=0.25) or less frequently (=0.1). We linked the exposure estimates with occupational histories of the HNRS participants and calculated inhalable Mn [$\mu g/m^3$ years] as the sum of the exposure in each job period with anticipated exposure using the product of the job-specific or welding-process average concentration [$\mu g/m^3$] and the corresponding duration [years], together with intensity scores for