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Original Article

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Occupational Exposure to Manganese and Fine Motor Skills in Elderly Men: Results from the Heinz Nixdorf Recall Study

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Abstract

Objectives: Exposure to manganese (Mn) may cause movement disorders, but less is known whether the effects persist after the termination of exposure. This study investigated the association between former exposure to Mn and fine motor deficits in elderly men from an industrial area with steel production.

Methods: Data on the occupational history and fine motor tests were obtained from the second follow-up of the prospective Heinz Nixdorf Recall Study (2011–2014). The study population included 1232 men (median age 68 years). Mn in blood (MnB) was determined in archived samples (2000–2003). The association between Mn exposure (working as welder or in other at-risk occupations, cumulative exposure to inhalable Mn, MnB) with various motor functions (errors in line tracing, steadiness, or aiming and tapping hits) was investigated with Poisson and logistic regression, adjusted for iron status and other covariates. Odds ratios (ORs) with 95% confidence intervals (CIs) were estimated for substantially impaired dexterity (errors >90th percentile, tapping hits <10th percentile).

Results: The median of cumulative exposure to inhalable Mn was 58 µg m^{-3} years in 322 men who ever worked in at-risk occupations. Although we observed a partly better motor performance of exposed workers at group level, we found fewer tapping hits in men with cumulative Mn exposure >184.8 µg m^{-3} years (OR 2.15, 95% CI 1.17–3.94). MnB ≥ 15 µg l^{-1}, serum ferritin ≥ 400 µg l^{-1}, and gamma-glutamyl transferase ≥74 U l^{-1} were associated with a greater number of errors in line tracing.
Conclusions: We found evidence that exposure to inhalable Mn may carry a risk for dexterity deficits. Whether these deficits can be exclusively attributed to Mn remains to be elucidated, as airborne Mn is strongly correlated with iron in metal fumes, and high ferritin was also associated with errors in line tracing. Furthermore, hand training effects must be taken into account when testing for fine motor skills.

Keywords: community-based cohort; ferritin; fine motor skills; manganese; welding

Introduction

Manganese (Mn) and iron (Fe) are major constituents of metal fumes in the production and processing of steel and ferroalloys (ATSDR, 2008). Due to growing evidence of neurotoxic effects of Mn even at relatively low concentrations, regulatory bodies have adopted occupational exposure limits (OELs). The German OELs were recently lowered to 20 µg m^{-3} for respirable Mn and 200 µg m^{-3} for inhalable Mn (http://www.baua.de/de/Themen-von-A-Z/Gefahrstoffe/TRGS-900.html). High-emission techniques, such as gas metal arc welding, require protective measures to comply with these OELs (Hobson *et al.*, 2011; Pesch *et al.*, 2012).

Airborne concentrations of Mn and Fe are strongly correlated in welding fumes (Pesch *et al.* 2012; Hedmer *et al.*, 2014). Therefore, potential neurotoxic effects cannot be exclusively attributed to Mn when exposure is assessed as inhalable Mn. Mn in blood (MnB) may serve as additional exposure metric (Baker *et al.*, 2014). Mn and Fe are essential redox-active metals and cofactors of multiple enzymes, including those associated with oxidative stress control (Aguirre and Culotta, 2012). Hence, their absorption, binding to biomolecules, and bilary excretion are strongly regulated as to maintain optimal levels and mitigate excessive oxidative damage. This tight regulation is reflected in a weak correlation between the systemic burden with Mn and Fe and with the parent metal concentration in welding fumes (Pesch *et al.*, 2012). Occupational exposure to metal fumes may cause dyshomeostasis in the systemic concentrations of both these metals, also liver dysfunction contributes to elevated blood levels (Rovira *et al.*, 2008; Pesch *et al.*, 2012; Casjens *et al.*, 2014).

Mn and Fe are essential for brain metabolism and can enter the brain–blood barrier by carrier-mediated processes (Yokel, 2006; McCarthy and Kosman, 2015a, b). Both metals preferentially accumulate in the basal ganglia, which are involved in the control of motor function (Guilarte, 2013). Elevated concentrations of redox-active forms of Fe and Mn in the basal ganglia can cause oxidative damage to biomolecules and neurons, with dysregulation of the dopaminergic system, a hallmark of movement disorders (Guilarte, 2010). The increase in the nigral Fe content and the loss of dopaminergic neurons are prominent features of Parkinson's disease (PD) (Ward *et al.*, 2014; Zucca *et al.*, 2017). Patients with PD, as well as workers with high Mn exposure suffering from manganism, are known to show motor deficits, albeit distinct clinical abnormalities have been ascribed to both conditions (Olanow, 2004). In contrast to PD, patients with manganism develop less frequently a resting tremor and do not respond to levodopa (Calne *et al.*, 1994). The latter observation lends support to the hypothesis that Mn, especially at low levels of exposure, may not damage dopaminergic neurons with persistent motor dysfunctions. However, a reduced uptake of 6-[^{18}F]fluoro-l-dopa was observed in a neuroimaging study of asymptomatic welders, indicating dysfunction of the nigrostriatal dopaminergic system, likely due to high cumulative Mn exposure, such as encountered in shipyards (Criswell *et al.*, 2011).

Occupational exposure to Mn has been associated with a continuum of extrapyramidal dysfunctions, ranging from subclinical fine motor impairments to clinical symptoms such as manganism or parkinsonism (Couper, 1837; Olanow, 2004). Less is known about the restoration of Mn-associated fine motor deficits after the cessation of occupational exposure (Lucchini *et al.*, 1995; Bouchard et al. 2007; Wastensson *et al.* 2012). Fine motor dysfunctions in conjunction with individual Mn exposure were primarily investigated in small cross-sectional studies, with conflicting results in meta-analyses (Greiffenstein and Lees-Haley, 2007; Meyer-Baron *et al.*, 2009). No excess morbidity from PD was observed in mostly former welders in previously published large

record-linkage studies (Fored *et al.*, 2006; Stampfer, 2009; Fryzek *et al.*, 2005; Kenborg *et al.*, 2012). However, each of these study designs suffered from methodological shortcomings, mainly in exposure assessment and control of confounders (Park, 2013).

Our analysis aimed to estimate fine motor deficits in elderly men from an area with a high volume of steel production in association with former occupational exposure to Mn. We obtained data on the occupational history and fine motor skills in the prospective Heinz Nixdorf Recall Study (HNRS). Exposure to Mn was assessed with multiple measures, including cumulative exposure to inhalable Mn based on measurements compiled in the German exposure database MEGA (Gabriel *et al.*, 2010).

Materials and Methods

Study population

The study was conducted with data from the second follow-up survey of HNRS (2011–2014). The design and conduct of HNRS and the investigation of Mn within the framework of this cohort have been previously described (Schmermund *et al.*, 2002; Casjens *et al.*, 2017). In brief, 4814 subjects (49.8% men, aged 45–75 years) participated at baseline (2000–2003). They were randomly selected from the general population of Bochum, Essen, and Mülheim with a response rate of 56%. This analysis investigated Mn-related fine motor deficits in 1232 men in association with exposure to Mn. Notably women were not employed as welders or steel workers. Our study population excluded 242 men with incomplete tests, missing information about handedness, or medical conditions known to affect dexterity. Approval for the study was obtained from the ethical commission of the Medical Faculty of the University Duisburg-Essen (approval number 11–4678). All participants signed an informed consent.

Fine motor tests

Finger tapping, line tracing, steadiness, and aiming were measured for each hand with the Motor Performance Series (Schuhfried, Mödling, Austria) using automated data generation and export into the project's database. The investigators were blinded to the exposure status. The handedness and the number of errors (E) or hits (H), respectively, were documented, together with the duration of errors (DE) and test time (TT) in seconds, where appropriate. Hits were recorded for tapping, which examines the wrist-finger speed by tapping a stylus as often as possible on a 40-mm^2 plate within 32 s. E, DE, and TT were measured for line tracing, which examines precision and speed of motor skills by drawing a stylus through a curvy course of a groove without touching the walls. E and DE were documented when testing steadiness measuring the ability to maintain a precise arm-hand position by holding a stylus for 32 s in a 5.8-mm hole without touching the boundary. Aiming specifically tests the ability of performing fast small-scale movements. Twenty holes with a diameter of 5 mm spaced at a distance of 4 mm had to be touched one by one with the stylus as fast as possible. E, DE, and TT were recorded.

Assessment of exposure to Mn

Job tasks with exposure to Mn

We assessed occupations with recognized exposures according to expert knowledge (C.v.T., B.P.) and scientific reports (ATSDR, 2008). A supplemental questionnaire was developed for regular and occasional welding (detailed by welding technique and materials), occupations in the production of steel and alloys, and in other settings, including the manufacture of dry-cell batteries, electroplating, and soldering.

The occupational history was documented as part of the main questionnaire. All jobs held during the entire working life were documented in calendar years (beginning and end) and coded according to the International Standard Classification of Occupations (ISCO-68) (International Labour Office, 1968). Blue-collar jobs included occupations coded with 7, 8, or 9 as first digit. In addition, we assessed non-exposed occupations that likely required fine motor skills (Supplementary Table S1, available at *Annals of Occupational Hygiene* online). All other non-exposed men with a blue-collar job as their last occupation constituted the reference group. The last occupation of the remaining group was considered as a white-collar job.

Calculation of cumulative exposure to inhalable Mn

The exposure assessment will be published elsewhere in greater detail. In brief, we established a job-exposure matrix (JEM) for occupations with Mn exposure using 5771 measurements compiled in MEGA from 1989 to 2015 according to a procedure developed for the use of exposure databases in community-based studies (Peters *et al.*, 2016). Mn was determined by inductively coupled plasma-mass spectrometry (ICP-MS) in personal samples of inhalable particles. About 10% of the concentrations was below the limit of quantification (LOQ) and multiply imputed (Lotz *et al.*, 2013). Textual information about workplaces was assigned to the corresponding at-risk occupations assessed with the supplemental questionnaire. We calculated the average annual shift concentration as geometric mean (GM) in these occupations with mixed-effects models according to an approach

applied to hexavalent chromium to adjust for sampling duration, analytical method, and calendar year where appropriate (Pesch *et al.*, 2015). The auxiliary data compiled in MEGA allowed detailing the shift concentrations of welders by major processes and Mn content of consumable electrodes. Although the overall exposure levels decreased due to new welding techniques and other changes, we failed to observe time trends within job tasks between 1989 and 2015 (data not shown).

The JEM with average shift concentrations in at-risk occupations was linked with the occupational history of the exposed workers. We calculated each worker's lifetime exposure to inhalable Mn (µg m^{-3} years) as the sum of the cumulative exposure levels in all of the exposure periods. The exposure level for each period was the product of the GM of the shift concentration (µg m^{-3}) and the years of working in this job. We weighted this product for occasional welding (frequently: 0.25, infrequently: 0.1), where appropriate.

Determination of Mn in archived whole blood samples

MnB was determined in aliquots of whole blood archived at baseline by means of ICP-MS as previously described (Casjens *et al.*, 2017). Plastic materials were used for sample preparation to prevent contamination. After thawing, 400 µl was diluted 1:12.5 with a 0.5% solution of ammonium hydroxide and 100 µl of a 0.2% solution of Triton-X. Analysis was carried out using a 7700 ICP-MS system from Agilent Technologies in He-mode (flow rate 5 ml min^{-1}) with a collision cell to avoid interferences. Skimmer and sampler cones were made of platinum. Materials from RECIPE (ClinChek Whole Blood Level, lyophil. for Trace Elements I and II, REF 8840, LOT 227) and SERONORM (Trace Elements Whole Blood Level I and II, LOT 1103129) served as internal control. Within-series and between-day imprecision were each lower than 8%. We used 15 µg l^{-1} as cut-off for an elevated concentration of MnB. This is the German biological reference value for MnB as the presumed 95th percentile of the distribution in the general population.

Markers of Fe status and liver dysfunction

Blood samples were collected at the second follow-up investigation and analyzed in the central laboratory of the University Hospital Essen without knowledge of the exposure status and with standard methods as previously described (Eisele *et al.*, 2013). In brief, hemoglobin (Hb) was measured with a STKR hematology analyzer (Beckman Coulter, Krefeld, Germany) and serum ferritin (SF), using the BN II nephelometer (Siemens Healthcare, Eschborn, Germany). We considered the Fe status as low if Hb < 13 g dl^{-1} and high if SF ≥ 400 µg l^{-1} (Casjens *et al.*, 2014). Gamma-glutamyl transferase (GGT) was determined with the ADVIA 1650 chemistry analyzer (Siemens Healthcare). GGT ≥ 90th percentile was considered as an indicator of a potential liver dysfunction.

Statistics

The distribution of continuous variables was presented with median and inter-quartile range (IQR), associations between variables with Spearman correlation coefficients (r_s). Poisson regression models were applied to errors or hits to estimate the factor of change for working in at-risk occupations, cumulative exposure to inhalable Mn, and MnB. Furthermore, odds ratios (ORs) with 95% confidence interval (CI) were estimated for the relative risk of a substantially impaired manual dexterity (errors >90th percentile, hits <10th percentile). We used the results from both hands (mixed regression models) and also from the non-dominant hand only to consider potential training effects of the dominant hand. We adjusted for age (per 10 years) and smoking status (never, former, and current), furthermore for occupational qualification (none or vocational, technician or foremen, university degree), and TT where appropriate. We did not include DE, which was correlated with E (r_s for steadiness: 0.89, line tracing: 0.71, and aiming: 0.94). We ran additional models for the effects of liver dysfunction and Fe status in men with laboratory values for GGT and SF. All calculations were done using SAS (version 9.4).

Results

Characteristics of the study population

Table 1 shows the characteristics of the 1232 male participants (median age 68 years) at the second HNRS follow-up examination (2011–2014). In total, 61% of all men were occupationally active at baseline and 27% at second follow-up. About 26% of all men had ever worked in at-risk occupations and showed a similar level of occupational qualification as the reference group of non-exposed, blue-collar workers. The fraction of never smokers was 29.8% in all men and varied between 50.0% in welders and 20.4% in men working in other occupations with Mn exposure. In this study population, none of the 24 regular welders presented with GGT above the 90th percentile (74 U l^{-1}). We observed SF ≥ 400 µg l^{-1} in 79 men (9.2%).

In occupationally exposed men, the median duration of working in at-risk occupations was 20 years (IQR 6–46), with on average 34 years since the last exposure to Mn at the second follow-up. The IQR of

Table 1. Characteristics of 1232 men at the second follow-up of the Heinz Nixdorf Recall Study, 2011–2014.

Characteristics	Total		Welders[a]		Occasional welding[a]		Other occupations with Mn exposure[a]		Manually skilled occupations[b]		Blue-collar jobs without Mn exposure[c]		White-collar occupations[b]	
N	1232		24		195		103		112		237		561	
Age (years) (*N* = 1232)														
Median (inter-quartile range)	68	62; 74	69	67; 73	68	63; 73	72	62; 77	70	62; 75	69	63; 74	67	62; 73
Occupational qualification (*N* = 1232)														
None/vocational	613	49.8%	16	66.7%	116	59.5%	62	60.2%	42	37.5%	158	66.7%	219	39.0%
Foreman/technician	269	21.8%	8	33.3%	58	29.7%	24	23.3%	35	31.3%	57	24.1%	87	15.5%
University	350	28.4%	0		21	10.8%	17	16.5%	35	31.3%	22	9.3%	255	45.5%
Employment at baseline (*N* = 1232)	753	61.1%	12	50.0%	109	55.9%	52	50.5%	66	58.9%	128	54.0%	386	61.1%
Employment at second follow-up (*N* = 1232)	335	27.2%	5	20.8%	39	20.0%	21	20.4%	31	27.7%	49	20.7%	190	33.9%
Smoking status (*N* = 1232)														
Never	367	29.8%	12	50.0%	50	25.6%	21	20.4%	40	35.7%	66	27.8%	178	31.7%
Former	687	55.8%	10	41.7%	112	57.4%	67	65.0%	62	55.4%	136	57.4%	300	53.5%
Current	178	14.4%	2	8.3%	33	16.9%	15	14.6%	10	8.9%	35	14.8%	83	14.8%
Gamma-glutamyl transferase [U/L] (*N* = 1123)														
≥74 (90th percentile)	121	9.9%	0		28	14.4%	14	13.7%	6	5.4%	18	7.6%	55	9.9%
Iron status (*N* = 861)														
Low (hemoglobin <13 g dl^{-1})	71	8.2%	3	15.0%	14	10.7%	5	6.8%	7	8.9%	13	7.4%	29	7.6%
Normal	711	82.6%	16	80.0%	99	75.6%	66	89.2%	64	81.0%	143	81.7%	323	84.6%
High (ferritin ≥ 400 µg l^{-1})	79	9.2%	1	5.0%	18	13.7%	3	4.1%	8	10.1%	19	10.9%	30	7.9%
Mn in blood (µg l^{-1}) at baseline (*N* = 1179)														
Median (inter-quartile range)	8.2	6.7; 9.8	8.6	7.1; 9.5	8.4	6.9; 10.4	8.3	6.9; 10.4	8.0	6.5; 9.8	8.4	6.7; 9.7	8.0	6.7; 9.6
Cumulative airborne exposure to Mn [µg m^{-3} years] (*N* = 322)														
Median (inter-quartile range)	58	18; 185	1177	619; 1847	69	25; 181	22	7; 79	0	0; 0	0	0; 0	0	0; 0
>1000	17	1.4%	16	66.7%	0		1	1.0%	0		0		0	
Working in at-risk occupation (years) (*N* = 319)														
Median (inter-quartile range)	20	6; 46	30	19; 40	10	3; 28	12	4; 33	0	0; 0	0	0; 0	0	0; 0
Duration since last Mn exposure of former workers (years) (*N* = 257)														
Median (inter-quartile range)	34	16; 46	19	13; 40	38	16; 48	34	19; 45	0	0; 0	0	0; 0	0	0; 0

[a]Ever exposed to Mn in regular or occasional welding, in other occupations with Mn exposure.

[b]Ever working in occupations that require manual skills (see Supplementary Table S1, available at *Annals of Occupational Hygiene* online).

[c]Blue- or white-collar occupation as last held job.

individual exposure periods spanned from 1961 to 1995. The median of the cumulative Mn exposure was 58 µg m^{-3} years, varying between 1177 µg m^{-3} years in welders and 22 µg m^{-3} years in men working in steel production and other at-risk occupations. Blue-collar workers had slightly higher MnB than men with a white-collar job as last occupation. We found a weak negative correlation between MnB and SF in the entire study population at baseline (r_s: −0.16; 95% CI −0.22 to −0.11, data not shown).

General results from the fine motor tests

We observed mostly significant correlations between all test variables, which were strongest for line tracing with steadiness (r_s: 0.42) and weakest for tapping and aiming (r_s: −0.06). Hits or errors made with the non-dominant hand were significantly correlated with the dominant hand (r_s for tapping: 0.65, line tracing: 0.56, steadiness: 0.58, aiming: 0.25). As shown in the mixed models, we noted greater number hits and fewer errors with the dominant hand, with the exception of steadiness (Table 2).

The covariates showed similar effects in all models. Age had the strongest influence on the test results (Table 3). In addition, current smoking was associated with greater number of errors (especially in line tracing) and fewer hits. The risk estimates of the exposure variables were not affected when adding pack-years to the models (data not shown). Low occupational qualification was associated with poorer test results. SF ≥ 400 µg l^{-1} was a significant predictor of more errors in line tracing. Men presenting with GGT ≥ 74 U l^{-1} made more errors in line tracing and steadiness.

Occupational exposure to Mn and fine motor skills

Having ever worked in occupations with exposure to Mn was not associated with fine motor deficits when exposure effects were evaluated at group level only. The test results with both hands indicated even a better performance in comparison to the reference group of non-exposed, blue-collar workers (Table 2). Mn-exposed workers made fewer errors in steadiness and all except regular welders made fewer aiming errors and more tapping hits. We found weaker effects for ever working in at-risk occupations with the data derived from the non-dominant hand (Supplementary Table S2, available at *Annals of Occupational Hygiene* online). In addition, logistic regression analysis of a substantial impairment of fine motor skills did not reveal significant impairments of dexterity for the non-dominant hand when comparing exposed versus non-exposed study groups (Supplementary Table S3, available at *Annals of Occupational Hygiene* online).

Eighteen men (2.2%) presented with MnB ≥ 15 µg l^{-1} at baseline. Similar to the results found for elevated SF and GGT, men with high MnB made more errors in line tracing (Table 3).

A cumulative exposure to inhalable Mn up to the 75th percentile (184.8 µg m^{-3} years) was not associated with fine motor deficits in regression models where dexterity was measured with hits or errors (Table 4 for 860 men with laboratory values and test results from both hands; Supplementary Table S4, available at *Annals of Occupational Hygiene* online, for 1232 men with test results of the non-dominant hand). Time since last exposure did not modify these effects (data not shown). In addition, we estimated potential predictors of substantially impaired test results with the non-dominant hand. Exposure >184.8 µg m^{-3} years was associated with an OR of 2.15 (95% CI 1.17–3.94) for achieving substantially fewer tapping hits (Table 5). This upper quartile of exposed men included 21 out of the 24 welders. They showed a substantially impaired line tracing among all men with laboratory values (Supplementary Table S5, available at *Annals of Occupational Hygiene* online).

Discussion

Mn is an important additive to increase the hardness of steel and is a major constituent of welding fumes. In this large prospective cohort study of 1232 elderly men from an industrial region with steel production, improved performance in several fine motor skills was observed when comparing Mn-exposed men with non-exposed, blue-collar workers. This observation likely reflects training effects of the hands and a weak exposure assessment when comparing study groups only. Using a quantitative assessment of cumulative exposure to inhalable Mn, we found a higher risk of substantially impaired tapping performance with increased levels of exposure. In this community-based cohort, cumulative Mn exposure was mainly encountered in steel production and lower than in a cohort of active welders, which developed a dose-dependent progression of parkinsonism (Racette *et al.*, 2017).

Due to the strong correlation between Mn and Fe in metal fumes, potential neurotoxic effects of both metals cannot be separated with airborne exposure variables by statistical means. In contrast to the tight correlation of airborne Mn and Fe, we confirmed a weak and even negative correlation between MnB and SF which was previously observed in other surveys (Meltzer *et al.*, 2010; Kim and Lee, 2011; Oulhote *et al.*, 2014).

Table 2. Occupation and other potential predictors of fine motor tests with both hands in 1232 men (mixed Poisson regression).

Variable	Value	N[a]	Tapping hits			Line tracing errors			Steadiness errors			Aiming errors		
			Exp(β)	95% CI		Exp(β)	95% CI		Exp(β)	95% CI		Exp(β)	95% CI	
Intercept		2464	267	253	281	9.27	7.86	10.9	0.88	0.61	1.28	0.08	0.03	0.18
Occupation	Blue-collar without Mn exposure (last occupation)	474	1			1			1			1		
	Welders	48	0.98	0.95	1.02	0.96	0.85	1.07	0.70	0.51	0.95	1.12	0.68	1.83
	Occasional welding	390	1.02	1.00	1.03	0.99	0.94	1.04	0.89	0.79	1.00	0.71	0.54	0.92
	Other potential Mn exposure	206	1.04	1.01	1.06	0.98	0.92	1.04	0.86	0.75	1.00	0.83	0.61	1.13
	Manually skilled	224	1.01	0.98	1.03	0.99	0.93	1.05	0.80	0.69	0.93	0.66	0.48	0.92
	White-collar	1122	1.03	1.02	1.05	0.98	0.94	1.02	0.96	0.88	1.06	0.77	0.63	0.94
Age [per 10 years]		2464	0.93	0.92	0.94	1.18	1.16	1.21	1.56	1.48	1.64	1.32	1.18	1.49
Smoking status	Never	734	1			1			1			1		
	Former	1374	1.00	0.99	1.01	1.02	0.98	1.06	1.02	0.94	1.11	1.16	0.96	1.40
	Current	356	0.97	0.95	0.98	1.06	1.01	1.11	1.26	1.13	1.42	1.23	0.95	1.60
Hand	Non-dominant	1232	1			1			1			1		
	Dominant	1232	1.11	1.09	1.12	0.89	0.86	0.92	0.98	0.91	1.05	0.36	0.30	0.43
Test time [sec]		2464				1.01	1.00	1.01				1.07	1.05	1.09

[a]Number of measurements.

Table 3. Blood concentrations of manganese (Mn), iron status, and other potential predictors of fine motor tests with both hands in 826 men (mixed Poisson regression).

Variable	Value	N[a]	Tapping hits			Line tracing errors			Steadiness errors			Aiming errors		
			Exp(β)	95% CI		Exp(β)	95% CI		Exp(β)	95% CI		Exp(β)	95% CI	
Intercept		1652	276	259	294	7.31	6.02	8.88	0.58	0.36	0.92	0.03	0.01	0.07
Mn in blood [µg/L]	< 15	1616	1			1			1			1		
	≥ 15	36	0.99	0.95	1.03	1.24	1.10	1.38	1.14	0.84	1.54	1.50	0.88	2.55
Iron status	Normal	1360	1.00			1.00			1.00			1.00		
	Hemoglobin < 13 g/dL	140	1.01	0.98	1.03	1.01	0.95	1.08	1.10	0.94	1.27	0.84	0.60	1.19
	Ferritin ≥ 400 µg/L	152	1.00	0.98	1.02	1.12	1.05	1.19	1.11	0.95	1.29	1.03	0.75	1.43
Occupational qualification	University	450	1			1			1			1		
	Foreman/technician	852	0.98	0.97	1.00	1.01	0.96	1.07	1.06	0.93	1.21	1.10	0.81	1.50
	None/vocational	350	0.97	0.95	0.98	1.08	1.04	1.13	1.15	1.03	1.29	1.51	1.18	1.93
Age [per 10 years]		1652	0.93	0.92	0.94	1.22	1.18	1.25	1.62	1.52	1.72	1.47	1.28	1.69
Smoking status	Never	488	1			1			1			1		
	Former	934	1.01	0.99	1.02	0.99	0.95	1.03	0.98	0.89	1.09	1.07	0.86	1.34
	Current	230	0.98	0.96	1.00	1.04	0.98	1.10	1.28	1.11	1.48	1.30	0.96	1.77
Gamma-glutamyl transferase [U/L]	< 74 (90th percentile)	1476	1			1			1			1		
	≥ 74	176	1.00	0.98	1.02	1.09	1.03	1.16	1.14	0.99	1.31	1.15	0.86	1.54
Hand	Non-dominant	826	1			1			1			1		
	Dominant	826	1.10	1.09	1.12	0.88	0.85	0.92	0.94	0.86	1.03	0.39	0.32	0.48
Test time [sec]		1652				1.00	1.00	1.01				1.07	1.05	1.09

[a]Number of measurements.

Table 4. Cumulative airborne exposure to manganese (Mn), iron status, and other predictors of fine motor tests with both hands in 860 men (mixed Poisson regression).

Variable	Value	N[a]	Tapping hits			Line tracing errors			Steadiness errors			Aiming errors		
			Exp(β)	95% CI		Exp(β)	95% CI		Exp(β)	95% CI		Exp(β)	95% CI	
Intercept	Intercept	1720	275	258	292	7.26	5.99	8.78	0.59	0.37	0.93	0.03	0.01	0.07
Cumulative Mn exposure	0	1270	1			1			1			1		
[µg/m^3 years]	>0–58	240	1.01	0.99	1.03	0.94	0.89	0.99	0.85	0.75	0.98	0.67	0.50	0.91
	>58–184.8	96	1.01	0.98	1.04	0.94	0.87	1.02	0.83	0.68	1.01	0.51	0.31	0.84
	>184.8	114	0.97	0.95	1.00	1.05	0.98	1.13	0.99	0.83	1.17	1.22	0.90	1.66
Iron status	Normal	1420	1			1			1			1		
	Hemoglobin < 13 g/dL	142	1.01	0.98	1.03	1.01	0.95	1.08	1.10	0.95	1.27	0.85	0.61	1.19
	Ferritin ≥ 400 µg/L	158	1.01	0.99	1.03	1.10	1.04	1.17	1.08	0.93	1.26	0.98	0.71	1.35
Occupational qualification	University	476	1			1			1			1		
	Foreman/technician	876	0.99	0.97	1.00	1.01	0.96	1.07	1.07	0.94	1.21	1.17	0.87	1.57
	None/vocational	368	0.97	0.96	0.99	1.07	1.03	1.12	1.16	1.04	1.29	1.58	1.24	2.01
Age [per 10 years]		1720	0.93	0.92	0.94	1.22	1.19	1.25	1.62	1.52	1.72	1.47	1.28	1.68
Smoking status	Never	500	1			1			1			1		
	Former	970	1.00	0.99	1.02	1.00	0.96	1.04	0.99	0.89	1.09	1.08	0.87	1.34
	Current	250	0.98	0.96	1.00	1.04	0.98	1.10	1.26	1.09	1.45	1.28	0.95	1.72
Gamma-glutamyl transfer-	< 74 (90th percentile)	1536	1			1			1			1		
ase [U/L]	≥ 74	184	0.99	0.97	1.01	1.10	1.04	1.16	1.16	1.01	1.33	1.20	0.90	1.61
Hand	Non-dominant	860	1			1			1			1		
	Dominant	860	1.10	1.09	1.12	0.89	0.85	0.92	0.95	0.87	1.04	0.39	0.32	0.48
Test time [sec]		1720				1.00	1.00	1.01				1.07	1.05	1.09

[a]Number of measurements.

Table 5. Odds ratios for cumulative Mn exposure and other potential predictors of substantially impaired fine motor tests with the non-dominant hand in 1232 men of the Heinz Nixdorf Recall Study, 2011–2014.

Variable	Value	Tapping hits			Line tracing errors			Steadiness errors			Aiming errors		
		n[a]	OR[b]	95% CI	n[a]	OR[b]	95% CI	n[a]	OR[b]	95% CI	n[a]	OR[b]	95% CI
Cumulative exposure to Mn [µg m^{-3} years]	0	85	1		89	1		89	1		129	1	
	> 0–58.0	16	1.02	0.57 1.83	19	1.17	0.66 2.06	16	0.97	0.54 1.73	16	0.62	0.36 1.09
	> 58.0–184.8	10	1.08	0.52 2.22	6	0.55	0.23 1.36	9	0.90	0.43 1.92	9	0.64	0.31 1.33
	> 184.8	17	2.15	1.17 3.94	14	1.93	0.99 3.75	13	1.44	0.74 2.78	14	1.01	0.54 1.89
Occupational qualification	University	24	1		31	1		25	1		35	1	
	Foremen/technician	26	1.25	0.68 2.28	27	1.08	0.60 1.92	24	1.15	0.63 2.11	25	0.94	0.54 1.62
	None/vocational	78	1.74	1.05 2.88	70	1.18	0.73 1.93	78	1.76	1.07 2.90	108	1.96	1.28 2.98
Age [per 10 years]		128	2.59	1.95 3.42	128	2.79	2.09 3.73	127	2.54	1.92 3.35	168	1.49	1.17 1.90
Smoking status	Never	35	1		36	1		34	1		47	1	
	Former	71	0.97	0.62 1.50	70	1.03	0.65 1.61	70	0.99	0.63 1.54	95	1.02	0.69 1.49
	Current	22	1.73	0.95 3.16	22	2.00	1.08 3.70	23	1.87	1.04 3.39	26	1.23	0.72 2.10
Test time [sec]					128	1.06	1.04 1.07				168	1.02	0.97 1.08

[a]Participants at risk.

[b]Odds ratio (OR) with 95% confidence interval (CI) as estimate of the relative risk for a substantially impaired dexterity (hits <10th percentile, errors >90th percentile).

To our knowledge, this is the first prospective, community-based study that observed a significant association between MnB and SF with fine motor tests, which is indicative for an independent effect of Fe in addition to the recognized neurotoxicity of Mn.

Major strengths of this community-based study are the prospective design, the application of a supplemental questionnaire on at-risk occupations, and the comprehensive modelling of Mn-associated effects, including the estimation of risks for a substantially impaired dexterity. The reference group comprised non-exposed men with a blue-collar job as last occupation. We separately tested men in white-collar occupations and jobs that require manual skills. Although we enrolled 322 men ever working in at-risk occupations, a general limitation of the community-based design is the low prevalence of high-risk occupations such as welders. Another limitation of this and of other studies is the lack of serial data for MnB and of lifetime individual measurements of airborne Mn. We adopted a model for other workplace substances in community-based studies to assess cumulative exposure to inhalable Mn in at-risk occupations based on a large dataset of measurements at German workplaces (Peters *et al.*, 2011; Pesch *et al.*, 2015, 2016). The detailed assessment of exposure will be published elsewhere.

Although Mn is mostly respirable in metal fumes, measurements of respirable Mn are scarce. Therefore, we calculated cumulative exposure for inhalable Mn. The median concentration of 5771 personal measurements of inhalable Mn compiled in the German exposure database MEGA was 35 µg m^{-3}, with a higher average concentration in welders (74 µg m^{-3}) than in foundry workers (7 µg m^{-3}). In contrast, 140 µg m^{-3} was estimated as average concentration of airborne Mn in a US cohort of active welders, where welding in confined space with high-emission techniques such as flux-cored arc welding could have resulted in much higher exposure levels (Racette *et al.*, 2017). We calculated 58 µg m^{-3} years as median cumulative exposure in Mn-exposed men enrolled in HNRS, varying between 1177 µg m^{-3} years in welders and 22 µg m^{-3} years in steel production and other at-risk occupations. The upper quartile of cumulative exposure (above 184.8 µg m^{-3} years) comprised 80 men, which had an increased OR for substantially fewer finger tapping hits and made a greater number of errors in line tracing. The corresponding 75th percentile of Mn exposure was 1100 µg m^{-3} years in the cohort of US welders.

Fine motor skills do not exclusively reflect damage to the basal ganglia where Mn preferentially accumulates (Lucchini *et al.*, 2009). We found evidence of training effects in particular of the dominant hand and in the low-dose range up to 58 µg m^{-3} years. Welding equipment has to be steadied for precise seams, which may explain an improved performance in steadiness observed also in other studies (Wastensson *et al.*, 2012). Locomotion, such as finger tapping, uses not only perceptual motor coordination, but also spatial cognition and memory (Anderson *et al.*, 2013). This may explain the effect of education on the test results. Deficits in finger tapping of exposed workers have been frequently reported in cross-sectional studies (Meyer-Baron *et al.*, 2009). Various versions of this test showed a strong activation of the basal ganglia (Witt *et al.*, 2008). Thus, our findings are consistent with previous reports in Mn-exposed workers but also corroborate the observation that less educational attainment is associated with neurobehavioral deficits (Anger *et al.*, 2000; Skrzek *et al.*, 2015). Whether the fine motor dysfunctions noted in current smokers are a causal effect of tobacco smoke or may have resulted from residual confounding for education remains to be elucidated.

This study is the first survey on MnB in a German population. Recently, MnB was determined within the framework of the US National Health and Nutrition Examination Survey (NHANES) 2011–2012 (Oulhote *et al.*, 2014). Although MnB is subject to a tight biological regulation, homeostasis may be compromised when welding with high-emission techniques (Pesch *et al.* 2012; Baker *et al.*, 2014). In HNRS, MnB was the highest in welders (median 8.6 µg l^{-1}), yet lower than in women (8.9 µg l^{-1}) (Bonberg *et al.*, 2017). Men with MnB ≥ 15 µg l^{-1} made a greater number of errors in line tracing. This cut-point is the German biological reference value, and concentrations above this value are considered to be influenced by occupational exposure. It is the presumed 95th percentile of the distribution of MnB in the general population, based on a narrative review of published studies. It is noteworthy that 15 µg l^{-1} was also the 95th percentile observed in HNRS, when women were included (Bonberg *et al.*, 2017). However, several other influencing factors such as liver cirrhosis may lead to high MnB and metal accumulation in the brain (Krieger *et al.*, 1995; Layrargues *et al.*, 1998). Neurobehavorial effects observed in Russian welders could be partially explained by alcohol consumption (Ellingsen *et al.*, 2014). Therefore, we estimated the effect of high GGT on dexterity as a proxy for a potential alcohol abuse or liver dysfunction. GGT is a significant predictor of advanced liver fibrosis, which may eventually progress to liver cirrhosis (Nishikawa *et al.*, 2016). GGT ≥ 74 U l^{-1}, the 90th percentile in this study population, was associated with a greater number of

errors in line tracing and steadiness. However, none of the former welders presented with elevated GGT at the second follow-up of the HNRS cohort.

In addition to Mn, fumes from the production or processing of steel contain large amounts of Fe (Flynn and Susi, 2010; Pesch *et al.*, 2012). Metal ions are of importance in brain function, and their primary route of uptake is across the blood–brain barrier (Yokel and Crossgrove, 2004; Yokel, 2006). However, excessive concentrations of redox-active Mn and Fe may propagate oxidative damage and lipid peroxidation in the brain. In particular, Fe plays a prominent role in brain function and neurodegeneration (Rouault, 2013; Ward *et al.*, 2014). Accordingly, we further controlled the effects of Mn on fine motor tests for the systemic Fe status, as this may also affect metal accumulation in the brain (Beard *et al.*, 2005; Bartzokis *et al.*, 2010). Men with SF ≥ 400 µg l^{-1} made significantly more errors in line tracing. In a study among a larger group of welders, high airborne Fe and GGT were predictive for elevated SF (Casjens *et al.*, 2014). Ferritin has multiple functions beyond being a biomarker of Fe stores and has been associated with liver dysfunction and inflammation (Wang *et al.*, 2010). Airborne Mn and Fe are closely correlated with the mass of particulate matter in welding fumes (Flynn and Susi, 2010; Hobson *et al.*, 2011; Pesch *et al.*, 2012), which may contribute to oxidative stress and neuroinflammation.

Conclusions

In this large cohort of elderly men from an industrial region with steel production, we show that high levels of cumulative exposure to inhalable Mn were associated with fine motor deficits. We found evidence of training effects in particular of the dominant hand and in the low-dose range, which requires a quantitative assessment of Mn exposure to identify dose-response trends. In addition, high concentrations of MnB, SF, and GGT were predictive of a greater number of errors in line tracing. We recommend that Fe metabolism, exposure to particulate matter, and liver dysfunction should be considered in addition to Mn when investigating neurobehavioral effects in welders and other workers with exposure to metal fumes.

Supplementary data

Supplementary data are available at *Annals of Work Exposures and Health* online.

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Conflict of Interest

Authors from the Institute for Prevention and Occupational Medicine (IPA) and Institute for Occupational Safety and Health (IFA) work for the German Social Accident Insurance. The authors are independent from the German Social Accident Insurance in study design, access to the collected data, responsibility for data analysis and interpretation, and the right to publish. K.-H.J. reports grants from the German Social Accident Insurance, during the conduct of the study. The views expressed in this paper are those of the authors and not necessarily those of the sponsor. All other authors have disclosed any potential conflicts of interests.

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