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# A large, nationwide, longitudinal study of central nervous system diseases among Korean workers exposed to manganese

Jin-Ha Yoon [a, b], Yeon-Soon Ahn [c, *]

[a] The Institute for Occupational Health, Yonsei University College of Medicine, Seoul, Republic of Korea
[b] Department of Preventive Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea
[c] Department of Occupational and Environmental Medicine, Dongguk University Ilsan Hospital, Ilsan, Goyang, Gyeonggi-do, 410-773, Republic of Korea

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ABSTRACT

*Introduction:* In occupational epidemiologic studies, the low incidence and chronic process of central nervous system (CNS) diseases has complicated the determination of the relationship between increased morbidity and manganese (Mn) exposure. Therefore, through this large cohort study, we evaluated CNS disease morbidity among Korean workers exposed to Mn

*Methods:* Data were collected from Mn-associated specialized medical check-up 2000 and 2004 in Korea. The number of workers admitted to hospital because of clinically diagnosed CNS disease was analyzed in male workers exposed to Mn ($n$ = 104,544). As a control reference population, 2% of Korean men were randomly selected and their hospital admission data were analyzed. For Mn-exposed workers, Standardized admission ratios (SARs) for CNS disease, as determined by ICD-10 classifications, were estimated in reference to the control population

*Results:* During follow up, 64 workers admitted because of CNS diseases. Chronic exposure to Mn (≥10 years) was significantly associated with the SAR (95% CI) of extrapyramidal and movement disorders (SAR: 2.03, 95% CI: 1.05–3.55), in particular, other extrapyramidal and movement disorders (SAR: 4.81, 95% CI: 1.29–12.32). Also borderline association (SAR = 4.88, 90% CI: 1.05–7.04) was noted for secondary Parkinsonism among workers with chronic Mn exposure. SARs (95% CI) for other degenerative nervous system diseases were significantly higher in Mn-exposed workers compared with the control population (SAR: 3.60, 95% CI: 1.16–8.40)

*Conclusion:* In conclusion, Mn-exposed workers exhibited significantly elevated SARs for degenerative nervous system diseases and extrapyramidal and movement disorders, compared to the age-matched reference population, suggesting a relatedness with Mn exposure



## 1. Introduction

Manganese (Mn), a naturally occurring metal, is an essential nutrient for humans, which is founded in both inorganic and organic compounds. Inorganic Mn is used for production of steel, welding rods, various Mn chemicals, glasses and batteries, hence workers in these industries are exposed to fumes and airborne particles of Mn [1]. Beyond occupational exposure, the general population are exposed to Mn from fungicides and pesticides, industrial air pollutants, combustion products of coal-burning plants and motor engines, and from contrast agents used for magnetic resonance imaging [2].

Inhalation of Mn during acute exposure to high levels can cause breathing discomfort, cough, and psychiatric symptoms such as headache, insomnia, emotional instability, and hallucinations [3]. Mn is selectively retained in brain, and the half-life of Mn in brain is longer than that in other organs [4]. Hence, during chronic exposure, workers may experience central nervous system (CNS) disorders, myasthenia [5], and Mn-induced Parkinsonism [6], which can include neuromotor manifestations of extrapyramidal symptoms such as muscle weakness, intentional tremor, and backward gait difficulties.

In a population living close to Mn-refinery, blood Mn levels were associated with deficiencies in individuals undergoing neurobehavioral testing (NBT) [7]. Neurologic examinations including the World Health Organization neurobehavioral core test battery [8] are used to investigate associations between low-dose Mn exposure and neurological symptoms. NBT can distinguish group

* Corresponding author. Tel.: +82 31 961 7518; fax: +82 31 961 7039.
*E-mail address:* ysahn@dongguk.ac.kr (Y.-S. Ahn).

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differences in neurological symptoms, but it is not clear whether the results are relevant to clinical neurological diseases [9]. Hence, an analysis of hospital data or death due to neurological disease in Mn-exposed groups is needed to confirm the association of Mn toxicity to neurological disease.

In a study of almost fifty thousand Mn-exposed welders, followed-up using death records and hospital discharge registers [10], no association could be made between Mn exposure and the risk of neurological disease. An analysis of hospital data from 25,000 workers based in the shipbuilding industry failed to show any association between Mn exposure and the risk of neurological diseases including Parkinson's disease (PD) [11]. Therefore, there is a lack of evidence from epidemiologic studies to demonstrate any association between actual CNS diseases (not NBT test) and chronic Mn exposure in cohort study. The aim of this study was to identify epidemiologic evidence of a relationship between CNS disease and the duration of Mn exposure in nationwide cohort study.

## 2. Materials and methods

### 2.1. Data collection and cohort definition

Annual specialized medical surveillance for exposure to occupational hazards including Mn has been conducted on Korean workers since 1972, and the data have been electronically stored and monitored since 2000 by the Korea Occupational Safety and Health Agency (KOSHA). These annual medical check-ups have been conducted for all Korean workers exposed to Mn in the form of dust and fumes by >100 medical centers nationwide. The medical check-up for Mn is composed of three parts. The first is a questionnaire and doctor's interview of Mn-related symptoms, signs, and exposure history. The second is a clinical examination including chest radiography (mandatory), grip power (not mandatory), and bMn levels (depending on the physician's decision, the bMn level in 17% of workers in this cohort was measured at last once over 5 years). The third consists of a documentation of the worker's personal information including their residence registration number (RRN: a unique 13-digit number assigned to all Korean citizens that includes gender and birth date) and the date of employment in the present company. Company information including industry type and the total number of workers is also included.

Using KOSHA data, we constructed the cohort for Mn-exposed male workers ($n$ = 104,544) who underwent more than one Mn-associated specialized medical check-up between January 1, 2000 and December 31, 2004. Female workers were excluded from the data analysis because the number of female Mn-exposed workers admitted to hospital with CNS diseases was too small to achieve significant statistical power. Number of female worker was 3952 and only 1 female worker experienced hospital admission due to neurologic diseases during follow up period.

For morbidity, rates related to neurological diseases according to hospital admission records of 2000–2005 were estimated using National Health Insurance Claim Data (NHICD). The completeness of the NHICD database is >99% because all Koreans have been covered by the Korea National Health Insurance Service (K-NHIS) since 1989. NHICD includes the RRN, admission and discharge date, and disease diagnosis. Diagnoses were classified according to the Korea Classification of Diseases and Causes of Death, 4th edition (KCD-4), using 3-character codes. Diseases of the nervous system classified by the KCD-4 are the same as those in the International Classification of Diseases, 10th revision (ICD-10: G00–G99). The corresponding ICD-10 codes were written in Table 1. All participants provided written informed consent for their participation in current cohort study. After constructing the cohort, the

**Table 1**
Morbidity of neurologic diseases by exposure duration of manganese (Reference: Korean general population).

| | | Manganese exposure (year) | | |
|---|---|---|---|---|
| | | ≥10 years ($n$ = 35,231) | <10 years ($n$ = 69,313) | Total ($n$ = 104,544) |
| Person-years (year) | | 200,915 | 237,778 | 438,693 |
| Systemic atrophies primarily affecting the central nervous system (G10-G13) | *N* | 1 | 0 | 1 |
| | SAR | 0.71 | – | 0.41 |
| | 95% CI | 0.01–3.97 | – | 0.01–2.29 |
| Spinal muscular atrophy and related syndromes (G12) | *N* | 1 | 0 | 1 |
| | SAR | 2.67 | – | 1.51 |
| | 95% CI | 0.03–14.87 | – | 0.02–8.42 |
| Extrapyramidal and movement disorders (G20-G26) | *N* | **12** | 2 | 14 |
| | SAR | **2.03** | 0.32 | 1.15 |
| | 95% CI | **1.05–3.55** | 0.04–1.15 | 0.63–1.93 |
| Parkinson's disease (G20) | *N* | 3 | 2 | 5 |
| | SAR | 0.51 | 0.32 | 0.41 |
| | 95% CI | 0.10–1.49 | 0.04–1.15 | 0.13–0.96 |
| Secondary parkinsonism (G21) | *N* | 3 | 1 | 4 |
| | SAR | 4.88 | 1.46 | 3.08 |
| | 95% CI | 0.98–14.26 | 0.02–8.13 | 0.83–7.88 |
| Other degenerative diseases of basal ganglia (G23) | *N* | 1 | 0 | 1 |
| | SAR | 2.96 | – | 1.26 |
| | 95% CI | 0.04–16.47 | – | 0.02–6.99 |
| Dystonia (G24) | *N* | 1 | 0 | 1 |
| | SAR | 0.88 | – | 0.50 |
| | 95% CI | 0.01–4.90 | – | 0.01–2.77 |
| Other extrapyramidal and movement disorders (G25) | *N* | **4** | 0 | 4 |
| | SAR | **4.81** | – | 2.54 |
| | 95% CI | **1.29–12.32** | – | 0.68–6.49 |
| Other degenerative diseases of the nervous system (G30-G32) | *N* | 2 | 3 | 5 |
| | SAR | 2.13 | 2.89 | 2.53 |
| | 95% CI | 0.24–7.69 | 0.58–8.45 | 0.82–5.91 |
| Other degenerative diseases of nervous system NEC (G31) | *N* | 2 | 3 | **5** |
| | SAR | 3.08 | 4.05 | **3.60** |
| | 95% CI | 0.35–11.13 | 0.81–11.84 | **1.16–8.40** |
| Demyelinating diseases of the central nervous system (G35-G37) | *N* | 5 | 6 | 11 |
| | SAR | 0.86 | 1.12 | 0.99 |
| | 95% CI | 0.28–2.02 | 0.41–2.43 | 049–1.76 |
| Multiple sclerosis (G35) | *N* | 1 | 2 | 3 |
| | SAR | 0.43 | 1.25 | 0.77 |
| | 95% CI | 0.01–2.41 | 0.14–4.51 | 0.15–2.44 |
| Other demyelinating diseases of central nervous system (G37) | *N* | 4 | 6 | 10 |
| | SAR | 1.14 | 1.64 | 1.39 |
| | 95% CI | 0.31–2.91 | 0.60–3.56 | 0.66–2.56 |

Abbreviation: *N*, number of cases; SAR, standardized admission rate; CI, confidence interval. Values in bold text were statistically significant.