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The association between blood lead level and clinical mental disorders in fifty thousand lead-exposed male workers

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ABSTRACT

Background: While there has been research into the relationship between blood lead (BPb) level and mental disorders, there have been few investigations that use clinically diagnosed mental disorders in the adult population with a **retrospective cohort** study design. Hence, our study investigated the association between BPb level and risk of clinically diagnosed mental disorders.
Methods: The data of male workers exposed to lead (Pb; n=54,788) were collected from annual Pb associated medical check-ups from 2000 to 2004 in Korea. The workers' hospital admission histories due to mental disorders (International Classification of Diseases, 10th revision, F00–F99) were used to identify clinically diagnosed mental disorders. After merging the data, the hazard ratio (HR) with a 95% confidence interval (95% CI) was calculated by survival analysis using the Cox proportional hazards model according to the quartile level of BPb (1st quartile < 4.10 μg/dl, 2nd quartile < 6.04 μg/dl, 3rd quartile < 10.00 μg/dl, and 4th quartile ≥ 10 μg/dl).
Results: In a total of 54,788 workers, there were 223 admission cases of mental disorders (F00–F99) during the follow-up period. The HR (95% CI) of total mental and behavioral disorders (F00–F99) was 1.63 (1.12–2.39) in the 4th quartile group compared to the HR of the 1st quartile group after adjusting for age. The HR (95% CI) of the 4th quartile group was 2.59 (1.15–5.82) for mood (affective) disorders (F30–F39).
Limitation: The hospital admission data, not outpatient data, were used for current study while almost affective disorder treated at outpatient clinic level.
Conclusion: Our study highlighted that Pb exposure can cause clinical mental disorders that require hospital admission in adult male workers. Our relatively large sample size strengthens the evidence of the association between BPb level and risk of clinically diagnosed mental disorders.

1. Introduction

Generally, developed countries have tried and succeeded in reducing levels of exposure to lead (Pb) (Muntner et al., 2005). However, certain occupations are still exposed to Pb at dangerous levels, In particular, smelting of Pb, welding and cutting materials containing Pb, painting, ship breaking, plumbing, storage battery manufacturing, and glass manufacturing are well-known occupations related to Pb exposure (Tong et al., 2000). In Korea, the blood lead (BPb) level of thirteen thousand workers in about one thousand factories nationwide was found to be 1.6 times higher than that of the general population. Moreover, half of the workers had more than 5 μg/dl BPb level and 1% of workers had more than 40 μg/dl (Kim et al., 2006), while the high BPb level related to various clinical diseases including mental illness (Rhodes et al., 2003).

It is known that Pb enters the bloodstream via respiratory tract exposure or oral consumption, and BPb is excreted via the urine and bile (Winship, 1989). The half-life of Pb in blood is almost 30 days, but the remaining Pb binds to red blood cells, eventually accumulating in the soft tissues and bone (Winship, 1989). The Pb in the bone is released steadily back into the bloodstream, and chronic exposure from the released Pb causes systemic damage. There have been numerous reports about organ damage due to Pb exposure, such as to the blood, kidneys, and central nervous system, and of death following severe excessive exposure (Papanikolaou et al., 2005).

Neurotoxicity is a well-known clinical feature of chronic Pb exposure (Flora et al., 2012). The Port Pirie Cohort Study, which is a prospective study, has found that prenatal exposure to Pb decreases the development of sensory and motor functions in infants (McMichael et al., 1988). In children and adults, Pb exposure

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decreases intellectual and cognitive functioning (Lucchini et al., 2012; Mazumdar et al., 2011). Numerous articles have shown that Pb toxicity affects neuropsychological functions, such as memory, executive functioning and attention, speech processing, language, and visual, spatial, and motor skills (Mason et al., 2014).

Psychological problems also emerge as a result of Pb exposure. Findings from the Normative Aging Study suggested that low-level Pb exposure is related to interpersonal characteristics, such as irritation, fatigue, anxiety, depression, and phobia (Rhodes et al., 2003). A study from the US using the National Health and Nutrition Examination Survey from 1999 to 2004 reported a strong association between BPb level and the clinical diagnosis of mental disorders, including depression and panic disorders (Bouchard et al., 2009). However, neither study can make a conclusion about the causality because a cross-sectional study design was used. One prospective study, which used a comprehensive set of questionnaires along with a physical examination to define the mental disorders, found a significant association between occupational Pb exposure and mental disorders such as depressive symptoms, confusion, anger and fatigue (Baker et al., 1983). Nevertheless, those studies were also limited because symptoms were assessed using self-report questionnaires, rather than using a clinical diagnosis (such as with hospital data) to define the psychological disorders. Therefore, an investigation with a **longitudinal** study design that uses clinical diagnostic methods is needed to elucidate the relationship between Pb exposure and mental disorders.

In the current study, we conducted a **retrospective cohort** study using 50,000 male workers to identify the relationship between Pb exposure and psychological problems. Furthermore, hospital admission data were linked to our cohort and clinically defined diagnoses were used to identify mental disorders. In particular, we examined the associations between Pb exposure and mental disorders that have not been investigated much in the adult population. Hence, we hope that our cohort study can contribute to the scientific knowledge about the relationship between occupational Pb exposure and risk of mental disorders in adult workers.

2. Methods

2.1. Ethics statement

All participants' private records were anonymized prior to analysis. The Institutional Review Board of Dongguk University Ilsan Hospital, South Korea, approved this study.

2.2. Cohort data and definition (Yoon and Ahn, 2015)

The annual specialized medical surveillance of workers' exposure to various chemicals has been conducted since 1972 in Korea. Electronic data processing was established in 2000, and the Korea Occupational Safety and Health Agency (KOSHA) has stored and monitored all exposure histories. According to the law of the Occupational Safety and Health Act, all workers exposed to chemical hazards should have an annual medical check-up conducted by nationwide medical centers, known as the workers' special medical check-up. The medical check-up for Pb has three parts: a focus interview by a medical doctor, biological monitoring of BPb level, and obtaining personal information, such as the residents' registration number (RRN; a unique 13-digit number for all Korean citizens, which includes an identification number for gender and date of birth). The RRN was anonymized prior to analysis.

A total of 54,788 male workers' BPb levels were stored by the KOSHA between January 1, 2000 and December 31, 2004. These data were merged with the morbidity data using the RRN. For morbidity, the National Health Insurance Claim Data (NHICD) was used to calculate the hospital admission history due to mental and behavioral disorders from 2000 to 2005. As all Koreans are covered by the Korea National Health Insurance Service system, the hospital admission history of all Koreans is captured by the NHICD. The NHICD holds the admission and discharge date, as well as disease diagnosis. The disease diagnosis was classified according to the standardized protocol of the Korea Classification of Diseases and Causes of Death (4th edition), and matched to the International Classification of Diseases, 10th revision (ICD-10). In the current study, all diseases are described according to the ICD-10.

2.3. Blood pb level, disease definition

BPb levels were measured during 5 years (from Jan 1, 2000 to Dec, 31, 2004) in each participant. The number of tests for measuring BPb varied from one to five times according to the number of participation for annual medical check-up. Hence the median values of BPb were used as proxy variable of cumulative exposure level in current study. The BPb levels were measured using an atomic absorption spectrometer after overnight fasting. Workers were categorized into **four groups** by BPb quartile level: 1st quartile < 4.10 μg/dl, 2nd quartile < 6.04 μg/dl, 3rd quartile < 10.00 μg/dl, and 4th quartile ≥ 10 μg/dl.

The three-digit ICD-10 codes from F00 to F99 (Mental and Behavioral disorders) were used to classify the mental disorders. Sub-classifications of diseases, such as F0, F1, and F2–F9, were also used to examine the association of BPb with specific mental disorders (Table 1). Workers could be admitted to hospital multiply due to the chronic nature of these mental and behavioral disorders. When there were multiple admissions for a patient due to disorders included in these ICD-10 codes, the admissions were considered as only one case of mental disorder. In the same context, the first admission date was considered the event date, and was used for calculating the follow-up period.

2.4. Statistical methods

The follow-up periods started from the date of enrollment in a factory in which the worker was exposed to Pb, and the event date was defined as the first admission date due to mental and behavioral disorders defined using the ICD-10 codes (F00–F99). The number of mental disorder cases was described according to the sub-classified diseases as well as the quartile BPb level (Table 1). Further statistical analyses of each sub-classified disease were undertaken when the number of mental disorder cases was greater than zero in every quartile level (Table 1). A trend analysis was performed using the Cochran–Armitage trend test. The hazard ratio (HR) and its 95% confidence interval (95% CI) were calculated by survival analysis using the Cox proportional hazards model with age adjustment. The HR with 95% CI was estimated according to the quartile increment of BPb level. All statistical analyses were performed using the ‘survival’ package of the R program (Therneau, 2013).

3. Results

The median and inter-quartile age range of the current study was 38 years (range 32–47). The geometric mean (95% CI) of BPb was 6.46 (6.42–6.50) μg/dl in current study. Among the 54,788 workers, there were 223 admission cases of mental disorders (F00–F99) during the follow-up period. There were zero cases in certain BPb level quartile groups for the following sub-classified diseases: admission cases number of organic, including symptomatic, mental disorders (F00–F09) was 8 in total, 0,2,1,5 in each