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

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

[a] The Institute for Occupational Health, Yonsei University College of Medicine, Seoul, South Korea
[b] Department of Preventive Medicine, Yonsei University College of Medicine, Seoul, South Korea
[c] Department of Occupational and Environmental Medicine, Dongguk University Ilsan Hospital, Goyang, South Korea

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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

* Corresponding auhor. Fax: +82 31 961 7039.
E-mail address: ysahn@dongguk.ac.kr (Y.-S. Ahn).

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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

Table 1
Hazard ratio (95% confidence interval) of mental and behavioral disorders according to tertile level of blood lead.

Disease	Number of hospital admission cases and Hazard Ratio (age adjusted)					
	Lead level*:	1st Quartile (n= 13,701)	2nd Quartile (n= 13,623)	3rd Quartile (n= 13,680)	4rd Quartile (n= 13,561)	P for trend
Total	F00–F99 (n=223)	42 1 (reference)	51 0.94 (0.62–1.42)	56 1.07 (0.72–1.61)	74 **1.63 (1.12–2.39)**	**0.002** **0.004**
Mental and behavioral disorders due to psychoactive substance use	F10–F19 (n=55)	8 1(reference)	8 0.55 (0.20–1.51)	18 1.54 (0.70–3.54)	21 1.96 (0.86–4.56)	**0.003** **0.009**
Schizophrenia, schizotypal and delusional disorder	F20–F29 (n=50)	12 1(reference)	14 0.97 (0.44–2.15)	8 0.70 (0.29–1.67)	16 1.30 (0.61–2.77)	0.693 0.621
Mood [affective] disorders	F30–F39 (n=62)	8 1 (reference)	15 1.35 (0.60–3.21)	16 1.53 (0.65–3.61)	23 **2.59 (1.15–5.82)**	**0.009** **0.012**
Neurotic, stress-related and somatoform disorders	F40–F48 (n=69)	13 1 (reference)	16 0.93 (0.45–1.95)	19 1.18 (0.58–2.40)	21 1.51 (0.76–3.04)	0.141 0.158
Behavioral syndromes associated with physiological disturbances and physical factors	F50–F59 (n=20)	7 1 (reference)	4 0.38 (0.11–1.33)	4 0.41 (0.12–1.41)	5 0.60 (0.19–1.91)	0.555 0.414
Disorders of adult personality and behavior	F60–F69 (n=7)	1 1 (reference)	1 0.86 (0.05–13.95)	2 1.82 (0.16–20.36)	3 3.04 (0.31–29.46)	0.234 0.227
Unspecified mental disorder	F99–F99 (n=53)	8 1 (reference)	7 0.47 (0.16–1.37)	18 1.56 (0.68–3.59)	20 1.91 (0.84–4.36)	**0.004** **0.009**

Hazard ration calculated (HR) with 95% confidence interval (95% CI) was calculated by Cox-Proportional Hazard model with age adjustment.
All models were adjusted by age.

* 1st Quartile: <4.10 μg/dl, 2nd Quartile <6.04 μg/dl, 3rd Quartile <10.00 μg/dl, 4th Quartile ≥ 10 μg/dl.

quartile from 1st to 4th, respectively that of mental retardation (F70–F79) was zero in total; disorders of psychological development (F80–F89) was zero in total; and behavioral and emotional disorders with onset usually occurring in childhood and adolescence (F90-F98) was 1 in total and 1 in 1st quartile. Hence, further analyses were not undertaken for these diseases categories.

There was an increased trend of total mental disorders according to quartile increment of BPb level. Numbers of hospital admission **cases** of Mental and behavioral disorders due to psychoactive substance use (F1), mood (affective) disorders (F30–F39), and unspecified mental disorder (F99) increased according to the quartile increment of BPb level (all p values for trends were below 0.05; Table 1).

The HR (95% CI) of total mental and behavioral disorders (F00–F99) was 1.63 (1.12–2.39) in 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). There were also an increment in the trend of the HR according to an increment of the quartile BPb level group for total mental and behavioral disorders (F00–F99), mental and behavioral disorders due to psychoactive substance use (F10–F19), mood (affective) disorders, and unspecified mental disorder (F99) (all p values for trend were below 0.05).

4. Discussion

Our cohort study for 54,788 lead exposed workers found that an increment of BPb level was related to the risk of mental disorders. Particularly, the risk of mood (affective) disorders increased according to BPb level, and the association showed a linear trend. Previous research used questionnaires to identify the mental disorder. Although various questionnaires and the Diagnostic and Statistical Manual of Mental Disorders (4th edition; DSM-IV) criteria can be used as screening and diagnostic tools for mental disorders in the community, it is not easy to determine the mental disorder clinically. In contrast to previous studies, we used hospital admission data to diagnose the mental disorders clinically. As such, our study should have obtained greater accuracy in defining mental disorders compared to other studies that used questionnaires only. Moreover, some studies have found a significant association between clinically diagnosed mental disorders and BPb level, but only with a relatively small sample size (n=61 and n=25) (Gonzalez-Estecha et al., 2011; Stanley and Wakwe, 2002). Our large sample size supports the relationship between Pb exposure and clinical mental disorders that needed hospital admission. Furthermore, to the best of our knowledge, the current study is the first to investigate and to show the association between Pb exposure and clinically diagnosed mental disorders in an Asian population exposed to Pb at workplace.

A systemic review has indicated that prenatal Pb exposure is related to mental disorders in children and adolescents (Williams and Ross, 2007). It also suggested that cognitive outcomes are affected and poor behavioral performance is worsened by Pb exposure. The Cincinnati Lead Study (Ris et al., 2004) compared the effect of prenatal and childhood BPb levels on neuropsychological outcomes, and found that post-natal exposure is also important to mental health, suggesting that BPb level affects the remote status of mental health outcomes. A cross-sectional study using 4704 children aged 5–15 years reported that there was a four-fold increased risk of attention deficit hyperactivity disorder in children with higher BPb levels compared to children with lower BPb levels

(Braun et al., 2006). A study in Spain using hospital-diagnosed data of this disorder also indicated its relationship to Pb exposure in children (Sanchez-Villegas Mdel et al., 2014). However, there are relatively few studies examining the elderly population and their mental health related to Pb exposure. Hence, our cohort study's focus on an adult working population might provide scientific knowledge that is supported by the childhood research.

A prospective cohort study of the elderly population, which followed 89 workers, showed that there was psychological change according to BPb level (Mantere et al., 1984). In addition, a cross-sectional study, the Normative Aging Study (Rhodes et al., 2003), showed that both Pb levels in the blood and bone are related to psychiatric symptoms in the adult population. However, they used the Brief Symptom Inventory to identify the psychiatric symptoms (Rhodes et al., 2003). Recently, a cross-sectional study that used the DSM-IV criteria to diagnose mental disorders reported an association between BPb level and mental disorder among young adults aged 20–39 years (Bouchard et al., 2009). Moreover, the Port Pirie cohort study undertook a prospective analysis to evaluate the association between childhood BPb level and mental disorder in adults (McFarlane et al., 2013). Hence, there was still controversy about the health effect of Pb exposure on adults' mental disorders. However, our relatively large cohort study of an adult working population showed a significant relationship between BPb level and risk of mental health disorders in adults. Furthermore, this association is strengthened by our study because clinically diagnosed hospital admission data were used to define the mental health outcome in current study.

There are possible biological mechanisms that can explain the relationship between BPb level and risk of mental health disorders. Pb is one of the most widely distributed heavy metals, and it can affect the normal physiology of the human system. The central nervous system, including the brain, is the main target organ of Pb toxicity (Wilson et al., 2000). Pb can cross the blood-brain barrier and can even be retained in the brain, including in the astroglial cells and neurons (Kerper and Hinkle, 1997). The half-life of Pb in the blood is almost one month, but in the brain is two years (Lidsky and Schneider, 2003). The presence of Pb in the brain can have various neurotoxic effects, such as neuronal cell death as well as disruption of intra-neuronal regulatory mechanisms (Lidsky and Schneider, 2003). The relationship of Pb with morphological and functional alterations of the brain has already been reported in various animal studies (Verina et al., 2007). A well-designed prospective study, which investigated the association between Pb exposure and neuro-degenerative changes in humans using magnetic resonance imaging measurement of the structural volume change of the brain, found a significant change in structural neuro-degeneration in the brain according to 1 μg Pb change per gram of bone mineral in the tibia (Stewart et al., 2006). Furthermore, some studies have suggested that Pb exposure can even alter the normal physiology of dopamine and serotonin metabolism in the brain (Verstraeten et al., 2008). Dopamine and serotonin are well-known neurotransmitters related to psychological disorders, including mood disorders (Verstraeten et al., 2008). In summary, Pb exposure can reach the brain across the blood-brain barrier, and cause brain damage that is related to psychological disorders. Such biological plausibility supports our current results in that the highest quartile BPb level (quartile $\geq$ 10 μg/dl) is related to a risk to mental health, particularly affective (mood) disorder.

The risk of the total mental health disorders (ICD-10 codes F00–F99) increased according to BPb level. In addition, affective (mood) disorder was sub-classified disease that had a significant relationship with BPb level in the current study. The category of mood (affective) disorders contains psychological disorders involving abnormal mood changes. Depression and manic episode are representative of mood (affective) disorders. As we described above, dopamine as well as serotonin are closely related to mood disorders. Hence, there is biological plausibility for our current result of an increased tendency of mood (affective) disorders related to high BPb levels. Mood disorders, including depression, are important diseases worldwide, and a major risk factor of mortality, including suicide (Parron et al., 1996). Because our current results show the harmful effect of Pb exposure in association with mood disorders, and mood disorders are related to mortality (Rapp et al., 2008), more careful attention is needed to reduce Pb exposure level.

Our study did not find a significant association with schizophrenia in the survival analysis, which is consistent with other **longitudinal** studies. Because schizophrenia has the symptoms of a lack of attention and neurocognitive impairment, and these symptoms are similar to a cognitive deficit due to Pb exposure, schizophrenia a plausible disease related to Pb exposure. A prospective study in the US (Opler et al., 2004) analyzed the relationship between Pb exposure and risk of schizophrenia, but there was no significant association. However, four years later, the author undertook a pooled analysis after adding more samples and found that the odds for schizophrenia was 1.92 times higher (p value was 0.03) in a high Pb-exposed group (Opler et al., 2008). Therefore, there is still controversy about the association between Pb exposure and the risk of schizophrenia.

Unspecified mental disorder (F99) includes any non-specific mental disorder, excluding organic mental disorders. Hence, atypical symptoms and psychological illnesses can be diagnosed as an unspecified mental disorder (F99). Our study found a significant elevated risk of unspecified mental disorder (F99) according to an increment in BPb level. Because we used hospital admission data to identify clinically diagnosed mental disorders, there might be a much lower prevalence compared to that shown in outpatient clinic data. Hence, the lack of association with other sub-classified mental disorders could be due to the low prevalence in the current cohort study.

Mental disorder increased sickness absence as well as presenteeism, and decreased the productivity of workers. For example, the economic cost of depression is greater than that of hypertension and diabetes in US (Druss et al., 2000). Some article suggested that mental disorder in workplace attenuate the job performances, and consequently productivity losses due to mental disorder are greater than cost of effective management (Wang et al., 2004). Hence, our study to investigate the new risk factor of mental disorder can help to improve the workers' health as well as to sustain the productivity in workplace. Furthermore, the geometric means of BPb was 6.46 (6.42–6.50) μg/dl in current study while that was 3.73 (3.68–3.78) μg/dl among general Korean population in 2000 (Moon et al., 2003), 2.61 (2.50–2.71) μg/dl among 1997 general Korean population in 2005 (Kim and Lee, 2011). The level of BPb in current study was almost 1.7 $\sim$2.5 times higher than Korean general population. Hence, our current results also suggested that psychological and psychiatric medical examination or screening test of mental disorder were needed for Pb high exposed workers.

4.1. Limitations

Although this large nationwide study included almost 55,000 Pb-exposed workers and used the clinical diagnosis of psychological disease as indicator of toxicity of Pb exposure, there were several limitations. First, the relatively young age of the cohort might be related to the relatively low incidence of mental disorder. Generally, there is a greater prevalence of mental disorders in the older age group (more than 70 years) (Stordal et al., 2001).

Second, we used hospital admission data to identify the mental

disorder. However, if workers have mild diseases or well-controlled mental disorders, they usually use outpatient clinics. Only serious cases are admitted to hospital for care or treatment of their mental disorders. This factor may have caused an underestimation of the risk of mental disorders in the current study. There was somewhat advantage of using admission data in current study. The diagnosis accuracy is greater in admission data comparing to outpatient data. For example, an article reported that outpatient setting easily show false positive rate. Actually, the NHICD data has almost more than 70% of validity in admission data while the outpatient data show below 50% of validity (Park, 2002). Hence our study design, using admission cases only, had strength to higher validity for clinical diagnosed mental disorder compare to outpatient data.

Third, the half-life of BPb is relatively short compared to that of bone, and Pb in bone is more closely related to a chronic or cumulative exposure history. Some studies have suggested that Pb in bone is related to mental disorders (Eum et al., 2012). However, we had no information about the Pb level in bone which reflects the chronic exposure of Pb. The BPb generally indicated the recent exposure history, and the BPb is related to hospital admission rate of mental disorder in current study. Hence, we cannot clarify whether chronic or acute exposure of Pb more closely related to mental illness.

Fourth, there was possibility of healthy worker effect that the worker who was not fit to work environment was excluded in current cohort. The worker who suffered from mental disorder hardly selected for work, and easily excluded from work place. This effect can weaken the relationship between BPb level and risk of disorder in this study.

Fifth, there are numerous risk factors for mental disorders, such as low socioeconomic status, physical illness, life style, and a family history of mental disorder (Cole and Dendukuri, 2003). As described above, pre- and post-natal environmental or childhood environmental exposure to Pb is also an important risk factor for developing mental disorder as adults. The daily life environmental is also important exposure source. Therefore, the high level of BPb might not be explained due to occupational exposure. The job characteristics such as low job security and long working week, personality as well as its conflict to work environment and social network are also related to mental illness (Skarsater et al., 2001; Theorell et al., 2015). Unfortunately, we had no information about this environmental exposure and other risk factors of depression such as job characteristics, personality and social network. However, our cohort consisted of Pb-exposed workers, who are usually manual workers, and might have a similar socioeconomic status. There was lack of information of smoking habit in current study while the smoking habit can be related to both BPb and mental disorder. Only 10% of data had information of smoking histories in current study. In that data, the smoking rate was 55.5% in men during 2000–2001. Furthermore, the smoking rate was somewhat greater in $< 10\ \mu g/dl$ BPb group and that was not statistically significantly differ between $\geq 10\ \mu g/dl$ and $< 10\ \mu g/dl$ BPb group. Hence, smoking effect might not affect our current results. This homogeneity in workers with large sample size of current study can attenuate the random error arisen from lack of information about such risk factors. Nevertheless, our cohort provided no information of such confounding factors, a more comprehensive study including potential confounding variables is needed to elucidate the association between Pb exposure and risk of mental disorder in workers.

Our study highlighted that Pb exposure can cause clinical mental disorders that require hospital admission in adult workers. Our relatively large sample size, which was followed-up for more than 55,000 workers, might overcome our limitation of a relatively young cohort population, and strengthen the association between Pb exposure and clinical mental disorders. Particularly, the risk of affective (mood) disorders increased according to BPb level. There were also trends for a risk of mental disorders according to the increment of BPb level. However, more studies with a longer follow-up period with older workers are needed to clarify the association in order to overcome the relatively low prevalence of clinical mental disorders in our cohort. Furthermore, a more comprehensive study design controlling mental disorder-related confounding variables is needed to construct scientific evidence of the association between Pb exposure and clinical mental disorders.

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