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The non-linear association between low-level lead exposure and maternal stress among pregnant women

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ABSTRACT

Background: Neuro-developmental impairments in the developing fetus due to exposure to low-level lead have been well documented. However, few studies have investigated the relation between maternal stress levels and low-level lead exposure among pregnant women.
Objectives: To investigate the relation between maternal blood lead and stress levels during index pregnancy.
Methods: 1931 pregnant women (gestational week 28–36) were investigated using stratified-cluster-sampling in Shanghai in 2010. Maternal life event stress and emotional stress were assessed using "Life-Event-Stress-Scale-for-Pregnant-Women" (LESPW) and "Symptom-Checklist-90-Revised" (SCL-90-R), respectively. Maternal whole blood lead levels were determined, and other data on covariates were obtained from maternal interviews and medical records. Two piecewise linear regression models were applied to assess the relations between blood lead and stress levels using a data-driven approach according to spline smoothing fitting of the data.
Results: Maternal blood lead levels ranged from 0.80 to 14.84 μg/dL, and the geometric mean was 3.97 μg/dL. The *P*-values for the two piecewise linear models against the single linear regression models were 0.010, 0.003 and 0.017 for models predicting GSI, depression and anxiety symptom scores, respectively. When blood lead levels were below 2.57 μg/dL, each unit increase in log10 transformed blood lead levels (μg/dL) was associated with about 18% increase in maternal GSI, depression and anxiety symptom scores ($P_{GSI} = 0.013$, $P_{depression} = 0.002$, $P_{anxiety} = 0.019$, respectively). However, no significant relation was found when blood lead levels were above 2.57 μg/dL (all *P*-values > 0.05).
Conclusion: Our findings suggested a nonlinear relationship between blood lead and emotional stress levels among pregnant women. Emotional stress increased along with blood lead levels, and appeared to be plateaued when blood lead levels reached 2.57 μg/dL.

1. Introduction

Although lead exposure has significantly decreased in many countries including China in recent years (Li et al., 2014), there still have been concerns about the impacts of low-level exposure to lead on the central nervous system (Min et al., 2007; Jusko et al., 2008; Téllez-Rojo et al., 2006). Neuro-behavioral deficits in children and the developing fetus, including impaired cognition, impulsivity, and hyperactivity, due to exposure to low-level lead have been well documented in previous studies (Hong et al., 2015; Huang et al., 2012; Liu et al., 2014a, 2014b; Sioen et al., 2013). However, compared with children, the impact of low-level lead exposure on adult neuropsychiatry was less focused and more controversial (Bouchard et al., 2009; Eum et al., 2012; Golub et al., 2010; Rajan et al., 2007; Rhodes et al., 2003).

No consistent conclusion has been made on the relationship between low-level lead exposure and adults' psychiatric symptoms. Bouchard et al. (2009) and Eum et al. (2012) found that higher lead levels were associated with higher odds of depression. Based on the Veterans Affairs Normative Aging Study, interquartile increments of lead in the tibia and patella were found to be associated with non-

Abbreviations: ACTH, adrenocorticotropic hormone; GSI, global Severity Index; LESPW, life-events-scale-for-pregnant-women; SCL-90-R, symptom-checklist-90-revised.

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significantly higher odds of psychiatric distress (Rajan et al., 2007). However, Golub et al. (2010) found that there was no significant increase in the risk for depression with increasing blood lead levels, whether blood lead was a categorical variable or a continuous one. In addition, current findings are all from studies performed in developed countries. The lead exposure level is generally lower in developed countries than developing countries, therefore, data from developing countries on the impacts of low-level lead exposure on psychiatric symptoms in adulthood is scarce.

The relation of lead exposure with psychiatric symptoms may also vary depending on the population characteristics. A previous study found that depressive symptoms increased with increased tibia bone lead concentrations among women who had received hormone replacement therapy during the perimenopausal period (Eum et al., 2012). As far as we know, no study so far has focused on the relationship between lead and anxiety and depression among pregnant women, despite the effects that stress may have on the vulnerable foetus. Maternal psychological distress during pregnancy has been recognised as a factor that may adversely alter pregnancy outcomes (Grote et al., 2010; Kramer et al., 2009).

Therefore, we aimed to describe the relation between environmental lead exposure and maternal stress among pregnant women in Shanghai, China.

2. Material and methods

2.1. Study population

Our study used stratified-cluster sampling in central and outlying districts of Shanghai. The sampling frame was made to select primary sampling units (districts) based on the information from 2010 Census. In 2010, Shanghai consisted of 19 districts. We randomly selected 2 districts (Xuhui and Yangpu) from the 9 central districts and 2 districts (Minhang and Chongming) from the 10 outlying districts. Within each sampled district, the largest maternity hospital was then selected. Therefore, 2 hospitals in the outlying districts and 2 hospitals in the central districts were included. Finally, a total of 1931 pregnant women during late pregnancy (28–36 gestational weeks) were investigated. According to prenatal care medical records, pregnant women with mental disabilities were excluded. After signing informed consent, each pregnant woman completed stress assessment questionnaires (Life-Event-Scale-for-Pregnant −Women [LESPW] and Symptom −Checklist-90-Revised [SCL-90-R]) and a blood lead test. Of the 1931 pregnant women, 230 individuals were excluded because of lack of blood lead data (their blood lead levels were not tested due to insufficient blood volumes or clots in the blood). Among the rest 1701 participants, 1696 had complete data on the SCL-90-R questionnaire and 1485 had complete data on the LESPW questionnaire.

The study was approved by the Medical Ethics Committee of Xinhua Hospital affiliated to Shanghai Jiao Tong University School of Medicine.

2.2. Maternal blood lead analysis

Whole blood samples were collected into vacutainer tubes pretreated with ethylene diamine tetra acetate at gestational week 28–36. Whole blood lead concentrations were determined using background-corrected graphite furnace atomic absorption spectrophotometry (PinAAcle 900Z, PerkinElmer, USA), and the detection limit was 0.01 μg/dL.

2.3. Maternal stress assessment

Maternal life event stress and emotional stress were assessed using the LESPW and SCL-90-R, respectively. The SCL-90-R, developed by Derogatis, is a multidimensional symptom self-rating inventory comprising of 90 items in nine primary symptom dimensions (somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism) (Derogatis, 1994). Items were scored on a five-point scale ranging from “not at all” to “extremely”. The Chinese version has been validated and widely used in previous studies (Tan et al., 2015; Srisurapanont et al., 2015). We used our study sample to gather validity and reliability evidence, and found that the Cronbach’s alpha coefficient was 0.96, and the validity coefficients including goodness-of-fit index, relative fit index, normed fit index, incremental fit index, and comparative fit index were 0.72–0.95. Previous researches reported that lead exposure was associated with the development of depression and anxiety (Bouchard et al., 2009; Rajan et al., 2007), therefore, stress levels belonging to the depression and anxiety subscales as well as the composite index (Global Severity Index, GSI) were specifically analysed in this study. GSI, as a quantitative indicator of the subjects' psychological distress level, was calculated by summing the scores of the nine dimensions and additional items, then divided by the total number of items. Depression and anxiety scores were calculated by summing the total scores of these two subscales, then divided by the number of respective items.

The LESPW is specifically designed for pregnant women, and asks women whether they have experienced 53 potentially stressful life events covering family life, work, study, and social relations during pregnancy. Weighted scores were calculated, and a higher total score indicated a higher life event stress level during pregnancy. The Cronbach’s coefficient of this scale was 0.96 (Zhang, 2005).

2.4. Potential confounders

Data on all confounders was collected during the maternal interview. The same set of confounders was used in all regression analyses, including maternal age at enrolment, ethnicity, maternal education, and family monthly income, which were widely used in the studies of neuropsychiatric changes due to lead exposure (Bjelland et al., 2008; Bouchard et al., 2009; Golub et al., 2010). We additionally adjusted for the number of years the women had lived in Shanghai, because we found significant differences in blood lead levels and maternal life event stress levels depending on how long the women had lived in Shanghai.

2.5. Statistical analyses

We used Empower(R) (version 2.13.9, X&Y solutions, MA, USA) and R (version 2.15.3, Robert Gentleman and Ross Ihaka, New Zealand) to statistically analyse the demographic characteristics of our study population, and the study population was analysed using analysis of variance, *t*-test (two-sided), Welch two sample *t*-test, Wilcoxon and Kruskal-Wallis rank sum tests.

We first used spline smoothing function (generalized additive models, GAMs) to visually inspect the shape of independent relationship between blood lead (log10-transformed) and maternal stress. The GAMs, a nonparametric regression, allowed us to examine possible nonlinear associations using a smoothing spline function. The smoothing spline is used to fit a smooth curve to a series of noisy observations through a spline function. Instead of being restricted to a linear relationship, it allows us to evaluate the functional relationship between the dependent and independent variables in a flexible, data-adaptive way (Ettinger et al., 2014; Hurley et al., 2004). Nonlinear relationships were observed between blood lead and the GSI, depression, and anxiety symptom scores of the SCL-90-R in both unadjusted and adjusted models. Then based on the shapes of the relationships, two piecewise linear