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Thyroid disruption and reduced mental development in children from an informal e-waste recycling area: A mediation analysis

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HIGHLIGHTS

- Median values of Pb, Cd, FT_4 and TSH in Guiyu were higher than that of the reference area.
- Guiyu children had lower cognitive Scores than those in the reference area.
- Pb was negatively correlated with both cognitive and language scores.
- Thyroid disruption isn't involved in the neurotoxicity induced by Pb-Cd co-exposure.

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ABSTRACT

This paper aims to evaluate the effects of thyroid disruption on the mental development of children. A total of 258 three-year-old children in Guiyu (e-waste-exposed group) and Nanao (reference group), China were examined. FT_3, FT_4, TSH, lead (BPb) and cadmium (BCd) in blood were determined, and cognitive and language scores of children were assessed based on the Bayley Scales of Infant Development III. Stepwise multiple regression was used to estimate the relationship between heavy metals and cognitive and language scores; mediation analysis was performed to determine whether thyroid disruption was mechanistically involved. Medians of BPb and BCd in Guiyu were higher than that of Nanao (11.30 ± 5.38 vs. 5.77 ± 2.51 μg/dL BPb; 1.22 ± 0.55 vs. 0.72 ± 0.37 μg/L BCd, both $p < 0.001$). Means of FT_4 and TSH in Guiyu were also higher than those in Nanao (16.65 ± 1.83 vs.16.06 ± 1.66 pmol/L FT_4, $p = 0.007$; 2.79 ± 1.30 vs. 2.21 ± 1.43 mIU/L TSH, $p = 0.001$). Guiyu children had lower cognitive scores (100.00 ± 25.00 vs. 120.00 ± 20.00, $p < 0.001$) and lower language scores (99.87 ± 7.52 vs. 111.39 ± 7.02, $p < 0.001$). Mediation analysis showed that Pb negatively correlated with both cognitive and language scores (both $p < 0.001$). However, FT_3, FT_4 and TSH did not significantly mediate the relationship between Pb and mental development of children (all $p > 0.05$). In contrast, Cd correlated with neither cognitive nor language scores (both $p > 0.05$). Results suggest exposure to heavy metal (Pb) reduces cognitive and language skills, and affects thyroid function, but fail to confirm that thyroid disruption is involved in the neurotoxicity induced by Pb–Cd co-exposure.

1. Introduction

The influence of thyroid hormone (TH) on brain development in children has been extensively studied (Chan and Kilby, 2000). The hypothalamus-pituitary-thyroid axis regulates thyroid function through thyrotropin-releasing hormone, also known as thyroid-stimulating hormone (TSH), and TH. It is clear that the fetus and neonate are quite sensitive to TH, and neurological growth and maturation can be compromised when disruptions in TH occur during fetal development (Zoeller et al., 2002). Studies have also revealed that relatively subtle deficits in circulating levels of TH, in pregnant women, could affect the neurological outcome of children (Ghassabian et al., 2011).

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Relevant abbreviations

BCd	blood cadmium
BMI	body mass index
BPb	blood lead
Cd	cadmium
FT_3	free triiodothyronine
FT_4	free thyroxine;
Pb	lead
PCBS	polychlorinated biphenyls
TH	thyroid hormone
TSH	thyroid stimulating hormone

Disposal of electronic waste, or e-waste, is an emerging global environmental issue. People living near hazardous waste sites can be exposed to soaring levels of toxic heavy metals and organic contaminants by breathing air, drinking water, eating food, or swallowing dust or dirt (Alabi et al., 2012; Heacock et al., 2016; Yekeen et al., 2016; Zhang et al., 2014; Zheng et al., 2016). Studies conducted in children have shown that developmental exposure to high levels of lead (Pb) and cadmium (Cd) can result in adverse neurocognitive and behavioral consequences in children, including mental retardation, lower neuropsychological test performance, lower child intelligence scores, and also decreasing child olfactory memory, which may extend into adulthood (Skerfving et al., 2015; Evens, et., 2015; Huang et al., 2012; Kippler et al., 2012; Zhang et al., 2017). Other studies show not only heavy metals, but also polybrominated flame retardants may lead to children suffering from lower scores of mental, or worse motor, cognitive and behavioral performance (Sagiv et al., 2015; Herbstman et al., 2010).

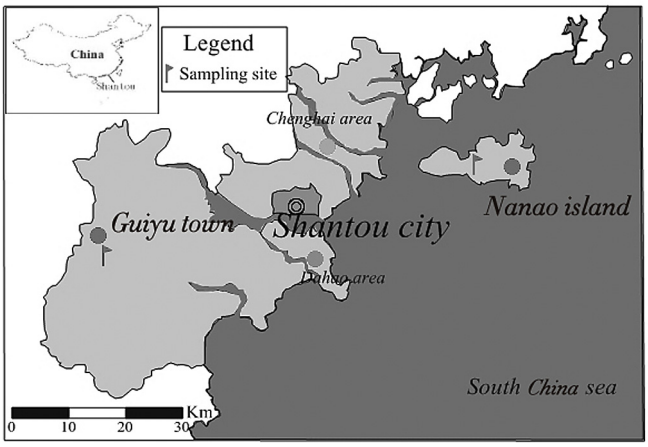
There is emerging evidence that children in informal recycling areas may have changes in TH and TSH concentrations. Especially relevant, concentrations of bisphenol A, polybrominated diphenyl ethers, polychlorinated biphenyls (PCBs) and hydroxylated PCBs correlate with TH and TSH levels (Lee et al., 2017; Eguchi et al., 2015; Xu et al., 2014). In recent years, a greater number of studies have focused on the relationship between levels of heavy metals and TH concentrations, although no consensus has been reached. Long-term, low-level Pb exposure resulting in low blood lead (BPb) levels (lower than 10 μg/dL), may lead to reduced free thyroxine (FT_4) levels without significant changes in TSH in adolescents (Dundar et al., 2006), and urinary Cd, but not associated with BPb, may be positively associated with free triiodothyronine (FT_3)(Chen et al., 2013). However, other studies report no statistically significant relationship between Pb concentrations and thyroid function (Siegel et al., 1989; Mendy et al., 2013).

Guiyu, is a crude and informal e-waste recycling town in Guangdong province. We have shown that concentrations of heavy metals, including Pb and Cd, are significantly higher and have adverse effects on the growth and development of the local neonates and children (Guo et al., 2010, 2012; Huo et al., 2007; Li et al., 2011, 2008a, 2008b; Wu et al., 2010, 2012; Xu et al., 2012, 2013, 2015, 2017; Zeng et al., 2016; Zhang et al., 2016, 2017; Zheng et al., 2013; Zheng et al., 2008). We recently showed child BPb and/or blood cadmium (BCd) correlate with certain behavioral abnormalities, such as alterations in temperament, conduct problems, antisocial behavior and decreased olfactory memory (Liu et al., 2011, 2014., Zhang et al., 2017). Studies are lacking on whether early childhood co-exposure to Pb and Cd directly affects the levels of TH and mental development of children in e-waste-contaminated areas, and what roles thyroid disruption plays in affecting child neurological outcomes. Therefore, we investigate whether thyroid disruption is involved in the mechanism of neurotoxicity induced by co-exposure to heavy metals. We measured BPb, BCd, FT_3, FT_4, and TSH in 258 three-year-old children in Guiyu and a reference location (Nanao), and assessed child cognitive and language scores based on the Bayley Scales of Infant Development III. In addition, we used mediation analysis, normally used to quantify and test the pathways of influence from causal variables to outcome variables (Hayes, 2013), to evaluate the effect of thyroid disruption on mental development in children co-exposed to Pb and Cd.

2. Material and methods

2.1. Study population

Volunteers from a selected kindergarten, in either the e-waste-exposed or reference area, were recruited, and screened based on the inclusion and exclusion criteria for this study. E-waste-exposed children were recruited from Guiyu in Shantou, China. Guiyu is a town with a more than 30-year history of informal e-waste recycling, which is often performed by family-run workshops. The soaring levels of toxic heavy metals and organic contaminants in the air, dust, soil, river sediment, surface water, and ground water of Guiyu have been previously reported (Zhang et al., 2014; Yekeen et al., 2016; Zheng et al., 2016). We recruited non-exposed subjects from Nanao Island, in Shantou, to serve as the reference group. This island is 104 km away from Guiyu, has a climate, cultural background, and socioeconomic status similar to the exposed area, and is populated with people of similar ethnicity and lifestyle. Because of its geographical isolation and lack of industrial workshops, Pb and Cd exposure is expected to be minimal among people living on this island.



Inclusion criteria were: (1) children approximately 3 years old (more than 30 months, but less than 42 months), (2) residence in Guiyu (or Nanao) for more than 2 years after birth, and (3) enrollment in a local regular kindergarten, which was a public daycare center, but with optional attendance. Exclusion criteria were: (1) mixed receptive-expressive language disorder, and (2) having been diagnosed with a severe neurologic or psychiatric disorder (cerebral palsy, seizure disorders, schizophrenia, obsessive-compulsive disorder). In total, two hundred eighty-four 3-year-old kindergarteners were recruited for our survey (135 in Guiyu and 149 in Nanao) from December 2011 to March 2012. After informed consent was obtained from the children's parents or guardians, blood samples were collected, and questionnaires were administered to the caretakers. Because of the shortage in volume