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Associations of lead and cadmium with sex hormones in adult males

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ABSTRACT

Heavy metal exposures are ubiquitous in the environment and their relation to sex hormones is not well understood. This paper investigates the associations between selected heavy metals (lead and cadmium) and sex hormones (testosterone, free testosterone, estradiol, free estradiol) as well as other major molecules in the steroid biosynthesis pathway (androstanedione glucuronide and sex-hormone binding globulin (SHBG)). Blood lead and cadmium were selected as biomarkers of exposure, and tested for associations in males using National Health and Nutritional Examination Survey (NHANES) data from 1999–2004. After adjustment for age, race, body mass index, smoking status, diabetes and alcohol intake, blood lead was positively associated with testosterone and SHBG while blood cadmium was positively associated with SHBG. After controlling for additional heavy metal exposure, the associations between lead and testosterone as well as cadmium and SHBG remained significant. Furthermore, the association between blood lead and testosterone was modified by smoking status (P for interaction = 0.011), diabetes (P for interaction = 0.021) and blood cadmium (P for interaction = 0.029). The association between blood cadmium and SHBG levels was modified by blood lead (P for interaction = 0.004). This study is the most comprehensive investigation to date regarding the association between heavy metals and sex hormones in males.

1. Introduction

Heavy metal exposures, such as lead and cadmium, are ubiquitous in our environment, with food, water, air, tobacco smoke and alcoholic drinks as possible exposure sources (Pizent et al., 2012). Lead can be found in old paints, soil, water, household dust, pottery, toys and traditional cosmetics (Mayo Clinic, 2014). For the general population, cadmium exposure often occurs through consumption of contaminated food, especially liver and kidney meats. Cigarette smoking is another major source of cadmium exposure, with smokers observed to have at least twice the amount of cadmium in their bodies than non-smokers (United States Agency for Toxic Substances and Disease Registry, 2008).

Animal and human studies have shown that exposure to cadmium and lead disrupts endocrine function (Colborn et al., 1993; Takiguchi and Yoshihara, 2006; Thomas, 1990). Endocrine disrupting chemicals can affect a range of hormone regulation activities, such as synthesis, metabolism and transport (Singleton and Khan, 2003). Sex hormones are regulated through the hypothalamus–pituitary–gonadal axis by negative feedback, stimulating synthesis of gonadotropin-releasing hormone, luteinizing hormone and follicle-stimulating hormone (Hall, 2010). Further, sex hormones are synthesized by the cytochrome P450 family of proteins (Nebert and Russell, 2002). Lastly, sex-hormone binding globulin (SHBG) is a plasma glycoprotein that transports both testosterone and estradiol throughout the body (Bond and Davis, 1987), its synthesis in the liver is under the control of androgens and estrogens, and its plasma levels are important in the regulation of free and albumin bound levels of these hormones. Dysregulation of any of these processes through exposure to heavy metals will likely affect sex hormone levels.

A previous study investigating the relationship between heavy metals and sex hormones in adult males found a synergistic effect between lead and cadmium on serum testosterone levels in both occupationally exposed (Telisman et al., 2000) and non-occupationally exposed populations (Telisman et al., 2007). Other studies observed positive associations between cadmium and testosterone and inverse associations between lead and testosterone (Dhooge et al., 2011; Jurasović et al., 2004; Lewis and Meeker, 2015; Rodamilans et al., 1988). These findings are inconsistent with other investigations that observed no association between cadmium and sex hormones (Menke et al., 2008). A study using a nationally representative sample found a positive association between blood cadmium and blood lead with testosterone (Lewis and Meeker,

Abbreviations: SHBG, sex-hormone binding globulin; NHANES, National Health and Nutrition Examination Survey; BMI, body mass index; LOD, limit of detection; HbA1C, gylcohemoglobin

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2015). Given the conflicting evidence and the variety of sample populations used, additional research into the role of heavy metals on sex hormone disruption is needed.

The purpose of our study is to investigate the associations between lead and cadmium exposures in relation to various sex hormones (i.e., testosterone, free testosterone, estradiol, free estradiol, androstanedione glucuronide and SHBG) in a nationally representative general population sample of adult men in the United States (US).

2. Methods

2.1. Study population

The National Health and Nutrition Examination Survey (NHANES) is a nationally representative sample of non-institutionalized civilians living in the US. This analysis combined three consecutive cycles of NHANES (1999–2000, 2001–2002 and 2003–2004) in which reproductive hormones were measured on a subsample of males to establish the study sample, according to the following eligibility criteria: (1) male sex, (2) aged >20 years, (3) no reported steroid or thyroid medication use, and (4) no reported thyroid disease. Additionally, only individuals without missing information on body mass index (BMI), diabetes status or the exposures and outcomes of interest were included in this analysis. The final study sample size was 869 participants (Fig. 1).

2.2. Exposure assessment

Blood lead and cadmium were measured from venous blood samples taken during examination visits following standard NHANES protocol. More information on specimen collection, analysis and quality assurance can be found in the NHANES protocol (National Health and Nutrition Examination Survey, 2002; National Health and Nutrition Examination Survey, 2006). Blood lead and cadmium were measured by atomic absorption spectrometry for the first two cycles (1999–2002), and inductively coupled plasma mass spectrometry in the third cycle (2003–2004). The limit of detection (LOD) varied across the different NHANES cycles. For 1999–2002, the LOD for blood lead was 0.6 μg/dL. After changing detection methods in 2003, the LOD was lowered to 0.025 μg/dL. A similar pattern was seen for blood cadmium; the LOD was 0.2 μg/L for 1999–2002 and 0.075 μg/L for 2003–2004. To

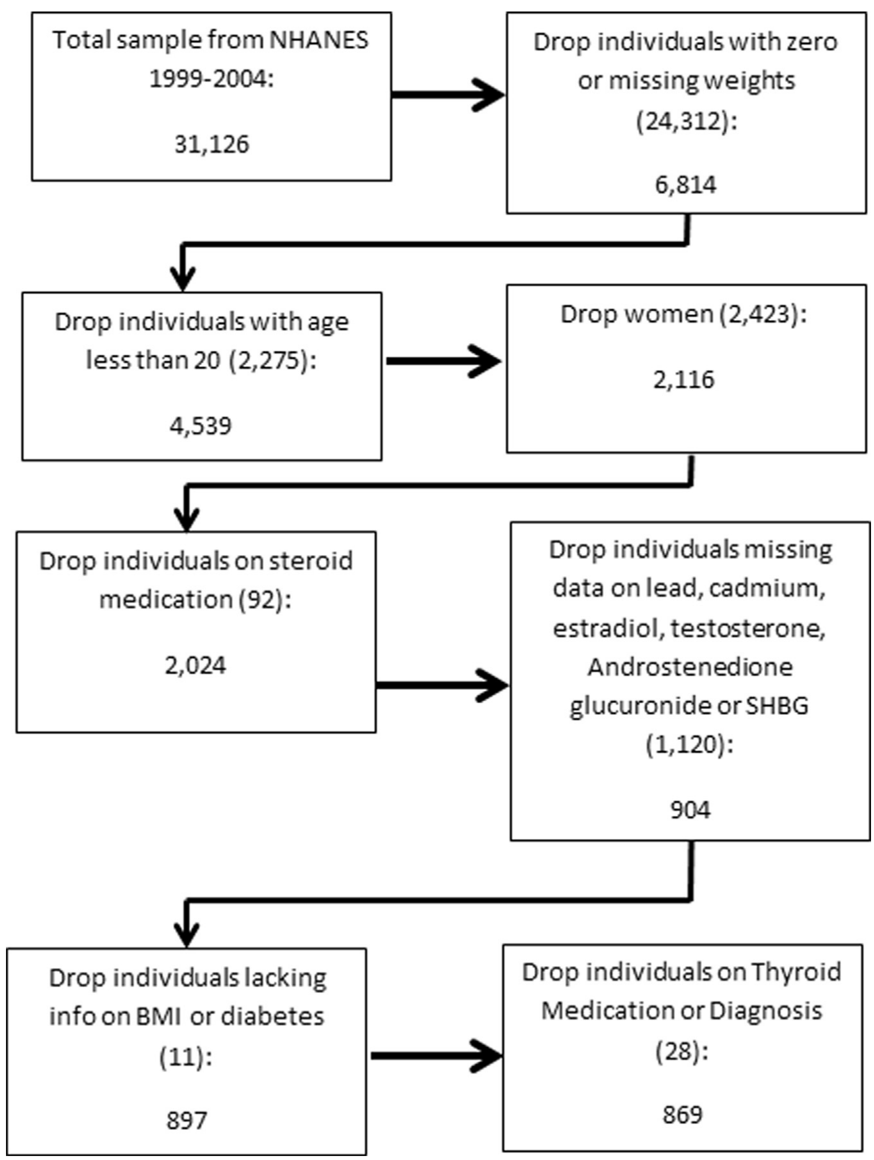

Fig.1. Flow chart displaying sample selection from NHANES 1999–2004.