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Exposure to acrylamide and the risk of cardiovascular diseases in the National Health and Nutrition Examination Survey 2003–2006

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ABSTRACT

Background: Long-term exposure to acrylamide (AA) from diet sources may induce oxidative stress and chronic inflammation. However, the association between AA exposure and the prevalence of cardiovascular diseases (CVD) remains unclear.

Objectives: We aimed to examine the association between blood exposure levels of AA biomarkers and the prevalence of main types of CVD in a general population of US adults.

Methods: We analyzed the associations between AA hemoglobin biomarkers [hemoglobin adducts of acrylamide (HbAA) and glycidamide (HbGA), sum of HbAA and HbGA (HbAA + HbGA), and ratio of HbGA to HbAA (HbGA:HbAA)] and self-reported diagnosis of CVD in 8290 adults (≥ 20 years of age) from the National Health and Nutrition Examination Survey (NHANES) 2003–2006. Multivariable logistic regression models were employed for estimating the associations in three groups classified by the combination of smoking status and serum cotinine levels.

Results: In people exposed to environmental tobacco smoke (n = 4670), HbGA, HbAA + HbGA, and HbGA:HbAA were significantly and inversely associated with the prevalence of total CVD ($p < 0.0001$, $p = 0.0155$, and $p = 0.0014$ for trend, respectively) after adjusting for various covariates. The odd ratios (ORs) for total CVD in the highest quartiles of HbGA, HbAA + HbGA, and HbGA:HbAA were 0.311 [95% confidence interval (CI): 0.193–0.500], 0.664 (95% CI: 0.485–0.911), and 0.495 (95% CI: 0.326–0.752) when compared with the individual lowest quartiles. In active smokers (n = 2432), HbAA was positively associated with CVD risk ($p = 0.0088$ for trend), while HbGA:HbAA was inversely related to total CVD ($p = 0.0137$ for trend). However, no significant associations of any AA hemoglobin biomarker with total and individual CVD prevalence were observed in the nonsmoking group (n = 1188).

Conclusions: AA hemoglobin biomarkers are significantly associated with CVD in the active smoking group and the group exposed to environmental tobacco smoke but not in the nonsmoking group. Further prospective studies should clarify the causal relationship between HbAA and HbGA and the prevalence of CVD.

1. Introduction

Cardiovascular diseases (CVD) are the most common cause of death and disability worldwide, accounting for an estimated 31.5% [95% confidence interval (CI): 30.3%–32.9%] of all global deaths in 2013 (Roth et al., 2015). Although the conventional risk factors, such as positive family history, diabetes mellitus, hypertension, dyslipidemia, and obesity have been identified as major contributors to increased risk of CVD, nearly 20% of individuals who suffer from CVD do not have any of these known risk factors (Khot et al., 2003). This suggests that emerging risk factors, such as exposure to environmental pollutants, also play a role in the augmentation or initiation of CVD because the cardiovascular system is highly vulnerable to a variety of environmental pollutants (Bhatnagar, 2004).

Acrylamide (AA), an α,β-unsaturated (conjugated) carbonyl compound with electrophilic reactivity, has recently been implicated as a possible risk factor from life development to senescence (Naruszewicz et al., 2008; Naruszewicz et al., 2009). AA is produced industrially

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worldwide and is used in plastics, grouts, water treatment products, and cosmetics (Friedman, 2003). As a Group 2A probable carcinogen (IARC, 1994), an international health alarm about AA was evoked in 2002 when it was widely found in carbohydrate-rich foods usually prepared at temperatures above 120 °C and low moisture, such as French fries, potato chips, bread, biscuits, and coffee (Mottram et al., 2002; Stadler et al., 2002; Tareke et al., 2002). As a component of tobacco smoke, smoking as well as passive smoking is also an important source of human exposure to AA (FAO/WHO, 2011; US-EPA, 2010).

The hemoglobin (Hb) adducts of AA (HbAA) and its major metabolite glycidamide (GA) (HbGA) at the N-terminal valine are well-established biomarkers of internal AA exposure after long-term exposure over the average lifespan of erythrocytes (Berger et al., 2011; Bergmark et al., 1993), which are widely employed to estimate the internal dose from workplace exposure as well as in the general population (BfR, 2011; EFSA, 2015; Shipp et al., 2006). Previous epidemiological data showed controversial associations of the Hb biomarkers of AA and GA with long-term cancer risk in cross-sectional human studies, such as the European Prospective Investigation into Cancer and Nutrition (EPIC) and the Nurses' Health Study (NHS) (Obon-Santacana et al., 2016; Vesper et al., 2008; Wilson et al., 2010; Xie et al., 2013). Besides cancer prevalence, oxidative stress and inflammatory states have been recognized as indicators of various chronic diseases like CVD. A pilot study reported the effect of potato chip consumption on markers of oxidative stress and inflammation via using HbAA as a biomarker of AA exposure (Naruszewicz et al., 2009). The findings indicated that long-term dietary intake of AA in high levels may cause chronic inflammation and contribute to the progression of early atherosclerosis as well as the increased risk of coronary artery disease, corresponding with numerous *in vivo* studies, indicating that AA could induce oxidative stress and proinflammatory states (Kim et al., 2015; Prasad and Muralidhara, 2012; Yousef and El-Demerdash, 2006). However, no epidemiological evidence has been reported to observe the associations between daily AA exposure and CVD. Therefore, the present study aimed to demonstrate whether daily AA exposure could pose risks of CVD prevalence to human health by examining data from the National Health and Nutrition Examination Survey (NHANES) collected from 2003 to 2004 and 2005 to 2006.

2. Methods

2.1. Study population

NHANES is a nationally representative survey to monitor the health status of the civilian noninstitutionalized U.S. population conducted annually by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC) (Johnson et al., 2013). Detailed survey operation manuals, consent documents, and brochures of each period are available on the NHANES website (CDC, 2009).

We merged data from the survey years 2003 to 2004 and 2005 to 2006, in which the levels of HbAA and HbGA were measured in two consecutive cycles. A total of 9794 samples from individuals with 4725 males and 5069 females between 18 and 85 years of age were available. Cardiovascular health was assessed only in respondents aged ≥20 years. A total of 8769 participants aged at least 20 years were available for analysis of HbAA and/or HbGA in their stored blood specimens. In addition, participants with missing information on assessment data of CVD were also excluded in the final model. Therefore, we obtained 8735 participants as the subsample of subjects.

Considering that AA is a major component of cigarette smoke and smoking is an important risk for CVD, we conducted the analyses in three groups with different smoking status, including an active smoker group, a group of those exposed to environmental tobacco smoke, and a nonexposed group, according to a combination of the smoking questionnaire and serum cotinine levels. In detail, active smokers were defined as those with cotinine levels > 10 ng/mL or those who reported a current smoking status of every day or some days (n = 2432). Those with serum cotinine levels that were detectable but < 10 ng/mL and who did not report current smoking status were considered as participants exposed to environmental tobacco smoke (n = 4670). Those with serum cotinine levels < 0.015 ng/mL, nonsmoking reported at home, and a self-reported nonsmoking status were considered as nonexposed participants (n = 1188). Finally, there were a total of 8290 participants enrolled in our analyses.

2.2. Assessment of HbAA and HbGA

The levels of HbAA and HbGA were measured in fresh or frozen erythrocytes or ethylenediaminetetraacetic acid (EDTA)-anticoagulated whole blood specimens as described previously (Vesper et al., 2010). In brief, two adducts at the N-terminal valine residues of hemoglobin were specifically cleaved from the protein chain based on a modified Edman reaction with fluorinated Edman reagent (Mowrer et al., 1986). Then, the thiohydantoin derivative products were extracted by liquid-liquid extraction and analyzed by high-performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS). The limits of detection (LODs) for the levels of HbAA and HbGA were 3 and 4 pmol/g Hb, respectively. A mean (± SD) recovery of (96.0 ± 1.9)% for HbAA and HbGA added externally into whole blood and red blood cells at different levels (0.5–20 pmol/200 μL) during an in-house recovery study. Each sample was measured in duplicate to reduce the laboratory measurement errors. More experimental details are available in the laboratory data of NHANES (CDC, 2008).

2.3. Assessment of CVD

CVD was ascertained by a composite of a self-reported physician diagnosis with a standardized medical condition questionnaire administered during the personal interview. Participants were asked the following: “Has a doctor or other health professional ever told you that you have congestive heart failure (CHF)/coronary heart disease (CHD)/angina pectoris/heart attack/stroke?” These were five separate questions with the same wording style. Answering “yes” to either of these questions was coded positive for CVD, while answering “yes” to a specific CVD case was coded positive for the relative individual type of CVD.

2.4. Covariates

Detailed information and data on potential confounders were available online (CDC, 2009). We considered the following covariates in our analyses, including information on age (years), sex (men or women), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, or others), education levels (< high school, =high school, or > high school), alcohol drinking status (never, former, or current), physical activity (never, moderate, or vigorous), family poverty-income ratio (PIR), family history of CVD (yes/no), history of physician-diagnosed hypertension (yes/no), history of physician-diagnosed diabetes (yes/no), taken anti-hypertensive agents (yes/no), taken anti-hyperglycemic agents (yes/no), and taken anti-hyperlipidemic agents (or told to take prescription for cholesterol, yes/no). The above information was obtained by a standardized questionnaire during a home interview. Total intake of caffeine, energy, saturated fatty acid, protein, carbohydrate, and sugar were measured by two consecutive 24-h dietary intake interviews conducted in person by trained interviewers. Total dietary *trans* fat intake was estimated via multiplying the amount of consumed individual food items by the concentrations of *trans* fat in these food items (Kris-Etherton et al., 2012; Storey and Anderson, 2015).

For the composite covariates, hypertension (yes/no) was defined as a history of physician-diagnosed hypertension, high systolic blood