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Associations of hemoglobin biomarker levels of acrylamide and all-cause and cardiovascular disease mortality among U.S. adults: National Health and Nutrition Examination Survey 2003–2006☆

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ABSTRACT

Background: The potential hazards of acrylamide (AA) have been proposed due to its lifelong exposure. However, the association between AA exposure and mortality remains unclear.
Objectives: We evaluated the prospective association of AA hemoglobin adducts (HbAA and HbGA) with all-cause and cardiovascular disease (CVD) mortality in U.S. population from National Health and Nutrition Examination Survey (NHANES) 2003–2006.
Methods: We followed 5504 participants who were ≥25 years of age for an average of 6.7 years at the baseline examination with annual linkage to the NHANES statistics database. Using AA hemoglobin biomarkers [HbAA, HbGA, sum of HbAA and HbGA (HbAA + HbGA), and ratio of HbGA to HbAA (HbGA/HbAA)], we determined mortality from all-causes and CVD through Cox proportional hazard regression analysis with multivariable adjustments both in non-smoker group and smoker group. In addition, subgroup analyses and sensitivity analyses were further conducted.
Results: After adjusting for sociodemographic, life behavioral and cardiovascular risk factors in non-smoker group, HbAA was positively associated with all-cause mortality (p for trend = 0.0197) and non-CVD mortality (p for trend = 0.0124). HbGA and HbGA/HbAA were inversely associated with all-cause mortality (p for trend = 0.0117 and 0.0098, respectively) and CVD mortality (p for trend=0.0009 and 0.0036, respectively). The multivariable adjusted hazard ratios (HRs) [95% confidence intervals (CIs)] of the upper three quartiles were 0.472 (95% CI: 0.283–0.786), 0.517 (95% CI: 0.299–0.894) and 0.470 (95% CI: 0.288–0.766) between HbGA/HbAA and all-cause mortality comparing with the lowest quartile, respectively. No significant associations were found between HbAA + HbGA and mortality in non-smoker group, and between all AA hemoglobin biomarkers and mortality in smoker group.
Conclusions: Hemoglobin biomarker levels of AA were strongly associated with mortality in general U.S. non-smoker adults. These findings proposed a continuous public health concern in relation to environmental and dietary exposure to AA.

1. Introduction

Acrylamide (AA) is a highly reactive chemical present in the environment (e.g., industrial wastewater, ground soil), consumer products (e.g., cosmetics, textiles), cigarette smoke and drinking water (Andersen, 2005; Bergmark, 1997; Junqua et al., 2015). Regarded as a neurotoxic compound (Erkekoglu and Baydar, 2014), AA is also a well-documented carcinogen in animals and a probable carcinogen in humans (Klaunig, 2008), which has been classified as a "Group 2A carcinogen" by the International Agency for Research on Cancer (IARC) (IARC, 1994). Worldwide attention has been attracted when high amount of AA was discovered in a variety of baking and frying of starchy foods commonly consumed by a large portion of the population in 2002 (Mottram et al., 2002).

Since then, numerous universities and institutions have extensively assessed the overall AA exposure of the general population to

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define the exposure extent and the possible associations with health effects. The updated human exposure assessment indicated that the mean and 95th percentile dietary AA intakes ranged 0.4–1.9 μg/kg b. w. per day, and 0.6–3.4 μg/kg b. w. per day, respectively (EFSA, 2015). However, much higher level ranging 1.4–18.6 μg/kg b. w. per day was estimated in occupational exposure from inhalation, while exposure from dermal uptake was still unknown due to the unavailable detection methods (Manson et al., 2005). Moreover, given the assessment in mainstream cigarette smoke which contains 1.0 μg or higher of AA per cigarette, smoking has become primary source of overall AA exposure for the population of smokers. (Moldoveanu and Gerardi, 2011).

After absorption, AA rapidly reaches the systemic circulation and can be extensively metabolized mostly by conjugation with glutathione (GSH), and some of AA can also be epoxidized to glycidamide (GA) by cytochrome P450 2E1 (Calleman et al., 1990; Sumner et al., 1999). Both AA and GA could also react with hemoglobin (Hb) (Fennell et al., 2005). The Hb adducts (HbAA and HbGA) could provide first-hand information about the amount of AA that has entered human bodies over the last three months based on the lifespan of erythrocyte (Fennell et al., 1992; Hartmann et al., 2008). Using HbAA and HbGA as well-established internal biomarkers, the associations of dietary AA intake with cancer risk have been particularly investigated in various epidemiologic studies but with controversial results (Obon-Santacana et al., 2016; Pelucchi et al., 2015; Xie et al., 2013).

In this study, we make a hypothesis that AA exposure would be associated with increased all-cause and cause-specific mortality, such as cardiovascular disease (CVD) mortality. We aimed to evaluate the prospective association of AA exposure with mortality in participants who were recruited in National Health and Nutrition Examination Survey (NHANES) from 2003 to 2006, with an interest in evaluating potential effect modification by demographic variables, life behaviors and other key risk factors.

2. Methods

2.1. Study population

NHANES consists of a series of large surveys, which aim to continuously monitor the nutrient and healthy condition of the non-institutionalized U.S. people (CDC, 2009). The study has been conducted every two years for a circle using nationally representative samples and complex multi-stage sampling designs. More details are provided in NHANES website by the National Center for Health Statistics (NCHS) (CDC, 2009).

For current analysis, the data we used consisted of 2003–2004 and 2005–2006 circles that were combined using NCHS recommendations. A total of 7897 adults aged ≥25 years participated in the NHANES 2003–2006 interviews and examinations. There were 1059 participants who had ever been diagnosed with CVD, 758 with cancer or malignancy, and 1251 with diabetes. Thus, the final sample size was 5504 subjects with 69.7% overall participation rate after excluding participants suffering from the above three types of diseases. Among them, measurement data about HbAA and HbGA levels were available in 5375 and 5376 participants, respectively, while both HbAA and HbGA levels were measured in 5247 participants. These participants had similar sociodemographic characteristics compared with the overall NHANES 2003–2006 population.

Considering AA is a major component of cigarette smoke, we conducted the analyses separately in non-smoker group and smoker group according to the combination of the smoking questionnaire and serum cotinine levels. In detail, smokers were defined as those with cotinine levels ≥10 ng/mL or those who reported currently smoking status every day or on some days ($n = 1570$). Those with serum cotinine levels that were detectable but <10 ng/mL and who did not report current smoking status were included in non-smoker group ($n = 3934$). Finally, there were total 5504 participants enrolled in our analyses.

2.2. HbAA and HbGA measurements

The detection of *N*-terminal hemoglobin adducts of AA and GA (HbAA and HbGA) in human whole blood or erythrocytes is commonly used in clinical chemistry based on the well-established procedure (Vesper et al., 2010). Based on the liquid-liquid extraction after modified Edman degradation reaction, HbAA and HbGA could be simultaneously measured in the Edman products through high-performance liquid chromatography combined with tandem mass spectrometry (HPLC-MS/MS) (Mowrer et al., 1986; Vesper et al., 2010). More details about the experiments were shown in laboratory manual provided by National Center for Environmental Health (NCEH) (CDC, 2008).

2.3. Baseline data collection

The information on socioeconomic and demographic characteristics [age, sex, race/ethnicity, family poverty-income ratio (PIR), and education levels], life-behavior variables (physical activity, smoking status, and alcohol drinking status), and other CVD risk factors (history of hypertension and history of family CVD) was based on self-reported information (CDC, 2009). Diet information (e.g. total energy intake) was obtained from 24-h dietary recall. Body parameters of height and weight were both measured to acquire the body mass index (BMI, kg/m^2). Serum total cholesterol was measured enzymatically while cotinine was determined through instrumental analysis, both of which were modeled as natural log-transformed continuous variables (CDC, 2009).

2.4. Follow-up and ascertainment of deaths

In our study, we mainly performed the analyses related to all-causes, CVD and non-CVD mortality. Theses data were obtained from the NHANES Linked Mortality public use files, which recorded the vital status and cause of death of NHANES participants from survey participation in 2003–2006 to the death or 31 December 2011 (NCHS, 2014). More information about the code, definition and principle of mortality status and death cause could refer the National Death Index (NDI) death certificate records, the 10th Edition of *International Classification of Diseases* (ICD-10), and the Clinical Modification System codes I00-I78 (WHO, 1992).

2.5. Statistical analysis

Using Cox proportional hazards regression, we calculated the hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause, CVD and non-CVD mortality, using “the lowest quartile of HbAA, HbGA, HbAA + HbGA, or HbGA/HbAA” as the reference group for the corresponding analyses in non-smoker group. In smoker group, the calculation was only available for all-cause mortality due to too few numbers of CVD and non-CVD deaths. We tested our models through 1 to 4 via step-by-step adjusting the risk factors. Model 1 was only adjusted for age, sex, and race/ethnicity, and model 2 was further adjusted for family PIR, education levels, BMI as well as health behaviors (physical activity and alcohol drinking status). Then, model 3 was simultaneously adjusted for the variables in model 2 plus the diseases risk factors, e.g. intake of total energy, history of hypertension, and family history of CVD. Finally, the full analysis model 4 were constructed and further adjusted for the