Environmental Science and Pollution Research (2022) 29:38425–38434
https://doi.org/10.1007/s11356-021-18342-0

RESEARCH ARTICLE

Total cholesterol: a potential mediator of the association between exposure to acrylamide and hypertension risk in adolescent females

Jingjia Liang[1,2] · Cheng Xu[1,2] · Qian Liu[1,2] · Zhenkun Weng[1,2] · Xin Zhang[1,2] · Jin Xu[1,2,3] · Aihua Gu[1,2]

Received: 8 September 2021 / Accepted: 21 December 2021 / Published online: 26 January 2022

Abstract

Acrylamide (AA) exposure is associated with a range of adverse health effects. However, whether AA exposure is related to hypertension in adolescents remains unclear. The associations of blood hemoglobin biomarkers of AA (HbAA) and its metabolite glycidamide (HbGA) with hypertension risk, diastolic blood pressure (DBP), and systolic blood pressure (SBP) were evaluated by multivariate logistic regression and linear regression. We identified a potential positive association between blood HbGA and hypertension risk in adolescent females (OR 1.81, 95% CI 1.00–3.30; *P* for trend = 0.022); however, there was no correlation in the non-linear model (*P* = 0.831). In the sex-stratified linear models, blood HbGA level had a strong positive association with SBP in adolescent females (beta 0.84, 95% CI 0.13–1.55, *P* = 0.020). Mechanistically, a one-unit increase in blood HbGA (ln transformed) was associated with a 2.83 mg/dL increase in total cholesterol (TC) among females in the fully adjusted model. Mediation analysis showed that TC mediated 24.15% of the association between blood HbGA level and the prevalence of hypertension in females. The present results provide epidemiological evidence that exposure to AA, mainly its metabolite glycidamide, is positively associated with the prevalence of hypertension or increased SBP in adolescent females.

Keywords Acrylamide · Glycidamide · Blood pressure · Adolescents · NHANES

Introduction

Hypertension, or elevated blood pressure (BP), is a global public health issue, with approximately 1 billion adults worldwide suffering from high blood pressure in 2008 (Forouzanfar et al. 2017). Furthermore, hypertension is a significant risk factor for adverse cardiovascular outcomes (Fuchs and Whelton 2020; Yu et al. 2019), and thus, it has become one of the leading causes of premature morbidity and mortality globally (Forouzanfar et al. 2017). With the pronounced increase in adolescent obesity, weight-related disease burdens, including that of adolescent hypertension, are becoming increasingly serious concerns (McNiece et al. 2007; Redwine et al. 2012). Epidemiological studies have indicated a substantial increase in hypertension in adolescents over the past few decades (Noubiap et al. 2017). Alarmingly, high BP in adolescence tracks across the life course; it not only increases susceptibility to hypertension or metabolic disorders in adulthood (Beckett et al. 1992) but also increases the risk of early cardiovascular disease (CVD) and related complications later in life (McCrindle et al. 2010). In addition to potential disease threats, the financial burden of hypertension is high despite the availability of low-cost pharmacotherapy (Mills et al. 2020). For these reasons, examining the risk factors for hypertension at the population level to develop and initiate effective interventions is critical, especially in teenagers. Several risk factors have been linked to hypertension, including overweight and obesity, dietary salt intake, male sex, older age, and ethnicity in adults

Responsible Editor: Lotfi Aleya

✉ Aihua Gu
aihuagu@njmu.edu.cn

[1] State Key Laboratory of Reproductive Medicine, School of Public Health, Nanjing Medical University, 101 Longmian Avenue, Nanjing 211166, China

[2] Key Laboratory of Modern Toxicology of Ministry of Education, Center for Global Health, Nanjing Medical University, Nanjing, China

[3] Department of Maternal, Child, and Adolescent Health, School of Public Health, Nanjing Medical University, Nanjing, China

as well as teenagers (Lo et al. 2013). In addition to the above risk factors, a number of studies have revealed that the impacts of environmental pollutants or gene/environment interactions on high BP are nonnegligible (Ma et al. 2019; Warembourg et al. 2019).

Acrylamide (AA), an industrially produced compound, is used to synthesize modified polyacrylamide, which is widely used in industries such as plastic manufacturing, cosmetics production, and wastewater treatment as well as molecular biological research, such as gel electrophoresis of proteins and nucleic acids (Beckett et al. 1992). AA was classified as a "Group 2A carcinogen" by international research institutions in 1994. In 2002, it received worldwide attention due to the large amount of AA found in processing at temperatures above 120 °C and in low-moisture foodstuff, such as fried potatoes, baked bread and cakes, and thermally processed cereals (Mottram et al. 2002). People are exposed to AA mainly through ingestion, inhalation, and skin contact during thermal-processed food intake, tobacco smoking, occupational production. and use (Vesper et al. 2010). The health threats of AA have been extensively reviewed in publications. An epidemiological study showed that dietary AA intake was associated with CVDs in the general US population (Zhang et al. 2018). A prospective association study reported a strong correlation between hemoglobin biomarker levels of AA (HbAA) and mortality in the general US population of nonsmoking adults (Huang et al. 2018a). It is well known that high BP is commonly and strongly associated with CVD and mortality in our globalized and industrialized societies (Oparil et al. 2018). However, the effects of AA exposure on high BP have rarely been investigated. Therefore, whether human exposure to AA causes BP to rise remains to be clarified.

As acrylamide exposure from food and smoking has become a worldwide concern, elucidation of the putative causal relationship between acrylamide exposure and hypertension risk is urgent. Epidemiological studies usually use HbAA and the hemoglobin adduct of the major metabolite of AA, glycidamide (HbGA), as internal biomarkers of the biochemical effect of AA to study the relationship between AA exposure and disease risk (Hartmann et al. 2008). In this study, our main analysis focused on using National Health and Nutrition Examination Survey (NHANES) data from 2003 through 2016 to explore the exposure–response relationship between blood HbAA and HbGA with hypertension and BP in adolescents aged 13–19 years.

Methods

Study population

The NHANES is a multicomponent, representative survey to monitor the health and nutritional conditions of the noninstitutionalized US civilian population with stratified, multistage, probability cluster sampling (Johnson et al. 2013). Written informed consent was obtained from all the participants, and the survey protocol was approved by the National Center for Health Statistics Research Ethics Review Board. Detailed information on biological sample collection, physical examinations, and questionnaire completion in each cycle is available on the NHANES website (https://www.cdc.gov/nchs/nhanes/).

We combined survey data from 2003 to 2006 and from 2013 to 2016, where HbAA and HbGA levels were measured in four consecutive cycles. A total of 3,981 samples were obtained from 2,041 boys and 1,940 girls aged between 13 and 19 years old at the time of examination. The stored blood samples of a total of 4,664 participants underwent analysis of HbAA and/or HbGA. In addition, participants who lacked BP assessment data were excluded from the final model. Therefore, we included 3,981 participants in the final analysis.

AA exposure markers: HbAA and HbGA

Blood samples of subjects were collected and stored at − 20 °C before analysis by the laboratory of the National Center for Environmental Health. The detection of N-terminal hemoglobin adducts of AA and GA (HbAA and HbGA, respectively) in human whole blood or erythrocyte specimens was based on a well-established procedure (Vesper et al. 2010). In brief, after a modified Edman degradation reaction with fluorinated Edman reagent, the thiohydantoin derivative products were extracted by liquid–liquid extraction; then, HbAA and HbGA were simultaneously analyzed by high-performance liquid chromatography tandem mass spectrometry. Every sample was measured in duplicate to decrease the likelihood of measurement errors.

Primary outcome: BP and hypertension

After the participants rested for 5 min in a seated position with feet flat on the floor, the designated personnel used a sphygmomanometer to measure up to 3 consecutive BP readings for each subject. BP was the average of ≤ 3 readings (Hara et al. 2015). In this study, hypertension was defined as BP ≥ 130/80 mmHg or the reported use of antihypertensive medication among adolescents aged 12–19 years according to new practical clinical guidelines released by the American Academy of Pediatrics in 2017 (Jackson et al. 2018).

Secondary outcome: blood lipid level and inflammation index

To observe possible causes of elevated BP risk caused by AA exposure, we conducted additional analyses with

laboratory data. We explored the associations between HbGA and markers of lipid metabolism (total cholesterol (TC), triglycerides (TGs), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C)) and markers of inflammatory state (white blood cell (WBC) and C-reactive protein (CRP)). Abnormalities of these parameters are known to increase the risk for high BP (Tzoulaki et al. 2018). Detailed information on sample collection and detection at the mobile examination center is available in previous studies (Phillips et al. 2018; Xu et al. 2021; Zang et al. 2018).

Covariates

In this study, the following variables were chosen as a priori covariates in the models because of their possible biological influence on AA exposure or outcomes: age; sex; ethnicity; body mass index (BMI); serum cotinine levels; dietary intake of calcium, sodium, and potassium; and poverty-income ratio (PIR, family income divided by the federal poverty threshold controlling for inflation and family size) (Carretero and Oparil 2000; Huang et al. 2018c; Rao 2016). Serum cotinine was a variable that served as a marker of exposure to environmental cigarette smoking and was ln transformed before inclusion in models. The PIR was used as an index to estimate socioeconomic conditions. The data concerning these variables were extracted from the NHANES questionnaires and laboratory detection.

Statistical analysis

Continuous variables are shown as the means ± standard deviations, while categorical variables are expressed as frequencies and proportions. The Mann–Whitney *U* test was used to test differences in continuous variables between sexes, while the χ^2 test was used to evaluate differences in categorical variables between sexes. Because the distributions of values of BP and AA hemoglobin biomarkers (HbAA or HbGA) are naturally skewed, a base-e logarithmic transformation was used for the data. Blood concentrations of HbAA or HbGA were categorized in quartiles according to the sample distribution. We used multivariate logistic regression models to estimate adjusted odds ratios (ORs) for hypertension status in association with HbAA or HbGA. We displayed effect estimates (ORs) and their 95% confidence intervals (CIs) for each quartile compared with the reference quartile (Q1 group). *P* for trend was determined by regarding the HbAA or HbGA category as a linear variable in the models. In addition, a multivariate linear regression model was performed to estimate the associations between markers of AA exposure (HbAA or HbGA) and systolic blood pressure (SBP) or diastolic blood pressure (DBP), and the results are presented as the regression coefficients (betas) and 95% confidence intervals (CIs). Potential non-linear relationships were assessed with restricted cubic spline (RCS) models. As sex is a particularly significant predictor, a separate analysis stratified by sex was conducted in both logistic regression and linear regression. Model 1 represented a crude model. Model 2 was additionally adjusted for age, sex and race/ethnicity, BMI, PIR, serum cotinine levels, and dietary intake of calcium, sodium, and potassium. To determine whether hypertension-related AA metabolites may affect BP by altering lipid levels or inflammation status, we conducted a multivariate linear regression as secondary analyses in a random subgroup with biochemical index data, including TGs, TC, HDL-C, LDL-C, WBC, and CRP. IBM SPSS software, version 20.0 (IBM Corp., Armonk, NY, USA), was utilized for all statistical analyses. All tests were two-sided, and a P value < 0.05 was regarded as the standard of statistical significance.

Results

Baseline characteristics of participants

The detailed characteristics of the study participants are illustrated in Table 1. This study included 3,981 subjects: 2,041 boys and 1,940 girls. The average age of the population was 16.0 ± 2.0 years old. Mexican Americans accounted for 30.2%, other Hispanic individuals accounted for 4.4%, non-Hispanic white individuals accounted for 26.9%, non-Hispanic black individuals accounted for 32.7%, and individuals of other races, including mixed race, accounted for 5.9%. No significant difference in age, race, or HbGA level was found with respect to sex. Among the other baseline characteristics, the distributions of BMI, PIR, and serum cotinine between boys and girls were as follows: 24.0 ± 5.8 and 24.8 ± 6.4; 2.1 ± 1.5 and 2.0 ± 1.5; and 22.3 ± 68.8 and 14.8 ± 54.7, respectively (all *P* values less than 0.05). The average HbAA level and HbAA/HbGA ratios in boys and girls were 70.0 ± 57.3 and 59.8 ± 40.1 pmol/g hemoglobin ($P < 0.001$) and 1.7 ± 3.9 and 1.4 ± 3.6 ($P < 0.001$), respectively. Daily intakes of calcium, sodium, and potassium in boys were significantly higher than those in girls ($P < 0.001$). Correspondingly, the prevalence of hypertension in boys ($n = 226$, 11.1%) was significantly higher than that in girls ($n = 121$, 6.2%, $P < 0.001$).

AA biomarkers and hypertension

The associations between blood HbAA/HbGA and hypertension or SBP/DBP among adolescents are shown in Table 2. Notably, the multivariate logistic regression models presented a positive association between HbGA and hypertension in the group of girls (*P* for trend = 0.022)

Table 1 Characteristics of the study subjects, grouped by gender, NHANES 2003 to 2016

Variable	Overall ($n=3,981$)	Boys ($n=2,041$)	Girls ($n=1,940$)	*P* value
Age (year)	16.0 ± 2.0	16.0 ± 2.0	15.9 ± 2.0	0.561
Race (%)				0.124
Mexican American	1201 (30.1%)	597 (29.3%)	604 (31.1%)	
Other Hispanic	174 (4.4%)	85 (4.2%)	89 (4.6%)	
Non-Hispanic white	1070 (26.9%)	547 (26.8%)	523 (27.0%)	
Non-Hispanic black	1301 (32.7%)	702 (34.4%)	599 (30.9%)	
Other race—including multi-racial	235 (5.9%)	110 (5.4%)	125 (6.4%)	
BMI (kg/m^2)	24.4 ± 6.1	24.0 ± 5.8	24.8 ± 6.4	0.001
PIR	2.0 ± 1.5	2.1 ± 1.5	2.0 ± 1.5	0.040
Cotinine (ng/mL)	18.6 ± 62.5	22.3 ± 68.8	14.8 ± 54.7	< 0.001
Calcium (mg)	961.5 ± 551.8	1087.3 ± 606.4	829.2 ± 451.7	< 0.001
Sodium (mg)	3431.4 ± 1595.1	3883.4 ± 1754.2	2955.8 ± 1242.4	< 0.001
Potassium (mg)	2334.1 ± 1086.7	2627.9 ± 1191.7	2024.9 ± 862.1	< 0.001
Acrylamide (pmol/g Hb)	65.0 ± 49.9	70.0 ± 57.3	59.8 ± 40.1	< 0.001
Glycidamide (pmol/g Hb)	57.5 ± 40.5	58.9 ± 45.0	56.0 ± 35.2	0.615
HbAA/HbGA	1.5 ± 3.8	1.7 ± 3.9	1.4 ± 3.6	< 0.001
Hypertension (%)	347 (8.7%)	226 (11.1%)	121 (6.2%)	< 0.001
SBP (mmHg)	110.5 ± 10.4	113.8 ± 10.6	107.6 ± 9.3	< 0.001
DBP (mmHg)	60.2 ± 11.7	58.9 ± 13.0	61.5 ± 9.9	< 0.001

Mean values with their standard deviation, or *n* (%)

BMI, body mass index; *PIR*, poverty-income ratio; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *Hb*, hemoglobin; *HbAA/HbGA*, acrylamide/glycidamide

after adjusting for age, race, BMI, PIR, serum cotinine, and dietary intake of calcium, sodium, and potassium. Compared with the lowest quartile, the ORs across increasing quartiles were 0.92 (95% CI: 0.49, 1.73), 1.35 (95% CI: 0.75, 2.43), and 1.81 (95% CI: 1.00, 3.30) for HbGA in girls. Figure 1 shows no non-linear relationship of HbGA level with hypertension in girls based on RCS regression models (*P* value = 0.831). A suggestive association was observed between HbGA and hypertension in girls. However, the association between hypertension and the concentrations of HbAA tended toward null in our study, regardless of sex.

In the multivariable-adjusted linear regression analysis, HbGA was found to be positively associated with SBP (beta = 0.49, 95% CI: 0, 0.97, *P* = 0.048 in the model that included all confounders) when all the participants were entered. After stratification analyses by sex, blood HbGA levels were positively associated with SBP among girls (beta = 0.84, 95% CI: 0.13, 1.55, *P* value = 0.020 in the model that included all confounders) but not boys. Figure 2 shows the continuous relationship of HbGA level with SBP or DBP in girls based on RCS regression models. A positive association was observed between HbGA level and SBP (*P* value = 0.028) in girls, while no linear association was detected between HbGA level and DBP (*P* value = 0.290) in boys. In addition, scatter plots and fitted lines with 95% CIs of the associations between HbGA level and SBP in girls are visualized in Supplementary Fig. 1.

AA biomarkers and serum lipid level and inflammation parameters

Because HbGA increases the risk of hypertension, especially in girls, we further explored the association between some serum biochemical indices and HbGA concentration, as exhibited in Table 3. In the multivariable-adjusted linear regression analysis conducted in girls for lipid levels, HbGA concentration was found to be positively associated with TC (beta = 2.83, 95% CI: 0.49, 5.18, *P* = 0.018) after adjusting for age, race, BMI, PIR, serum cotinine, and dietary intake of calcium, sodium, and potassium. Furthermore, mediation analysis results showed that 25.47% of the association between HbGA level and hypertension risk was statistically accounted for by TC (Fig. 3).

Discussion

Although there are large numbers of studies on the relationship between AA exposure and health outcomes, the association of AA levels with BP abnormalities in a representative sample from a general population has never been explored.

Table 2 Multivariate analysis of the association of acrylamide biomarkers in hemoglobin and hypertension and blood pressure in teenagers from the NHANES, 2003 to 2014

	Case/control	Hypertension					SBP		DBP	
		Q1	Q2	Q3	Q4	*P* for trend	Bp and 95% CI	*P*	Bp and 95% CI	*P*
		14/343	18/370	21/356	27/342					
Overall	Acrylamide									
	Model 1	Ref	0.66 (0.47, 0.92)	0.81 (0.59, 1.12)	1.17 (0.87, 1.57)	0.165	0.90 (0.29, 1.51)	0.004	−0.05 (−1.74, 0.63)	0.878
	Model 2	Ref	0.70 (0.49, 0.99)	0.85 (0.61, 1.19)	1.01 (0.72, 1.42)	0.794	0.27 (−0.37, 0.90)	0.413	−0.39 (−1.18, 0.39)	0.325
	Glycidamide									
	Model 1	Ref	0.78 (0.56, 1.09)	0.95 (0.69, 1.30)	1.17 (0.86, 1.58)	0.182	0.74 (0.24, 1.24)	0.004	−0.20 (−0.76, 0.37)	0.493
	Model 2	Ref	0.81 (0.57, 1.14)	0.94 (0.67, 1.31)	1.01 (0.71, 1.42)	0.795	0.49 (0, 0.97)	0.048	−0.59 (−1.19, 0)	0.051
Males	Acrylamide									
	Model 1	Ref	0.59 (0.39, 0.90)	0.56 (0.37, 0.86)	0.98 (0.69, 1.40)	0.971	0.76 (−0.02, 1.55)	0.057	0.45 (−0.52, 1.42)	0.367
	Model 2	Ref	0.61 (0.40, 0.94)	0.57 (0.36, 0.88)	0.85 (0.56, 1.28)	0.375	0.29 (−0.56, 1.14)	0.500	−0.60 (−1.73, 0.51)	0.286
	Glycidamide									
	Model 1	Ref	0.75 (0.50, 1.12)	0.80 (0.54, 1.18)	0.95 (0.65, 1.38)	0.829	0.68 (0.01, 1.34)	0.046	−0.37 (−1.19, 0.45)	0.376
	Model 2	Ref	0.76 (0.50, 1.16)	0.77 (0.51, 1.17)	0.75 (0.49, 1.15)	0.192	0.23 (−0.43, 0.89)	0.494	−0.88 (−1.78, 0.01)	0.052
Females	Acrylamide									
	Model 1	Ref	0.81 (0.46, 1.45)	1.41 (0.85, 2.36)	1.39 (0.81, 2.38)	0.075	−0.01 (−0.90, 0.88)	0.985	−0.31 (−1.25, 0.63)	0.521
	Model 2	Ref	0.90 (0.49, 1.65)	1.58 (0.91, 2.74)	1.43 (0.77, 2.67)	0.084	0.03 (−0.94, 1.00)	0.947	−0.10 (−1.20, 0.99)	0.853
	Glycidamide									
	Model 1	Ref	0.99 (0.54, 1.82)	1.50 (0.86, 2.63)	1.87 (1.08, 3.24)	0.007	0.88 (0.18, 1.58)	0.014	0.02 (−0.72, 0.77)	0.957
	Model 2	Ref	0.92 (0.49, 1.73)	1.35 (0.75, 2.43)	1.81 (1.00, 3.30)	0.022	0.84 (0.13, 1.55)	0.020	0.02 (−0.78, 0.81)	0.965

Model 1, crude model

Model 2, age; race; gender (overall); PIR; BMI; dietary intake of calcium, sodium, and potassium; and serum cotinine levels

Acrylamide concentration: Q1 2.12–42.1 pmol/g Hb; Q2 42.2–52.6 pmol/g Hb; Q3 52.7–67.2 pmol/g Hb; Q4 67.3–499 pmol/g Hb

Glycidamide concentration: Q1 2.83–35.6 pmol/g Hb; Q2 35.8–48.8 pmol/g Hb; Q3 48.9–66.2 pmol/g Hb; Q4 66.4–400 pmol/g Hb

N_c, the number of participants free of hypertension; N_h, the number of participants with hypertension

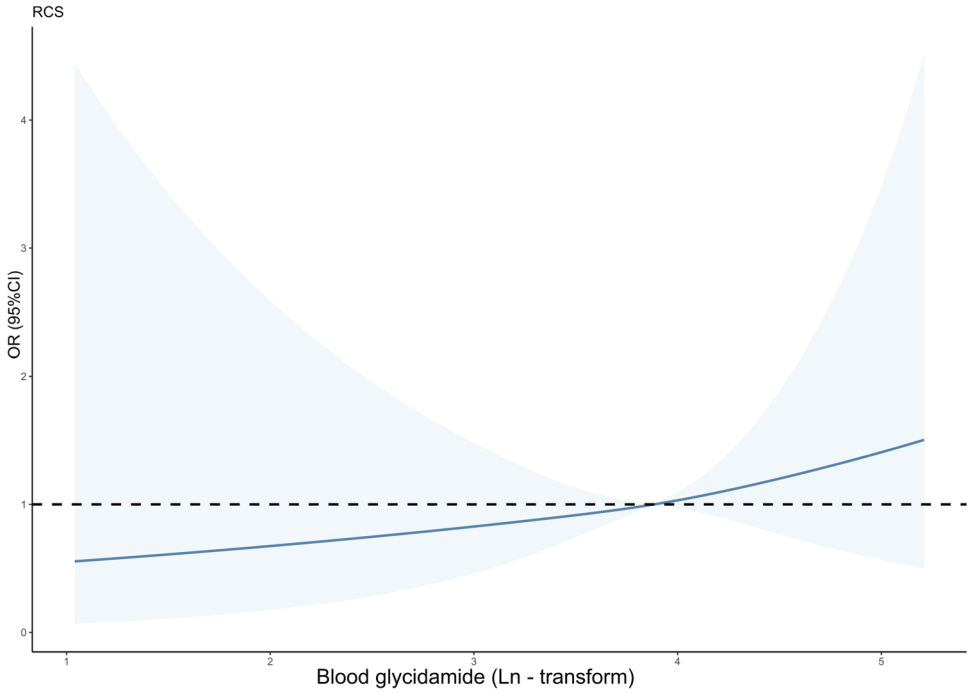

Fig. 1 Predicted spline curves for the association of hypertension with blood HbGA concentrations using restricted cubic spline regression models. HbGA, hemoglobin biomarker of glycidamide. The model was adjusted for age; race; PIR; BMI; dietary intake of calcium, sodium, and potassium; and serum cotinine levels

In the present study, we first found that GA, rather than its parent agent AA, was significantly associated with hypertension in adolescent females, which was mainly reflected in the risk of increased SBP. The results of the mediation analysis showed that disordered lipid levels and inflammatory responses mediated the association of blood GA concentration and hypertension risk. These findings have added to the evidence that AA exposure plays a crucial role in the risk of hypertension in adolescence. Greater cardiovascular benefits would be obtained from early prevention of and screening for AA exposure in adolescence, particularly among girls.

Studies have shown that AA may be produced by the Maillard reaction in foods containing asparagine and reduced sugar (Zhang et al. 2009). The intensity of AA formation depends on the initial concentration of its precursors or their ratio, temperature, duration of heat treatment, humidity, etc. (Hedegaard et al. 2008). Once ingested, AA can be rapidly disseminated to all body tissues and metabolized under the action of the cytochrome CYP2E1 enzyme to produce a more active epoxide, namely, GA (Kadry et al. 1999). GA can react with DNA molecules to form purine base adducts, which may explain the mutagenicity of AA in humans and experimental animals (Besaratinia and Pfeifer 2004). Our study showed that GA may substantially contribute to AA-induced BP increases.

A cross-sectional study in general adults from the Wuhan-Zhuhai cohort demonstrated that urinary AA metabolites, namely, N-acetyl-S-(2-carbamoyl-2-hydroxyethyl)-l-cysteine (GAMA), were significantly associated with heart rate variability reduction (Wang et al. 2020), a marker of cardiac autonomic nervous dysfunction, suggesting the early occurrence of cardiovascular injury (Feng et al. 2015). Consistent with our study, this article also highlights the high priority of addressing cardiovascular injury associated with AA, especially the adverse effect of its metabolite GA. Additionally, another recent epidemiological study conducted in the representative US adults have found significant associations between AA hemoglobin biomarkers and CVD in active smokers (Zhang et al. 2018). Unlike our finding that HbGA increases the risk of hypertension, in their study, HbGA was a protective factor for total CVD risk in people exposed to environmental tobacco smoke. However, according to their study, the protective effect of HbGA was not found in active smokers or nonexposed people. The results of another previous study in children with early stages of chronic kidney disease showed that urinary AA levels were negatively associated with high SBP and DBP levels according to 24-h ambulatory BP monitoring (Hsu et al. 2020). This discrepancy between our results and the results from previous studies is probably due to divergent age groups, health states, or exposure levels. In contrast to adults, whose main exposure is smoking, children and adolescents are mainly exposed to AA by consuming French fries, biscuits, and breakfast cereals, as they are the main consumers of these foods (Lambert et al. 2018). Previous studies have shown that AA has potential endocrine-disrupting effects (Duke et al. 2018; Matoso et al. 2019). In addition, individuals aged 12–21 years are 2–3 times more sensitive to endocrine disruption (McMullen et al. 2017). Therefore, AA may affect the health of children and adolescents through endocrine-disrupting effects.

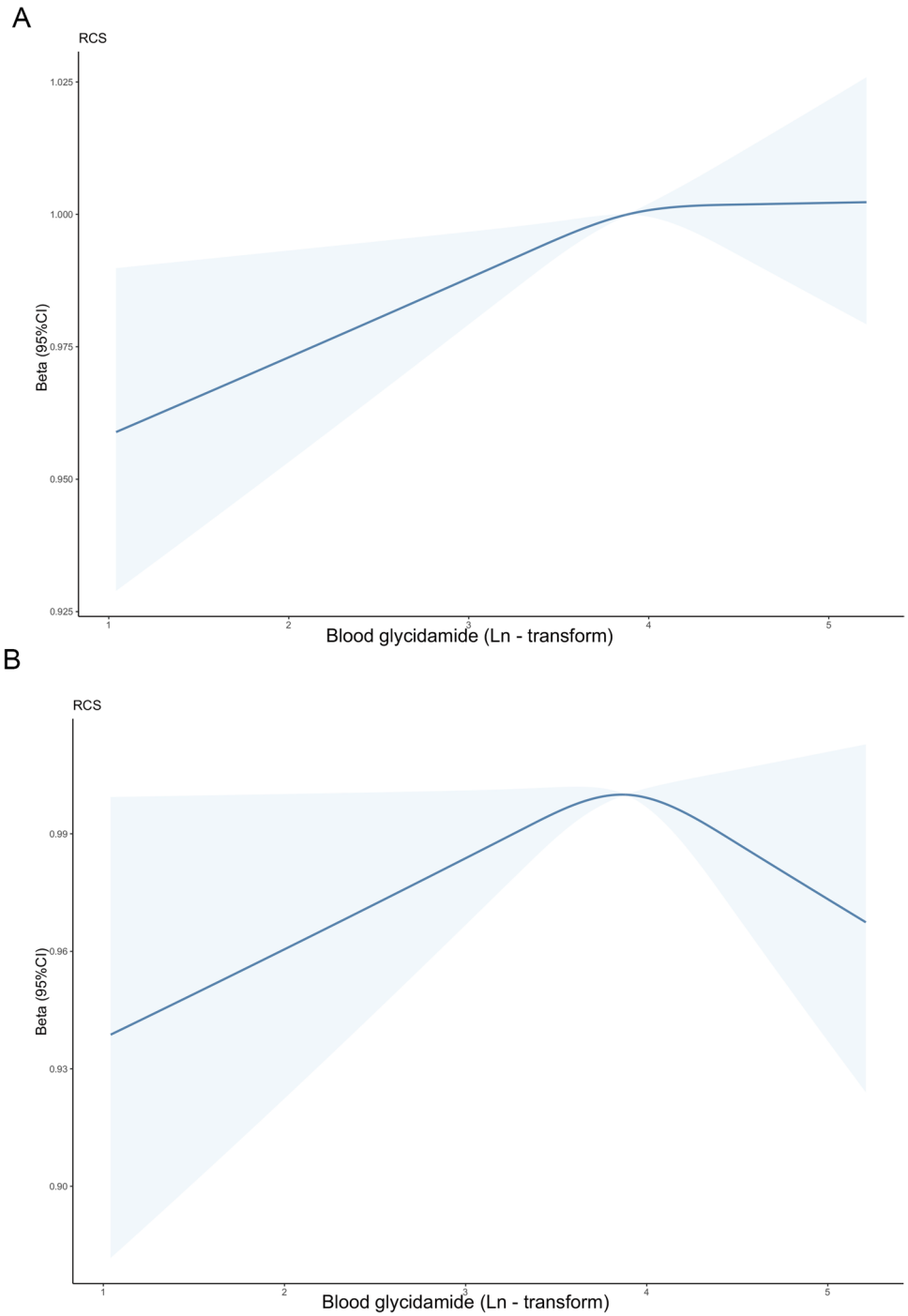

Fig. 2 Predicted spline curves for the relationships between SBP (**A**) or DBP (**B**) and blood HbGA concentrations using restricted cubic spline regression models. HbGA, hemoglobin biomarker of glycidamide. The model was adjusted for age; race; PIR; BMI; dietary intake of calcium, sodium, and potassium; and serum cotinine levels

In recent decades, the toxicological effects of AA on neurogenesis, reproduction, development, carcinogenesis, and mutagenesis have been well elucidated (Besaratinia & Pfeifer 2004; Huang et al. 2019; Matoso et al. 2019). However, the cardiovascular effects of AA have only been confirmed in a few studies. A study in zebrafish embryos showed that treatment with AA at 2.0 mM by 96 hpf resulted in a deficient cardiovascular system with a weak contractile function of the cardiac chambers and a lowered heart rate (Huang et al. 2018b), which was associated with oxidative stress status and disordered lipid distribution in the heart region of developing zebrafish. Another in vitro study revealed that AA could lead to lipoprotein metabolism disorder by modifying the functional and structural properties of lipoproteins or enhancing the oxidation and degradation of LDL and the uptake of LDL by macrophages, which both ultimately promote the exacerbation of atherosclerosis (Kim et al. 2015). Another previous animal study found that rat plasma TC and

Table 3 Multivariate analysis of the association of the HbGA levels and mean changes (95% CI) in the blood lipids and inflammation parameters in girls

	Mean	95% CI	*P* value
Blood lipids (mg/dL)			
Serum triglyceride	5.23	−0.65, 11.11	0.081
HDL cholesterol	0.65	−0.33, 1.63	0.192
LDL cholesterol	1.52	−1.59, 4.63	0.337
Total cholesterol	2.83	0.49, 5.18	0.018
Inflammation parameters			
WBC (10^9/L)	0.13	−0.03, 0.19	0.105
CRP (mg/dL)	0.02	−0.03, 0.07	0.451

Adjust as age, race, PIR, serum cotinine, BMI, calcium, sodium, and potassium

Hemoglobin biomarker of glycidamide (HbGA) levels were ln transformed

WBC, white blood cell; *CRP*, C-reactive protein

LDL-C levels were increased, while HDL-C and TGs were decreased when administered both aluminum and AA daily for 21 days (Ghorbel et al. 2015). These experimental results suggest that the cardiovascular toxicity caused by AA may be related to abnormal lipoprotein metabolism, which is in accordance with our results. Through mediation analysis, we observed that the increase in HbGA was related to the increase in TC.

In the present study, we discovered a significant sex difference in the associations between AA exposure and hypertension prevalence in adolescents. To our knowledge, this is the first study to uncover this difference in adolescents. This finding may be related to the potential impact of AA on the sex hormone system, in which girls have higher estrogen levels than boys (Nagata et al. 2018). Sex hormones were deemed to play a critical role in BP (Marrocco and McEwen 2016). In addition, a greater susceptibility of females to environmental pollutants was speculated. More epidemiological and mechanistic studies are warranted to verify the sex difference in the AA exposure effect and to elucidate the potential reasons.

The present study has some critical strengths. First, the NHANES data provide a relatively large, general population sample and are nationally representative. In addition, AA intake was measured by hemoglobin adducts in the laboratory, while some previous studies evaluated it by food frequency questionnaires (Freisling et al. 2013), which may ignore exposure pathways such as smoking. Furthermore, we conducted separate analyses stratified by sex, which can explore the sensitivity of different groups to environmental chemicals. The limitations of this study need to be addressed. First, the cross-sectional design hindered the confirmation of causal relationship between AA exposure and hypertension outcomes. Second, AA and GA concentrations are usually standardized by hemoglobin concentration, but hemoglobin status is probably affected by age, sex, smoking, and alcohol consumption, which may increase the risk of misclassification of population samples. A previous study in the US NHANES population verified that sex, age, and race had no significant effect on acrylamide exposure, and hemoglobin adducts of HbAA and HbGA could be used to estimate relative exposure and validate intake estimates (Vesper et al. 2010). Additionally, measurement of HbAA and HbGA only at one time point may not reflect the long-term average exposure level of the population (Obon-Santacana et al. 2016). Finally, although covariates were adjusted for in the models, possible effects of residual confounding factors, such as early life factors (e.g., maternal smoking and premature delivery) and school status, could not be ruled out. Many environmental chemical exposures may be associated with hypertension risk, and other chemicals were not

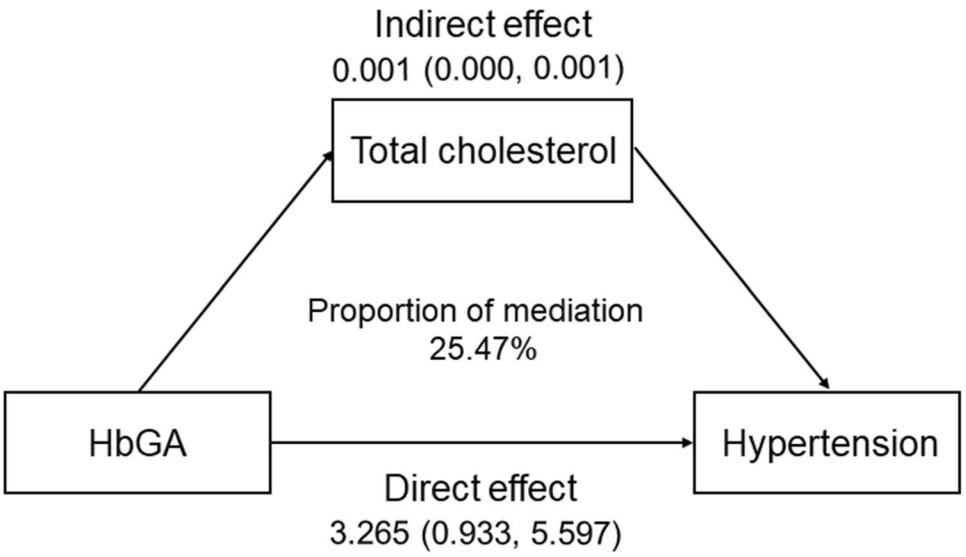

Fig. 3 Assessment of the mediating effects of serum TC on the association between serum HbGA level and hypertension in girls. The model was adjusted for age; race; PIR; BMI; dietary intake of calcium, sodium, and potassium; and serum cotinine levels

assessed in our analysis. Future studies may need to further assess the impact of the interaction of different chemicals on the risk of hypertension.

Conclusion

Higher AA exposure is associated with increased SBP and risk for hypertension, and these associations may be stronger among girls. In particular, our findings indicate that the TC may be a mediator of the SBP increase caused by AA exposure. In view of this study, universal AA screening beginning during or before adolescence is advocated. Furthermore, it is necessary to explore the causal relationship between AA exposure and hypertension and further reveal its related mechanism.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11356-021-18342-0.

Acknowledgements The authors are grateful to members of the National Center for Health Statistics (NCHS) of the Centers for Disease Control (CDC) and Prevention and the participants who enrolled in the National Health and Nutrition Examination Survey.

Author contribution Aihua Gu, Cheng Xu, and Jingjia Liang conceived and designed the study and the model, performed the analyses, and drafted the manuscript. Jingjia Liang, Qing Yan, Qian Liu, and Zhenkun Weng supported the model parameterization, conducted the statistical analyses, and participated in the drafting of the article. Xin Zhang and Jin Xu revised the manuscript. All authors have read and approved the final manuscript.

Funding This work was supported by funding from the National Key Research and Development Program (2019YFA0802701); the National Science Foundation of China (81900281, 91839102, 91943301); and the China Postdoctoral Science Foundation (2021M691641).

Data availability All data generated or analyzed during this study are included in this published article and its supplementary files.

Declarations

Ethics approval and consent to participate Survey participants signed consent forms and agreed to storage of their blood samples for future research. The CDC/NCHS Ethical Review Board approved the NHANES study and approved its dissemination to the public.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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