The association between coronary artery disease and glyphosate exposure found in pesticide factory workers

Liping Pan[1*], Ming Xu[1*], Dandan Yang[1*], Boshen Wang[1,2], Qiuni Zhao[1,3], En-Min Ding[1], Baoli Zhu[1]

[1]Jiangsu Provincial Center for Disease Prevention and Control, Nanjing 210009, China; [2]Department of Occupational and Environmental Medicine, School of Public Health, Nantong University, Nantong 226000, China; [3]Department of Occupational and Environmental Medicine, School of Public Heath, Southeast University, Nanjing 210000, China

Contributions: (I) Conception and design: B Zhu, L Pan, B Wang; (II) Administrative support: D Yang, B Zhu ; (III) Provision of study materials or patients: M Xu; (IV) Collection and assembly of data: B Wang; (V) Data analysis and interpretation: M Xu, L Pan; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*These authors contributed equally to this work.

Correspondence to: Baoli Zhu. Institute of Occupational Disease Prevention, Jiangsu Provincial Center for Disease Prevention and Control, No. 172 Jiangsu Road, Nanjing 210009, China. Email: zhubl@jscdc.cn.

Background: Glyphosate is a widely used herbicide in the world. Coronary artery disease (CAD) has been recognized as widespread causes of death and disability. In our study, we aimed to investigate the difference in results of health examination among people whether exposed to glyphosate or not.

Methods: We recruited workers from glyphosate production line as the exposed group and workers without doing pesticide production as the non-exposed group. All the participants have taken health examination as well as finished personal health questionnaires. A total of 42 patients with CAD were found among the return patients. Individual and fix-point samplings were performed to monitor the level of glyphosate in workplace air around the production line. Glyphosate and AMPA in the plasma were measured by gas chromatography combined with GC/MS method. The association between measured variables and the incidence of CAD was evaluated in unconditional logistic regression models.

Results: The highest levels of permissible concentration-time weighted average (PC-TWA) (0.01–94.59 mg/m^3) and permissible concentration-short term exposure limit (PC-STEL) (0.01–20 mg/m^3) were separately presented in the jobs like packing and drying. The average concentration of glyphosate and its metabolin aminomethylphonic acid (AMPA) 85481 in blood plasma was 9.13 and 4.20 ng/mL, respectively. Forty-two percent of glyphosate workers admitted wearing gauze mask or spectacles seldom worn when they worked. The incidence rates of hypertension, CAD, abnormal rate of ECG, total liver function index [including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein (TP)] and summary of renal function index were found significantly higher in the exposed group than non-exposed group (P<0.05). According to the regression analysis, variables entered into the equation of logistic regression model were glyphosate exposure (P=0.032, OR =2.300, 95% CI =1.075–4.920), BMI (P=0.008, OR =1.135, 95% CI =1.034–1.245), hyperlipemia (P=0.049, OR =2.085, 95% CI =1.005–4.328) and alcohol user (P<0.001, OR =9.755, 95% CI =4.127–23.057). The regression model fitting test of glyphosate was also showed statistically significance (P<0.05).

Conclusions: Our results suggested that glyphosate might be a potential hazard factor to CAD.

Keywords: Coronary artery disease (CAD); glyphosate exposure; aminomethylphonic acid (AMPA)

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Introduction

Glyphosate (N-phosphonomethyl glycine) is an herbicide against problems of annual and perennial weeds, which is widely used in agricultural, forestry, and residential markets (1). In the U.S. agriculture, glyphosate was the second most commonly used pesticide, with a rising consumption based on the evolution of glyphosate-resistance crops. In China, more than twenty glyphosate production enterprises existed, which occupied 70% of the global capacity. Though glyphosate accounted for the biggest chunk of herbicides utilized in China, its exposure was not monitored.

Glyphosate is primarily released into the environment during its application, and unintentional release of glyphosate from wind-drift and accident spillage can result in its spreading to air, surface and underground water, soil and plants (2). Furthermore, glyphosate and its degradation product-aminomethylphonic acid (AMPA) could be detected to depths up to 1 m. Toxicity studies and poisoning cases of glyphosate were reported constantly (3). As reported, glyphosate had low oral acute mammalian toxicity [lethal dose for 50% of rats (LD50) >4,320 mg/kg] (1). Meanwhile, studies conducted the no-observed-effect level (NOEL) for systemic chronic toxicity was 8,000 ppm (1). The regulatory agencies have concluded that it was not a mutagen, carcinogen, teratogen, or reproductive or developmental toxicant till now (4). In 1973, the World Health Organization (WHO) suggested that 500,000 cases of acute serious pesticide poisoning occurred annually, and 3 million cases hospitalized with 220,000 deaths in 1985 (5). Millions of farmers and workers suffered from poisoning and death in developing countries, and occupational exposures and also suicide made glyphosate based herbicides toxicity a worldwide concern.

Coronary disease was the top cause of death in American and many other developed countries in 20 century. In China, the number of CAD patients reached 290 million now, which might even tend to an increasing trend in the future. More than 17 million died on this account (6-8). Based on the Global Burden of Disease Study, cardiovascular and circulatory diseases took over 11.8% of global DALYs (disability-adjusted life years), mainly including anemic heart disease (5.2%), hemorrhagic apoplexy (2.5%), cerebral arterial thrombosis (1.6%), and hypertensive heart disease (0.6%) (7). The leading pathophysiology mechanisms of CAD was atherosclerosis (9) a chronic process characterized by the sedimentation of excessive cholesterol in the arterial intima (10). Elevated serum levels of total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL) etc. were the most imperative risk factors for atherosclerotic vascular diseases (11-16). Till now, the acute clinical impairments of glyphosate were described variously, especially gastrointestinal, cardiovascular, respiratory, hematological, hepatonephric, metabolic, neurological, dermal, and ophthalmological diseases with high doses (17-19). Lots of studies have researched an association between glyphosate intoxication and cardiovascular (20-24). Life-threatening arrhythmias might be the cause of death in glyphosate based herbicides intoxication. QTc prolongation and arrhythmias along with first-degree atrioventricular block were observed after glyphosate based herbicides intoxication. However, the potential chronic impacts of glyphosate with low dose were still unidentified. In our study, we intended to investigate whether there were associations between chronic exposure of glyphosate and CAD.

Methods

Study population

Six representative glyphosate enterprises in two Province with an average annual output ranging from 30,000 to 70,000 ton were chosen as the study area. The workers from glyphosate production line were recruited as the exposed group and workers without pesticide production as the non-exposed group in March 2013. People with history of liver and kidney disease, angiocardiopathy, or hypotensor drug users were excluded from the study.

Data collection

The study has lasted for two years. All the participants took a health examination including department of internal medicine examination, blood biochemistry, routine urine test, type-B ultrasonic, chest X-ray, and electrocardiogram. Height, weight, and sitting blood pressure were measured at the same time. Fasting blood samples were taken from the subjects, and the sera was isolated and stored at –80 ℃ until analysis. Each enrolled individual was asked to complete a questionnaire that included general demographic data, personal life habit such as smoking and drinking disease history, family disease history, occupational exposure and protective measures. Smoking history referred to at least one cigarette per day for more than six months. Drinking history referred to drinking at least once a week, lasting for more than one year. An informed consent with appropriate forms was signed to enable the use of resulting data on research purposes.

Field monitoring and sample detection

Individual sampling was performed by putting a small sampling instrument in the worker's pocket with clips containing filter paper on their collar, as close as possible to their breathing zone, sampling for 8 hours with a flow of 2 L/min. Short time sampling was carried out at each sampling point during production line running, which would take 15 minutes with a flow of 5 L/min. Ultra-fine glass fiber filter paper was used to collect glyphosate with Dust Sampler from the workplace air. After having been ultrasonically eluted with deionized water, samples were determined by ion chromatography using a conductivity detector. Monitoring sites were in the line of glyphosate production including centrifugation, crystallization, oxidation, sucking filtration, drying, and packing. Samples could be stored at room temperature for at least seven days. The minimum detectable concentration of this method was 0.00041 mg/m^3 (calculated by sampling 75 L of air). Within the range of 0.05–1.00 mg/L, a linear relationship was found with mean values of the peak area and concentration of glyphosate. The sampling efficiency was 100%. The elution efficiency ranged from 94.5% to 96.7%. The recovery rate ranged from 94.8% to 97.4%.

Plasma samples were dried completely after being derivatized with trifluoroacetic anhydride (TFAA) and heptafluorobutanol (HFB), and then being dissolved by 0.2% citral ethyl acetate solution. Glyphosate and AMPA in the extracts were measured by gas chromatography combined with mass spectrometry (GC/MS) method with DB-5MS capillary column and EI ion-source. The calibration curves of glyphosate and AMPA in the samples were linear over the concentration ranges of 10–400 ng/mL. The limits of detection were 4.05, 1.87 ng/mL for glyphosate and AMPA, respectively. The limit of quantitation (LOQ) of glyphosate was 14.34 ng/mL, and the LOQ of AMPA was 4.31 ng/mL. Recovery rate of glyphosate in this study ranged from 70.56–106.28%, and recovery rate of AMPA ranged from 90.06–100.76%.

Diagnostic for coronary artery disease (CAD)

The diagnosis of CAD was based on typical clinical diagnosis, electrocardiographic changes and coronary angiography. Coronary angiography was performed among patients with further consultation. The selected CAD patients were subjects to significant coronary stenosis (≥50%) in at least either one of the three main coronary arteries or their major branches. In addition, angiographic severity of disease was defined as single or multi-vessel disease on the basis of a number of involved artery (luminal narrowing ≥50%) in the three major coronary arteries (25,26).

Statistical analyses

Categorical variables were presented as frequencies and percentages. Continuous variables were summarized in terms of means and standard deviations, or medians and geometric means of variables with skewed distributions. The difference in composition ratio and rate was compared by using Trend chi square test or Fisher's exact test. The association between measured variables and the presence of CAD were evaluated in an unconditional logistic regression model. Statistical analyses were performed with SPSS statistical package (SPSS Inc., Chicago, Illinois). $P<0.05$ were considered to be statistically significant.

Results

Characteristics of the study population

The baseline characteristics of exposed group and non-exposed group are compared in *Table 1*. Overall, the incidences of hypertension, CAD were significantly higher in exposed group than non-exposed group (34.1% *vs.* 15.5% and 8.0% *vs.* 3.7%, respectively). Compared to the non-exposed group, workers exposed to glyphosate had significantly higher abnormal rate of ECG (32.1% *vs.* 20.1%), total liver function index (33.2% *vs.* 9.2%), ALT (13.2% *vs.* 5.7%), AST (4.1% *vs.* 1.4%), TP (10.4% *vs.* 6.0%), and summary of renal function index (22.5% *vs.* 16.0%).

Although, data from the questionnaires showed that most of subjective symptoms occurred more seriously in the exposed group than non-exposed group, no statistically significant difference in incidence was calculated between these two groups. Incidence rates of headache, insomnia and dreamful sleep, palpitate, irritability, whole body fatigue, anorexia, cough or bronchitis, nausea and vomiting, pruritus or dermatitis, bellyache were 9.6%, 7.1%, 4.4%, 6.0%, 6.3%, 4.1%, 3.8%, 2.5%, 5.8%, 2.2%, in exposed group, and 7.4%, 5.7%, 3.2%, 3.7%, 5.9%, 3.2%, 5.4%, 2.0%, 4.9%, 1.7% in non-exposed group, respectively (shown in *Table 1*).

Field monitoring results

Description analysis of permissible concentration-

Table 1 Demographic, clinical characteristics of exposed group and non-exposed group

Group	Non-exposed group (n=349)	Exposed group (n=364)	χ^2	P value
Gender (male/female)	277/72	281/83	0.494	0.482
Age, years	41.16±7.56	42.21±8.20	–	0.075
Working age, years	13.23±9.48	10.81±9.68	–	0.110
Exposed years	–	5.00±4.18	–	–
BMI, kg/m^2	24.83±3.92	25.04±3.72	–	0.455
Electrocardiographic abnormality, n (%)	70 (20.1)	117 (32.1)	13.450	<0.001
Hypertension, n (%)	54 (15.5)	124 (34.1)	32.881	<0.001
SP, mmHg	118.12±16.38	125.18±19.98	–	<0.001
DP, mmHg	77.66±11.30	83.91±11.11	–	<0.001
Diabetes, n (%)	9 (2.6)	6 (1.6)	0.749	0.387
Lipid levels, n (%)				
TG	115 (33.0)	98 (26.9)	3.091	0.079
TC	90 (25.8)	107 (29.4)	1.160	0.282
LDL	42 (12.0)	56 (15.4)	1.687	0.094
Total	164 (46.9)	165 (45.3)	0.198	0.656
Abnormal chest X-ray, n (%)	9 (2.6)	17 (4.7)	2.218	0.136
Abnormal liver function, n (%)				
ALT	20 (5.7)	48 (13.2)	11.481	0.001
AST	5 (1.4)	15 (4.1)	4.723	0.030
TBIL	24 (6.9)	34 (9.3)	1.447	0.229
TP	21 (6.0)	38 (10.4)	4.591	0.032
A/G	16 (4.6)	27 (7.4)	2.523	0.112
Total	32 (9.2)	121 (33.2)	61.261	<0.001
Abnormal renal function, n (%)				
BUN	24 (6.9)	37 (10.2)	2.462	0.117
Cr	5 (1.4)	3 (0.8)	Fisher	0.497
UA	35 (10.0)	52 (14.3)	3.014	0.083
Total	56 (16.0)	82 (22.5)	5.618	0.018
CAD (+) , n (%)	13 (3.7)	29 (8.0)	5.784	0.016
Smoke, n (%)	103 (29.5)	116 (31.9)	0.464	0.496
Alcohol user, n (%)	26 (7.4)	35 (9.6)	1.068	0.301
Subjective symptoms, n (%)				
Headache	26 (7.4)	35 (9.6)	1.068	0.301
Insomnia and dreamful sleep	20 (5.7)	26 (7.1)	0.589	0.443
Palpitate	11 (3.2)	16 (4.4)	0.756	0.384
Irritability	13 (3.7)	22 (6.0)	2.053	0.152
Whole body fatigue	20 (5.9)	23 (6.3)	0.109	0.742
Anorexia	11 (3.2)	15 (4.1)	0.476	0.490
Cough or bronchitis	19 (5.4)	14 (3.8)	1.031	0.310
Nausea and vomiting	7 (2.0)	9 (2.5)	0.123	0.726
Pruritus or dermatitis	17 (4.9)	21 (5.8)	0.285	0.594
Bellyache	6 (1.7)	8 (2.2)	0.212	0.645

Table 1 (*continued*)

Table 1 (*continued*)

Group	Non-exposed group (n=349)	Exposed group (n=364)	χ^2	P value
Occupational protection, n (%)				
Always	202 (58.0)			
Less than 1 h	83 (24.0)			
Never	64 (18.0)			

Note: data are mean ± SD for continuous variables, or frequency and percentage for categorical variables. Abbreviations: BMI, body mass index; SP, systolic pressure; DP, diastolic pressure; TG, total glyceride; TC, total cholesterol; LDL, low-density lipoprotein; ALT, alanine aminotransferase; AST, aspartate transaminase; TBIL, total bilirubin; TP, total protein; A/G, ALB/GLB; BUN, blood urea nitrogen; Cr, creatinine; UA, uric acid; CAD, coronary artery disease.

Table 2 Results of field monitoring in workplace air

Item	PC-TWA (mg/m^3)	PC-STEL (mg/m^3)
Number of samples	56	100
Range	0.01–94.59	0.01–20.68
Median	0.40	0.05
Geometric mean	0.41	0.10

Note: data are geometric mean, median and range for continuous variables. Abbreviations: PC-TWA, permissible concentration-time weighted average; PC-STEL, permissible concentration-short term exposure limit.

time weighted average (PC-TWA) and permissible concentration-short term exposure limit (PC-STEL) are shown in *Table 2*. We collected 56 samples by individual sampling, and 100 samples by fixed point sampling along the glyphosate production line. The geometric mean and median of PC-TWA were 0.41 and 0.40 mg/m^3, respectively (ranging from 0.01 to 94.59 mg/m^3). The geometric mean of PC-STEL was 0.10 mg/m^3, and its median was 0.05 mg/m^3 (ranging from 0.01 to 20 mg/m^3). The highest levels of PC-TWA and PC-STEL were separately presented in jobs like packing and drying. Besides, data from work habits in questionnaires also revealed the occupational protective information in working hours (*Table 1*). Among the subjects working in the glyphosate production line, 202 workers (58%) wore gauze mask, protective spectacles and gloves at work all the time, 83 workers (24%) less than one hour a day, and 64 workers (18%) neither gauze mask nor protective spectacles at their work time.

Determination of glyphosate

Blood plasma was collected from workers at the same time when they were taking health examinations, which stored at –80 ℃ until analysis. By the GC/MS method described above, the average concentration of glyphosate and its metabolin AMPA in blood plasma were 11.73 and 5.29 ng/mL, respectively. The median concentration of glyphosate in plasma was 5.51 ng/mL, ranging from undected to 45.16 ng/mL. And the median concentration of AMPA was 2.30 ng/mL, ranging from undected to 20.03 ng/mL.

The association between coronary artery disease (CAD) and glyphosate

In order to do further identification of the association between glyphosate exposure and CAD, logistic regression analysis was performed (*Table 3*). Variables entered into the equation of unconditional logistic regression model were glyphosate exposure, BMI, hyperlipemia and alcohol user following the protocol (P<0.10). The regression model fitting test was statistically significant (P<0.05). We considered glyphosate exposure (P=0.032, OR =2.300, 95% CI =1.075–4.920), BMI (P=0.008, OR =1.135, 95% CI =1.034–1.245), hyperlipidemia (P=0.049, OR =2.085, 95% CI =1.005–4.328) and alcohol (P<0.001, OR =9.755, 95% CI =4.127–23.057) as risk factors of CAD.

Discussion

Recently, mounting researches about glyphosate's damages on cardiovascular disease had been carried out. However, most studies evaluated the outcomes of acute glyphosate exposure. In the present study, we firstly intended to investigate the clinical impact of chronic glyphosate exposure with low dose. Our study suggested the chronic glyphosate might be a significant risk factor of CAD in China population.

Frequent toxic consequences of glyphosate were

Table 3 Logistic regression analysis of factors influencing prevalence of CAD in workers

Factors	N (%)	P value	OR (95% CI)
Exposure			
No	364 (51.1)	–	1.000
Yes	349 (48.9)	0.032	2.300 (1.075–4.920)
Gender			
Male	558 (78.3)	–	1.000
Female	155 (21.7)	0.572	0.743 (0.265–2.081)
Age, years			
<45	399 (56.0)	–	1.000
≥45	314 (44.0)	0.485	1.016 (0.972–1.062)
BMI, kg/m^2			
<24	242 (33.9)	–	1.000
≥24	471 (66.1)	0.008	1.135 (1.034–1.245)
Diabetes			
No	698 (97.9)	–	1.000
Yes	15 (2.1)	0.149	2.995 (0.675–13.291)
Hyperlipemia			
No	535 (75.0)	–	1.000
Yes	178 (25.0)	0.049	2.085 (1.005–4.328)
Chest X-ray			
Normal	687 (96.4)	–	1.000
Abnormal	26 (3.6)	0.369	0.376 (0.045–3.177)
Liver function			
Normal	560 (78.5)	–	1.000
Abnormal	153 (21.5)	0.886	1.062 (0.470–2.397)
Renal function			
Normal	575 (80.6)	–	1.000
Abnormal	138 (19.4)	0.717	1.154 (0.531–2.511)
Smoke			
No	494 (69.3)	–	1.000
Yes	219 (30.7)	0.541	0.782 (0.354–1.724)
Alcohol use			
No	652 (91.4)	–	1.000
Yes	61 (8.6)	0.000	9.755 (4.127–23.057)

Assignment: exposure (exposed group =2, non-exposed group =1); sex (male =1, female =2); diabetes (yes =2, no =1); hyperlipemia (yes =2, no =1); abnormal chest X-ray (yes =2, no =1); abnormal liver function (yes=2, no=1); abnormal renal function (yes =2, no =1); smoker (yes =2, no =1); alcohol user (yes =2, no =1).

investigated after suicide or accidence. In these situation, hepatic and kidney toxicity were the primary endpoint of glyphosate intoxications. In rat experiments, degenerative changes in hepatocytes especially in portal area were observed after administered glyphosate with a high dose. Meanwhile, glomerular degeneration, mononuclear cells infiltration were also found in kidney organs (27). In the present study, we also noticed the abnormal liver and renal functions in the glyphosate exposure group (P<0.001 and P=0.018). These results also suggested that chronic glyphosate exposure with a low dose also might cause the damage of metabolic system.

Based on recent studies, the association between glyphosate intoxication and cardiovascular were distinctly revealed. In a suicidal case, up to 500 mL of glyphosate ingestion leading to a QTc prolongation and life-threatening arrhythmias was considered as the cause of death (19). However, data in human reporting cardiovascular effects on chronic glyphosate exposure with a low dose were quite few. In our study, higher morbidity of CAD in glyphosate group reminded us that glyphosate was a hazardous factor for workers and farmers. As reported by Lakshmi *et al.*, the down-regulation of ES-SOD, because of its hypermethylation, could finally resulted in CAD (28), which was consistent with the consequence of Roundup (glyphosate 41%) (induced 27% decrease of SOD activity) (29). Based on these studies, the mechanism of glyphosate leading to CAD might involve the suppression of SOD.

In our study, there were several limitations. First, the research was based on a professional cohort study. However, this cohort population has been established for only two years. There were few patients for further investigation of glyphosate molecular poisonousness in CAD. Second, lack of sample in different dose exposure of glyphosate limited us to a trend testing. Third, for ethical reasons, we did not identify our statistical analysis results in normal cardiac tissue.

Conclusions

In conclusion, glyphosate exposure along with BMI, hyperlipemia and alcohol use was found a risk factor of CAD, which reminded us the potential chronic effects on human-beings of glyphosate herbicide.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jphe.2016.12.04). BZ serves as an Editor-in-Chief of *Journal of Public Health and Emergency* from Jan. 2017 to Dec. 2022. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).The study was approved by the ethics institutes. An informed consent with appropriate forms was signed to enable the use of resulting data on research purposes.

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