

Association Between Blood Ethylene Oxide Levels and The Prevalence of Hypertension

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Abstract

The relationship of blood ethylene oxide levels with hypertension and blood pressure has not been addressed. A total of 5005 participants from the National Health and Nutrition Examination Survey (NHANES) 2013–2016 were enrolled. Hypertension was defined as a mean systolic blood pressure (SBP) of at least 140 mmHg, a mean diastolic blood pressure (DBP) of at least 90 mmHg, or both, and/or the self-reported use of prescription drugs for diagnosed hypertension. Generalized linear regression models and restricted cubic spline plots were performed to explore the associations of ethylene oxide levels with hypertension and blood pressure. The prevalence of hypertension in the study sample was 27.6%. After adjusting for confounding factors, compared with the lowest quantile, the odds ratios (ORs) with 95% confidence intervals (CIs) of hypertension across the quantiles of ethylene oxide levels were 0.80 (0.63, 1.03), 0.91 (0.71, 1.16), and 1.39 (1.06, 1.82), respectively (P for trend 0.001). Compared with the lowest quantile, the highest quantile of blood ethylene oxide levels was significantly associated with the worst DBP profile by approximately 2.67 mmHg. Blood ethylene oxide levels showed a strong nonlinear and positive association with DBP, while no significant association was observed between blood ethylene oxide levels and SBP. These results provide epidemiological evidence of elevated blood levels of ethylene oxide in relation to a higher prevalence of hypertension and higher DBP. Further study is warranted to address these issues.

1. Introduction

Hypertension is a global health problem that can lead to serious consequences, including renal failure, cardiovascular disease (CVD), stroke and other chronic diseases (Hamrahian and Falkner, 2017; Lackland and Weber, 2015; Lamprea-Montealegre et al., 2018). Hypertension was also identified as a vital influential risk factor contributing to disability-adjusted life-years worldwide (Virani et al., 2021). Therefore, the discovery and reduction of hypertension exposure factors have significant public health benefits.

Ethylene oxide is an important industrial and environmental chemical and has been classified as a Group 1 human carcinogen by the International Agency for Research on Cancer (Yang et al., 2018). There are two pathways of ethylene oxide exposure, endogenous and exogenous pathways, and the endogenous pathway is a major source of exposure among the general population (Rasool and Malik, 2021). Environmental exposure to ethylene oxide occurs during its production and use, such as gaseous sterilant for medical devices and as a fumigant to disinfect food products such as spices. Ethylene oxide is a gas at room temperature, and inhalation is the primary method of human exposure. After inhalation, ethylene oxide is easily absorbed into the blood and rapidly distributed throughout the human body (Jinot and Fritz, 2018). As described in the previous literature, ethylene oxide is directly responsible for increased oxidative stress and related disorders (Rasool and Malik, 2021), while increased oxidative stress is a central mechanism contributing to elevated blood pressure (Prado et al., 2021). In view of the former considerations, we hypothesize that ethylene oxide is positively correlated with hypertension.

Thus, in the present study, we aimed to explore whether elevated blood ethylene oxide levels were independently associated with an increased prevalence of hypertension and blood pressure using nationally representative data from the National Health and Nutrition Examination Survey (NHANES) series.

2. Methods

2.1. Study population

Our study included 20146 participants from the 2013–2016 NHANES conducted by the Centers for Disease Control and Prevention (CDC) National Center for Health Statistics (NCHS). We retrieved all data from the website of the NCHS (<https://www.cdc.gov/nchs/nhanes/index.htm>). To analyze the effects of ethylene oxide on hypertension, we excluded subjects with missing ethylene oxide (n=14700), systolic blood pressure (SBP) and diastolic blood pressure (DBP) data (n=404). We also excluded pregnant women (n=37). Finally, a total of 5005 participants were included in our analysis (Fig. 1). All participants provided written informed consent, and the study protocol was approved by the Research Ethics Review Board of the NCHS.

2.2. Assessment of ethylene oxide levels

Human whole blood samples were collected in a mobile examination center. Blood ethylene oxide levels were measured by a modified Edman reaction method. The detailed measurement of blood ethylene oxide concentrations is described in detail elsewhere (wwwn.cdc.gov/nchs/data/nhanes/2015-2016/labmethods/AMDGYD_ETHOX_I_MET.pdf). The limit of detection (LOD) for blood ethylene oxide concentrations was 12.90 pmol/g Hb, while the analytic results below the LOD were recorded as the LOD values divided by the square root of 2.

2.3 Blood pressure measurements

Trained physicians used a calibrated mercury sphygmomanometer using a standardized protocol to measure arterial blood pressure, and 3 consecutive blood pressure readings were taken for each participant on the same arm. Hypertension was defined as a mean SBP of at least 140 mmHg, a mean DBP of at least 90 mmHg, or both, and/or the self-reported use of prescription drugs for diagnosed hypertension (Muntner et al., 2020).

2.4 Additional Data

We selected data consistent with previous studies (Liao et al., 2020; Liu et al., 2021) and current NHANES guidelines. Data on demographic characteristics, body examinations, medication use, and socioeconomic background were selected as appropriate. Data on age, sex (male/female), race/ethnicity (Mexican

American, other Hispanic, non-Hispanic White, non-Hispanic Black, other race), education (<9th grade, 9–11th grade, high school,

college, and graduate), smoking status (smoking more than 100 cigarettes during their lifetime or not), diabetes mellitus (yes/no), alcohol use (consumed at least 12 drinks in the last 12 months or not), poverty-to-income ratio, and physical activity level (none, moderate and vigorous) was based on self-reports. Body mass index (BMI, kg/m²) was calculated as body weight divided by height squared. Information on dietary intake of calories, sodium, and potassium was also considered as covariates in our analysis models.

2.5. Statistical analysis

All statistical analyses were performed by R software (v3.6.0; R Foundation for Statistical Computing). Baseline characteristics were compared across the quantiles of blood ethylene oxide levels using 1-way ANOVA for continuous variables and χ^2 tests for categorical variables. Since the ethylene oxide levels were skewed, we log₂ transformed the data. Simple and multiple generalized linear regression models were performed to explore the associations of ethylene oxide levels with hypertension and blood pressure. Restricted cubic spline plots with 3 knots located at the 10th, 50th, and 90th percentiles of the distribution were generated to explore the potential nonlinear relationship between ethylene oxide levels and hypertension and blood pressure. Participants who reported taking antihypertensive medications were omitted from further separate statistical models, and adjusted regression coefficients (β) were obtained to estimate the association of ethylene oxide levels with SBP and DBP (n=3994). Generalized linear regression models and restricted cubic spline models were all adjusted for age, sex, education level, race, diabetes mellitus, smoking status, alcohol use, body mass index, poverty-income ratio, energy intake, sodium intake, potassium intake, and physical activity level. Subgroup analysis stratified by age, sex, diabetes, obesity, and physical activity level was performed because they were important confounding factors of hypertension. A *P* value < 0.05 was regarded as statistically significant in our study.

3. Results

3.1 Baseline characteristics

The baseline characteristics of the study subjects across the quantiles of blood ethylene oxide levels are shown in Table 1. Differential significance was found for age, sex, education level, race/ethnicity, smoking status, alcohol use, BMI, dietary energy intake, dietary sodium intake, dietary potassium intake, poverty-to-income ratio, and physical activity level. The prevalence of hypertension in the study sample was 27.6%, and the prevalence of hypertension across the quantiles of blood ethylene oxide levels was 28.5%, 23.2%, 24.8% and 33.7%, respectively.

Table 1
Characteristics of the study population.

Variable	Overall (n=5005)	≤24.6 pmol/g Hb (n=1265)	>24.6 to ≤34.3 pmol/g Hb (n=1248)	>34.3 to ≤98.4 pmol/g Hb (n=1241)	98.4 pmol/g Hb (n=1251)	<i>P</i> value
Age, years	40.6 (21.2)	41.8 (21.7)	37.6 (23.0)	38.0 (22.6)	44.7 (15.9)	<0.001
Male, %	2495 (49.9%)	562 (44.4%)	596 (47.8%)	631 (50.8%)	706 (56.4%)	<0.001
Education level, %						<0.001
<9th grade	447 (8.9%)	119 (9.4%)	123 (9.9%)	113 (9.1%)	92 (7.4%)	
9–11th grade	674 (13.5%)	113 (8.9%)	136 (10.9%)	139 (11.2%)	286 (22.9%)	
High school	1185 (23.7%)	270 (21.3%)	250 (20.0%)	296 (23.9%)	369 (29.5%)	
College	1550 (31.0%)	399 (31.5%)	389 (31.2%)	365 (29.4%)	397 (31.7%)	
Graduate	1149 (23.0%)	364 (28.8%)	350 (28.0%)	328 (26.4%)	107 (8.6%)	
Race/ethnicity, %						<0.001
Mexican American	812 (16.2%)	225 (17.8%)	268 (21.5%)	233 (18.8%)	86 (6.9%)	
Other Hispanic	538 (10.7%)	165 (13.0%)	172 (13.8%)	114 (9.2%)	87 (7.0%)	
Non-Hispanic White	1897 (37.9%)	531 (42.0%)	418 (33.5%)	341 (27.5%)	607 (48.5%)	
Non-Hispanic Black	1044 (20.9%)	195 (15.4%)	210 (16.8%)	275 (22.2%)	364 (29.1%)	
Other race	714 (14.3%)	149 (11.8%)	180 (14.4%)	278 (22.4%)	107 (8.6%)	
Diabetes mellitus, %	511 (10.2%)	114 (9.0%)	119 (9.5%)	146 (11.8%)	132 (10.6%)	0.110

Data are presented as mean (SD) or n (%).

Variable	Overall (n=5005)	≤24.6 pmol/g Hb (n=1265)	>24.6 to ≤34.3 pmol/g Hb (n=1248)	>34.3 to ≤98.4 pmol/g Hb (n=1241)	98.4 pmol/g Hb (n=1251)	<i>P</i> value
Smoker, %	2214 (44.2%)	326 (25.8%)	297 (23.8%)	416 (33.5%)	1175 (93.9%)	<0.001
Alcohol user, %	3515 (70.2%)	867 (68.5%)	777 (62.3%)	807 (65.0%)	1064 (85.1%)	<0.001
Body mass index, kg/m ²	27.7 (7.43)	28.8 (7.67)	27.5 (7.89)	26.4 (6.88)	28.1 (7.02)	<0.001
Energy intake (kcal/day)	1914 (1461- 2457)	1848 (1443- 2340)	1902 (1439-2410)	1917 (1470-2444)	1998 (1503- 2657)	<0.001
Sodium intake, mg/day	3114 (2334- 4117)	3046 (2333- 3985)	3064 (2270-4061)	3208 (2415-4188)	3147 (2312- 4258)	0.007
Potassium intake, mg/day	2312 (1725- 3024)	2289 (1759- 2931)	2326 (1746-3057)	2348 (1739-3069)	2265 (1631- 3036)	0.050
Poverty-income ratio	2.10 (1.52)	2.41 (1.57)	2.22 (1.54)	2.17 (1.55)	1.60 (1.27)	<0.001
Physical activity						<0.001
Never	2996 (59.9%)	749 (59.2%)	785 (62.9%)	793 (63.9%)	669 (53.5%)	
Moderate	1041 (20.8%)	277 (21.9%)	263 (21.1%)	272 (21.9%)	229 (18.3%)	
Vigorous	968 (19.3%)	239 (18.9%)	200 (16.0%)	176 (14.2%)	353 (28.2%)	
Systolic blood pressure, mmHg	120 (18.3)	121 (17.8)	118 (17.6)	118 (18.4)	124 (18.6)	<0.001
Diastolic blood pressure, mmHg	66.7 (13.5)	67.0 (12.8)	65.2 (13.6)	65.0 (14.0)	69.8 (13.0)	<0.001
Hypertension, %	1380 (27.6%)	361 (28.5%)	290 (23.2%)	308 (24.8%)	421 (33.7%)	<0.001
Data are presented as mean (SD) or n (%).						

3.2 Associations between ethylene oxide levels and hypertension

The fully multivariable adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for hypertension across the quantiles of blood ethylene oxide levels compared with the lowest quartile were 0.80 (0.63, 1.03), 0.91 (0.71, 1.16), and 1.39 (1.06, 1.82), respectively (P for trend 0.001, Table 2). Cubic spline plots of the association between blood ethylene oxide levels and the prevalence of hypertension were approximately nonlinear (Figure 2); however, the tests for nonlinearity were not significant.

Table 2

Adjusted odds ratios for associations between ethylene oxide and the prevalence of hypertension.

Ethylene oxide	Cases	N	Model 1	Model 2	Model 3
			OR (95% CI)	OR (95% CI)	OR (95% CI)
Q1	361	1265	Ref.	Ref.	Ref.
Q2	290	1248	0.82 (0.65, 1.04)	0.81 (0.63, 1.03)	0.80 (0.63, 1.03)
Q3	308	1241	0.93 (0.74, 1.17)	0.92 (0.72, 1.17)	0.91 (0.71, 1.16)
Q4	421	1251	1.36 (1.10, 1.68)	1.42 (1.09, 1.85)	1.39 (1.06, 1.82)
P for trend			<0.001	0.001	0.001
Bolding indicates significant ($P < 0.05$).					
Model 1 was adjusted for age and sex.					
Model 2 was adjusted for age, sex, education level, race, diabetes mellitus, smoking status, alcohol use, body mass index.					
Model 3 was adjusted for age, sex, education level, race, diabetes mellitus, smoking status, alcohol use, body mass index, poverty-income ratio, energy intake, sodium intake, potassium intake, and physical activity.					
OR, Odd ratio; CI, confidence interval.					

3.3 Associations between ethylene oxide levels and blood pressure.

In the full multiple generalized linear regression, no significant association between blood ethylene oxide levels and SBP was observed (P for trend = 0.869, Table 3 and Fig. 3A). Participants in the highest quartile, in comparison with the lowest quartile of blood ethylene oxide levels, showed increased DBP by 2.67 mmHg. The restricted cubic spline plot displayed a J-shape between blood ethylene oxide levels and DBP (P for nonlinearity = 0.021, Fig. 3B).

Table 3
Association between ethylene oxide and systolic and diastolic blood pressure.

	Systolic blood pressure	Diastolic blood pressure
	β (95% CI)	β (95% CI)
Ethylene oxide, pmol/g Hb		
Q1	Ref.	Ref.
Q2	-0.41(-1.57, 0.75)	-0.27(-1.31, 0.76)
Q3	-1.15(-2.34, 0.04)	-0.73(-1.79, 0.33)
Q4	0.00(-1.44, 1.43)	2.67(1.38, 3.95)
<i>P for trend</i>	0.869	<0.001
Bolding indicates significant ($P<0.05$). Analyses was adjusted for age, sex, education level, race, diabetes mellitus, smoking status, alcohol use, body mass index, poverty-income ratio, energy intake, sodium intake, potassium intake, and physical activity		

3.4 Subgroup analysis

Stratified analysis confirmed a stronger association between blood ethylene oxide levels and the prevalence of hypertension among participants aged ≤ 60 years, female participants, nondiabetic participants, participants with BMIs >30 kg/m², and participants with poor physical activity levels (Table 4). Since the interaction of blood ethylene oxide levels with age groups was significant, age-stratified models suggested that the association of blood ethylene oxide levels with the prevalence of hypertension was significant among participants aged ≤ 60 years but not participants aged >60 years.

Table 4

Subgroups analysis for the associations of ethylene oxide with the prevalence of hypertension.

	Q1	Q2	Q3	Q4	<i>P</i> for trend	<i>P</i> for interaction
	OR	OR(95% CI)	OR (95% CI)	OR(95% CI)		
Age						0.040
>60 years	1.00	0.94(0.66, 1.35)	1.00(0.69, 1.44)	1.14(0.74, 1.73)	0.481	
≤60 years	1.00	0.69(0.52, 0.93)	0.76(0.56, 1.02)	1.34(0.97, 1.84)	0.003	
Sex						0.572
Male	1.00	0.63(0.44, 0.89)	0.86(0.61, 1.22)	1.34(0.92, 1.93)	0.006	
Female	1.00	1.05(0.75, 1.49)	0.97(0.68, 1.40)	1.50(1.01, 2.25)	0.043	
Diabetes						0.411
Yes	1.00	0.82(0.44, 1.53)	0.89(0.48, 1.66)	1.19(0.60, 2.36)	0.420	
No	1.00	0.78(0.60, 1.01)	0.91(0.69, 1.20)	1.36(1.01, 1.82)	0.006	
Obesity						0.843
BMI>30 kg/m ²	1.00	1.04(0.74, 1.46)	0.96(0.67, 1.38)	1.38(0.92, 2.05)	0.096	
BMI≤30 kg/m ²	1.00	0.64(0.45, 0.90)	0.78(0.56, 1.10)	1.20(0.84, 1.72)	0.051	
Physical activity						0.307
Never	1.00	0.88(0.64, 1.20)	0.99(0.73, 1.36)	1.63(1.15, 2.32)	0.001	
Moderate	1.00	0.68(0.38, 1.20)	0.99(0.55, 1.77)	1.39(0.73, 2.63)	0.145	
Vigorous	1.00	0.75(0.42, 1.34)	0.68(0.37, 1.25)	0.89(0.50, 1.59)	0.992	

Bolding indicates significant ($P<0.05$). Analyses was adjusted for age, sex, education level, race, diabetes mellitus, smoking status, alcohol use, body mass index, poverty-income ratio, energy intake, sodium intake, potassium intake, and physical activity when they were not the strata variables. OR, Odd ratio; CI, confidence interval.

4. Discussion

Using the national representative survey in America, this analysis is the first to demonstrate that the concentration of blood ethylene oxide is positively associated with the prevalence of hypertension and DBP. The significant association between elevated blood ethylene oxide levels and the prevalence of hypertension and DBP persisted even after adjustment for a wide range of established confounding factors, including age, sex, education level, race, diabetes mellitus, smoking status, alcohol use, body mass index, poverty-income ratio, energy intake, sodium intake, potassium intake, and physical activity level.

Previous studies regarding the cardiotoxicity of ethylene oxide exposure in the general population are sparse. Collectively, our findings corroborate the findings of the few previously published studies (cross-sectional study) that reported the association between ethylene oxide exposure and cardiovascular disease in the general population (Zeng et al., 2021). Specifically, in a cross-sectional study of 3,410 participants from the NHANES, the authors found that elevated blood levels of ethylene oxide were independently associated with an increased prevalence of cardiovascular disease in the general population (Zeng et al., 2021). However, there was little evidence of any ethylene oxide relationship to all-cause and cardiovascular mortality in a cohort of 18 235 ethylene oxide-exposed workers (Steenland et al., 2004). The results of our study suggest the possible cardiotoxic effects of ethylene oxide exposure on blood pressure.

The biological mechanisms linking ethylene oxide levels to a higher prevalence of hypertension and higher DBP are not fully understood. Data from animal studies have suggested that the metabolism of ethylene oxide hydrolysis produced ethylene glycol and 2-chloroethanol (Koga et al., 1987). Accumulating evidence suggests that ethylene oxide and its metabolism promote increased oxidative stress and inflammation, two possible determinants of hypertension (Adedara and Farombi, 2010; Kuiper et al., 2008; Rasool and Malik, 2021). Ethylene glycol forms a conjugate with glutathione (GSH), resulting in its excretion through urine, forms S-carboxymethyl GSH and S-carboxymethyl cysteine, and disrupts the formation of thiol (-SH) groups (Rasool and Malik, 2021). Both increases in the formation of S-carboxymethyl GSH and S-carboxymethyl cysteine and decreases in thiol (-SH) groups contribute to decreases in the GSH level, further leading to oxidative stress damage.

There are several limitations in the present study. First, given the observational nature of this cross-sectional study, causality cannot be determined. Second, we used a single measurement of ethylene oxide levels in the blood to reflect chronic exposure to ethylene oxide, while dynamic changes in blood ethylene oxide levels may lead to exposure misclassification. Finally, although the data were tested with multiple adjustments, unmeasured confounding factors may also play a role in the relationship of blood ethylene oxide levels with hypertension and blood pressure.

5. Conclusion

In summary, our study demonstrates that exposure to ethylene oxide is related to an elevated prevalence of hypertension and higher diastolic blood pressure in the general population. The mechanism underlying the effect of ethylene oxide levels on blood pressure needs further exploration.

Declarations

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Contributions

Yuxing Wang and Ningtao Wu designed the research. Ningtao Wu performed the data analysis. Wenya Cao wrote and edited the original draft of the paper. Yuxing Wang and Xiaoqing Liu took responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the interpretation of the results, and all authors read and approved the final manuscript.

Ethics declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The data we used and analyzed in our study are available from <https://www.cdc.gov/nchs/nhanes>.

Competing interests

The authors declare that they have no competing interests.

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Figures

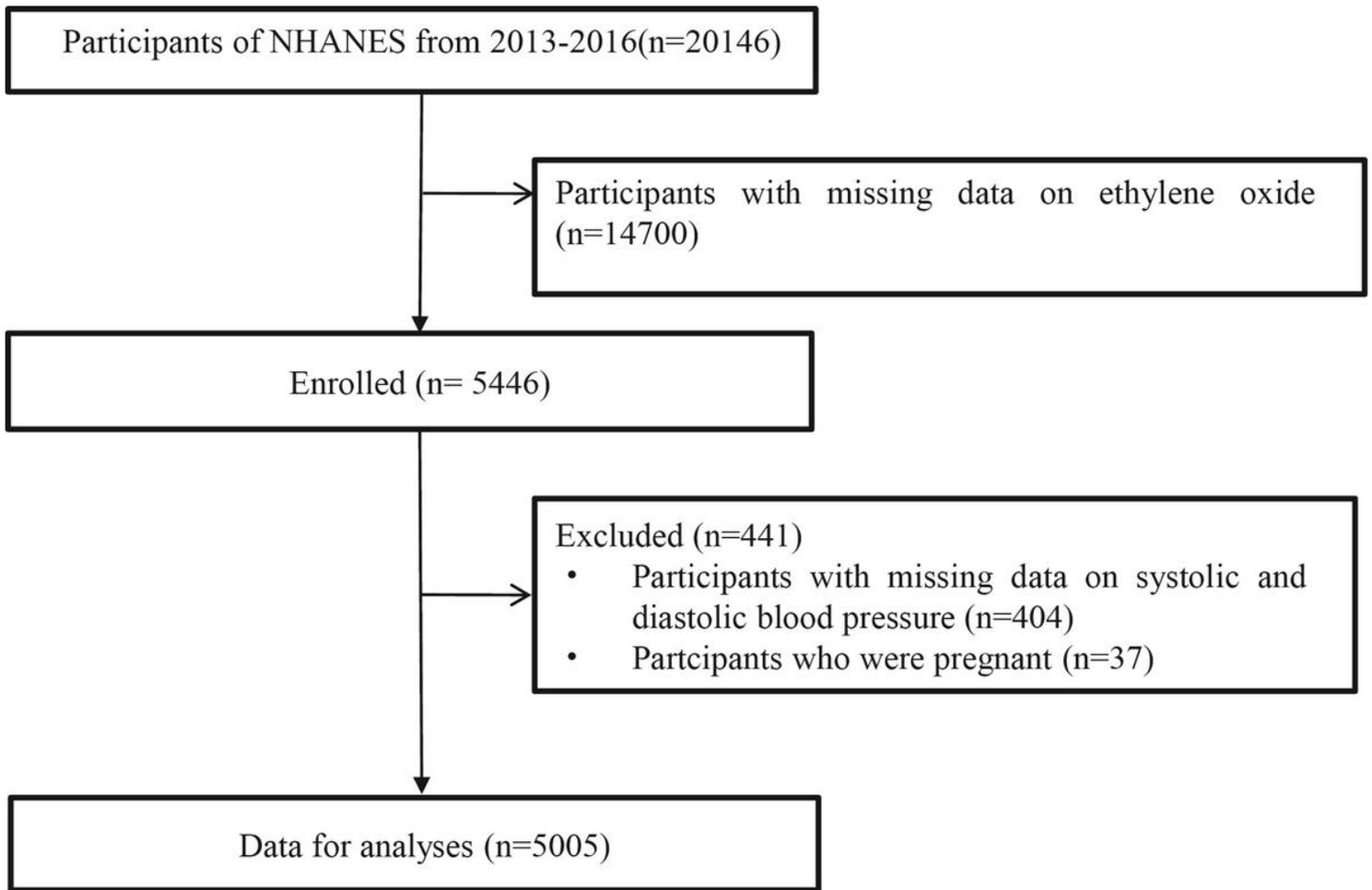


Figure 1

Study flow chart.

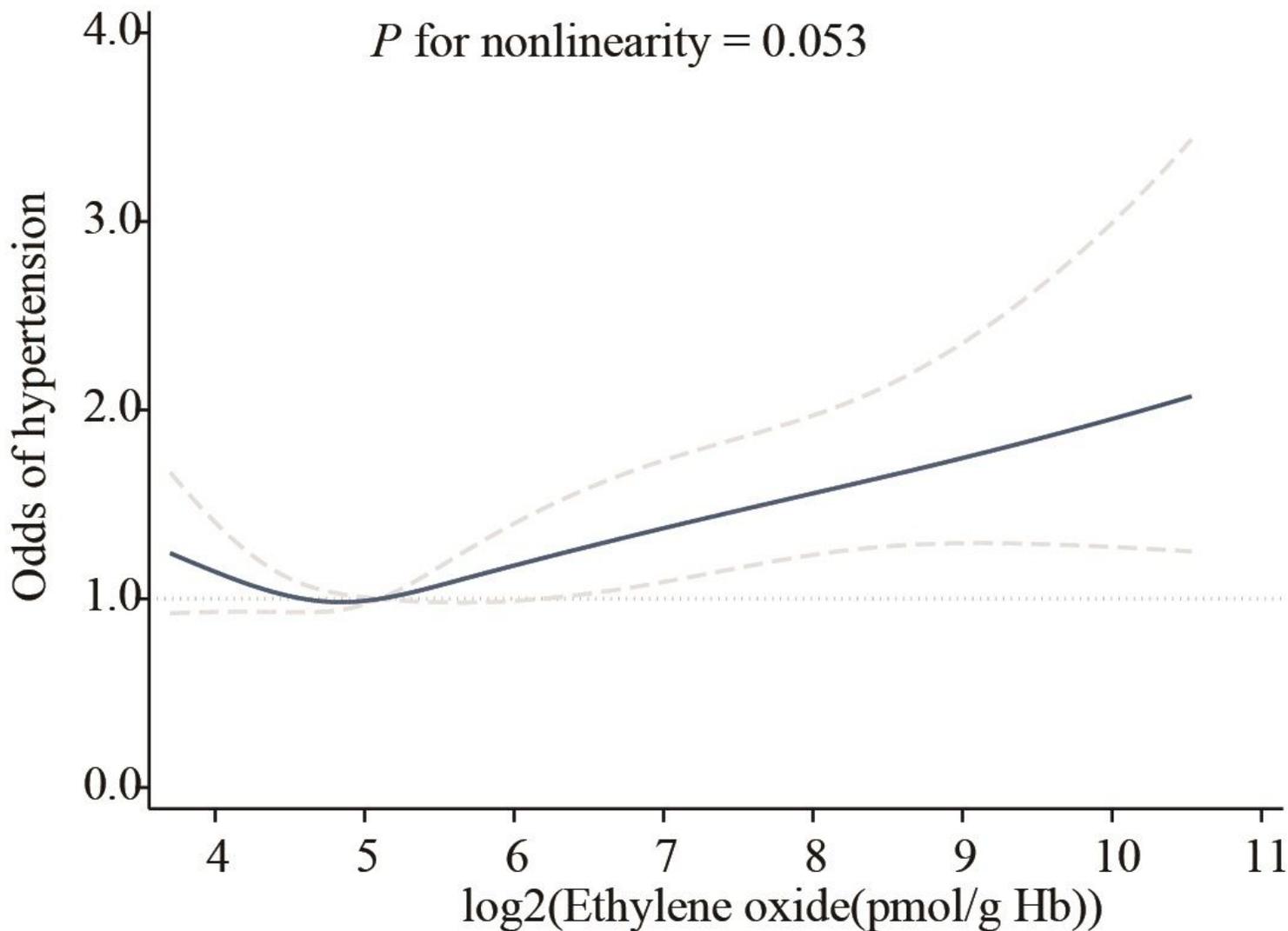


Figure 2

Restricted cubic spline plots of the associations between blood ethylene oxide and hypertension. Analyses were adjusted for age, sex, education level, race, diabetes mellitus, smoking status, alcohol use, body mass index, poverty-income ratio, energy intake, sodium intake, potassium intake, and physical activity. The solid line and dashed line represent the odds ratios of hypertension and corresponding 95% confidence intervals.

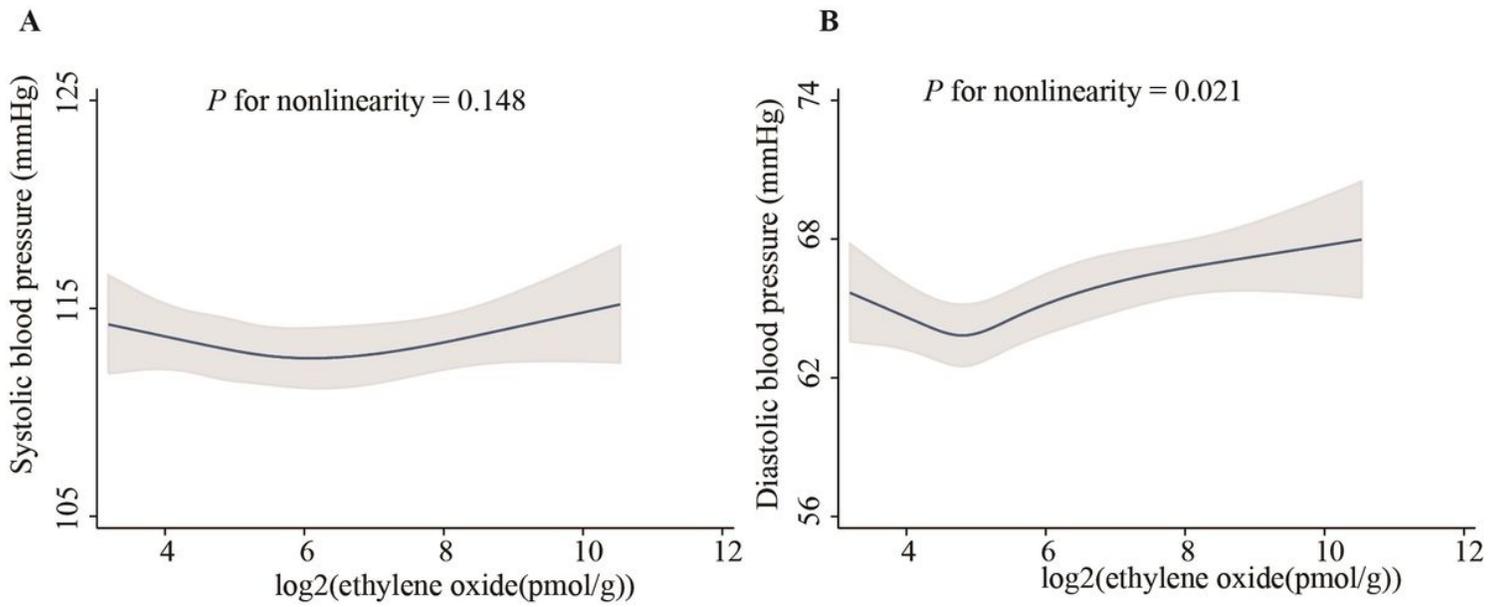


Figure 3

Restricted cubic spline plots of the associations between blood ethylene oxide and systolic (A) and diastolic blood pressure (B). Analyses were adjusted for age, sex, education level, race, diabetes mellitus, smoking status, alcohol use, body mass index, poverty-income ratio, energy intake, sodium intake, potassium intake, and physical activity. The solid line and dashed line represent the predicted value of blood pressure and corresponding 95% confidence intervals.