Association between ethylene oxide and the risk of depression symptoms in US adults: a cross-sectional study from NHANES

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Abstract

Ethylene oxide (EO) is an organic compound widely distributed in the environment. However, the association between EO exposure and the risk of depression remains uncertain. The objective of our study was to evaluate the potential link between EO exposure and depression risk. In this cross-sectional study, a total of 5,120 persons aged 20 years or older from 2013 to March 2020 NHANES database were included. Depression was assessed using the Patient Health Questionnaire (PHQ-9) and scored by asking respondents about the frequency of depressive symptoms in the past two weeks, with a total score of ≥ 10 considered clinically relevant depression. Logistic regression, restricted cubic spline regression modeling, and sensitive analyses were used to assess whether hemoglobin adducts of blood ethylene oxide (HbEO) were associated with depression. In this study, the overall prevalence of depression was 7.8%, and the prevalence was 6.2% in male vs 9.3% in female. Regression analysis using log2-transformed HbEO as a continuous and quartile variable revealed that blood HbEO levels were associated with the risk of depression, not only different depressive symptoms, but the different factor models.

Introduction

Depression is a common and growing mental disorder characterized by significant and persistent low mood accompanied by lack of interest in things, decreased concentration, decreased appetite, feelings of guilt, and suicidal ideation. It exhibits a high prevalence, frequent recurrence, and a risk of disability. Among the world's top 10 disabling diseases, disability due to depression takes the most toll, and stands as the principal contributor to the global burden of disease. A Lancet study showed that the global prevalence of depression has increased 0.6-fold over the last 30 years and is expected to become the number one global disease burden by 2030. The burden of depression seems to be particularly severe in developed countries. Furthermore, depression can result in serious consequences, including increased rates of disability, mortality, and societal costs. Hence, early identification and detection of depression, along with timely intervention, are particularly crucial.

Spitzer et al developed the Patient Health Questionnaire-9 (PHQ-9) for assessing the severity of depression in 2001. The questionnaire is recognized as a dependable and effective screening instrument for evaluating symptoms of depression. It is built upon the diagnostic criteria for severe depressive symptoms outlined in DSM-IV, and its core standards are also applicable to DSM-V. The study by Negeri et al. indicates that, compared to semi-structured interviews, the PHQ-9 achieves a sensitivity and specificity of 85%, demonstrating excellent internal reliability. Through Confirmatory Factor Analysis (CFA), a two-factor model has been proposed for the PHQ-9 questionnaire, where the first factor reflects cognitive and emotional symptoms, and the second factor reflects somatic symptoms. Through multiple CFA studies, it has been found that the use of PHQ-9 is acceptable in major demographic groups within the United States. This allows for comparisons of overall, cognitive/emotional, and somatic depressive symptoms within these populations, facilitating the extension of PHQ-9 usage from clinical settings to community contexts.

With increasing global environmental pollution, environmental factors have become particularly important in the development of depression. More and more researchers are focusing on the impact of environmental factors on depression and suggesting that environmental factors are important risk factors for depression. Ethylene oxide (EO) is a colorless, odorless, reactive epoxide used primarily in the manufacture of plastics, textiles, antifreeze, and in the sterilization of food and medical supplies. In addition, ethylene oxide is emitted from the combustion of fuels such as oil, coal, and natural gas, as well as from tobacco products. Ethylene oxide is classified as one of the 189 hazardous air pollutants under the U.S. Environmental Protection Agency's Clean Air Act. Additionally, the
International Agency for Research on Cancer categorizes ethylene oxide as a Group 1 carcinogen, and commercial sterilization and fumigation operations are required to comply with standards that limit emissions. The general population may be exposed to ethylene oxide through the air, vehicle exhaust, and fumes\textsuperscript{15,16}. Due to its short half-life, it is difficult to accurately measure EO levels in the human body. However EO can bind to hemoglobin to produce hemoglobin adducts of ethylene oxide (HbEO), which are distributed to a variety of tissues. The half-life of HbEO is approximately 4 months, longer than the half-life of EO in the body (less than 1 hour), so it can be used as a sensitive and stable blood biomarker for assessing EO exposure\textsuperscript{17,18}.

Several studies have shown that excessive EO exposure increases the risk of developing cancer, cardiovascular disease, chronic obstructive pulmonary disease (COPD), and neurologic dysfunction \textsuperscript{19-22}. However there are fewer studies on the association between ethylene oxide exposure and risk of depression. By analyzing data from the National Health and Nutrition Examination Survey (NHANES), we evaluated the association between blood ethylene oxide hemoglobin adducts and depression in U.S. adults to better understand environmental risk factors for depression.

**Materials and Methods**

**Study population and design**

The National Health and Nutrition Examination Survey database is a cross-sectional survey conducted by the Centers for Disease Control and Prevention (CDC) to assess the health and nutritional status of the non-institutionalized population of the US using a stratified, multistage probability survey\textsuperscript{22}. NHANES collects demographic and in-depth health information through home-visit screenings and laboratory tests conducted by mobile examination centers (MECs). NHANES is administered by the National Center for Health Statistics (NCHS) Ethics Review Board authorization, and all participants completed a written informed consent form prior to participation\textsuperscript{20}. No additional institutional review board approval was required for secondary analyses \textsuperscript{23}. NHANES data are available through the NHANES website (http://www.cdc.gov/nchs/nhanes.htm). This cross-sectional study used data from three cycles, 2013-2014, 2015-2016, and 2017- March 2020, finally enrolling a total of 20,720 participants 20 years older. Then we excluded pregnant women (n=222), subjects EO exposure deficient (n=12,108), PHQ-9 deficient (n=2,862), and other covariates deficient (n=4,08), resulting in a total of 5,120 participants enrolled in the study. The process of inclusion and exclusion is shown in Figure 1.

**Measurement of EO**

Information on endogenous and exogenous EO exposure in the general population is very limited, and ethylene oxide hemoglobin adducts, with their long half-life, are highly sensitive methods for determining EO exposure\textsuperscript{24,25}. The following HbEO measurements are based on the NHANES Laboratory/Medical Technician Procedures Manual: Washed-packed red blood cell specimens were processed, stored, and shipped to the Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, GA for analysis. Vials are stored under appropriate frozen (−30°C) conditions until they are shipped to National Center for Environmental Health for testing. The NHANES quality assurance and quality control protocols (QA/QC) meet the 1988 Clinical Laboratory Improvement Amendments mandates. Detailed quality control and quality assurance instructions are discussed in the NHANES LPM. This procedure describes a method based on the modified Edman reaction to measure hemoglobin adducts of EO in human whole blood or erythrocytes. Specifically, the reaction products with the N-terminal valine residue of the hemoglobin protein chains (N-[2-carbamoyl ethyl] valine and N-[2-hydroxycarbamoyl-ethyl] valine EO adducts) are measured. Analysis of Edman products by high-performance liquid
chromatography coupled with tandem mass spectrometry (HPLC-MS/MS) and results processing. The above measurements were conducted by the NHANES laboratory. For analytes with results below the lower limit of detection (ex., LBDEOALC =1), an imputed value was provided. This value is the lower limit of detection divided by the square root of 2 (LLOD/sqrt[2]). The procedure is available on the NHANES website (http://www.cdc.gov/Nchs/Nhanes/2013-2014/ETHOX_H.htm).

Assessment of Depressive Symptoms

Depression was assessed by a nine-item depression screening instrument, the Patient Health Questionnaire (PHQ-9) that asked questions about the frequency of depression symptoms over the past 2 weeks. The following are the nine questions: (1) have little interest in doing things; (2) feeling down, depressed, or hopeless; (3) trouble sleeping or sleeping too much; (4) feeling tired or having little energy; (5) poor appetite or overeating; (6) feeling bad about yourself; (7) trouble concentrating on things; (8) moving or speaking slowly or too fast; (9) thought you would be better off dead. Response categories for the nine-item instrument "not at all," "several days," "more than half the days," and "nearly every day" were given a point ranging from 0 to 3. A total score is based on the sum of the points in each item ranging from 0 to 27\(^{11}\). A total score \(\geq 10\) was considered to be clinically relevant depression according to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)\(^{26,27}\). The score for the cognitive/emotional factor subscale can be computed by summing the responses to items 1 (lack of pleasure), 2 (depressed mood), 6 (low self-esteem), 7 (difficulty concentrating), 8 (psychomotor agitation/retardation), and 9 (suicidal ideation). The score for the somatic factor subscale can be calculated by summing the responses to items 3 (sleep disturbance), 4 (fatigue), and 5 (appetite changes)\(^{11}\).

Assessment of covariates

Various covariates were assessed according to previous references and NHANES guidelines, including gender, age, race, education level, marital status, family income, body mass index (BMI), smoking status, sedentary time, sleep time and medical history, including hypertension, diabetes mellitus (DM), coronary heart disease (CHD), stroke, cancer, asthma and liver disease\(^{20,28,29}\). Smoking status was defined as having smoked at least 100 cigarettes in a lifetime. Cigarette smoking and exposure to environmental tobacco smoke, have been proven to elevate EO levels\(^{15}\). Cotinine, the principal metabolite of nicotine, serves as a reliable indicator for both active smoking and exposure to secondhand smoke. Therefore, serum cotinine was considered a potential confounding factor in the analysis. Race was categorized as Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, Other Race. Marital status was categorized as living with a partner and living alone. Educational level was categorized as less than 9 years, 9-12 years, and more than 12 years. Body mass index was based on a standardized count of weight and height to calculate BMI. According to a US government report, family incomes were classified into three groups based on poverty-to-income ratios (PIR): low (PIR \(\leq 1.3\)), medium (1.3 < PIR \(\leq 3.5\)), and high (PIR > 3.5). Sedentary time was defined as time spent sitting per day, categorized as < 3 h/day, 3-6 h/day, > 6 h/day. Sleep time was defined as time spent sleeping per day, categorized as < 7h/day, 7-9h/day, \(\geq 9h/day\). The identification of preexisting underlying conditions re- inquiring whether participants had previously informed these conditions to their physicians, including diabetes mellitus (DM), hypertension, coronary heart disease (CHD), stroke, cancer, asthma and liver disease.

Data analysis

Normally distributed continuous variables are described using mean \pm standard deviation (Mean \pm SD), and non-normally distributed continuous variables are described using median (inter-quartile spacing). Categorical variables were expressed as absolute values (n) or percentages (%). Because of the uneven distribution of HbEO levels, HbEO
was log 2 transformed to normalize the distribution into quartiles. In order to compare differences between groups, one-way analysis of variance (ANOVA, normal distribution), Kruskal-Wallis test (skewed distribution) and chi-square test (categorical variables) were performed. Logistic regression models were used to determine the ratio of odd (OR) and 95% confidence intervals (95% CI) for the association between HbEO exposure and depression. Linear regression models were used to determine the $\beta$ coefficients and a 95% confidence interval for relationship between EO and the total score of depression, cognitive/emotional score and somatic score. In addition, sensitivity analysis was used to further assess the relationship between HbEO and depression, as well as the association between EO and depressive symptoms. Restricted cubic spline (RCS) regression with 4 nodes at the 5th, 35th, 65th, and 95th percentiles of log 2-transformed HbEO was performed to assess the nonlinear association of HbEO levels with depression and every symptoms. Subgroup analyses were used to assess the robustness of the relationship between log 2-transformed HbEO levels and depression, stratified by factors including: sex, age (20-60 years vs $\geq$ 60 years), marital status (living with a partner vs living alone), education level (9 years, 9-12 years and more than 12 years), family income (low, medium and high), BMI (<25 vs $\geq$ 25 Kg/m$^2$), smoking status and medical history.

All the analyses were performed with the statistical software packages R (http://www.R-project.org, The R Foundation) and Free Statistics software version 1.9. A two-sided P-value of <0.05 was statistically significant.

Results

Characteristics of the population

As is shown in table 1, among the 5,120 individuals, 49.5% were male, and 50.5% were female, with a mean age of 50.0± 17.2 years. The overall prevalence of depression was 7.8%, with prevalence rates of 6.2% and 9.3% among males and females respectively. Compared to the group without depressive symptoms, the depression group tends to be female, middle education level, living alone, lower income levels and higher BMI, HbEO levels, serum cotinine levels and medical conditions (P<0.001).

Table S.1 shows the baseline characteristics of the population following stratification into quartiles based on EO levels. Based on log2-transformed HbEO
<table>
<thead>
<tr>
<th>Variables</th>
<th>No-depression (n = 4722)</th>
<th>Depression (n = 398)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender n (%)</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Male</td>
<td>2375 (50.3)</td>
<td>158 (39.7)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2347 (49.7)</td>
<td>240 (60.3)</td>
<td></td>
</tr>
<tr>
<td>Age(years), Mean ± SD</td>
<td>50.0 ± 17.2</td>
<td>50.4 ± 16.9</td>
<td>0.634</td>
</tr>
<tr>
<td>Race/ethnicity, n (%)</td>
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<td></td>
<td>0.164</td>
</tr>
<tr>
<td>Mexican American</td>
<td>642 (13.6)</td>
<td>47 (11.8)</td>
<td></td>
</tr>
<tr>
<td>Other Hispanic</td>
<td>472 (10)</td>
<td>47 (11.8)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>1814 (38.4)</td>
<td>167 (42)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>1036 (21.9)</td>
<td>88 (22.1)</td>
<td></td>
</tr>
<tr>
<td>Other Race</td>
<td>758 (16.1)</td>
<td>49 (12.3)</td>
<td></td>
</tr>
<tr>
<td>Education level, n (%)</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>&lt; 9</td>
<td>372 (7.9)</td>
<td>41 (10.3)</td>
<td></td>
</tr>
<tr>
<td>9–12</td>
<td>1599 (33.9)</td>
<td>185 (46.5)</td>
<td></td>
</tr>
<tr>
<td>&gt;12</td>
<td>2751 (58.3)</td>
<td>172 (43.2)</td>
<td></td>
</tr>
<tr>
<td>Marital status, n (%)</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Living with partner</td>
<td>2899 (61.4)</td>
<td>182 (45.7)</td>
<td></td>
</tr>
<tr>
<td>Living alone</td>
<td>1823 (38.6)</td>
<td>216 (54.3)</td>
<td></td>
</tr>
<tr>
<td>PIR, n (%)</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Low</td>
<td>1352 (28.6)</td>
<td>196 (49.2)</td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>1807 (38.3)</td>
<td>142 (35.7)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>1563 (33.1)</td>
<td>60 (15.1)</td>
<td></td>
</tr>
<tr>
<td>BMI(kg/m2), Mean ± SD</td>
<td>29.5 ± 7.1</td>
<td>31.6 ± 9.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sleep duration on weekdays (hours),Mean ± SD</td>
<td>7.4 ± 1.5</td>
<td>7.5 ± 5.0</td>
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</tr>
<tr>
<td>DM, n (%)</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>No</td>
<td>4076 (86.3)</td>
<td>313 (78.6)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>646 (13.7)</td>
<td>85 (21.4)</td>
<td></td>
</tr>
<tr>
<td>CHD, n (%)</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>No</td>
<td>4558 (96.5)</td>
<td>371 (93.2)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>164 (3.5)</td>
<td>27 (6.8)</td>
<td></td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>No</td>
<td>4547 (96.3)</td>
<td>362 (91)</td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>-------------</td>
<td>----------</td>
<td></td>
</tr>
<tr>
<td>Cancer, n (%)</td>
<td></td>
<td>0.015</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>4272 (90.5)</td>
<td>345 (86.7)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>450 (9.5)</td>
<td>53 (13.3)</td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td></td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>3367 (71.3)</td>
<td>225 (56.5)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1355 (28.7)</td>
<td>173 (43.5)</td>
<td></td>
</tr>
<tr>
<td>Asthma, n (%)</td>
<td></td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>4044 (85.6)</td>
<td>281 (70.6)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>678 (14.4)</td>
<td>117 (29.4)</td>
<td></td>
</tr>
<tr>
<td>Liver disease, n (%)</td>
<td></td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>4531 (96)</td>
<td>348 (87.4)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>191 (4)</td>
<td>50 (12.6)</td>
<td></td>
</tr>
<tr>
<td>Cotinine, Median (IQR)</td>
<td>0.0 (0.0, 4.6)</td>
<td>0.5 (0.0, 183.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>log2EO, Median (IQR)</td>
<td>4.4 (4.0, 5.3)</td>
<td>4.8 (4.1, 7.1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sedentary time (hours), Median (IQR)</td>
<td>6.0 (4.0, 8.0)</td>
<td>6.0 (4.0, 8.0)</td>
<td>0.006</td>
</tr>
<tr>
<td>cognitive/emotional score, Median (IQR)</td>
<td>0.0 (0.0, 1.0)</td>
<td>8.0 (6.0, 10.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Somatic score, Median (IQR)</td>
<td>1.0 (0.0, 2.0)</td>
<td>6.0 (5.0, 8.0)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Table 1. Characteristics of participants.

**Abbreviations:** PIR: Ratio of family income to poverty; MI: body mass index; DM: diabetes mellitus; CHD: coronary heart disease; log2EO: log2-transformed ethylene oxide.

Levels, we divided participants equally into 4 groups: group Q1 (2.536 pmol/g Hb ≤ log2 HbEO < 3.991 pmol/g Hb, n = 877), group Q2 (3.994 pmol/g Hb ≤ log2 HbEO < 4.459 pmol/g Hb, n = 880), Q3 group (4.461 pmol/g Hb ≤ log2 HbEO < 5.423 pmol/g Hb), and Q4 group (5.429 pmol/g Hb ≤ log2 HbEO < 10.512 pmol/g Hb). Higher HbEO levels were primarily observed in the youngers, males, living alone, lower PIR, a history of stroke, hypertension, asthma, liver disease, and patients with high cotinine levels. The study also revealed elevated depression scores, cognitive/emotional scores and somatic scores in the group with higher HbEO levels.

**Relationship between ethylene oxide hemoglobin adducts and depression**

Multiple logistic analysis (Table S.2) showed that as a continuous variable, HbEO levels were positively associated with the risk of depression, (Crude ratio OR 1.26, 95% confidence interval 1.19~1.34, p<0.001). This relationship persisted after different model adjustments, Model I (OR=1.19, 95% CI 1.12~1.27, p<0.001), Model II (OR=1.23, 95% CI
1.12~1.35, p<0.001), and Model III (OR=1.19, 95% CI 1.09~1.31, p<0.001). Model I was adjusted for socio-demographic characteristics including gender, age, race, education level, marital status, and annual family income (PIR). Model II was further adjusted for BMI, serum cotinine, sedentary time, and log2-transformed HbEO was categorized into four groups, the adjusted OR for ethylene oxide adducts and depression were 1.09(95%CI:0.78~1.51),1.02(95%CI:0.72~1.43),2.11 (95%CI:1.49~2.97) for Q2, Q3, and Q4 respectively, when compared to Q1, the group with low level of ethylene oxide in model II.

Furthermore, we performed regression analyses to examine the association between HbEO levels and various aspects of depression, including PHQ total scores, individual symptom phenotypes of depression, as well as cognitive/emotional scores and somatic score. In the linear regression analysis with the total score of PHQ-9 as a continuous variable, it was observed that HbEO levels show a positive correlation with PHQ-9 scores. As HbEO levels increase, there is a corresponding increase in PHQ-9 scores(β=0.36,95%CI:0.25~0.46 in Model II). This relationship persists even after stratifying ethylene oxide levels into quartiles and adjusting the model accordingly(β=1.25,95%CI:0.85~1.63 in Model II)(Table 2). Moreover, cognitive/emotional scores and somatic scores also increase with the elevation of EO levels. This result maintains its robustness, even EO as a continuous or categorical variable.(Table S.3, Table S.4)

The results of the multivariate logistic regression analysis indicate that with the increase in HbEO levels, the risk for 1 (lack of pleasure), 2 (depressed mood), 3 (sleep disturbance), 4 (fatigue), 5 (appetite changes), 6 (low self-esteem), 7 (difficulty concentrating), 8 (psychomotor agitation/retardation) increases, while PHQ-9-suicidal ideation does not show a corresponding increase(Table S.5-S.13). The results of cubic spline curve indicate a linear relationship between EO and depressed mood, sleep disturbance, fatigue, low self-esteem, difficulty concentrating, psychomotor agitation/retardation(Figure S.1-S.8). Additionally, there is a curvilinear relationship between HbEO levels and two item– lack of pleasure and appetite changes, with inflection points at 4.08 and 4.71, respectively. (Table S.14-S.15).

### Table 2. Association between log2-transformed HbEO and total score of PHQ-9.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Crude</th>
<th>p-value</th>
<th>Model I</th>
<th>Model II</th>
<th>Model III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>p-value</td>
<td>p-value</td>
<td>p-value</td>
<td>p-value</td>
</tr>
<tr>
<td>Log2HbEO</td>
<td>0.36 (0.28~0.44)</td>
<td>&lt;0.001</td>
<td>0.3 (0.22~0.38)</td>
<td>&lt;0.001</td>
<td>0.36 (0.25~0.46)</td>
</tr>
<tr>
<td>Q1 group</td>
<td>1(Ref)</td>
<td>1(Ref)</td>
<td>1(Ref)</td>
<td>1(Ref)</td>
<td>1(Ref)</td>
</tr>
<tr>
<td>Q2 group</td>
<td>0.09 (-0.24~0.42)</td>
<td>0.596</td>
<td>0.09 (-0.23~0.42)</td>
<td>0.576</td>
<td>0.1 (-0.22~0.43)</td>
</tr>
<tr>
<td>Q3 group</td>
<td>0.01 (-0.32~0.34)</td>
<td>0.956</td>
<td>0.07 (-0.26~0.4)</td>
<td>0.683</td>
<td>0.16 (-0.17~0.49)</td>
</tr>
<tr>
<td>Q4 group</td>
<td>1.32 (0.98~1.65)</td>
<td>&lt;0.001</td>
<td>1.12 (0.78~1.46)</td>
<td>&lt;0.001</td>
<td>1.24 (0.85~1.63)</td>
</tr>
<tr>
<td>p for trend</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Notes: Crude model adjusted for none.

Model I: Adjust for gender, age, race, education, marital status, and PIR.

Model II: Adjust for the variables in Model I plus BMI, Cotinine, sedentary time and sleep duration on weekdays.
**Model III:** Adjust for the variables in Model II plus hypertension, CHD, stroke, cancer, DM, asthma, liver.

The cubic spline curve between blood EO levels and depression showed a linear relationship ($p$ for nonlinearity > 0.05) (Figure 2). Subgroup analyses were used to test

the consistency of the relationship between HbEO levels and depression in different groups of the population. As is shown in the figure 3, no significant interactions were found in any subgroups after stratification by gender, age, race, education level, marital status, household income, BMI, alcohol consumption, and smoking. Given multiple calibration issues, $p$-values less than 0.05 for the gender interaction may not be statistically significant.

**Discussion**

Using a retrospective survey study from the NHANES database, we observed a positive association between blood HbEO levels and the risk of depression. This association remained persistent even after adjusting for various factors, consistent with Jiang’s study 30. Moreover, our study reveals that with an increase in HbEO levels, there is a corresponding rise in the risk of depressive symptom, cognitive/emotional factor, and somatic factor.

Ethylene oxide is a toxic industrial chemical that was reclassified as a known human carcinogen by the U.S. Environmental Protection Agency (EPA) in 2016, and studies have found that cancer incidence rates in residents exposed to ethylene oxide are up to 24 times higher than national levels 31. Ethylene oxide has long been recognized as harmful to occupationally exposed populations, particularly workers sterilizing medical devices. And studies have shown that the general population is exposed to increased levels of ethylene oxide due to cigarette smoking, renovations, burning of fossil fuels, and use of residential ethylene oxide facilities. Additionally, many studies have demonstrated a correlation between blood ethylene oxide, cigarette smoking and exposure to environmental tobacco smoke 15,32–34. In our study, we found that those with higher HbEO levels also exhibited elevated cotinine levels. Hence, reducing tobacco use can mitigate the risk of depression to some extent. Besides, several recent studies have found that high levels of HbEO are significantly associated with a high prevalence of diabetes, obesity, heart disease, hypertension, chronic obstructive pulmonary disease in the general population 19,20,22,35–36. Therefore the potential adverse effects of HbEO exposure should be of concern not only to occupationally exposed persons but also to the general population.

Depression is a mental disorder influenced by multiple factors, including genetic, social, and environmental elements. Depression is projected to be the leading cause of disease burden by 2030, so it is critical to identify potential modifiable risk factors. Social and environmental factors are often modifiable, thus mitigating environmental risk factors for depression through public health measures is feasible. Recently, many studies have found that air pollution exposure is associated with the development of depression, particularly airborne particulate matter and gaseous pollutants 30,37–40. In our study, we not only identified a correlation between HbEO levels and the risk of depression, but also observed associations between HbEO and depression symptoms, cognitive/emotional factors, and somatic factors. Both the total score of PHQ-9 and two-factor models of depression scores indicate that there is an association between HbEO levels and the risk of depression. In general, the incidence of depression in females is reported to be twice compared to males 41. In our study, there were more females among the individuals with depression. Symptoms in females may manifest as loss of pleasure, negative emotions, sleep disorders, appetite and weight disruption, forgetfulness and guilt. In contrast, males may exhibit depressive behavior through violence, aggression, and substance use, thereby increasing the risk of somatic illnesses 42. The two-factor model of depression reflects the somatic and cognitive/emotional dimensions of depression. Several studies have indicated an
association between somatic factors and cardiovascular disease prognosis, inflammation, obesity, hyperlipidemia, atherosclerosis\textsuperscript{43–45}.

The biological mechanisms between air pollution and depression are not very clear. Previous studies have suggested several potential pathways, including systemic inflammation, oxidative stress, and cerebrovascular injury, which in turn are associated with neurotransmitter and hormone dysregulation leading to depression\textsuperscript{46–48}. A prospective study from the United Kingdom noted that anxiety and depression were associated with a significantly increased risk of air pollution scores, and that reducing exposure to air pollutants would reduce the disease burden of anxiety and depression\textsuperscript{49}. A cross-sectional study in Spain also found that increased levels of air pollution increased the risk of depression in adults\textsuperscript{50}, and a longitudinal study conducted in Korea showed similar results\textsuperscript{51,52}. Animal studies in mice have shown that exposure to particles emitted from diesel engines can lead to neuroinflammation and oxidative stress, which can subsequently cause the onset of depression\textsuperscript{53}. Air pollution affects the central nervous system through inflammation and oxidative stress in olfactory receptor neurons, trigeminal nerve, or somatic circulation\textsuperscript{54}. An imbalance of 5-hydroxytryptamine and tryptophan in the central nervous system is a recognized etiological mechanism for depression\textsuperscript{55}. Excessive inflammation can cause neurotransmitter dysfunction by accelerating the degradation of tryptophan, which is necessary for the synthesis of 5-hydroxytryptophan\textsuperscript{56}. Lynch et al found that ethylene oxide exposure causes inflammatory damage to exposed organs in rodents\textsuperscript{57}, and evidence from several studies has shown that ethylene oxide induces inflammatory responses in a variety of diseases\textsuperscript{22,36,58}. Zhu et al in a study of US adults found that inflammatory level increased with increasing levels of HbEO\textsuperscript{59}. In addition ethylene oxide exposure leads to decreased intracellular glutathione levels and increased hepatic lipid peroxidation. Both increased lipid peroxidation and disruption of the glutathione redox cycle are associated with oxidative stress in vivo\textsuperscript{60}. However the potential biological mechanisms between ethylene oxide exposure and depression remain to be further investigated.

In this study, we explored the association between ethylene oxide and the risk of depression, depressive symptoms, and the two-factor model of depression. The results consistently indicated a correlation between ethylene oxide levels and the occurrence of depression in a representative U.S population. Notably, even after adjustment for potential confounding factors and sensitive analyses, the results remained robust. However, there are some limitations in this study. First, due to the cross-sectional study design, it was not possible to infer a causal relationship between ethylene oxide exposure and depression; second, despite the inclusion of as many confounding variables as possible, there were still some residual confounding factors such as other pollutants that could have affected the results; and third, we used data from a single episode of blood ethylene oxide, whereas a more comprehensive evaluation of the relationship between cumulative ethylene oxide exposure and the prevalence of depression would be better.

Conclusions

In a nationally representative sample of U.S adults, we have discovered a significant link between higher EO levels and an increased prevalence of depression, depressive symptoms, and different depressive models. Additional prospective studies are needed to confirm these findings and further elucidate potential mechanisms of action.

Declarations

Author Contribution
Z.Z and H.L.Z concepted the research; Z.Z, H.L.Z and C.Y. W analysed and studied the design; H.L.Z wrote the main manuscript text; Z.Z edited the manuscript. All authors have read and agreed to the published version of the manuscript.

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Data availability

The original data were accessed from https://www.cdc.gov/nchs/nhanes/about_nhanes.

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Competing interests

There are no competing interests among all authors.

Additional information

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8. Diagnostic and Statistical Manual of Mental Disorders. DSM Library 


**Figures**

![Figure 1](image-url)
Flow chart of study participants. NHANES, National Health and Nutrition Examination survey; PIR, Ratio of family income to poverty; BMI, Body Mass Index; DM, Diabetes mellitus; CHD: Coronary heart disease.

Figure 2

Association between log2-transformed HbEO and depression. Solid and dashed lines represent the predicted value and 95% confidence intervals. They were adjusted for gender, age, race, education, marital status, PIR, BMI, cotinine, sedentary time and sleep duration on weekdays, hypertension, CHD, stroke, cancer, DM, asthma, liver. Only 99% of the data is shown.

Abbreviations: PIR: Ratio of family income to poverty; MI: body mass index; DM: diabetes mellitus; CHD: coronary heart disease; log2EO: log2-transformed ethylene oxide; Ref, reference.
The forest plots of sub-group.

**Abbreviations:** PIR: Ratio of family income to poverty; MI: body mass index; DM: diabetes mellitus; CHD: coronary heart disease.

**Supplementary Files**

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