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Associations of long-term exposure to ambient nitrogen dioxide with indicators of diabetes and dyslipidemia in China: a nationwide analysis

Qingli Zhang[a], **Cong Liu**[a], **Yafeng Wang**[b], **Jinquan Gong**[b], **Gewei Wang**[b], **Wenzhen Ge**[c], **Renjie Chen**[a,d,*], **Xia Meng**[a,d,*], **Yaohui Zhao**[e], **Haidong Kan**[a]

[a]School of Public Health, Key Lab of Public Health Safety of the Ministry of Education and NHC Key Lab of Health Technology Assessment, Fudan University, Shanghai 200032, China;

[b]Institute of Social Surveys, Peking University, Beijing, China;

[c]Regeneron Pharmaceuticals Inc., New York 10591, USA;

[d]Shanghai Typhoon Institute/CMA, Shanghai Key Laboratory of Meteorology and Health, Shanghai, 200030, China.

[e]National School of Development, Peking University, Beijing, China;

Abstract

Background: The associations between ambient NO_2 and diabetes and dyslipidemia have been controversial, and data is especially lacking in developing countries.

Objective: This study aimed to assess the associations of long-term exposure to NO_2 with diabetes and dyslipidemia in China.

[*]**Correspondence:** Dr. Xia Meng, Department of Environmental Health, School of Public Health, Fudan University, P.O. Box 249, 130 Dong-An Road, Shanghai 200032, China. mengxia@fudan.edu.cn; or Dr. Renjie Chen, Department of Environmental Health, School of Public Health, Fudan University, P.O. Box 249, 130 Dong-An Road, Shanghai 200032, China. chenrenjie@fudan.edu.cn.

CRediT author statement

Qingli Zhang: Investigation, Formal analysis, Writing - Original Draft
Cong Liu: Methodology, Validation
Yafeng Wang: Data curation
Jinquan Gong: Data curation
Gewei Wang: Data curation
Wenzhen Ge: Writing - Review & Editing
Renjie Chen: Conceptualization, Writing - Review & Editing, Supervision
Xia Meng: Conceptualization, Writing - Review & Editing, Supervision
Yaohui Zhao: Resources, Funding acquisition
Haidong Kan: Funding acquisition, Supervision, Project administration

Conflict of interests

The authors declared no conflicts of interest.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Methods: We conducted a cross-sectional study including 13,013 participants from the China Health and Retirement Longitudinal Study. The annual average concentrations of NO_2 were estimated based on land-use regression, satellite measurements, and universal kriging. We applied logistic regression models to evaluate the associations of NO_2 with diabetes and dyslipidemia, and linear regression models to assess the associations with blood biomarkers.

Results: A total of 1,933 diabetes cases (14.85%) and 1,935 (14.87%) dyslipidemia cases were identified. Significant associations were observed between NO_2 and risk of diabetes and dyslipidemia independent of $PM_{2.5}$ and O_3. For an interquartile range (IQR) increase in NO_2 (12.39 μg/m^3), we observed a 13% [odds ratio (OR): 1.13; 95% confidence interval (CI): 1.01, 1.26] increased risk of diabetes, 1.48% (95%CI: 0.51%, 2.46%) increase in glucose, 0.74% (95%CI: 0.19%, 1.29%) increase in glycosylated hemoglobin (HbA1c), 17% (OR: 1.17; 95% CI: 1.05, 1.31) increased risk of dyslipidemia, 4.62% (95%CI: 2.49%, 6.79%) increase in triglyceride, and a decrease of 2.96% (95%CI: 2.13%, 3.79%) in high-density lipoprotein. The associations of NO_2 with glucose disorders were stronger among smokers.

Conclusions: Our study indicated long-term exposure to NO_2 might contribute to the development of diabetes and dyslipidemia, and the associations were potentially independent of O_3 and $PM_{2.5}$.

Keywords

air pollution; nitrogen dioxide; diabetes; dyslipidemia; glucolipid metabolism

Introduction

Glucose and lipid metabolism disorders are the primary risk factors for cardiovascular and cerebrovascular diseases, the leading cause of deaths worldwide. The prevalence of glucose and lipid metabolism-related diseases, including diabetes and dyslipidemia, has been rising rapidly, especially in developing countries (World Health Organization, 2016). It was estimated that the overall prevalence of diabetes and dyslipidemia were as high as 11.6% and 34.0%, respectively, among the Chinese adult population in 2010 (Xu et al., 2013; Pan et al., 2016).

Accumulating studies indicated that long-term exposure to air pollution can act as facilitators of glucose and lipid metabolism-related diseases (Pearson et al., 2010; Liu et al., 2016; Wang et al., 2018; Lao et al., 2019). While most previous studies put more emphasis on particulate matter, air pollution is a rather complex mixture consisting of both solid particles and various toxic gases. NO_2 is a noxious gaseous pollutant and an important precursor in the formation of secondary aerosols and ozone, with ubiquitous sources mainly from fossil fuels. Only a limited number of studies were available on the toxicity of NO_2 on glucose and lipid metabolic diseases, and the results were mixed, with positive associations found in some (Cai et al., 2017; Yang et al., 2018b) but null in others (Chen et al., 2016; Eze et al., 2017). It is also unclear whether the associations between NO_2 and health outcomes are independent or are rather indicators of the impact of other air pollutants. In an integrated science assessment for NO_2 in 2016, the United States Environmental Protection Agency concluded that “Available studies have not distinguished an independent effect of NO_2 on

cardiovascular diseases and diabetes." However, recent studies demonstrated that the adverse health effects caused by NO_2 were likely to be independent of other co-pollutants such as fine particulate matter ($PM_{2.5}$) and ambient ozone (O_3) (Wooding et al., 2019).

The associations between NO_2 and blood biomarkers of glucose and lipid metabolism (e.g., HbA1c, cholesterol) were only investigated in a few studies and mostly in developed countries (Cai et al., 2017; Lucht et al., 2018). China's rapid economic development has been accompanied by massive consumption of fossil fuels, resulting in high levels of air pollution. However, only a few single-center studies have explored the associations of long-term exposure of NO_2 with health outcome in China (Yang et al., 2018a; Yang et al., 2018b; Mao et al., 2020). Most of these studies used the single-pollutant model without adjustment for the confounding co-pollutants such as $PM_{2.5}$ and O_3, thus they were unable to isolate the independent role of NO_2. Also, some previous studies relied on self-report for case identification of diabetes and dyslipidemia, which would inevitably be biased due to the poor sensitivity of self-report (Yuan et al., 2015). It was estimated that nearly 50% of diabetes cases failed to be diagnosed (International Diabetes Federation, 2017). Therefore, national studies on associations between long-term NO_2 exposure and metabolic diseases are needed in China, where air pollution levels are high, and prevalence rates of diabetes and dyslipidemia have been accelerating.

In this study, we utilized data from the third wave of a nationwide project, the China Health and Retirement Longitudinal Study (CHARLS), to investigate the associations of long-term exposure to NO_2 with glucose and lipid metabolic diseases and six key biomarkers.

2. Materials and Methods

2.1 Study population

CHARLS aims to collect a high quality nationally representative sample of Chinese residents. Using a four-staged, stratified, cluster sampling method, participants were selected randomly from 450 villages or neighborhoods (the smallest administrative unit in China) in 150 counties or districts within 28 provinces (Zhao et al., 2014). Baseline information was collected during 2011 and 2012 through in-person interviews, and follow-up was conducted every two years. In this study, we used data collected in the third wave of CHARLS in 2015. A total of 21,095 participants completed face-to-face interviews and were encouraged to donate venous blood samples for blood tests. A standardized questionnaire was used to obtain individual information including demographics (e.g., age, sex, educational level, body mass index [BMI]), behavioral factors (smoking status, pack-years of smoking, and alcohol consumption), types of energy used for heating and cooking, and history of chronic diseases (e.g., diabetes and dyslipidemia) (Chen et al., 2019a). Finally, 13,013 participants who completed both questionnaires and blood tests were included in the current analysis.

2.2 Health data

A total of 13,013 participants donated blood samples, among which 85% (11,025) reported to have fasted overnight as required. Both fasting and non-fasting subjects were included in the current study. The transportation and storage of blood samples were strictly in

accordance with the protocol (Chen et al., 2019a). Boronate affinity high-performance liquid chromatography method was used to examine glycosylated hemoglobin (HbA1c) level. Standard enzymatic colorimetric methods were used to measure levels of glucose (Hexokinase), HDL (Direct method), LDL (Direct method), cholesterol (Oxidase method), and triglyceride (Oxidase method).

The primary definition of diabetes was meeting at least one of the following criteria: a fasting blood glucose > 126 mg/dl, a non-fasting blood glucose > 200 mg/dl, HbA1c > 6.5%, or using antidiabetic medications including insulin, modern medicine or traditional Chinese medicine (Yuan et al., 2015). These cut-off points were in accordance with the recommendation from the American Diabetes Association (American Diabetes Association, 2014). Self-reported diabetes was defined as answering “Yes” to the question “Have you been diagnosed with diabetes or high blood sugar?”. The primary definition for dyslipidemia was the ratio of cholesterol to HDL ≥ 5.0 (Allison et al., 2008) or using lipid-lowering medications(Wang et al., 2017). Self-reported dyslipidemia was evaluated based on the question: “Have you ever been diagnosed with dyslipidemia?”.

2.3 Air pollution data

The annual average concentrations of NO_2 in 2015 at the participants’ residential addresses were estimated using a national empirical model. Details on the exposure model has been described elsewhere (Xu et al., 2019). Briefly, this model was built incorporating land-use and meteorological data, ground-level NO_2 concentrations from China’s regulatory monitors, and satellite-based measurements of NO_2, at 1 km× 1 km spatial resolution. The model showed good predictive power with a 10-fold CV R^2 of 0.78. We obtained the concentrations of $PM_{2.5}$ and O_3 in 2015 at a spatial resolution of 0·1° × 0·1° (approximately 11 km x 11 km at the equator) fro m the Global Burden of Disease project. The annual average concentrations of $PM_{2.5}$ were estimated by combining satellite-based aerosol optical depth (AOD) data and simulations from chemical transport models, and the predictions were calibrated with ground-level monitoring data (Shaddick et al., 2018). The concentrations of O_3 were estimated using the global chemical transport models and corrected with ground measurements (Shaddick et al., 2018). The concentrations of NO_2, $PM_{2.5,}$ and O_3 in the grids were assigned to the participants if their residential addresses fell into the corresponding grids.

2.4 Statistical analysis

We used multivariable logistic regression models to examine the associations between NO_2 and diabetes/dyslipidemia and multivariable linear regression models to investigate the associations between NO_2 and glucose levels (glucose and HbA1c) and lipid levels (HDL, LDL, cholesterol, and triglyceride). All biomarkers were log transformed to improve the normality before statistical analysis. We established four models to explore these associations. Model 1 adjusted for age, sex, educational level (low, ≤ 5years; medium, 6–9 years; high, >9 years), body mass index (BMI, <18.5 kg/m^2,18.5 – 24.9 kg/m^2, ≥ 25 kg/m^2), smoking status (current smokers, ex-smoker and non-smoker), pack-years for current smokers (pack per day multiplied by years of smoking), frequency of alcohol consumption (never, < 1 / month, > 1 / month), energy types for cooking and heating (clean, central

heating, solar energy, electricity natural gas; unclean, coal or biomass). We additionally adjusted for ambient O_3 (model 2), $PM_{2.5}$ (model 3), or both (model 4, the primary model). There was no significant collinearity among the three air pollutants according to the variance inflation factor, so they could be simultaneously adjusted in the models.

In order to evaluate potential effect modifiers, we conducted stratification analyses by age (21–64 years and ≥65 years), sex (male and female), BMI (<18.5 kg/m^2,18.5 – 24.9 kg/m^2, ≥ 25 kg/m^2), smoking status (current or former smokers, never smokers), and alcohol consumption (ever/never). The statistical significance of the potential effect modifier was tested by calculating the 95% CIs of the effect differences between strata using the following formula $(Q_1 - Q_2) \pm 1.96\sqrt{Se_1^2 + Se_2^2}$, where Q_1 and Q_2 were the estimates in each strata and Se_1 and Se_2 were the corresponding standard errors (Schenker and Gentleman, 2001; Payton et al., 2003). P values for the potential effect modifiers were calculated based on 95% CIs (Altman and Bland, 2011).

We did sensitivity analyses by repeating the above analyses using self-reported diabetes and dyslipidemia. We also did sensitivity analyses by excluding diabetes cases defined only by non-fasting glucose to test the stability of the associations.

The effect estimates were presented per interquartile range (IQR) increase in NO_2. We reported odds ratios (ORs) and 95%CIs for logistic regression models and percent changes (95%CI) for all biomarkers. All statistical tests were two-sided, and a p-value less than 0.05 was considered statistically significant.

3. Results

3.1 Descriptive statistics

Location of the CHARLS study sites distributed in 450 villages or neighborhoods (the smallest administrative unit in China) in 150 counties or districts within 28 provinces (Figure 1). Baseline characteristics, the prevalence of diabetes and dyslipidemia, mean concentrations of biomarkers, and air pollutants were summarized in Table 1. A total of 13,013 subjects were included in the current analysis. The mean age was 61.88 years, 46.04% were men, and the mean BMI was 23.95 kg/m^2. A total of 1,933 (14.85%) diabetes cases and 1,935 (14.87%) dyslipidemia cases were identified using the primary outcome definitions. The average levels of glucose, HbA1c, HDL, LDL, cholesterol, and triglyceride were 103.6 mg/dl, 5.98%, 51.21 mg/dl, 102.22 mg/dl, 183.94 mg/dl, and 143.20 mg/dl, respectively. Strong correlations were observed between LDL and cholesterol (r=0.87) as well as between glucose and HbA1c (r=0.70). The remaining correlations among the biomarkers were weak (Table S1). The demographic characteristics of the excluded population were similar to those of the included population (Table S2). The annual average concentrations of NO_2 varied greatly among participants from 6.77 μg/m^3 to 58.41 μg/m^3, with a mean of 24 μg/m^3 (IQR, 12.39 μg/m^3). The average of the annual mean concentrations of $PM_{2.5}$ and O_3 at residential addresses were 57.32 μg/m^3 and 68.27 μg/m^3, respectively. There were moderate to high correlations among air pollutants (r = 0.72 for NO_2 and $PM_{2.5}$, r = 0.56 for NO_2 and O_3, r= 0.71 for $PM_{2.5}$ and O_3) (Table S3).

3.2 Regression results

Table 2 presents the associations between NO_2 exposure and diabetes and dyslipidemia. We found significant positive associations of NO_2 concentration and diabetes, blood glucose, and HbA1c in all models. The associations remained after adjustment of O_3, while were attenuated but remained statistically significant after adjustment of $PM_{2.5}$. In model 4, an IQR increase in NO_2 was associated with a 13% increase in risk of diabetes (OR=1.13, 95%CI: 1.01, 1.26), a 1.48% (95%CI: 0.51%, 2.46%) increment in glucose, and a 0.74% (95%CI: 0.19%, 1.29%) elevation in HbA1c. Higher NO_2 exposure was also associated with increased risk of dyslipidemia, increased concentrating of triglyceride, and decreased concentration of HDL. Each IQR increase in NO_2 was associated with a 17% (OR 1.17, 95%CI, 1.05, 1.31) increased risk of dyslipidemia, a 4.62% (95%CI: 2.49%, 6.79%) increase in triglyceride and a 2.96% (95%CI: 2.13%, 3.79%) decrease in HDL (model 4). No associations were observed between NO_2 exposure and LDL or cholesterol after full adjustment.

Results of stratified analyses were shown in Table 3 and Table 4. For dyslipidemia or related biomarkers, we did not find any significant modifying effects based on current stratified analysis. However, we found the associations between NO_2 and glucose disorders were significantly stronger among smokers (Table 3)

When using self-report for definitions, the prevalence of diabetes was appreciably lower (9.00%) than that using the primary definition (14.85%). The sensitivity of self-reported diabetes was 49%, and the specificity was 81%. While the prevalence of dyslipidemia remained similar, the sensitivity and specificity of self-reported dyslipidemia were 62% and 63%, respectively. The associations between NO_2 and both self-reported diabetes and self-reported dyslipidemia remained significant (Table S4). After excluding diabetes cases that were diagnosed only by non-fasting glucose, the association remained stable. An IQR increase in NO_2 was associated with a 13% increase in risk of diabetes (OR=1.13, 95%CI: 1.01, 1.26) (Table S4).

4. Discussion

In this nationwide cross-sectional study, we found that exposure to NO_2 air pollution was significantly associated with diabetes and dyslipidemia independent of other co-pollutants ($PM_{2.5}$ and O_3). The associations were consistent when using different definitions of diabetes and dyslipidemia. The associations between NO_2 and risks of diabetes and glucose biomarkers were stronger among ever smokers compared to never smokers. To our knowledge, this is the largest nationwide study to explore the associations between long-term exposure of NO_2 and glucose and lipids levels in developing countries.

The association between ambient NO_2 exposure and diabetes has been investigated in several epidemiological studies (Andersen et al., 2012; Yang et al., 2018b; Yang et al., 2020). A recent meta-analysis including 11 studies primarily from developed countries reported that the OR of diabetes was 1.07 (95%CI: 1.04, 1.11) per 10 μg/m^3 increment in NO_2 exposure (Yang et al., 2020). In line with these results, our study in China also suggested a significantly positive association between NO_2 and diabetes with a comparable

effect size (OR=1.13, 95%CI: 1.01, 1.26, per an IQR (12.39 μg/m^3) increment of NO_2). Fasting glucose and HbA1c are both important biomarkers of glucose-homeostasis and are used for diabetes diagnosis. However, very few studies have assessed the associations of NO_2 with blood glucose and HbA1c, and the results were inconsistent. Consistent with our results, Chuang et al., found elevated fasting glucose and HbA1c were positively associated with long-term exposure to NO_2 in an analysis among 1,023 elderly subjects in Taiwan (Chuang et al., 2011). Similarly, in a cross-sectional study including 15,477 adults from mainland China, Yang et al., observed NO_2 was associated with a higher concentration of plasma glucose (Yang et al., 2018b). In contrast, a study including 7,108 observations in Germany found no association between NO_2 and blood glucose or HbA1c (Lucht et al., 2018). The inconsistency of these results might be attributable to differences in geographic locations, study populations, and exposure levels. The associations of NO_2 with diabetes and glucose metabolism appear to be biologically plausible. Preliminary evidence from toxicological studies and some epidemiological studies suggested that long-term exposure to NO_2 was positively associated with low-grade systemic inflammation (including adipose tissue inflammation) and oxidative stress (Li et al., 2011; Riedl et al., 2012). These effects can further lead to impaired insulin signaling, which plays a key role in glucose homeostasis (Sun et al., 2009; Chen et al., 2016).

Dyslipidemia plays a key role in the development of cardiovascular diseases (Brunham et al., 2008). The positive associations we observed between NO_2 exposure and dyslipidemia were largely consistent with previous studies, though mixed findings existed. The Chinese Health Study of 33 Communities found that long-term NO_2 exposure was associated with risk of hypercholesterolemia, higher cholesterol and triglyceride levels, and lower HDL-C level (Yang et al., 2018a). Consistent results were also reported from the Korean Community Health Survey (Shin et al., 2019). A pooled study of 144,082 European participants reported that NO_2 was significantly associated with elevated triglycerides and HDL cholesterol, but not with total cholesterol (Cai et al., 2017). Another study among 1,023 Mexican Americans reported no associations between NO_2 exposure and any lipids concentration (Chen et al., 2016). The geographic differences, varying health status of participants, and variables included in statistical models complicated the comparison across studies. The biological mechanism underlying these associations remains unclear. One possible explanation is that systemic inflammation and oxidative stress induced by inhaled NO_2 might trigger lipid oxidation and impair lipid metabolism (Chen et al., 2019b).

In this study, we observed that associations between NO_2 and glucose disorders appeared to be stronger among smokers than non-smokers, which were consistent with the findings from an Italian study (Orioli et al., 2018). On the contrary, another study in Denmark that investigated the modification effect of smoking status reported stronger associations among non-smokers (Andersen et al., 2012). Smoking and air pollution were both identified as important risk factors for diabetes and shared similar biological pathways triggering glucose metabolic disorder, such as systemic inflammation and oxidative stress. Some studies also suggested preexisting subclinical inflammation might enhance the diabetogenic effects of air pollution (Kramer et al., 2010). These findings, along with our results, supported that smokers, who had chronic low-level inflammation, might be more susceptible to NO_2.

Few epidemiological studies explored whether the associations of NO_2 with diabetes or dyslipidemia were independent of other co-pollutants. A study conducted in Northwest China among 3,912 type-2 diabetes patients found that the associations between NO_2 and triglyceride disappeared after adjustment of $PM_{2.5}$ and sulfur dioxide, while the associations with HDL and LDL remained statistically significant (Wang et al., 2018). In the current study, adjustment for O_3 did not materially change the associations between NO_2 and glucose and lipid indicators. The associations with glucose disorders weakened after adjustment for $PM_{2.5}$ but remained statistically significant even in three-pollutants models. The results in this study supported that the associations of NO_2 with glucose and lipid metabolism could be potentially independent of O_3 or $PM_{2.5}$.

Some limitations of this study should be noted. First, exposure misclassification was likely as we obtained the exposure of NO_2 from a prediction model rather than personal monitoring, and indoor environment air pollution was not considered. Second, although our study adjusted for multiple individual-level confounders, residual confounding from unmeasured factors such as physical activity, noise, and other traffic-related pollutants, could not be ruled out. Finally, this study was based on a cross-sectional design, thus it was not possible to determine temporal precedence or to establish causality. Future studies with prospective cohort study design and full adjustment of co-pollutants would be valuable to verify the associations between NO_2 and glucose and lipid metabolic diseases.

Conclusion

Our study suggests that long-term exposure to NO_2 air pollution was significantly associated with glucose and lipids metabolic diseases in China, and the associations were potentially independent of O_3 and $PM_{2.5}$. The associations of NO_2 with diabetes and glucose biomarkers were stronger among smokers. Our findings have important public health implications for the prevention of diabetes and dyslipidemia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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Highlights

- Long-term exposure to NO_2 was associated with diabetes and dyslipidemia.
- Associations of NO_2 with blood glucose and lipid were independent of O_3 and $PM_{2.5}$.
- The associations between NO_2 and glucose disorders were stronger among smokers.

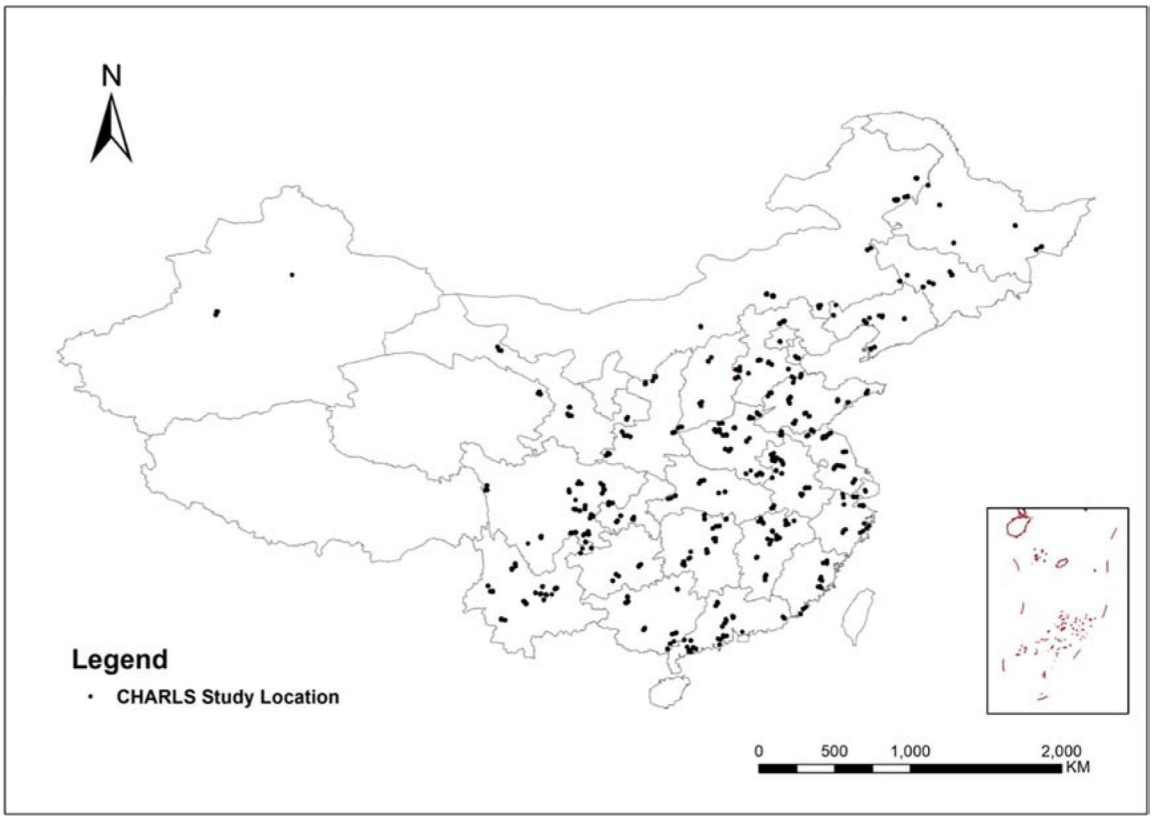

Figure 1 :
Locations of the study sites in the CHARLS project.

Table 1.

Baseline characteristics of the study participants.

Characteristics	Value
Age (year, mean ± SD)	61.88 ± 10.02
Sex N (%)	
Female	7021 (53.96)
Male	5991 (46.04)
Educational level N (%)	
Low	2927 (27.40)
Medium	4418 (41.36)
High	3336 (31.23)
BMI (kg/m^2, mean ± SD)	23.94 ± 3.74
Smoking status N (%)	
Never	7758 (59.68)
Former	1746 (13.43)
Current	3496 (26.89)
Pack-years of cigarette for current smokers	32.73 ± 10.02
Drinking frequency N (%)	
Never	8481 (65.26)
<1/month	1134 (8.73)
>1/month	3380 (26.01)
Type of energy N (%)	
Clean (central heating, solar energy, electricity, natural gas)	6657 (51.42)
Unclean (coal or biomass)	6290 (48.58)
Diabetes	
Prevalence of diabetes (%)	1933 (14.85)
Glucose (mg/dL mean ± SD)	103.6 ± 35.4
HbA1c (%, mean ± SD)	5.98 ± 0.99
Dyslipidemia	
Prevalence of dyslipidemia (%)	1935 (14.87)
HDL (mg/dL mean ± SD)	51.21 ± 11.58
LDL (mg/dL mean ± SD)	102.22 ± 29.01
Cholesterol (mg/dL mean ± SD)	183.94 ± 36.62
Triglyceride (mg/dL mean ± SD)	143.20 ± 91.30
Exposure to air pollutants	
NO_2 ($\mu g/m^3$, mean (IQR))	24.00 (17.84 – 30.22)
$PM_{2.5}$ ($\mu g/m^3$, mean (IQR))	57.32 (40.31 – 71.78)
O_3 ($\mu g/m^3$, mean (IQR))	68.27 (60.30 – 74.41)

Abbreviations: SD, standard deviation; BMI, Body mass index; HbA1c, glycosylated hemoglobin, %; HDL, high density lipoprotein; LDL, low density lipoprotein; IQR, interquartile range (P_{75}–P_{25}); NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than or equal to 2.5 μm; O_3, ozone

Table 2.

Changes (point estimates and 95% confidence intervals) in health indicators associated with an interquartile range increase in NO_2.

Health indicators	point estimates and 95% confidence intervals			
	Model1	**Model2**	**Model3**	**Model4**
Diabetes				
Prevalence of diabetes (odds ratio)	1.17 (1.09, 1.26)	1.17 (1.06, 1.28)	1.12 (1.01, 1.25)	1.13 (1.01, 1.26)
Fasting glucose (% change)	2.25 (1.59, 2.91)	2.23 (1.42, 3.05)	1.38 (0.43, 2.35)	1.48 (0.51, 2.46)
HbA1c (% change)	0.85 (0.48, 1.22)	1.00 (0.55, 1.46)	0.66 (0.11, 1.20)	0.74 (0.19, 1.29)
Dyslipidemia				
Prevalence of dyslipidemia (odds ratio)	1.14 (1.06, 1.23)	1.26 (1.15, 1.38)	1.13 (1.01, 1.26)	1.17 (1.05, 1.31)
HDL (% change)	−2.57 (−3.13, −2.01)	−3.12 (−3.80, −2.44)	−2.76 (−3.57, −1.94)	−2.96 (−3.79, −2.13)
LDL (% change)	−1.86 (−2.62, −1.09)	0.61 (−0.35, 1.58)	0.08 (−1.07, 1.23)	0.85 (−0.32, 2.03)
Cholesterol (% change)	−1.81 (−2.32, −1.30)	−0.06 (−0.70, 0.58)	−0.65 (−1.40, 0.12)	−0.08 (−0.85, 0.70)
Triglyceride (% change)	0.49 (−0.88, 1.89)	3.42 (1.68, 5.19)	3.83 (1.74, 5.95)	4.62 (2.49, 6.79)

Abbreviations:NO_2, nitrogen dioxide; HbA1c, glycosylated hemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein. Note: Model1, adjusted age, sex, educational level (low, medium, high), BMI (<18.5, 18.5–24.9, ≥25), smoking status (current smokers, ex-smoker and non-smoker), pack-years for current smokers, drinking frequency (never, < 1 / month, > 1 / month), energy types for cooking and heating (clean, unclean); Model2, Model1 + O3; Model3, Model1 + $PM_{2.5}$; Model4, Model1 + O_3 + $PM_{2.5}$. All biomarkers were log transformed in the association analysis.

Table 3.

Changes (point estimates and 95% confidence intervals) in health indicators for diabetes associated with an interquartile range increase in NO2 stratified by potential modifiers.

Variables	Categories	N	Diabetes		Fasting glucose		HbA1c	
			OR (95% CI)	p	% change (95% CI)	p	% change (95% CI)	p
Age	21–64	7844	1.19 (1.02, 1.39)	0.43	1.46 (0.20, 2.74)	0.76	0.94 (0.22, 1.66)	0.58
	≥65	5023	1.09 (0.93, 1.28)		1.80 (0.27, 3.36)		0.61 (−0.24, 1.47)	
Sex	Female	7021	1.06 (0.91, 1.24)	0.27	1.28 (−0.04, 2.63)	0.66	0.35 (−0.42, 1.12)	0.12
	Male	5991	1.21 (1.02, 1.42)		1.74 (0.31, 3.19)		1.22 (0.44, 2.01)	
BMI kg/m^2	<18.5	717	1.21 (0.60, 2.44)		5.52 (0.87, 10.39)		1.36 (−1.37, 4.17)	
	18.5–24.9	7442	1.11 (0.95, 1.31)	0.83	1.45 (0.21, 2.70)	0.10	0.81 (0.12, 1.50)	0.72
	≥25	4854	1.12 (0.96, 1.31)		1.12 (−0.55, 2.81)		0.55 (−0.41, 1.51)	
Smoking status	No	7758	**1.01 (0.87, 1.17)**	**0.03**	**0.55 (−0.70, 1.82)**	**0.03**	**0.25 (−0.47, 0.97)**	**0.04**
	Yes	5242	**1.29 (1.09, 1.54)**		**2.78 (1.24, 4.34)**		**1.40 (0.55, 2.25)**	
Drinking	No	8481	1.11 (0.97, 1.27)	0.69	1.44 (0.20, 2.69)	0.89	0.82 (0.11, 1.54)	0.80
	Yes	4514	1.17 (0.96, 1.42)		1.59 (0.02, 3.18)		0.67 (−0.17, 1.52)	

Abbreviations: NO^2, nitrogen dioxide; BMI, Body mass index; HbA1c, glycosylated hemoglobin; OR, odds ratio.

Note: categories for education (low ≤ 9 years; high ≥ 9 years); models adjusted for age, sex, educational level (low, medium, high), BMI (<18.5 kg/m2, 18.5–24.9 kg/m^2, ≥25 kg/m^2), smoking status (current smokers, ex-smoker and non-smoker), pack-years for current smokers, drinking frequency (never, < 1 / month, > 1 / month), energy types for cooking and heating (clean, unclean), O_3, $PM_{2.5}$. All biomarkers were log transformed in the association analysis.

Table 4.

Changes (point estimates and 95% confidence intervals) in health indicators for dyslipidemia associated with an interquartile range increase in NO_2 stratified by potential modifiers.

Variables	Categories	N	Dyslipidemia		HDL		LDL		Cholesterol		Triglyceride	
			OR and 95%CI	p	% change (95% CI)	p	% change (95% CI)	p	% change (95% CI)	p	% change (95% CI)	p
Age	21–64	7844	1.10 (0.95, 1.28)	0.16	−2.96 (−4.02, −1.89)	0.92	1.51 (−0.04, 3.08)	0.33	−0.06 (−1.08, 0.96)	0.89	3.71 (0.84, 6.67)	0.38
	≥65	5023	1.29 (1.09, 1.52)		−3.05 (−4.36, −1.72)		0.31 (−1.47, 2.12)		0.06 (−1.13, 1.26)		5.67 (2.56, 8.86)	
Sex	Female	7021	1.11 (0.95, 1.29)	0.35	−2.30 (−3.38, −1.20)	0.08	1.29 (−0.26, 2.87)	0.38	0.20 (−0.82, 1.24)	0.33	3.15 (0.33, 6.04)	0.20
	Male	5991	1.24 (1.05, 1.46)		−3.79 (−5.04, −2.52)		0.23 (−1.52, 2.01)		−0.57 (−1.72, 0.59)		5.94 (2.77, 9.21)	
BMI kg/m^2	<18.5	717	1.17 (0.48, 2.85)		−3.93 (−8.27, 0.61)		−1.40 (−6.94, 4.48)		−2.58 (−6.27, 1.27)		5.49 (−2.88, 14.58)	
	18.5–24.9	7442	1.18 (1.00, 1.39)	0.99	−3.37 (−4.51, −2.23)	0.82	0.56 (−0.97, 2.12)	0.53	−0.13 (−1.15, 0.89)	0.23	6.01 (3.19, 8.92)	0.92
	≥25	4854	1.16 (0.99, 1.34)		−2.10 (−3.32, −0.86)		1.45 (−0.45, 3.38)		0.28 (−0.97, 1.55)		2.44 (−1.02, 6.02)	
Smoking status	No	7758	1.11 (0.95, 1.29)	0.21	−2.76 (−3.78, −1.72)	0.59	0.99 (−0.49, 2.49)	0.69	−0.23 (−1.21, 0.76)	0.88	2.73 (0.05, 5.48)	0.08
	Yes	5242	1.24 (1.05, 1.46)		−3.24 (−4.60, −1.87)		0.48 (−1.40, 2.39)		−0.10 (−1.34, 1.15)		6.66 (3.25, 10.18)	
Drinking	No	8481	1.17 (1.02, 1.33)	0.92	−2.87 (−3.86, −1.86)	0.69	0.69 (−0.75, 2.15)	0.68	−0.06 (−1.03, 0.92)	0.91	4.59 (1.98, 7.27)	0.88
	Yes	4514	1.18 (0.97, 1.44)		−3.24 (−4.70, −1.77)		1.23 (−0.75, 3.24)		−0.15 (−1.42, 1.13)		4.20 (0.59, 7.94)	

Abbreviations: NO_2, nitrogen dioxide; BMI, Body mass index; HDL, high density lipoprotein; LDL, low density lipoprotein.

Note: categories for education (low ≤ 9 years; high ≥ 9 years); models adjusted for age, sex, educational level (low, medium, high), BMI (<18.5 kg/m^2, 18.5–24.9 kg/m^2, ≥25 kg/m^2), smoking status (current smokers, ex-smoker and non-smoker), pack-years for current smokers, drinking frequency (never, < 1 / month, > 1 / month), energy types for cooking and heating (clean, unclean), O_3, $PM_{2.5}$. All biomarkers were log transformed in the association analysis. All biomarkers were log transformed in the association analysis.