# Risk analysis of air pollutants and types of anemia: a UK Biobank prospective cohort study

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## Abstract

# Background:

Previous studies have suggested that exposure to air pollutants may be associated with specific blood indicators or anemia in certain populations. However, there is insufficient epidemiological data and prospective evidence to evaluate the relationship between environmental air pollution and specific types of anemia.

# Methods:

We conducted a large-scale prospective cohort study based on the UK Biobank. Annual average concentrations of $NO_2$, $PM_{2.5}$, $PM_{2.5-10}$, and $PM_{10}$ were obtained from the ESCAPE study using the Land Use Regression (LUR) model. The association between atmospheric pollutants and different types of anemia was investigated using the Cox proportional hazards model. Furthermore, restricted cubic splines were used to explore exposure-response relationships for positive associations, followed by stratification and effect modification analyses by gender and age.

# Results:

After adjusting for demographic characteristics, 3–4 of the four types of air pollution were significantly associated with an increased risk of iron deficiency, vitamin B12 deficiency and folate deficiency anemia, while there was no significant association with other defined types of anemia. After full adjustment, we estimated that the hazard ratios (HRs) of iron deficiency anemia associated with each 10μg/$m^3$ increase in $NO_2$, $PM_{2.5}$, and $PM_{10}$ were 1.04 (95%CI: 1.02, 1.07), 2.00 (95%CI: 1.71, 2.33), and 1.10 (95%CI: 1.02, 1.20) respectively. The HRs of folate deficiency anemia with each 10μg/$m^3$ increase in $NO_2$, $PM_{2.5}$, $PM_{2.5-10}$, and $PM_{10}$ were 1.25 (95%CI: 1.12, 1.40), 4.61 (95%CI: 2.03, 10.47), 2.81 (95%CI: 1.11, 7.08), and 1.99 (95%CI: 1.25, 3.15) respectively. For vitamin B12 deficiency anemia, no significant association with atmospheric pollution was found. Additionally, we estimated almost linear exposure-response curves between air pollution and anemia, and interaction analyses suggested that gender and age did not modify the association between air pollution and anemia.

# Conclusion

Our research provided reliable evidence for the association between long-term exposure to $PM_{10}$, $PM_{2.5}$, $PM_{2.5-10}$, $NO_2$, and several types of anemia. $NO_2$, $PM_{2.5}$, and $PM_{10}$ significantly increased the risk of iron deficiency anemia and folate deficiency anemia. Additionally, we found that the smaller the PM diameter, the higher the risk, and folate deficiency anemia was more susceptible to air pollution than iron deficiency anemia. No association was observed between the four types of air pollution and hemolytic anemia, aplastic anemia, and other types of anemia. Although the mechanisms are not well understood, we emphasize the need to limit the levels of PM and $NO_2$ in the environment to reduce the potential impact of air pollution on folate and iron deficiency anemia.

## Introduction

Anemia is a disease defined by a lack of hemoglobin (Hb) in the blood, affecting approximately one-third of the global population, resulting in increased morbidity and mortality, decreased work productivity, and impaired neurological development (Chaparro and Suchdev 2019). There are two main types of anemia: insufficient production of red blood cells (erythrocytes) by the bone marrow, and an increase in the rate of red blood cell breakdown (hemolysis). The former may be due to a lack of hematopoietic raw materials. The latter occurs in specific hemolytic anemias, the prevalence of which has increased from approximately 308 million in 1990 to approximately 506 million in 2017 (The 2018; Nations within a nation: variations in epidemiological transition across the states of India, 1990–2016 in the Global Burden of Disease Study 2017). Anemia posed significant risks and leads to different adverse outcomes in individuals of all age groups. Studies have found that older adults with anemia are at a higher risk for many severe adverse health outcomes, including mortality (Ezekowitz et al. 2003; Wu et al. 2001), impaired functional status (Lipschitz 2003; Denny et al. 2006), impaired cognitive function 7, and cognitive disorders such as Alzheimer's disease (Beard et al. 1997; Atti et al. 2006). Anemia was associated with increased morbidity and mortality in women and children (Kassebaum et al. 2014), resulting in adverse birth outcomes (Haider et al. 2013), decreased work productivity in adults (Haas and Brownlie 2001), and impaired cognitive and behavioral development in children (Walker et al. 2007).

Air pollutants may be a potential factor leading to anemia. Studies have shown that exposure to $PM_{2.5}$ and $NO_2$ can increase systemic inflammation and affect bone marrow hematopoietic function (Dabass et al. 2016; Orona et al. 2016; Mukae et al. 2000). Short-term exposure to atmospheric pollutants was associated with elevated markers of circulatory inflammation, while long-term exposure to particulate pollutants might have led to sustained chronic inflammation, triggering cardiovascular events or chronic disease states (Brook et al. 2010). Importantly, systemic inflammation reduced the production of erythropoietin, exacerbated the intractable response of hematopoietic precursors to endogenous erythropoietin, ultimately led to a decrease in Hb content/red blood cell count (Ferrucci and Balducci 2008; Quay et al. 1998). Moreover, more than half of the PM deposited in the nasal cavity ultimately enters the digestive tract and may affect iron absorption efficiency(Quay et al. 1998; Agency ; D'Angelo 2013rány 2001; Ganz 2019). Particles of molecular size are directly absorbed into the bloodstream and compete with host cells for available iron (Czechowski et al. 2004; Town et al. 2012; Yamamoto et al. 2010; Yang and Van den Berg 2009). Although the mechanism is unclear, environmentally-related particulate matter β-particle radiation (PRβ) may lead to a decrease in Hb concentration (Vieira et al. 2020). Folic acid plays an important role in hematopoiesis, and the main source of folic acid in the human body is dietary

intake. Studies have shown a positive correlation between the use of polluting cooking fuel by rural residents and folic acid deficiency (Xia et al. 2023; Kwag et al. 2021).

Although studies have investigated the association between PM and indicators of anemia, most of them focus on specific populations, such as the elderly, children, and pregnant women (Elbarbary et al. 2020; Honda et al. 2017; Mehta et al. 2021; Morales-Ancajima et al. 2019). The impact of air pollution on anemia in the general population has received little attention, and there is a lack of large-scale prospective studies evaluating the association between long-term air pollution exposure and anemia subtypes. To provide more statistical evidence and fill the knowledge gap, our study assessed the association between long-term PM and $NO_2$ exposure and the occurrence of 11 types of anemia. We further explored the corresponding exposure-response curves and identified susceptible populations through stratified analysis.

## Methods

# 4.1 Data source

UK Biobank is a large, forward-looking cohort that recruited approximately 500,000 people from England, Wales, and Scotland from 2006 until 2010 (Palmer 2007). All participants will have their basic information recorded, such as gender, age, etc., during the recruitment process. They will also undergo physical measurements and other assessments. The UK Biobank received ethical approval from the North West Multi-centre Research Ethics Committee (Ref: 11/NW/0382). Information on the UK Biobank protocol can be found on the website (https://www.UK Biobankiobank.ac.uk/). The UK Biobank application number of this study is 99732.

# 4.2 Ambient Air Pollution Measurement

To estimate the annual average concentrations of $PM_{10}$, $PM_{2.5-10}$, and $PM_{2.5}$, we used land-use regression (LUR) models developed in the European Study of Cohorts for Air Pollution Effects (ESCAPE), which investigated the effects of air pollution on 119 European cohorts (Eeftens et al. 2012; Development of NO2 and NOx land use regression models for estimating air pollution exposure in 36 study areas in Europe – The ESCAPE project 2013). Specifically, we estimated the annual average air pollutant concentrations by using pollutant-specific LUR models and predictive variables in a geographic information system, combined with participant residential addresses obtained from baseline information collection. The official description of the UK Biobank indicates that data from different air pollution models should not be averaged. Therefore, based on previous research, we used the air pollution data from the ESCAPE project in 2010 to represent long-term exposure to PM in our analysis (Luo et al. 2022). In addition, considering that population mobility leads to inaccurate results, participants who had moved away from their original residential address were excluded from the study.

# 4.3 Anemia

The relevant results of the first diagnosis of anemia were determined based on the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) codes D50-D64. In the UK Biobank, there are seven sources for reporting the date of first onset, including death registration only, primary care data, primary care data plus other sources, hospital inpatient data only, hospital inpatient data plus other sources, self-report data, and self-report data plus other sources. For more detailed information, please refer to http://content.digital.nhs.uk/services. Acquired pure red cell aplasia (D60) and anemia due to enzyme disorders (D55) were excluded from further analysis due to insufficient positive cases. In addition, individuals with anemia at recruitment and those who developed anemia within two years of follow-up were excluded to prevent reverse causality. Furthermore, self-report cases were also excluded to increase the accuracy of the results. The duration of follow-up was calculated from the baseline assessment date to the date of first diagnosis of anemia. For individuals who did not develop anemia, the endpoint was the date of death, loss to follow-up, or the last occurrence of specific anemia, whichever came first.

# 4.4 Covariates

A series of confounding factors such as social demographics, behavior, and diet were determined based on existing literature. The demographic characteristics included in this study are as follows: baseline age was determined based on date of birth and baseline assessment, with participants divided into two groups: 60 years and above, and below 60 years old. Gender was self-reported at baseline. Education level was categorized into college/university or other. Ethnicity was divided into White and Other. Townsend Deprivation Index (TDI) was divided into low/high economic level based on the median (Dolan et al. 1995). Lifestyle factors included physical activity, smoking status, alcohol consumption, and healthy diet. The International Physical Activity Questionnaire (IPAQ) was mainly used to evaluate the physical activity levels of adults and classify the population into low, moderate, and high levels (Lee et al. 2011). Smoking status was categorized into never, occasional, and regular. Alcohol consumption was self-reported and categorized as never, past, and current. In terms of diet, we referred to the definition of healthy diet from a previous study in UK Biobank (Rutten-Jacobs et al. 2018). Increasing intake of fruits, vegetables, and fish, and decreasing consumption of processed and red meats were determined to be healthy foods (intake of fruits and vegetables: >4.5 servings/week; fish intake: >2 times/week; meat intake: processed meats ≤2 times/week, and red meats ≤5 times/week). A healthy diet was defined as meeting at least two of the above healthy food criteria, otherwise it was considered unhealthy. In addition, we also considered dietary iron, vitamin B12, and folate intake, as well as supplement use. The former was calculated based on 5-day 24-hour dietary recall, while the latter was self-reported by participants. Body measurements included BMI, which was defined as weight in kilograms divided by height in meters squared ($kg/m^2$). Past medical history included mental health status, cancer, hypertension, diabetes, stroke, heart failure, digestive disease, and respiratory disease. Digestive diseases considered in this study included gastroesophageal reflux disease, ulcer, gastritis, dyspepsia, and inflammatory bowel disease. Respiratory diseases included chronic obstructive

pulmonary disease, asthma, emphysema, and bronchiectasis. Mental health status (diagnosed with nervousness, anxiety, tension, or depression by a physician) was obtained through questionnaires. Cancer was determined based on the diagnosis date from the National Cancer Registration. Other past medical histories such as hypertension and diabetes were determined based on ICD-10 codes.

## 4.5 Statistical analysis

In the statistical analysis, we applied the Cox proportional hazards regression model to estimate the hazard ratios (HRs) of long-term PM exposure on the risk of anemia. We used the Schoenfeld residual test to check the proportional hazards assumption in the model. Based on previous related research, we pre-assumed that the exposure-response relationship between long-term PM exposure and the risk of anemia incidence is linear, in order to estimate the hazard ratios (HRs) and 95% confidence intervals (95%CIs) associated with each 10μg/$m^3$ increase in long-term PM and $NO_2$ exposures.

Only demographic characteristics were adjusted in the preliminary analysis to screen for positive anemia outcomes related to air pollution. Due to a certain proportion of missing values for dietary iron, vitamin B12 and folate, as well as supplement use, the "MICE" package in R software was used for multiple imputation (MI) of the data (Su et al. 2011). Five complete datasets were obtained through MI, and the effect estimates from these five datasets were combined to report HR and CI. We constructed multiple models, taking into account the effects of multiple variables, and conducted stratified analysis by gender and age. Interaction terms between pollutant variables and stratification variables were included in the model, and their interaction was tested through likelihood ratio tests. We also explored the non-linear exposure-response association relationship using restricted cubic spline (RCS) models with 3 knots (the 25th, 50th, 75th percentile) for PM and $NO_2$ exposures (Gauthier et al. 2020). Finally, several sensitivity analyses were conducted: 1) Excluding cases of anemia occurring within 3 years of follow-up; 2) Excluding participants with baseline tumors, 3. Including family smokers and history of digestive system surgery to further validate the robustness of the model.

The Cox proportional hazard regression model was constructed using the “survival” package. We estimated the HRs of anemia associated with 10μg/$m^3$ increase in PM10, $PM_{2.5-10}$, $PM_{2.5}$ and $NO_2$ in all the analyses, and we performed test for trend based on variable containing median value for each quartile. All the above were achieved by R4.2.3 (http://www.r-project.org) and two-sided $p < 0.05$ was considered statistically significant.

## Results

After adjusting for demographic characteristics, only three clearly defined types of anemia (iron-deficiency anemia, vitamin B12 deficiency anemia, and folate deficiency anemia) showed a significant association with air pollutants (p<0.05), and strict exclusion was performed based on this. Among the total 502,370 participants in the UK Biobank cohort, we excluded 155,064 participants in this study: 1) Other 11 types of anemia (n=24,503) , Self-reported anemia (n=4,908), baseline anemia and anemia occurring within 2 years of recruitment (n=11,849) and anemia reported after death or loss of visit (n=8); 2) Subjects with missing air pollutant data (n=38,234) and participants who have moved away from their original place of residence (n=65,429); 3) Pregnant participants (n=114); 4) Lack of covariates (n=10,019) (Figure 1). Finally, a total of 347,306 participants with complete data were included.

After strict screening, the baseline characteristics of the participants were described in Table 1. During an average follow-up period of 13.41 years, 17,260 new cases of anemia were identified among all 347,306 participants, including 15,908 cases of iron-deficiency anemia, 866 cases of vitamin B12-deficiency anemia, and 486 cases of folate-deficiency anemia. Compared with participants who had not experienced any type of anemia, anemic patients were older, less likely to be white, had higher education levels, worse economic conditions, higher smoking rates, lower current alcohol consumption, and exercised less. Meanwhile, anemic individuals had a higher proportion of obesity, more psychological problems, a less healthy diet, and a higher incidence of previous diseases (including cancer, hypertension, diabetes, stroke, heart failure, respiratory diseases, and digestive diseases) (all p-value <0.001). In addition, the annual average concentrations of $NO_2$, $PM_{2.5}$, $PM_{2.5-10}$, and $PM_{10}$ in 2010 were 26.65 ± 7.66 μg/$m^3$, 9.99 ± 1.06 μg/$m^3$, 6.43 ± 0.90 μg/$m^3$, and 16.25 ± 1.90 μg/$m^3$, respectively, all of which exceeded the thresholds recommended by the World Health Organization's 2021 global air quality guidelines (annual levels: $NO_2$, 10μg/$m^3$; $PM_{2.5}$, 5μg/$m^3$; $PM_{10}$, 15μg/$m^3$). Furthermore, the annual average pollutant exposure of anemic patients was slightly higher than that of non-anemic participants (p value<0.01, respectively). Figure S1 presents the Pearson correlation results between air pollutants, indicating a positive correlation between $NO_2$, $PM_{10}$, $PM_{2.5-10}$, and $PM_{2.5}$, with Pearson coefficients ranging from 0.50 to 0.86, except for the weaker correlation of $PM_{2.5-10}$ with other indicators.

Schoenfeld residual tests showed all models met the proportional hazards assumption. After adjusting only demographic characteristics (gender, age, ethnicity, education level), atmospheric pollutants increased the risk of three distinctly defined nutrition-related anemias, while four pollutants showed no significant associations with other types of anemias (Figure 2). Multiple models were used to assess the risk relationships (Table 2). After full adjustment, it was estimated that for each 10μg/$m^3$ increase in $NO_2$, $PM_{2.5}$, and $PM_{10}$, the hazard ratios (HRs) of iron deficiency anemia were 1.04 (95%CI: 1.02, 1.07), 2.00 (95%CI: 1.71, 2.33), and 1.10 (95%CI: 1.02, 1.20) respectively; and the HRs of folate deficiency anemia for each 10μg/$m^3$ increase in NO2, PM2.5, PM2.5-10, and PM10 were 1.25 (95%CI: 1.12, 1.40), 4.61 (95%CI: 2.03, 10.47), 2.81 (95%CI: 1.11, 7.08), and 1.99 (95%CI: 1.25, 3.15) respectively. No significant association with pollutants was found for vitamin B12 deficiency anemia. Additionally, as described in Figure 3 and Table 2, we estimated almost linear exposure-response curves between pollutants and anemia.

Stratified analysis and effect modification tests showed that gender and age did not modify the association between pollutants and anemia (all P interaction > 0.05) (Table 3), and as described in Table S1 and Table S2, consistent with the main model, several sensitivity analyses suggested robust associations between several air pollutants and anemia.

## Discussion

Based on a large prospective cohort study from the UK Biobank, we systematically investigated the association between long-term exposure to particulate matter (PM) and $NO_2$ and the risk of 11 types of anemia in the general population. After preliminary analysis, three clearly defined nutrition-related anemias were significantly associated with air pollutants. After considering all potential confounding factors, we found that folate-deficiency anemia risk increased significantly with long-term exposure to $NO_2$, $PM_{2.5}$, $PM_{2.5-10}$, and $PM_{10}$; iron-deficiency anemia risk increased with long-term exposure to $NO_2$, $PM_{2.5}$, and $PM_{10}$; however, vitamin B12 deficiency anemia was not associated with any of the four environmental exposures. Furthermore, these associations remained robust after excluding anemia occurring within three years of follow-up, removing participants with tumors, considering family environmental particulate exposure and history of digestive tract surgery. We also explored the linear relationship curve between exposure to pollutants and the risk of anemia, and the results suggested an almost linear association. Overall, the associations of anemia risk with $PM_{2.5}$, $PM_{2.5-10}$, $PM_{10}$, and $NO_2$ decreased in sequence, and in terms of anemia types, the risk of folate-deficiency anemia was most strongly associated with pollutant exposure. Finally, although not statistically significant, stratified analysis and effect modification tests suggest that older age and male may be more susceptible to the development of anemia due to these pollutants.

Our study provides strong evidence of an association between long-term exposure to $PM_{2.5}$, $PM_{10}$, and $NO_2$ and the risk of nutrition-related anemia in the general population. Despite the lack of prospective cohort studies on atmospheric pollution and anemia subtypes, several observational studies support our conclusions. In 2020, survey data from 252 cities in China showed a significant positive correlation between hospitalization for anemia and concurrent exposure levels of $PM_{2.5}$ on the same day (Gu et al. 2020). Similarly in 2020, another cross-sectional study in China indicated significant associations of $PM_{10}$, $PM_{2.5}$, $PM_1$, and $NO_2$ with the risk of anemia and decreased hemoglobin (Hb) levels in the elderly (Elbarbary et al. 2020). Trenton et al. suggested that $NO_2$ and $PM_{2.5}$ were significantly associated with an increased prevalence of anemia and reduced Hb levels in older Americans, that there were dose-response relationship, and that acute response protein significantly mediates this effect of $PM_{2.5}$ (Honda et al. 2017). Consistent with our study, a cross-sectional study of Korean housewives showed that while the overall effect of $PM_{2.5}$ exposure was a decrease in mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH), $PM_{2.5}$ was also significantly negatively correlated with serum folate levels (Kwag et al. 2021). A recent survey of rural Chinese women also supports the idea that long-term use of solid fuels such as coal or wood may lead to insufficient red blood cell folate levels (Xia et al. 2023). Several studies from India revealed that $PM_{2.5}$ and other respirable particulate matter (RPM) have adverse effects on the hematological characteristics of anemic children, trained and sedentary male athletes (Mishra and Retherford 2007) (Mehta et al. 2021; Das and Chatterjee 2015). Interestingly, a retrospective birth cohort study from western China aimed at investigating the relationship between $PM_{2.5}$ and late-pregnancy Hb levels showed a slight association between $PM_{2.5}$ and decreased Hb levels and mild anemia. However, this association disappeared in primiparous women, and the study seems to suggest that the mild impact of $PM_{2.5}$ on late-pregnancy Hb levels may not rise to the level of anemia (Xie et al. 2022). We hypothesize that there are several possible reasons for this, one being that primiparous women are relatively young in age and have more active gastrointestinal tract function and greater nutrient absorption, and the other being that they may be more attentive to a rational diet and use of supplements. There is evidence that plasma iron and B vitamin concentrations or the use of dietary supplements modify the association of PM with several diseases(Chen et al. 2022; Gaskins et al. 2019; Loftus et al. 2019). Third, short-term exposures may lead to subtle fluctuations in Hb levels, and anemia is more likely to be a result of long-term exposure to PM. In our study, we also found no significant association between four atmospheric pollutants and vitamin B12 deficiency anemia, which is consistent with an early animal study where rats exposed to $NO_2$ (7 hours/day, 5 days/week, for 21 days) maintained normal serum vitamin B12 levels (Kripke and Sherwin 1984). Furthermore, a study of pediatric emergency room visits for sickle cell disease in children and adolescents in São Paulo, Brazil, from September 1999 to December 2004, showed that $NO_2$ and $PM_{10}$ were associated with a higher total number of emergency room visits for sickle cell disease, and that high $PM_{10}$ exposure increased by 40.3% in sickle cell patients with pain symptoms (Barbosa et al. 2015). However, in our study, there was no evidence to support the association between several exposures and the risk of sickle cell anemia.

In this study, stratified analysis shows that, despite the lack of statistical differences in interaction tests, our results suggest that males may enhance the association of all four pollutants with three types of anemia. Contrary to our study, Sørensen et al. studied 68 students aged between 20 and 33, collecting four instances of $PM_{2.5}$ exposure data within a year, and found that $PM_{2.5}$ in males was unrelated to Hb concentration, while in females, it was positively correlated with Hb concentration (Sørensen et al. 2003). However, this study did not classify the causes of anemia, and the study design type was also inconsistent. Importantly, the average follow-up time for anemia in our study was greater than 8 years, and studies have suggested that the effects of short-term pollutant exposure on hematology and hematopoiesis may differ from long-term exposure (Medzhitov 2008). Nevertheless, it still needs to be pointed out that, based on published studies, the pathophysiological mechanisms of gender differences in the association between PM and anemia are still unclear. On the other hand, there are many reasons for the decrease in Hb in the elderly population, but usually, there is no clear cause (Guralnik et al. 2004). In this study, we also found that almost all stratified models showed a relatively stronger association in the subgroup over 60 years of age. Studies indicated that 71% of PM deposited in the nasal cavity will eventually enter the digestive tract (Agency). Due to the degeneration of gastrointestinal function in the elderly population, PM exposure may more easily limit the digestive and absorptive capacity of nutrients in this population, thereby increasing the likelihood of anemia. Furthermore, it should be noted that particulate matter has low-level environmental radioactivity, and the elderly may be more sensitive to radiation because their ability to repair its effects is reduced (Hernández et al. 2015).

Mechanistically, firstly, chronic inflammation mediates the inhibition of hematopoietic function by $PM_{2.5}$ and $NO_2$, and long-term chronic inflammation leads to insufficient secretion of erythropoietin by the kidneys and increased resistance of the bone marrow to erythropoietin (Hsu et al. 2001rány 2001). Secondly, air pollution upregulates the levels of IL-6 in alveolar macrophages, which has been shown to increase the production of hepatic iron regulatory protein, which may hinder the absorption of iron in the gastrointestinal tract (D'Angelo 2013; Quay et al. 1998). Thirdly, Honda et al. demonstrated that C-reactive protein may mediate the association between $PM_{2.5}$ but not $NO_2$ and hemoglobin levels in the elderly population in the United States, although it is still unclear whether this holds true for young individuals (Honda et al. 2017). Fourthly, natural organic matter accounts for the majority of inhalable particulate matter in ambient

air, and some components of particulate matter such as Humic-Like Substances (HULIS) are rich in oxygen-containing functional groups, including carboxylates and phenolates, which facilitate the formation of stable complexes with metals, with a particularly strong affinity for iron. Inhaled particles compete with host cells for available iron, leading to chronic host response ("iron competition") (Ghio et al. 2020; Erdogan et al. 2007; Yamamoto et al. 2010). Fifthly, inhaled radioactive nuclides attached to PM can be transported throughout the body, and studies have shown an association between environmental ionizing radiation released by particulate matter and lower Hb concentration (Porstend?Rfer 1994). It is evident that many mechanisms could be inferred as effects on iron metabolism. Considering that iron-deficiency anemia is the most common type among populations, this is understandable. However, there is currently a lack of research on the population and mechanisms linking environmental pollution with folate deficiency. We hypothesize that some of the aforementioned mechanisms may also mediate folate deficiency. However, more evidence is needed to reveal this in the future.

In this study, we used a single-pollutant model to assess the associations between four environmental exposures and anemia. We also found that as particle diameter increased, the risks of folate deficiency anemia and iron-deficiency anemia were reduced. The following factors can explain this result. Firstly, due to the potentially higher content of HULIS in $PM_{2.5}$, their impact on the "iron competition" effect may be stronger. Secondly, the concentration of radioactive isotopes emitting beta and alpha particles in the environment appears to be influenced by the size of PM. $PM_{2.5}$ has a larger specific surface area, allowing it to accumulate more radioactive substances while also delaying the decay of unattached particles, thereby posing more persistent harm to the human body (Porstend?Rfer 1994). However, strangely, both $PM_{2.5}$ and $PM_{10}$ increased the risk of iron deficiency, while $PM_{2.5-10}$ did not, suggesting that the effect of $PM_{10}$ is mainly derived from $PM_{2.5}$.

Another interesting finding is that, among different types of nutrition-related anemia, folate deficiency anemia shows the strongest environmental susceptibility while vitamin B12 deficiency anemia is not affected. One possible explanation is that, unlike slight variations in Hb levels, individuals diagnosed with anemia require Hb levels below a specific threshold, which means long-term environmental exposure is necessary. Folate has limited storage in the body and can only meet the body's needs for 3–4 months without intake, whereas the storage of vitamin B12 can often meet the body's needs for several years, and the iron storage of healthy adults can provide for several months to about a year. If PM and $NO_2$ mainly affect the absorption of these nutrients leading to anemia, our study is highly consistent with this background. In addition, according to official data from UK Biobank (https://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=41270), the proportions of iron-deficiency anemia, vitamin B12 deficiency anemia, and folate deficiency anemia without clear causes (D50.9, D52.9, and D53.9) among the three main types of nutrition-related anemia diagnosed by ICD10 are 69%, 21%, and 97%, respectively. Our study may provide some clues for revealing these causes.

## Advantages and Limitations

To our knowledge, this is the first prospective cohort study exploring the causal relationship between atmospheric pollution and anemia subtypes. The study has a large sample size, long follow-up duration, and standardized data collection protocol, effectively balancing multiple confounding factors. In addition, several sensitivity analyses also validated the reliability of the conclusions.

However, there are also some limitations. Firstly, there is a possibility of delayed diagnosis of anemia, which may introduce some bias in the overall effect assessment. Secondly, due to the temporal limitation of PM exposure data in the UK Biobank, we used the annual average concentration of pollution data from 2010 as a proxy for long-term exposure. Thirdly, over half of the participants lacked information on vitamin and mineral supplementation. Considering the small number of cases of folate deficiency anemia, excluding missing values directly would render some studies unable to proceed. For this contradiction, we constructed multiple models and included the covariate in the fully adjusted model, thus caution is needed when interpreting these results. Fourthly, the annual average concentrations of PM and $NO_2$ in the UK are relatively low, and thus we were unable to investigate the effects of higher concentrations of PM exposure on anemia subtypes. Further research is still needed in heavily polluted developing countries. Fifthly, due to the lack of exposure data, we did not consider the effects of PM components on anemia. Lastly, the age range of the participants assessed was between 37 and 73 years old, and pregnant participants were excluded. Therefore, the conclusions of this study may not be extrapolated to special populations such as pregnancy and children.

## Conclusion

In summary, PM and $NO_2$ increase the risk of iron deficiency anemia and folate deficiency anemia, while this association is not significant in other well-defined anemias. The smaller the PM diameter, the stronger its association, and folate deficiency anemia is also more susceptible to air pollution. For the human body, B vitamins and mineral supplements have potential for environmental pollution resistance. In addition to necessary prevention measures to reduce pollution, the general population may also benefit from appropriate supplementation of these nutrients.

## Abbreviations

BMI, body mass index

CI, confidence interval

ESCAPE, European Study of Cohorts for Air Pollution Effects

Hb, hemoglobin

HR, Hazard Ratio

HULIS, Humic-Like Substances

ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th Revision

IL-6, Interleukin-6

IPAQ, International Physical Activity Questionnaire

LUR, Land Use Regression

NO2, nitrogen dioxide

PM10, inhalable particulate matter

PM2.5, fine particulate matter

PM2.5-10, coarse particulate matter

RCS, restricted cubic spline

## Declarations

Author Contributions

LFL wrote the main part of the paper. YR and YZ make a Critical revision of the manuscript for important intellectual content. LLW, YTS and FCY responsible for proper layout of images. SWL, LM and YN revised the manuscript appropriately. FD conceived and supervised this manuscript. All authors read and approved the final manuscript.

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Conflict of Interest Disclosures

*The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.*

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## Tables

## Table 1: Baseline characteristics of the included participants.

| Characteristics | Total (n = 347306) | Healthy (n = 330046) | Anemia (n = 17260) | P |
|---|---|---|---|---|
| Follow-up time (years), (Mean, SD) | 13.41 (1.52) | 13.66 (0.80) | 8.61 (3.16) | < 0.001 |
| $NO_2$ (μg/$m^3$) (Mean, SD) | 26.65 (7.66) | 26.61 (7.66) | 27.42 (7.73) | < 0.001 |
| $PM_{10}$ (μg/$m^3$) (Mean, SD) | 16.25 (1.90) | 16.25 (1.90) | 16.35 (1.88) | < 0.001 |
| $PM_{2.5}$ (μg/$m^3$) (Mean, SD) | 9.99 (1.06) | 9.98 (1.05) | 10.12 (1.08) | < 0.001 |
| $PM_{2.5-10}$ (μg/$m^3$) (Mean, SD) | 6.43 (0.90) | 6.43 (0.90) | 6.45 (0.91) | 0.009 |
| Sex, n (%) | | | | 0.759 |
| Female | 188062 (54) | 178736 (54) | 9326 (54) | |
| Male | 159244 (46) | 151310 (46) | 7934 (46) | |
| Age, n (%) | | | | < 0.001 |
| < 60 years | 192523 (55) | 185886 (56) | 6637 (38) | |
| ≥ 60 years | 154783 (45) | 144160 (44) | 10623 (62) | |
| Ethnicity, n (%) | | | | < 0.001 |
| Others | 20486 (6) | 19136 (6) | 1350 (8) | |
| The white | 326820 (94) | 310910 (94) | 15910 (92) | |
| Education attainment, n (%) | | | | < 0.001 |
| Less than a college degree | 329373 (95) | 313122 (95) | 16251 (94) | |
| College degrees or higher | 17933 (5) | 16924 (5) | 1009 (6) | |
| Townsend deprivation index[1], n (%) | | | | < 0.001 |
| High economic level | 168865 (49) | 161758 (49) | 7107 (41) | |
| Low economic level | 178441 (51) | 168288 (51) | 10153 (59) | |
| Smoke, n (%) | | | | < 0.001 |
| Never smoked | 309161 (89) | 294027 (89) | 15134 (88) | |
| Smoke regularly | 28391 (8) | 26719 (8) | 1672 (10) | |
| Smoke occasionally | 9754 (3) | 9300 (3) | 454 (3) | |
| Alcohol, n (%) | | | | < 0.001 |
| Never | 15377 (4) | 14074 (4) | 1303 (8) | |
| Previous | 12410 (4) | 11230 (3) | 1180 (7) | |
| Current | 319519 (92) | 304742 (92) | 14777 (86) | |
| IPAQ[2], n (%) | | | | < 0.001 |
| Low | 52153 (15) | 49163 (15) | 2990 (17) | |
| Moderate | 113067 (33) | 107727 (33) | 5340 (31) | |
| High | 114511 (33) | 109652 (33) | 4859 (28) | |
| Unknown | 67575 (19) | 63504 (19) | 4071 (24) | |
| Body mass index, n (%) | | | | < 0.001 |
| < 25 kg/$m^2$ | 111523 (32) | 107234 (32) | 4289 (25) | |
| ≥ 25 kg/$m^2$ | 235783 (68) | 222812 (68) | 12971 (75) | |
| Mental health status[3], n (%) | | | | < 0.001 |
| No | 307288 (88) | 292767 (89) | 14521 (84) | |
| Yes | 40018 (12) | 37279 (11) | 2739 (16) | |
| Cancer, n (%) | | | | < 0.001 |

| | | | | |
|---|---|---|---|---|
| No | 315569 (91) | 300305 (91) | 15264 (88) | |
| Yes | 31737 (9) | 29741 (9) | 1996 (12) | |
| Hypertension, n (%) | | | | < 0.001 |
| No | 254599 (73) | 244629 (74) | 9970 (58) | |
| Yes | 92707 (27) | 85417 (26) | 7290 (42) | |
| Type II Diabetes, n (%) | | | | < 0.001 |
| No | 338883 (98) | 323292 (98) | 15591 (90) | |
| Yes | 8423 (2) | 6754 (2) | 1669 (10) | |
| Stroke n (%) | | | | < 0.001 |
| No | 342693 (99) | 326012 (99) | 16681 (97) | |
| Yes | 4613 (1) | 4034 (1) | 579 (3) | |
| Heart failure, n (%) | | | | < 0.001 |
| No | 345615 (100) | 328593 (100) | 17022 (99) | |
| Yes | 1691 (0) | 1453 (0) | 238 (1) | |
| Healthy diet[4], n (%) | | | | < 0.001 |
| No | 91412 (26) | 86502 (26) | 4910 (28) | |
| Yes | 255894 (74) | 243544 (74) | 12350 (72) | |
| Respiratory disease[5], n (%) | | | | < 0.001 |
| No | 336745 (97) | 320207 (97) | 16538 (96) | |
| Yes | 10561 (3) | 9839 (3) | 722 (4) | |
| Digestive diseases[6], n (%) | | | | < 0.001 |
| No | 296760 (85) | 284096 (86) | 12664 (73) | |
| Yes | 50546 (15) | 45950 (14) | 4596 (27) | |
| Gas or solid-fuel cooking, n (%) | | | | < 0.001 |
| None | 60633 (17) | 57280 (17) | 3353 (19) | |
| Clean fuel | 277418 (80) | 263879 (80) | 13539 (78) | |
| Solid fuel | 9255 (3) | 8887 (3) | 368 (2) | |

**Notes:** 1, High economic level was defined as Townsend Deprivation Index < -2.23 (median value) while low economic level was defined as Townsend Deprivation Index ≥ -2.23. 2, Physical activity was categorized as low, moderate and high based on the International Physical Activity Questionnaire (IPAQ). 3, Mental health status were assessed according to the touchscreen question (“Have you ever seen a psychiatrist for nerves, anxiety, tension or depression?”). 4, Healthy diet was defined as at least two of the healthy food (fruit and vegetable intake: > 4.5 pieces or servings a week; fish intake: > 2 per week; meat intake: processed meat ≤ 2 per week & red meat ≤ 5 per week), otherwise unhealthy. 5, Respiratory disease included chronic obstructive pulmonary disease, asthma, emphysema, and bronchiectasis. 6, Digestive diseases considered in this study included gastroesophageal reflux disease, ulcer, gastritis, dyspepsia, and inflammatory bowel disease. $PM_{10}$, inhalable particulate matter; $PM_{2.5-10}$, coarse particulate matter; $PM_{2.5}$, fine particulate matter. $NO_2$, nitrogen dioxide.

## Table 2 Association between per 10μg/m$^3$ increase in air pollutants exposure and the risk of anemia incidence.

| | Crude model | | Model 1 | | Model 2 | | Model 3 | | | Mod |
|---|---|---|---|---|---|---|---|---|---|---|
| **Iron deficiency anemia** | HR (95%CI) | P | 95%CI | P | HR (95%CI) | P | HR (95%CI) | P | p trend | HR ( |
| $NO_2$ | 1.13(1.11,1.15) | <0.0001 | 1.14(1.12,1.16) | <0.0001 | 1.05(1.03,1.08) | <0.0001 | 1.04(1.02,1.07) | <0.001 | 0.001 | 1.04 |
| $PM_{2.5}$ | 3.26(2.83,3.74) | <0.0001 | 3.58(3.11,4.12) | <0.0001 | 2.14(1.84,2.49) | <0.0001 | 2.05(1.76,2.38) | <0.0001 | <0.0001 | 2.00 |
| $PM_{2.5-10}$ | 1.24(1.05,1.47) | 0.01 | 1.23(1.04,1.46) | 0.02 | 1.06(0.89,1.27) | 0.48 | 1.08(0.91,1.29) | 0.36 | / | 1.08 |
| $PM_{10}$ | 1.30(1.20,1.41) | <0.0001 | 1.29(1.19,1.40) | <0.0001 | 1.10(1.02,1.20) | 0.02 | 1.11(1.02,1.20) | 0.02 | 0.045 | 1.10 |
| **VitaminB12 deficiency anemia** | | | | | | | | | | |
| $NO_2$ | 1.11(1.02,1.21) | 0.01 | 1.13(1.04,1.23) | 0.004 | 1.03(0.94,1.13) | 0.55 | 1.03(0.93,1.13) | 0.58 | / | 1.02 |
| $PM_{2.5}$ | 3.38(1.86,6.14) | <0.0001 | 3.86(2.12,7.04) | <0.0001 | 2.09(1.09,4.01) | 0.03 | 1.95(1.02,3.74) | 0.04 | / | 1.86 |
| $PM_{2.5-10}$ | 0.80(0.38,1.70) | 0.57 | 0.83(0.39,1.75) | 0.62 | 0.69(0.32,1.48) | 0.34 | 0.68(0.31,1.47) | 0.32 | / | 0.68 |
| $PM_{10}$ | 1.40(1.00,1.98) | 0.05 | 1.44(1.02,2.03) | 0.04 | 1.21(0.85,1.72) | 0.30 | 1.18(0.83,1.69) | 0.36 | / | 1.17 |
| **Folate deficiency anemia** | | | | | | | | | | |
| $NO_2$ | 1.36(1.23,1.50) | <0.0001 | 1.42(1.29,1.57) | <0.0001 | 1.26(1.13,1.41) | <0.0001 | 1.25(1.12,1.40) | <0.0001 | <0.001 | 1.25 |
| $PM_{2.5}$ | 9.58(4.54,20.19) | <0.0001 | 12.87(6.16,26.90) | <0.0001 | 4.94(2.19,11.16) | <0.001 | 4.70(2.08,10.65) | <0.001 | 0.013 | 4.61 |
| $PM_{2.5-10}$ | 3.06(1.24,7.53) | 0.01 | 3.32(1.36,8.14) | 0.01 | 2.68(1.06,6.75) | 0.04 | 2.74(1.09,6.91) | 0.03 | 0.006 | 2.81 |
| $PM_{10}$ | 2.36(1.52,3.68) | <0.001 | 2.56(1.65,3.98) | <0.0001 | 1.97(1.24,3.11) | 0.004 | 1.98(1.25,3.14) | 0.004 | 0.04 | 1.99 |

**Notes:** Crude model, unadjusted; Model 1, adjusted for age, sex, ethnicity, education level; Model 2, further adjusted for Townsend Deprivation Index, Smoke, Alcohol, IPAQ, BMI and mental health status; Model 3, further adjusted for cancer, hypertension, type II Diabetes, stroke, heart failure, healthy diet, assessment center, respiratory diseases, digestive diseases, gas or solid-fuel cooking; Model 4, further adjusted for iron/vitamin B12/folate intake and Vitamin or mineral supplements. IPAQ, International Physical Activity Questionnaire; BMI, body mass index; HR, Hazard Ratio; CI, confidence interval; $PM_{10}$, inhalable particulate matter; $PM_{2.5-10}$, coarse particulate matter; $PM_{2.5}$, fine particulate matter. $NO_2$, nitrogen dioxide.

## Table 3: HR estimates for the association between per 10μg/$m^3$ increase in air pollutants and anemia in gender and age subgroups.

| | | Iron deficiency anemia | | | Vitamin B12 deficiency anemia | | | Folate deficiency anemia | | |
|---|---|---|---|---|---|---|---|---|---|---|
| $NO_2$ | | HR (95%CI) | P | P int | HR (95%CI) | P | P int | HR (95%CI) | P | P int |
| | Sex | | | 0.633 | | | 0.749 | | | 0.631 |
| | Male | 1.057(1.023,1.092) | <0.001 | | 1.034(0.897,1.193) | 0.643 | | 1.281(1.118,1.468) | <0.001 | |
| | Female | 1.036(1.005,1.068) | 0.023 | | 1.019(0.895,1.159) | 0.777 | | 1.199(0.985,1.458) | 0.070 | |
| | Age | | | 0.827 | | | 0.166 | | | 0.183 |
| | ≥ 60 | 1.044(1.015,1.074) | 0.003 | | 1.112(0.981,1.259) | 0.096 | | 1.333(1.171,1.518) | <0.0001 | |
| | < 60 | 1.049(1.013,1.087) | 0.007 | | 0.924(0.797,1.072) | 0.298 | | 1.071(0.863,1.329) | 0.534 | |
| $PM_{2.5}$ | | | | | | | | | | |
| | Sex | | | 0.35 | | | 0.633 | | | 0.718 |
| | Male | 2.097(1.673,2.627) | <0.0001 | | 1.939(0.722,5.212) | 0.189 | | 5.436(1.980,14.92) | 0.001 | |
| | Female | 1.945(1.576,2.399) | <0.0001 | | 1.859(0.767,4.507) | 0.170 | | 3.55(0.872,14.45) | 0.077 | |
| | Age | | | 0.955 | | | 0.081 | | | 0.519 |
| | ≥ 60 | 2.042(1.674,2.490) | <0.0001 | | 3.748(1.581,8.887) | 0.003 | | 5.939(2.230,15.82) | <0.001 | |
| | < 60 | 1.998(1.567,2.547) | <0.0001 | | 0.796(0.289,2.194) | 0.660 | | 2.602(0.588,11.526) | 0.208 | |
| $PM_{2.5-10}$ | | | | | | | | | | |
| | Sex | | | 0.157 | | | 0.015 | | | 0.478 |
| | Male | 1.297(1.007,1.671) | 0.044 | | 1.924(0.663,5.583) | 0.229 | | 3.674(1.177,11.474) | 0.025 | |
| | Female | 0.932(0.734,1.183) | 0.561 | | 0.261(0.086,0.796) | 0.018 | | 1.726(0.352,8.46) | 0.501 | |
| | Age | | | 0.477 | | | 0.913 | | | 0.738 |
| | ≥ 60 | 1.14(0.914,1.423) | 0.245 | | 0.714(0.257,1.983) | 0.518 | | 2.6(0.851,7.942) | 0.094 | |
| | < 60 | 1(0.755, 1.324) | 0.999 | | 0.661(0.205,2.125) | 0.487 | | 3.289(0.630,17.166) | 0.158 | |
| $PM_{10}$ | | | | | | | | | | |
| | Sex | | | 0.524 | | | 0.062 | | | 0.523 |
| | Male | 1.176(1.039,1.331) | 0.010 | | 1.768(1.049,2.979) | 0.032 | | 2.246(1.266,3.984) | 0.006 | |
| | Female | 1.05(0.936,1.178) | 0.405 | | 0.834(0.510,1.364) | 0.470 | | 1.607(0.737,3.504) | 0.233 | |
| | Age | | | 0.456 | | | 0.357 | | | 0.583 |
| | ≥ 60 | 1.139(1.023,1.268) | 0.017 | | 1.409(0.882,2.253) | 0.151 | | 2.188(1.262,3.791) | 0.005 | |
| | < 60 | 1.06(0.925,1.214) | 0.402 | | 0.929(0.532,1.619) | 0.794 | | 1.563(0.668,3.66) | 0.303 | |

**Notes:** Models were adjusted for age/sex, ethnicity, education level, Townsend Deprivation Index, Smoke, Alcohol, IPAQ, BMI, mental health status, cancer, hypertension, type II Diabetes, stroke, heart failure, healthy diet, assessment center, respiratory diseases, digestive diseases, gas or solid-fuel cooking, iron/vitamin B12/folate intake and Vitamin or mineral supplements. IPAQ, International Physical Activity Questionnaire; BMI, body mass index; P int, p for interaction; HR, Hazard Ratio; CI, confidence interval; $PM_{10}$, inhalable particulate matter; $PM_{2.5-10}$, coarse particulate matter; $PM_{2.5}$, fine particulate matter. $NO_2$, nitrogen dioxide.

## Figures

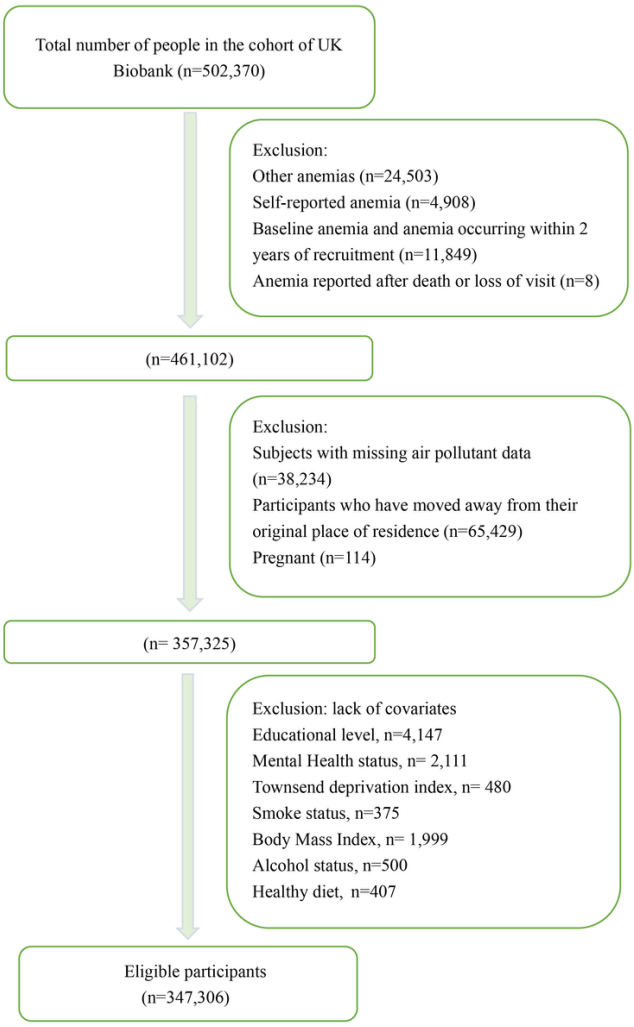


**Figure 1**

Process flowchart of inclusion and exclusion criteria.

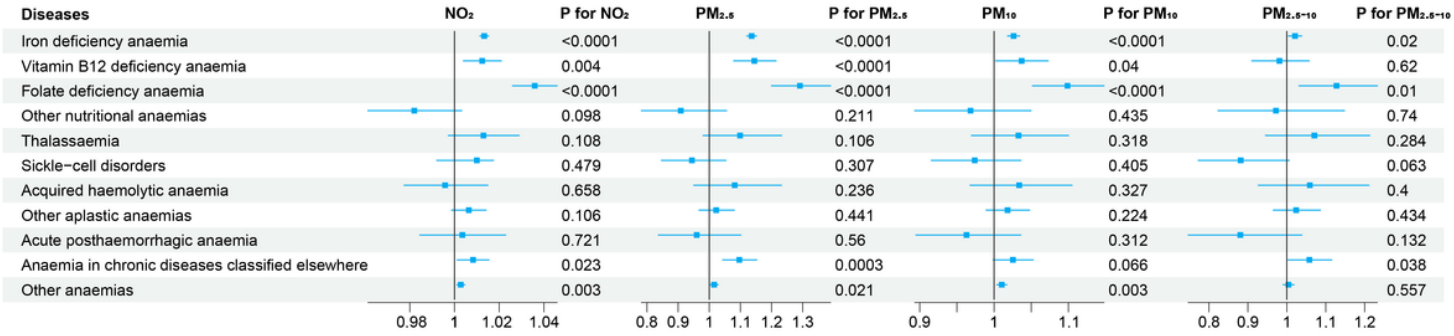


**Figure 2**

Multivariate Cox regression analysis for predicting anemia risk per 1μg/$m^3$ of air pollutants.

**Notes:** Model was adjusted for age, sex, ethnicity, education level. $NO_2$, nitrogen dioxide; $PM_{2.5}$, fine particulate matter; PM10, inhalable particulate matter; $PM_{2.5\text{-}10}$, coarse particulate matter.

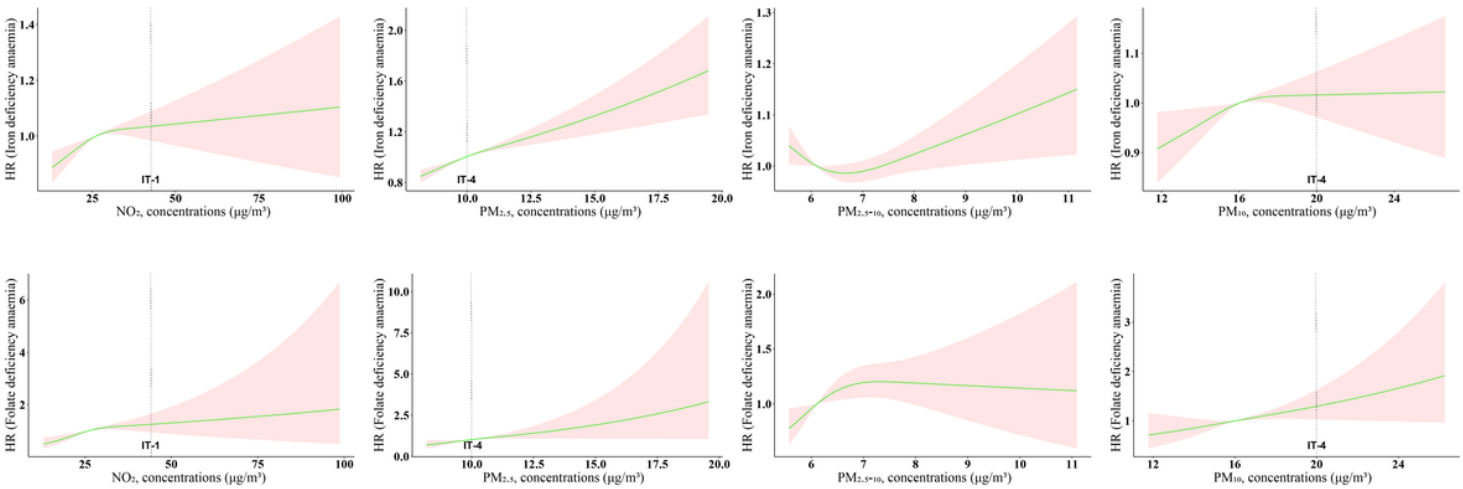


**Figure 3**

Exposure and response curve of long-term air pollutants exposure and hazard risk of anemia incidence.

**Notes:** $NO_2$, nitrogen dioxide; $PM_{2.5}$, fine particulate matter; $PM_{10}$, inhalable particulate matter; $PM_{2.5\text{-}10}$, coarse particulate matter; IT-1, AQG recommended annual mean interim target 1; IT-4, AQG recommended annual mean interim target 4; HR, hazard ratio; AQG, Air Quality Guidelines. Model was adjusted for demographic factors, lifestyle, economic situation, physical indicators, past medical history, daily intake of dietary iron or folic acid and vitamin/mineral use.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymaterials.docx