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Associations of ambient air pollution and lifestyle with the risk of NAFLD: a population-based cohort study

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Abstract

Background Both ambient air pollution and lifestyle factors contribute to the incidence of non-alcoholic fatty liver disease (NAFLD), but previous studies usually focused on single-factor associations. We aimed to assess the joint associations of ambient air pollution and lifestyle with the NAFLD risk and investigate whether lifestyle modifies the association of air pollution with NAFLD risk.

Methods A total of 417,025 participants from the UK Biobank were included in this study. Annual average concentrations of NO_2, NO_x, $PM_{2.5}$, PM_{10}, and $PM_{2.5-10}$ were estimated. A composite lifestyle score was determined based on physical activity, alcohol intake, smoking status, dietary patterns, sedentary time, and sleep duration. Cox proportional hazards regression models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs), as well as the population attributable fraction (PAF). Potential additive interactions of air pollution with lifestyle were also examined by the relative excess risk due to the interaction (RERI) and the attributable proportion due to the interaction (AP).

Results 4752 (1.14%) incident NAFLD events were recorded. Long-term exposure to air pollutants and an unhealthy lifestyle were significantly associated with the increased risk of incident NAFLD. Lifestyle was the primary factor of incident NAFLD, with a PAF of 37.18% (95% CI: 29.67%, 44.69%). In addition, a significant additive interaction between air pollution and lifestyle for NAFLD risk was observed (RERI: 0.36, 95% CI: 0.09–0.63).

Conclusions Long-term exposure to ambient air pollutants and poor lifestyle were jointly associated with a higher risk of NAFLD.

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Keywords Air Pollution, Lifestyle, Non-alcoholic fatty liver disease, Association, UK Biobank

Background

Non-alcoholic fatty liver disease (NAFLD) is one of the most common liver diseases, with a worldwide prevalence of 32.4%. Meanwhile, it continues to be a leading cause of cirrhosis and hepatocellular carcinoma [1, 2]. Given the increasing prevalence and potential complications associated with NAFLD, it has become a significant public health concern [3]. Understanding the underlying risk factors associated with NAFLD is crucial for developing effective prevention and treatment strategies.

Increasing studies have suggested that genetic susceptibility plays a crucial role in developing NAFLD [4–6] and helps to identify high-risk individuals effectively [7, 8]. Besides these intrinsic risks, accumulating evidence has indicated that exposure to ambient air pollutants and poor lifestyle, such as smoking, drinking, poor diet habits, lack of physical exercise, and poor sedentary behavior, may be associated with the risk of NAFLD [9–13]. However, the available evidence is limited and inconclusive. Previous studies were mainly designed as cross-sectional and primarily conducted in the East Asia populations and were almost only restricted to $PM_{2.5}$ exposure [9, 10]. Besides, few studies detect the association between lifestyle and the risk of NAFLD using synthetical lifestyle measures even though there are internal connections among the lifestyle factors [14, 15]. In addition, previous studies mainly focused on the separate associations of air pollutants and lifestyle factors with the NAFLD risk [13, 15, 16], ignoring the joint associations and potential modification effects that might provide valuable insights into the development of disease and enable to develop effective strategies for NAFLD prevention.

Therefore, based on the prospective population-based cohort (UK Biobank), this study aimed to investigate: (1) the associations and population attributable fraction (PAF) of ambient air pollutants exposure and lifestyle with NAFLD risk; (2) whether ambient air pollutants exposure and lifestyle jointly contribute to the risk of NAFLD, as well as the possible interactions between ambient air pollutants exposure and lifestyle.

Methods

Study population

The UK Biobank is a large, population-based prospective study, approved by the North West Multicenter Research Ethics Committee (Application No.92675). Details of the design and investigation methods of the UK Biobank have been described elsewhere [17]. Briefly, this large prospective cohort study recruited more than 500,000 participants aged 37–73 between 2006 and 2010. Participants were invited to complete a self-reported touchscreen questionnaire at one of the 22 assessment centers in England, Wales, and Scotland. Baseline demographics, socioeconomics, lifestyle, and health information were obtained through touchscreen questionnaires, face-to-face interviews, and physical health measurements [18]. Informed written consent for the study was collected from all participants.

For the present analyses, we excluded participants with NAFLD (n=547), previous cancer (n=38,616), liver disease (hepatitis, infective/viral hepatitis, non-infective hepatitis, and liver failure/cirrhosis) (n=2,464), or other viral infections including HIV, HBV, and HCV (n=264) at baseline. Those with sex mismatch (n=372), alcohol dependency (n=3,590), lack of demographic information (n=2,777), or missing air pollution information (n=41,299) were also excluded. Finally, 417,025 participants were involved in the association analyses of ambient air pollutants and NAFLD risk, and 321,930 participants were involved in lifestyle and air pollution relevant analyses by excluding participants with inaccessible information on lifestyle (n=95,095) (Fig. 1).

Air pollution assessment

The annual average estimates of particulate matter with aerodynamic diameter≤2.5 μm ($PM_{2.5}$), the coarse particulate matter between 2.5 μm and 10 μm in aerodynamic diameter ($PM_{2.5-10}$), particulate matter with aerodynamic diameter≤10 μm (PM_{10}), nitrogen dioxide (NO_2), and nitrogen oxides (NO_x) concentrations for the year 2010 were modeled for each address using a Land Use Regression (LUR) model, which developed as part of the European Study of Cohorts for Air Pollution Effects (ESCAPE: http://www.escapeproject.eu/). Air pollution estimates for 2005–2007 were available only for NO_2 and PM_{10} from EU-wide air pollution maps [19]. The UK Biobank website recommended that the estimates from different air pollution models should not be averaged to avoid introducing bias (https://biobank.ctsu.ox.ac.uk/crystal/label.cgi?id=114). Therefore, we used the estimates from the ESCAPE project (2010) for the primary analyses and the estimates from EU-wide air pollution maps (2005–2007) for the supplementary analyses. More detailed view of information was provided in Additional file 1: eMethod.

To better assess the joint exposure to multiple air pollutants, we obtained PC1-PC5 by principal components analysis (PCA) and estimated the β coefficients for PC1-PC5 in the adjusted Cox models, then calculated the weighted air pollution score (wAPS) by $\sum_{i=1}^{5}\beta\,[\mathrm{PCi}]\times\mathrm{PCi}$. The concentrations of air

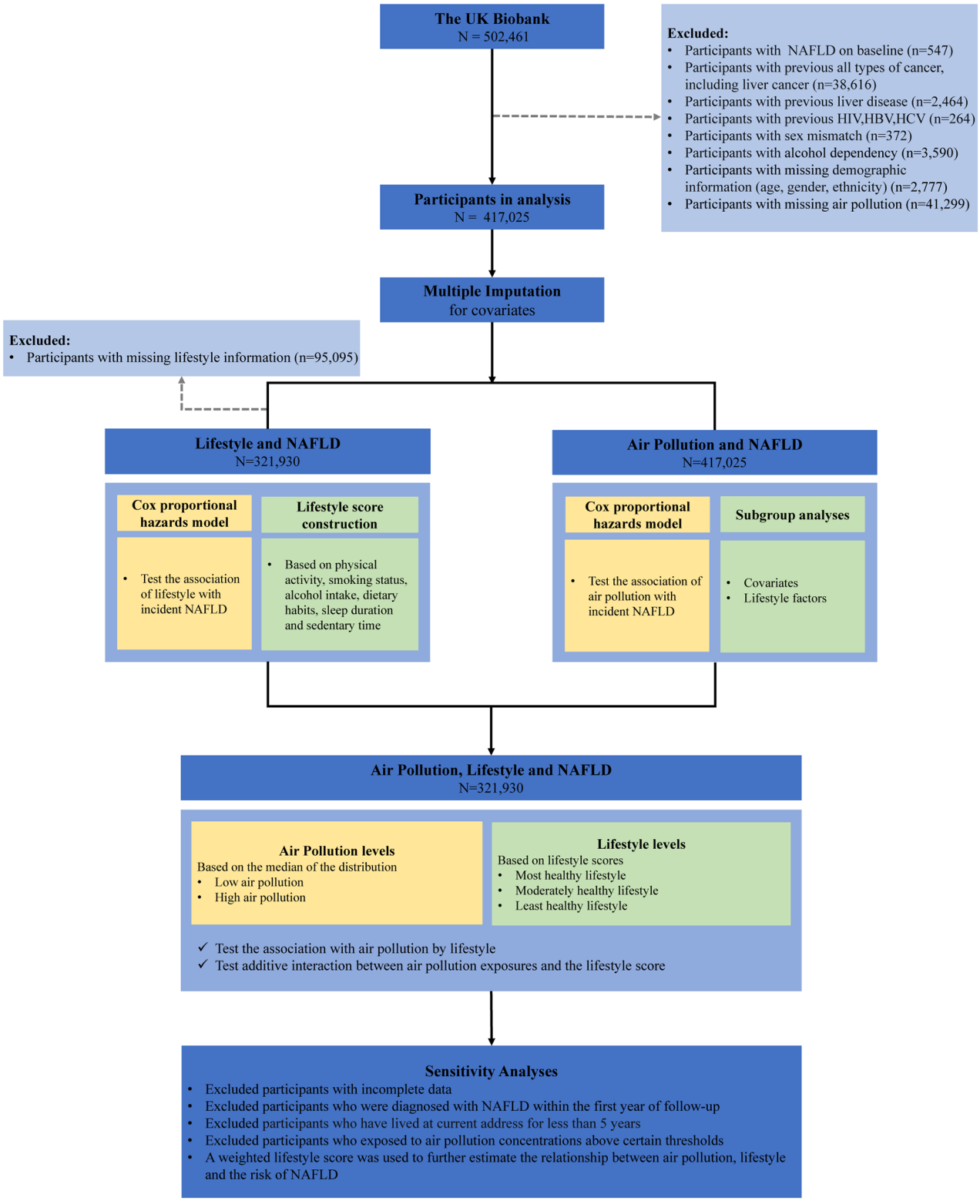

Fig. 1 Study design and workflow. Abbreviations: NAFLD, non-alcoholic fatty liver disease; HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus

pollutants were categorized as low or high levels based on the median of the distribution.

Lifestyle score assessment

According to the published studies, the definition of lifestyle contained the following six components: physical activity, alcohol intake, smoking status, dietary patterns, sedentary time, and sleep duration [20, 21]. Ideal physical activity was defined as vigorous activities ≥ 75 min per week or moderate activities ≥ 150 min per week. Alcohol intake was considered unhealthy if the frequency of drinking was daily or almost daily. The smoking status was divided into current smokers and non-current smokers, with the latter defined as ideal smoking status. According to the diet score, the dietary pattern was divided into healthy and unhealthy diets [21], and details of the calculation of the diet score were provided in the online supplementary (Additional file 1: Table S1). Sedentary time ≥ 7 h per day was considered unhealthy, where the sedentary time was calculated by summing up time spent watching TV, using computers, and driving [20]. Regarding sleep duration, participants were considered unhealthy if the sleep duration was < 7 h/day or > 9 h/day. Details about the definition of lifestyle were presented in the online supplementary (Additional file 1: Table S2).

An unweighted score, ranging from 0 to 6, was calculated by summing up each component score (0 or 1), with higher scores indicating an unhealthier lifestyle. Based on the unweighted score, participants were subsequently classified into three categories: most healthy (scored 0), moderately healthy (scored 1 or 2), and least healthy (scored 3, 4, 5 or 6).

Ascertainment of outcome

The outcome of this study was incident NAFLD, defined according to the International Classification of Diseases, Tenth Revision (ICD-10) coding system through linkage with diagnoses made during hospital inpatient admissions, and NAFLD was ascertained by the ICD-10 codes K75.8 and K76.0, as presented in Additional file 1: Table S3 [13]. Participants were followed up from the recruitment until the date of NAFLD first occurrence or censoring. Censoring was defined as loss to follow-up, death, or the end of follow-up (August 15, 2021), whichever came first.

Covariates

A directed acyclic graph (DAG) illustrating the association between air pollution, lifestyle and NAFLD is presented in Additional file 1: Figure S1. The DAG was constructed to identify potential confounding variables that should be adjusted in the analysis [22]. According to DAG, a sufficient number of variables were retained for adjustment, including sociodemographic factors (age, sex, ethnicity, and BMI), socioeconomic status (Townsend deprivation index, household income, education level [23], and employment status [24]), and local environmental exposure (24-hour weighted average noise [13], greenspace percentage in 1000 m buffer and proximity to major roads [24]), which were collected at baseline. The detailed information for covariates was described in the Additional file 1: eMethods. Multiple imputation by chained equations was performed to impute missing covariates data (Additional file 1: eMethods) [25].

Statistical analyses

Continuous variables were reported as mean ± standard deviation (SD), or median with interquartile range (Q1, Q3), and categorical variables were described using frequency and proportion (%) by the NAFLD group and non-NAFLD group, respectively. Cox proportional hazard models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the single-factor and joint associations of ambient air pollutants and lifestyle score with incident NAFLD, adjusting for age, sex, ethnicity, BMI, education level, employment status, household income, TDI, 24-hour weighted average noise, greenspace percentage in 1000 m buffer and proximity to major roads. Moreover, the air pollutant concentrations were adjusted when the single-factor association of lifestyle was analyzed. The assumption of proportional hazards was confirmed by Schoenfeld residual plots. The population-level fractions of incident NAFLD hazard rate due to risk factors (i.e., ambient air pollution and lifestyle) were estimated by calculating PAF with 95% CI [26]. Restricted cubic spline functions with four predetermined knots (5%, 35%, 65%, and 95%) were used to depict the exposure-response curves between ambient air pollutants and the risk of NAFLD after excluding participants with the top 1% of exposure due to poor accuracy [27]. Potential interactions for ambient air pollutants and lifestyle with NAFLD risk were reported on the additive scale by two indexes: the relative excess risk due to the interaction (RERI) and the attributable proportion due to the interaction (AP) [28]. Multivariate delta method was used to estimate the 95% CI of the RERI and AP, and the Wald overall test was used to examine the overall additive interaction.

We performed several sensitivity analyses to verify the robustness of the results. First, we excluded participants who developed NAFLD within the first year of follow-up. Second, we restricted analyses among participants who had lived at their current address for five or more years to consider the effects of reliable cumulative exposures. Third, we limited the analyses to participants with complete covariate data to compare with the results based on multiple imputations [29]. Fourth, to investigate whether the associations between air pollutants and NAFLD risk

were significantly lower than desired thresholds, we only included participants exposed to air pollutant concentrations below the specified thresholds ($PM_{2.5}$: 25 μg/m^3, PM_{10}: 40 μg/m^3, NO_2: 40 μg/m^3) [23, 30]. Fifth, a weighted lifestyle score was considered by summing the products of each component score and the corresponding coefficient [31].

All analyses were performed by R software (version 4.2.3), and the statistical significance was defined as two-sided $P<0.05$.

Results

Baseline characteristics

Over a median follow-up of 12.38 years (Q1, Q3: 11.68, 13.04 years), there were 4,752 (1.14%) incident NAFLD events recorded, with a median onset time of 7.38 years (Q1, Q3: 3.82, 10.93 years). Table 1 shows the baseline characteristics of all participants. The average age at baseline was 56.30±8.12 years, and 53.7% were females. Median (Q1, Q3) air pollutants (NO_2, NO_x, $PM_{2.5}$, PM_{10}, $PM_{2.5-10}$) exposure levels were 26.13 (21.38, 31.21), 42.23 (34.22, 50.72), 9.93 (9.29, 10.56), 16.03 (15.25, 17.01) and 6.11 (5.84, 6.64) μg/m^3 respectively. The description after excluding missing data is presented in Additional file 1: Table S4. Participants with incident NAFLD tended to have a poorer lifestyle than NAFLD-free ones ($P<0.001$). There were statistically significant positive correlations among five air pollutants to varying degrees ($0.2<r<0.92$) (Additional file 1: Table S5).

Associations of air pollutants and lifestyle with incident NAFLD

Participants with incident NAFLD were exposed to higher levels of air pollution and unhealthier lifestyles. Additional file 1: Table S6 shows the HR (95% CI) for high NO_2, NO_x, $PM_{2.5}$, PM_{10}, $PM_{2.5-10}$, wAPS, and least healthy lifestyle, respectively. The exposure-response relationships of ambient air pollutants (as a continuous variable) with the risk of NAFLD did not observe a significant nonlinear trend (P-nonlinear>0.05, Additional file 1: Figure S2). We observed an increased risk of NAFLD across the lifestyle score (P-trend<0.001; Additional file 1: Figure S3), which did not change with additional adjustment for wAPS (Additional file 1: Table S7). The results of supplementary analyses were robust when we conducted the analyses using the air pollution estimates from 2005 to 2007 (Additional file 1: Table S8).

Lifestyle was the leading factor for incident NAFLD, with a PAF of 37.18% (95% CI: 29.67%, 44.69%) (Fig. 2). Ambient air pollutants were also significant risk factors [PAF of wAPS: 9.91% (95% CI: 6.12%, 13.70%)]. Specifically, when high levels of air pollutants (NO_2, NO_x, and $PM_{2.5}$) were reduced to low levels, there were 10.19% (95% CI: 6.42%, 13.96%), 8.18% (95% CI: 4.72%, 11.64%), and 5.82% (95% CI: 2.36%, 9.29%) of NAFLD risk would be potentially reduced, respectively.

Joint associations of air pollutants and lifestyle with incident NAFLD

We observed that the overall NAFLD risk increased as both air pollutants exposure and lifestyle risk score increased (Fig. 3). Compared with those with low air pollutants exposure and the most healthy lifestyle, the highest NAFLD risk was observed in participants with the least healthy lifestyle and high air pollutants exposure (NO_2: HR: 2.30, 95% CI: 1.65–3.22; NO_x: HR: 2.24, 95% CI: 1.61–3.13; $PM_{2.5}$: HR: 2.15, 95% CI:1.54–3.01; PM_{10}: HR: 2.09, 95% CI:1.50–2.91; $PM_{2.5-10}$: HR: 2.18, 95% CI:1.56–3.03; wAPS: HR: 2.35, 95% CI:1.68–3.28).

Additionally, we observed significant risk stratification at different levels of air pollutant exposure and lifestyle (Additional file 1: Figure S4). The results of sensitivity analyses and supplementary analyses were also robust (Additional file 1: Table S9-S13).

Interactions of air pollutants with lifestyle on NAFLD risk

The additive interactions were indicated by the Wald overall test of RERI and AP (Table 2), which showed statistically significant interactions between air pollutants (including NO_2 and wAPS) and lifestyle. Unhealthy lifestyle and high air pollutant levels, particularly NO_2, significantly impact the risk of NAFLD. In general, with high ambient air pollutants exposure (wAPS) with a moderately healthy lifestyle, the RERI was 0.36 (95% CI: 0.09–0.63), suggesting that there would be a 0.36 relative excess risk because of the additive interaction, accounting for 19% (95% CI: 4%–35%) of the risk of NAFLD in participants exposed to both moderately healthy lifestyle and high air pollutants exposure.

Discussion

In this population-based cohort study, we observed that long-term exposure to air pollutants (NO_2, NO_x, $PM_{2.5}$, and PM_{10}) and an unhealthy lifestyle were significantly associated with the increased risk of incident NAFLD. Lifestyle was the primary factor of incident NAFLD, accounting for about 37% of population-level risk. Furthermore, the most significant NAFLD risk was observed among those with high exposure to air pollutants and the most unhealthy lifestyle. Meanwhile, lifestyle might modify the impact of long-term exposure to air pollutants on the risk of NAFLD.

In this study, we used air pollution estimates from 2010 to capture long-term air pollutant exposure since air pollution levels in the UK have been relatively stable over the years [32]. The associations between air pollutant exposure and NAFLD risk align with the previous report [9, 10, 13]. However, we did not find the same

Table 1 Population characteristics included in the study

Characteristics	Total (*n* = 417,025)	Individuals without NAFLD (*n* = 412,273)	Individuals with NAFLD (*n* = 4,752)	*P* value
Sex [n (%)]				0.002
Female	223,892 (53.7)	221,446 (53.7)	2446 (51.5)	
Male	193,133 (46.3)	190,827 (46.3)	2306 (48.5)	
Age [mean ± SD]	56.30 ± 8.12	56.29 ± 8.12	56.82 ± 7.93	< 0.001
Age [n (%)]				0.017
< 60	241,067 (57.8)	238,401 (57.8)	2666 (56.1)	
≥ 60	175,958 (42.2)	173,872 (42.2)	2086 (43.9)	
Ethnicity [n (%)]				0.005
White	392,478 (94.1)	388,051 (94.1)	4427 (93.2)	
Others	24,547 (5.9)	24,222 (5.9)	325 (6.8)	
BMI [mean ± SD]	27.44 ± 4.79	27.39 ± 4.76	31.45 ± 5.69	< 0.001
BMI [n (%)]				< 0.001
Normal (< 25 kg/m^2)	136,727 (32.8)	136,261 (33.1)	466 (9.8)	
Overweight (25–29.9 kg/m^2)	176,670 (42.4)	175,008 (42.4)	1662 (35.0)	
Obesity (≥ 30 kg/m^2)	101,353 (24.3)	98,781 (24.0)	2572 (54.1)	
Missing	2275 (0.5)	2223 (0.5)	52 (1.1)	
24-h weighted average noise [n (%)]				0.130
≤ 55 dB[A]	215,380 (51.6)	212,934 (51.6)	2446 (51.5)	
> 55 to ≤ 60 dB[A]	150,445 (36.1)	148,716 (36.1)	1729 (36.4)	
> 60 to ≤ 65 dB[A]	24,576 (5.9)	24,327 (5.9)	249 (5.2)	
> 65 dB[A]	26,624 (6.4)	26,296 (6.4)	328 (6.9)	
Household income [n (%)]				< 0.001
Less than £31,000	168,999 (40.5)	166,633 (40.4)	2366 (49.8)	
Equal to or above £31,000	184,468 (44.2)	182,963 (44.4)	1505 (31.7)	
Missing	63,558 (15.2)	62,677 (15.2)	881 (18.5)	
TDI [n (%)]				< 0.001
Tertile1	138,845 (33.3)	137,691 (33.4)	1154 (24.3)	
Tertile2	138,852 (33.3)	137,472 (33.3)	1380 (29.0)	
Tertile3	138,857 (33.3)	136,644 (33.1)	2213 (46.6)	
Missing	471 (0.1)	466 (0.1)	5 (0.1)	
Education level [n (%)]				< 0.001
Degree or professional education	131,228 (31.5)	130,240 (31.6)	988 (20.8)	
Other levels	277,924 (66.6)	274,288 (66.5)	3636 (76.5)	
Missing	7873 (1.9)	7745 (1.9)	128 (2.7)	
Employment status [n (%)]				< 0.001
Paid	243,407 (58.4)	241,062 (58.5)	2345 (49.3)	
Not employed or not in paid	171,958 (41.2)	169,572 (41.1)	2386 (50.2)	
Missing	1660 (0.4)	1639 (0.4)	21 (0.4)	
Greenspace percentage in 1000 m buffer [n (%)]				< 0.001
Low	197,043 (47.2)	194,516 (47.2)	2527 (53.2)	
High	197,052 (47.3)	194,938 (47.3)	2114 (44.5)	
Missing	22,930 (5.5)	22,819 (5.5)	111 (2.3)	
Proximity to major road [n (%)]				0.034
Low	208,440 (50.0)	206,138 (50.0)	2302 (48.4)	
High	208,585 (50.0)	206,135 (50.0)	2450 (51.6)	
Lifestyle factor				
Lifestyle score [n (%)]				< 0.001
0	45,380 (10.9)	45,136 (10.9)	244 (5.1)	
1	98,862 (23.7)	98,039 (23.8)	823 (17.3)	
2	100,798 (24.2)	99,683 (24.2)	1115 (23.5)	
3	54,888 (13.2)	54,122 (13.1)	766 (16.1)	
4	18,193 (4.4)	17,872 (4.3)	321 (6.8)	

Table 1 (continued)

Characteristics	Total (*n* = 417,025)	Individuals without NAFLD (*n* = 412,273)	Individuals with NAFLD (*n* = 4,752)	*P* value
≥ 5	3768 (0.9)	3685 (0.9)	83 (1.7)	
Missing	95,136 (22.8)	93,736 (22.7)	1400 (29.5)	
Lifestyle [n (%)]				< 0.001
Mostly healthy	45,380 (10.9)	45,136 (10.9)	244 (5.1)	
Moderately healthy	199,660 (47.9)	197,722 (48.0)	1938 (40.8)	
Least healthy	76,849 (18.4)	75,679 (18.4)	1170 (24.6)	
Missing	95,136 (22.8)	93,736 (22.7)	1400 (29.5)	
Air pollution, μg/m^3				
NO_2 [median (Q1, Q3)]	26.13 (21.38, 31.21)	26.12 (21.37, 31.19)	27.80 (22.91, 32.51)	< 0.001
NO_x [median (Q1, Q3)]	42.23 (34.22, 50.72)	42.20 (34.19, 50.69)	44.72 (36.69, 53.55)	< 0.001
$PM_{2.5}$ [median (Q1, Q3)]	9.93 (9.29, 10.56)	9.93 (9.29, 10.56)	10.11 (9.49, 10.79)	< 0.001
PM_{10} [median (Q1, Q3)]	16.03 (15.25, 17.01)	16.03 (15.25, 17.01)	16.11 (15.42, 17.15)	< 0.001
$PM_{2.5-10}$ [median (Q1, Q3)]	6.11 (5.84, 6.64)	6.11 (5.84, 6.64)	6.14 (5.86, 6.72)	< 0.001

Abbreviations: NO_2, nitrogen dioxide; NO_x, nitrogen oxides; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤ 2.5 μm; PM_{10}, particulate matter with aerodynamic diameter ≤ 10 μm; $PM_{2.5-10}$, particulate matter with aerodynamic diameter in 2.5–10 μm; BMI, body mass index; SD, standard deviation; Q, quartile

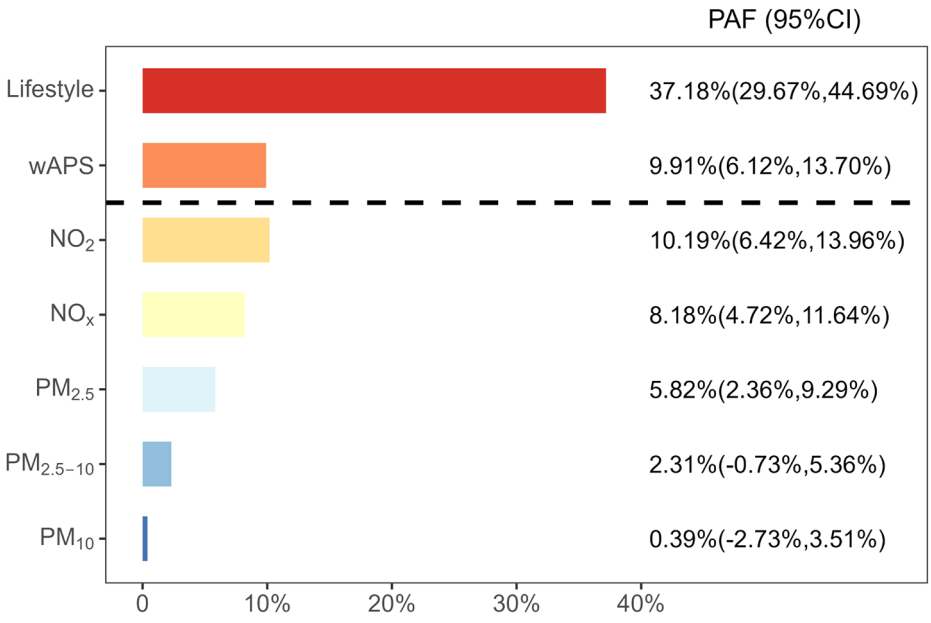

Fig. 2 PAF for NAFLD risk factors in the UK Biobank. Abbreviations: NO_2, nitrogen dioxide; NO_x, nitrogen oxides; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤ 2.5 μm; PM_{10}, particulate matter with aerodynamic diameter ≤ 10 μm; $PM_{2.5-10}$, particulate matter with aerodynamic diameter in 2.5–10 μm; wAPS, weighted air pollution score; PAF, the population attributable fraction; CI, confidence interval. The above factors were calculated separately in the Cox Proportional Hazard model.Lifestyle model: adjusted for age, sex, ethnicity, BMI, education level, employment status, household income, Townsend deprivation index, 24-hour weighted average noise, greenspace percentage in 1000 m buffer, and proximity to major roads.Air pollution model: adjusted for age, sex, ethnicity, BMI, education level, employment status, household income, Townsend deprivation index, 24-hour weighted average noise, greenspace percentage in 1000 m buffer, and proximity to major roads

strong association between PM_{10} and NAFLD risk as in the previous report (HR: 1.14, 95% CI: 1.09–1.20, per IQR), which used the air pollution average estimates for the years 2005–2010 with different air pollution models [13]. It is worth noting that the UK Biobank does not recommend using the average estimates of air pollution from different models, as it may introduce bias (https://biobank.ctsu.ox.ac.uk/crystal/label.cgi?id=114).

We constructed a lifestyle risk score to evaluate the potential impact of a modifiable lifestyle, confirming that an unhealthy lifestyle plays an essential role in the increased risk of NAFLD. Previous studies also discovered that some lifestyle factors, such as long sedentary time [33], night shift work [34], physical activity [15], high-fat diet [35], and smoking [35], are associated with increased risk of NAFLD. Nevertheless, the complexity and interconnectedness of health behaviors suggest that

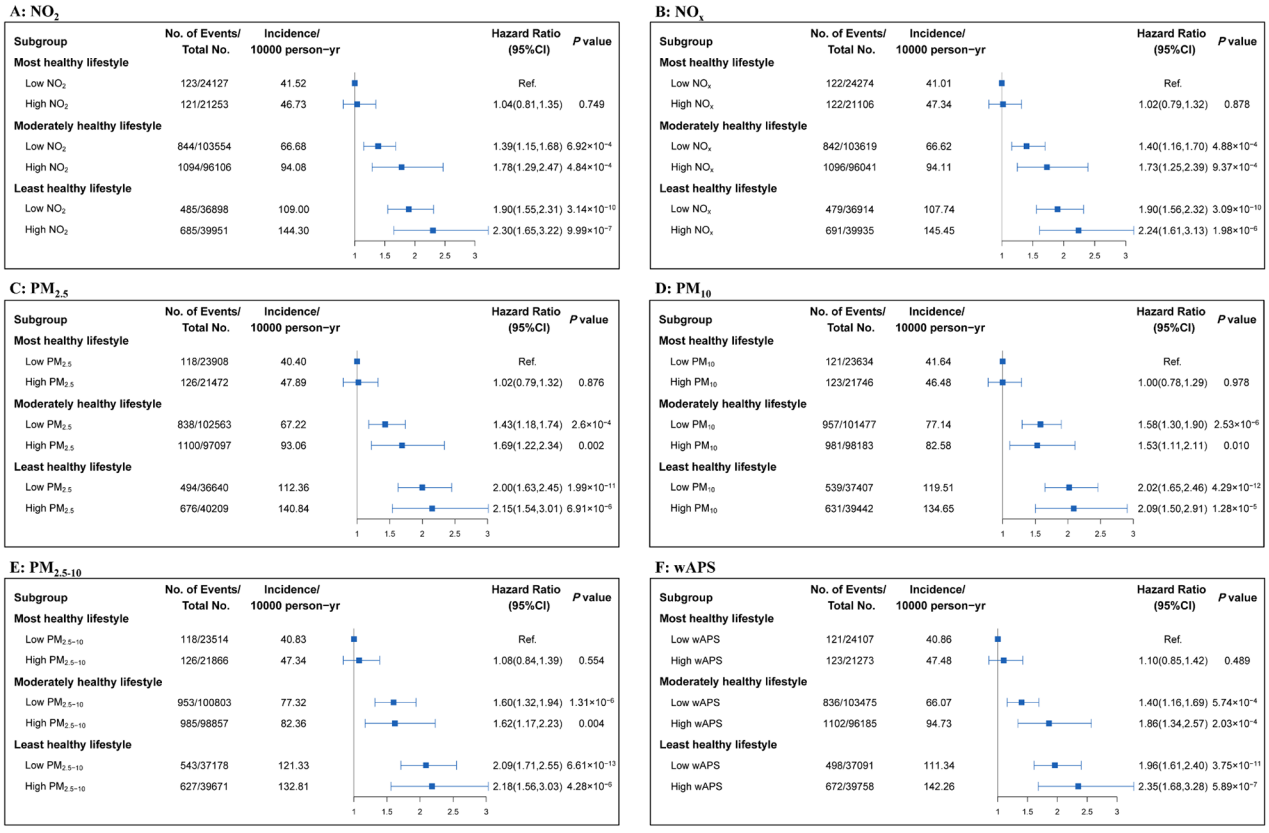

Fig. 3 Risk of incident NAFLD according to air pollution and lifestyle categories. Abbreviations: NO_2, nitrogen dioxide; NO_x, nitrogen oxides; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤ 2.5 μm; PM_{10}, particulate matter with aerodynamic diameter ≤ 10 μm; $PM_{2.5-10}$, particulate matter with aerodynamic diameter in 2.5–10 μm; wAPS, weighted air pollution score; HR, hazard ratio; CI, confidence interval; Ref., reference. The hazard ratios for NAFLD according to (*A*) NO_2, (*B*) NO_x, (*C*) $PM_{2.5}$, (*D*) PM_{10}, (*E*) $PM_{2.5-10}$, (*F*) wAPS, and lifestyle risk score categories were estimated by using Cox proportional hazard models with adjustment for age, sex, ethnicity, BMI, education level, employment status, household income, Townsend deprivation index, 24-hour weighted average noise, greenspace percentage in 1000 m buffer and proximity to major roads. Definition of lifestyle categories: most healthy (scored 0), moderately healthy (scored 1 or 2), and least healthy (scored 3, 4, 5, or 6)

the lifestyle risk score we used, which incorporates multiple lifestyle factors, may better reflect the impact of a healthy lifestyle than separate analyses using only a specific single factor.

The current study also identified several less-established associations. The combined effects and interactions of ambient air pollutants and lifestyle on the risk of incident NAFLD have not been investigated. This study incorporating the joint association enables ascertaining the collective contribution of individual risk factors and their cumulative effect on the development of NAFLD, which facilitates the acquisition of more precise risk stratification and identification of high-risk populations. Additionally, the current study demonstrated that 36% of NAFLD risk could be attributed to the additive interaction between lifestyle and aggregate air pollutants exposure (surrogated by the wAPS), suggesting that lifestyle choices may modulate the impacts of ambient air pollutants on NAFLD risk.

Indeed, long-term air pollutant exposure and lifestyle factors have been found to be associated with elevated levels of systemic inflammation [36–38]. Consequently, higher levels of systemic inflammatory markers may contribute to the development of NAFLD [39]. Therefore, it is plausible that populations exposed to high air pollutants and a poor lifestyle may experience an amplified impact. These findings indicate that both ambient air pollutants and lifestyle play a vital role in the development of NAFLD and highlight the importance of lifestyle improvement that can provide valuable insights for formulating personalized prevention strategies aimed at mitigating the risk of NAFLD incidence, thereby helping to reduce the health burden of NAFLD.

We note that due to NAFLD has principal limitations that rely on exclusionary confounder terms and the use of potentially stigmatising language, an international panel of experts proposed a new concept, metabolic dysfunction associated steatotic liver disease (MASLD), which requires the presence of both hepatic steatosis and

Table 2 RERI and AP for additive interaction between air pollutants and lifestyle categories

Exposure	Interaction	Lifestyle		
		Moderately healthy	Least healthy	*P*-overall
High pollution of wAPS	RERI (95% CI)	0.36(0.09,0.63)	0.29(-0.06,0.64)	0.033
	AP (95% CI)	0.19(0.04,0.35)	0.12(-0.03,0.27)	0.055
High pollution of NO_2	RERI (95% CI)	0.35(0.09,0.62)	0.37(0.03,0.70)	0.024
	AP (95% CI)	0.20(0.04,0.36)	0.16(0.01,0.31)	0.045
High pollution of NO_x	RERI (95% CI)	0.30(0.04,0.57)	0.32(-0.01,0.65)	0.057
	AP (95% CI)	0.18(0.01,0.34)	0.14(-0.01,0.30)	0.092
High pollution of $PM_{2.5}$	RERI (95% CI)	0.24(-0.03,0.50)	0.14(-0.21,0.48)	0.206
	AP (95% CI)	0.14(-0.03,0.31)	0.06(-0.10,0.22)	0.244
High pollution of PM_{10}	RERI (95% CI)	-0.05(-0.34,0.24)	0.07(-0.27,0.41)	0.699
	AP (95% CI)	-0.03(-0.22,0.16)	0.03(-0.13,0.20)	0.691
High pollution of $PM_{2.5-10}$	RERI (95% CI)	-0.07(-0.37,0.24)	0.01(-0.35,0.37)	0.820
	AP (95% CI)	-0.04(-0.23,0.14)	0.01(-0.16,0.17)	0.816

Abbreviations: NO_2, nitrogen dioxide; NO_x, nitrogen oxides; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤ 2.5 μm; PM_{10}, particulate matter with aerodynamic diameter ≤ 10 μm; $PM_{2.5-10}$, particulate matter with aerodynamic diameter in 2.5–10 μm; wAPS, weighted air pollution score; RERI, relative excess risk due to the interaction; AP, attributable proportion due to the interaction; CI, confidence interval

Lifestyle model: adjusted for age, sex, ethnicity, BMI, education level, employment status, household income, Townsend deprivation index, 24-hour weighted average noise, greenspace percentage in 1000 m buffer, and proximity to major roads

Definition of lifestyle categories: most healthy (scored 0), moderately healthy (scored 1, or 2), and least healthy (scored 3, 4, 5, or 6)

To estimate the RERI and AP, the low air pollution category and the most healthy lifestyle (scored 0) groups were the reference categories

metabolic dysfunction for diagnosis [40, 41]. However, follow-up outcomes were defined according to ICD-10 in the UK Biobank. Therefore, the definition of NAFLD is still used in this study. Song et al. studied the data of 1016 subjects who underwent proton magnetic resonance spectroscopy in a randomly selected community in Hong Kong between 2008 and 2010 and found that only 6 out of 261 NAFLD patients did not meet the metabolic criteria for MASLD [42]. In addition, an expert panel analysis of the European LITMUS Consortium showed that 98% of registered cases of NAFLD met the new criteria for MASLD [41]. Therefore, it is reasonable to assume that the old NAFLD findings are still valid under the new MASLD definition.

To our knowledge, this study is the first to report the joint and interactive associations of ambient air pollutants and lifestyle with the risk of NAFLD while adjusting for a wide range of potential confounders identified by the casual DAG. Major strengths of this study include the population-based prospective design and standardized individual air pollution exposure assessments. Moreover, we analyzed aggregate air pollution exposure using a weighted air pollution score and overall lifestyle using both unweighted and weighted lifestyle scores, further reinforced by several sensitivity analyses.

However, the present study still has some limitations when interpreting our results. First, the assessment of air pollution exposure based on a single address does not account for other potentially influential long-term exposures, such as occupational exposure and indoor air pollution. Second, data on lifestyle composition were self-reported and thus may be subject to recall bias, and changes in lifestyle over time were not accounted for in the analyses. Third, we conducted the primary analyses with the imputed covariate values using the multiple imputations(MI) method based on the missing at random (MAR) assumption. The results might be biased from the actual ones even though we found they were similar to ones based only on complete cases. Fourth, we excluded approximately 23% cases with missing data when analyzing the lifestyle score as an exposure variable. Thus, it can decrease statistical power and potentially limit the generalizability of the findings. Fifth, although we have adjusted for a range of potential confounders using causal DAG in our analysis, residual confounders may still exist. Sixth, We chose the time-scale over the age-scale for Cox regression; however, this approach might not be appropriate if there is no direct relationship between the entry time into the cohort and the observed outcome. Finally, the population in UK Biobank is not universally representative, which may have had some volunteer bias, and most of the participants in our study were of European descent, limiting the generality of the results.

Conclusions

We found that long-term exposure to ambient air pollutants and poor lifestyle were jointly associated with a higher risk of NAFLD in this population-based cohort study. Poor lifestyle may exacerbate the impact of ambient air pollutants on NAFLD risk, highlighting the importance of developing a healthy lifestyle to reduce the hazards of air pollution. Government interventions to improve air quality and individuals' adherence to a healthy lifestyle are essential for preventing NAFLD.

Abbreviations

NAFLD	Non-alcoholic fatty liver disease
NO_2	Nitrogen dioxide
NO_x	Nitrogen oxides
$PM_{2.5}$	Particulate matter with aerodynamic diameter ≤ 2.5 μm
PM_{10}	Particulate matter with aerodynamic diameter ≤ 10 μm
$PM_{2.5-10}$	Particulate matter with aerodynamic diameter in 2.5–10 μm
PAF	the population attributable fraction; RERI, relative excess risk due to the interaction
AP	Attributable proportion due to the interaction
IQR	Interquartile range
CI	Confidence interval
wAPS	the weighted air pollution score
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
LUR	Land use regression model
ESCAPE	the European Study of Cohorts for Air Pollution Effects
PCA	Principal component analysis
ICD-10	International Classification of Diseases, Tenth Revision
DAG	Directed acyclic graph
BMI	Body mass index
TDI	Townsend deprivation index
SD	Standard deviation
HR	Hazard ratio
OR	Odds ratio
MASLD	Metabolic dysfunction associated steatotic liver disease
MI	the multiple imputations
MAR	Missing at random

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-024-19761-7.

Supplementary Material 1

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Author contributions

J.B., S.N., and Z.Z. designed the study. X.K., R.H., R.G., and S.N. conducted the data analysis. Y.Z., D.Y. and Y.W. contributed to the acquisition of the data. X.K. and R.H. drafted the manuscript. S.N., Z.Z., J.W., J.L., H.Y., M.D., L.L., and J.B. critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript.

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Data availability

This research has been conducted using the UK Biobank Resource (Application Number 92675). The authors do not have permission to share data. The data used in this current study are available from the UK Biobank data resources. Permissions are required to gain access to the UK Biobank data resources, subject to successful registration and application process. Further information can be found on the UK Biobank website (https://www.ukbiobank.ac.uk/).

Declarations

Competing interests

The authors declare no competing interests.

Ethical approval and consent to participate

Ethical approval of the UK Biobank study was given by the North West Multicenter Research Ethics Committee, the National Information Governance Board for Health & Social Care, and the Community Health Index Advisory Group. The present analyses were conducted under UK Biobank application number 92675.

Consent for publication

Not applicable.

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References

1. Friedman SL, Neuschwander-Tetri BA, Rinella M, Sanyal AJ. Mechanisms of NAFLD development and therapeutic strategies. Nat Med. 2018;24(7):908–22.
2. Riazi K, Azhari H, Charette JH, Underwood FE, King JA, Afshar EE, Swain MG, Congly SE, Kaplan GG, Shaheen AA. The prevalence and incidence of NAFLD worldwide: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2022;7(9):851–61.
3. Powell EE, Wong VW, Rinella M. Non-alcoholic fatty liver disease. Lancet. 2021;397(10290):2212–24.
4. Eslam M, Valenti L, Romeo S. Genetics and epigenetics of NAFLD and NASH: clinical impact. J Hepatol. 2018;68(2):268–79.
5. Kahali B, Halligan B, Speliotes EK. Insights from Genome-Wide Association Analyses of Nonalcoholic Fatty liver disease. Semin Liver Dis. 2015;35(4):375–91.
6. Loomba R, Schork N, Chen CH, Bettencourt R, Bhatt A, Ang B, Nguyen P, Hernandez C, Richards L, Salotti J, et al. Heritability of hepatic fibrosis and steatosis based on a prospective twin study. Gastroenterology. 2015;149(7):1784–93.
7. Jonas W, Schürmann A. Genetic and epigenetic factors determining NAFLD risk. Mol Metab. 2021;50:101111.
8. Sharma D, Mandal P. NAFLD: genetics and its clinical implications. Clin Res Hepatol Gastroenterol. 2022;46(9):102003.
9. Sun S, Yang Q, Zhou Q, Cao W, Yu S, Zhan S, Sun F. Long-term exposure to air pollution, habitual physical activity and risk of non-alcoholic fatty liver disease: a prospective cohort study. Ecotoxicol Environ Saf. 2022;235:113440.
10. Deng P, Tang H, Zhu L, Duan J, Li F, Li Y, Wang J, Wu J, Meng C, Wang W, et al. Association of long-term ambient fine particulate matter (PM(2.5)) and incident non-alcoholic fatty liver disease in Chinese adults. Environ Pollut. 2023;329:121666.
11. Guo B, Guo Y, Nima Q, Feng Y, Wang Z, Lu R, Baimayangji, Ma Y, Zhou J, Xu H, et al. Exposure to air pollution is associated with an increased risk of metabolic dysfunction-associated fatty liver disease. J Hepatol. 2022;76(3):518–25.
12. VoPham T, Kim NJ, Berry K, Mendoza JA, Kaufman JD, Ioannou GN. PM(2.5) air pollution exposure and nonalcoholic fatty liver disease in the Nationwide Inpatient Sample. Environ Res. 2022;213:113611.
13. Li FR, Liao J, Zhu B, Li X, Cheng Z, Jin C, Mo C, Wu X, Li Q, Liang F. Long-term exposure to air pollution and incident non-alcoholic fatty liver disease and cirrhosis: a cohort study. Liver Int. 2023;43(2):299–307.
14. Petermann-Rocha F, Wirth MD, Boonpor J, Parra-Soto S, Zhou Z, Mathers JC, Livingstone K, Forrest E, Pell JP, Ho FK, et al. Associations between an inflammatory diet index and severe non-alcoholic fatty liver disease: a prospective study of 171,544 UK Biobank participants. BMC Med. 2023;21(1):123.
15. Ge X, Wang X, Yan Y, Zhang L, Yu C, Lu J, Xu X, Gao J, Liu M, Jiang T, et al. Behavioural activity pattern, genetic factors, and the risk of nonalcoholic fatty liver disease: a prospective study in the UK Biobank. Liver Int. 2023;43(6):1287–97.

16. He P, Zhang Y, Ye Z, Li H, Liu M, Zhou C, Yang S, Gan X, Zhang Y, Qin X. A healthy lifestyle, Life's essential 8 scores and new-onset severe NAFLD: a prospective analysis in UK Biobank. Metabolism. 2023;146:155643.
17. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, Downey P, Elliott P, Green J, Landray M, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 2015;12(3):e1001779.
18. Collins R. What makes UK Biobank special? Lancet. 2012;379(9822):1173–4.
19. Vienneau D, de Hoogh K, Bechle MJ, Beelen R, van Donkelaar A, Martin RV, Millet DB, Hoek G, Marshall JD. Western European land use regression incorporating satellite- and ground-based measurements of NO2 and PM10. Environ Sci Technol. 2013;47(23):13555–64.
20. Foster HME, Celis-Morales CA, Nicholl BI, Petermann-Rocha F, Pell JP, Gill JMR, O'Donnell CA, Mair FS. The effect of socioeconomic deprivation on the association between an extended measurement of unhealthy lifestyle factors and health outcomes: a prospective analysis of the UK Biobank cohort. Lancet Public Health. 2018;3(12):e576–85.
21. Said MA, Verweij N, van der Harst P. Associations of Combined Genetic and Lifestyle Risks With Incident Cardiovascular Disease and Diabetes in the UK Biobank Study. JAMA Cardiol. 2018;3(8):693–702.
22. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology. 1999;10(1):37–48.
23. Huang Y, Zhu M, Ji M, Fan J, Xie J, Wei X, Jiang X, Xu J, Chen L, Yin R, et al. Air Pollution, genetic factors, and the risk of Lung Cancer: a prospective study in the UK Biobank. Am J Respir Crit Care Med. 2021;204(7):817–25.
24. Yang T, Wang J, Huang J, Kelly FJ, Li G. Long-term exposure to Multiple Ambient Air Pollutants and Association With Incident Depression and anxiety. JAMA Psychiatry. 2023;80(4):305–13.
25. Greenland S, Finkle WD. A critical look at methods for handling missing covariates in epidemiologic regression analyses. Am J Epidemiol. 1995;142(12):1255–64.
26. Chen L, Lin DY, Zeng D. Attributable fraction functions for censored event times. Biometrika. 2010;97(3):713–26.
27. Liang H, Zhou X, Zhu Y, Li D, Jing D, Su X, Pan P, Liu H, Zhang Y. Association of outdoor air pollution, lifestyle, genetic factors with the risk of lung cancer: a prospective cohort study. Environ Res. 2023;218:114996.
28. Li R, Chambless L. Test for additive interaction in proportional hazards models. Ann Epidemiol. 2007;17(3):227–36.
29. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, Wood AM, Carpenter JR. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009;338:b2393.
30. Raaschou-Nielsen O, Andersen ZJ, Beelen R, Samoli E, Stafoggia M, Weinmayr G, Hoffmann B, Fischer P, Nieuwenhuijsen MJ, Brunekreef B, et al. Air pollution and lung cancer incidence in 17 European cohorts: prospective analyses from the European study of cohorts for Air Pollution effects (ESCAPE). Lancet Oncol. 2013;14(9):813–22.
31. Lourida I, Hannon E, Littlejohns TJ, Langa KM, Hyppönen E, Kuźma E, Llewellyn DJ. Association of Lifestyle and genetic risk with incidence of Dementia. JAMA. 2019;322(5):430–7.
32. Wang M, Zhou T, Song Y, Li X, Ma H, Hu Y, Heianza Y, Qi L. Joint exposure to various ambient air pollutants and incident heart failure: a prospective analysis in UK Biobank. Eur Heart J. 2021;42(16):1582–91.
33. Li J, Hua S, Chen GC, Strizich G, Kuniholm MH, Shan Z, Talavera GA, Castañeda SF, Gellman MD, Cai J, et al. Objectively measured sedentary time, physical activity and liver enzyme elevations in US Hispanics/Latinos. Liver Int. 2020;40(8):1883–94.
34. Huang H, Liu Z, Xie J, Xu C. Association between night shift work and NAFLD: a prospective analysis of 281,280 UK Biobank participants. BMC Public Health. 2023;23(1):1282.
35. Fouda S, Khan A, Chan SMH, Mahzari A, Zhou X, Qin CX, Vlahos R, Ye JM. Exposure to cigarette smoke precipitates simple hepatosteatosis to NASH in high-fat diet fed mice by inducing oxidative stress. Clin Sci (Lond). 2021;135(17):2103–19.
36. Shiels MS, Katki HA, Freedman ND, Purdue MP, Wentzensen N, Trabert B, Kitahara CM, Furr M, Li Y, Kemp TJ, et al. Cigarette smoking and variations in systemic Immune and inflammation markers. JNCI: J Natl Cancer Inst. 2014;106(11):dju294.
37. Zheng Z, Xu X, Zhang X, Wang A, Zhang C, Hüttemann M, Grossman LI, Chen LC, Rajagopalan S, Sun Q, et al. Exposure to ambient particulate matter induces a NASH-like phenotype and impairs hepatic glucose metabolism in an animal model. J Hepatol. 2013;58(1):148–54.
38. Xu MX, Ge CX, Qin YT, Gu TT, Lou DS, Li Q, Hu LF, Feng J, Huang P, Tan J. Prolonged PM2.5 exposure elevates risk of oxidative stress-driven nonalcoholic fatty liver disease by triggering increase of dyslipidemia. Free Radic Biol Med. 2019;130:542–56.
39. Parthasarathy G, Revelo X, Malhi H. Pathogenesis of nonalcoholic steatohepatitis: an overview. Hepatol Commun. 2020;4(4):478–92.
40. Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, Zelber-Sagi S, Wai-Sun Wong V, Dufour JF, Schattenberg JM, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. J Hepatol. 2020;73(1):202–9.
41. Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, Romero D, Abdelmalek MF, Anstee QM, Arab JP, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. Ann Hepatol. 2024;29(1):101133.
42. Song SJ, Lai JC, Wong GL, Wong VW, Yip TC. Can we use old NAFLD data under the new MASLD definition? J Hepatol. 2024;80(2):e54–6.

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