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Original Contribution

Combined effect of biological age and fine particulate matter pollution with risk of nonalcoholic fatty liver disease in the UK Biobank: a prospective cohort study

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Abstract

Aging and long-term exposure to fine particulate matter ($PM_{2.5}$) are associated with a higher risk of nonalcoholic fatty liver disease (NAFLD), but evidence on their combined effect is limited. We thus evaluated the joint effects of accelerated biological aging and $PM_{2.5}$ exposure on incident NAFLD in a UK cohort. We included 296 917 UK Biobank participants without NAFLD at baseline. Annual mean $PM_{2.5}$ concentration was evaluated using a land use regression model. Biological age was assessed using the Klemera–Doubal method (KDM-BA) and PhenoAge algorithm. Cox proportional hazards models were used to assess the effects on incident NAFLD. Both chronic $PM_{2.5}$ exposure and older biological age were linked to higher risk of NAFLD, with HRs of 1.07 (95% CI, 1.04-1.10) per SD increase in $PM_{2.5}$, 1.47 (95% CI 1.43-1.52) in per SD increase KDM-BA, and 1.38 (95% CI 1.35-1.41) in per SD increase PhenoAge-BA, respectively. Participants with low PhenoAge and low $PM_{2.5}$ had a lower NAFLD risk than those with high PhenoAge and high $PM_{2.5}$. Positive additive interactions were observed. This study suggests that both $PM_{2.5}$ exposure and biological aging increase NAFLD risk, with simultaneous exposure to high levels potentially intensifying their effects.

Key words: air pollution; biological aging; nonalcoholic fatty liver disease; cohort study; Cox proportional hazards model; public health.

Introduction

Nonalcoholic fatty liver disease (NAFLD), driven by metabolic syndrome (eg, obesity, insulin resistance, and hyperlipidemia), has been considered a hepatic feature of a systemic metabolic disorder during the last few decades.[1,2] It has been suggested that NAFLD is one of the most prevalent metabolic liver diseases and estimated to affect 25%-45% of adults globally.[3] Therefore, identifying emerging risk factors contributing to NAFLD might help to identify high-risk individuals and develop prevention and treatment strategies.

Air pollution is globally ubiquitous and has been identified as a leading environmental contributor to the global disease burden. Several studies have evaluated the relationships of long-term exposure to air pollution with metabolic dysfunction-associated fatty liver disease (such as NAFLD),[4,5] liver enzymes,[5-8] hepatic steatosis,[9,10] and liver cancer.[11] A dynamic cohort study of 17 106 patients showed a significant positive association between $PM_{2.5}$ and NAFLD in the Chinese population.[12] Moreover, a cohort study with 456 687 Britons showed that long-term exposure to air pollution was associated with a higher risk of developing NAFLD and cirrhosis.[13]

Aging is a general concept characterized by progressive functional and structural loss of tissue and organs. Several epidemiologic studies showed a positive relationship between aging-related disease and NAFLD.[14-17] However, no evidence was considered on the effect of biological aging on NAFLD. In addition, no evidence of the interactive effects of biological aging and $PM_{2.5}$ has been reported. Given that both aging and ambient $PM_{2.5}$ may have irritated effects on NAFLD, we hypothesized that biological aging and ambient $PM_{2.5}$ may have both independent and interactive associations with the risk of NAFLD.

Thus, a prospective cohort study using the UK Biobank database to investigate whether biological aging and environmental $PM_{2.5}$ are associated with NAFLD and to examine their combined effects on NAFLD.

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Methods

Study population

The UK Biobank recruited over half a million participants aged 37-73 years throughout 22 centers in the United Kingdom from 2006 to 2010.[18] All participants completed a touch-screen questionnaire, undertook physical measurements, and provided blood, urine, and saliva samples at baseline. More information about the UK Biobank protocol can be found online (http://www.ukbiobank.ac.uk). For this analysis, participants with valid data on air pollution exposure and biological age were included in this study. In brief, we excluded participants who were refused to participate in or those with missing data on air pollution exposure or biological age, or with NAFLD at baseline, resulting in a total of 296 917 participants being included (Figure S1). Compared with the original population, the participants included were more educated, less likely to be smoking, more likely to take physical activity (Table S1). Ethical Approval UK Biobank was approved by the North West Multi-Centre Research Ethics Committee (Ref: 11/NW/0382).

$PM_{2.5}$ exposure assessment

In the UK Biobank, the annual average concentration of $PM_{2.5}$ in 2010 was evaluated using the land use regression (LUR) model developed by the European Study Cohorts for Air Pollution Effects (ESCAPA). Briefly, this model was combined with Geographic Information System (GIS)-derived predictors including traffic, land use, and topography. The annual average concentrations of $PM_{2.5}$ (available for the year 2010) for each participant were linked to their residential addresses provided at the baseline visit (2006-2010). Both the continuous (per SD increase) and categorical data (low/moderate/high) of $PM_{2.5}$ were used for data analysis. We categorized the participants into three groups based on the tertile cut-off values of $PM_{2.5}$ concentrations as low, moderate, and high, respectively.

Biological age assessment

The biological age for each participant was calculated using KDM-BA and the PhenoAge, respectively. The KDM-BA was evaluated using forced expiratory volume in 1 second (FEV1), systolic blood pressure, and 7 blood chemistry parameters (ie, albumin, alkaline phosphatase, blood urea nitrogen, creatinine, C-reactive protein, glycated hemoglobin, and total cholesterol). The PhenoAge was calculated using 9 blood chemistries: albumin, alkaline phosphatase, creatinine, C-reactive protein, glucose, mean cell volume, red cell distribution width, white blood cell count, and lymphocyte proportion. Both KDM-BA and PhenoAge were originally trained using data from the National Health and Nutrition Examination Survey (NHANES) following the methods previously described by Klemera et al.[19] and Levine et al.[20] KDM-BA models biological age as the average biological state associated with a particular chronological age in a reference population. This model assumes biological age increases linearly with time. PhenoAge models biological age as the average biological state associated with a particular level of mortality risk in a reference population. This model assumes biological age increases exponentially with time.[21]

Ascertainment NAFLD

The health outcome of this study was the incident NAFLD, which was defined as hospitalization or death due to NAFLD and was ascertained from the linked hospital and death databases.[22] The date and cause of death were obtained from death certificates held by the National Health Service (NHS) Information Centre (England and Wales) and the NHS Central Register Scotland (Scotland). Dates and causes of hospital admissions were identified via record linkage to Health Episode Statistics (England and Wales) and the Scottish Morbidity Records (SMR01) (Scotland). Details of the linkage procedure can be found at http://content.digital.Nhs.uk/services. Using the International Classification of Diseases, 10th revision (ICD-10), and the latest Expert Panel Consensus Statement, NAFLD was defined as ICD-10 K76.0 and K75.8.[23]

Covariate data

Information on age at baseline (continuous), sex (female/male), education (with/without a college/university degree or other professional qualification), ethnicity (White/non-White), smoking status (never/previous/current), drinking status (never/previous/current), and income was collected from the UKB touchscreen questionnaire, where participants were asked corresponding questions. The type and duration of physical activity were recorded by International Physical Activity Questionnaire (IPAQ) and categorized as low (<600 MET-min/week), moderate (600-3000 MET-min/week), and high (≥3000 MET-min/week). Townsend deprivation index (area-based socioeconomic status) was derived from the postcode of residence, using the Townsend score.

Statistical analysis

The characteristics of continuous variables were described by means (SD), and categorical variables were depicted using numbers (percentages). The missing covariates were imputed by R package "mice".

Cox proportional hazards model used to evaluate the relationship of $PM_{2.5}$ and biological aging (ie, KDM-BA and PhenoAge, referred to as biological aging hereafter) with incident NAFLD. Three models were gradually adopted: model 1 was the crude model; model 2 adjusted for age and sex; and model 3 further adjusted for ethnicity, physical activity, education, employment status, smoking status, drinking status, body mass index (BMI), cancer, and cardiovascular disease. To evaluate the joint effects of biological aging and $PM_{2.5}$, participants were categorized into 9 groups according to the biological aging status and $PM_{2.5}$ exposure level: low biological aging-low $PM_{2.5}$, low biological aging-moderate $PM_{2.5}$, low biological aging-high $PM_{2.5}$, moderate biological aging-low $PM_{2.5}$, moderate biological aging-moderate $PM_{2.5}$, moderate biological aging-high $PM_{2.5}$, high biological aging-low $PM_{2.5}$, high biological aging-moderate $PM_{2.5}$, and high biological aging-high $PM_{2.5}$. The HRs with their 95% CI of NAFLD in model 3 were calculated with high biological aging and high $PM_{2.5}$ exposure as the reference. Relative excess risks due to interaction (RERI) using the delta method and multiplicative interaction terms using likelihood tests were calculated to evaluate the additive and multiplicative interaction effects between biological aging and $PM_{2.5}$, respectively. Subgroup analyses were also performed separately with stratification by the tertile categories of $PM_{2.5}$ exposure and biological aging to examine the associations of the NAFLD risk with the $PM_{2.5}$ concentration or biological aging in each stratum.

A series of sensitivity analyses were performed to examine the robustness of our effect estimates: (1) excluding participants who were followed up for less than 2 years to control reverse causation; (2) excluding individuals with cancer or cardiovascular disease at baseline; (3) restricting the analysis to male participants to examine whether the combined effects of $PM_{2.5}$ and biological aging differed by sex.

All statistical analyses were performed in R statistical Software, version 4.3.3. Two-tailed P <.05 indicated statistical significance.

Table 1. Baseline characteristics of the study participants by NAFLD.

Characteristics	Participants with NAFLD (*N* = 5109)	Participants without NAFLD (*N* = 291 608)	Overall (*N* = 296 917)
Age (years), mean (SD)	57.53 (7.89)	56.65 (8.06)	56.67 (8.06)
Sex, *n* (%)			
Female	2612 (51.1)	159 287 (54.6)	161 899 (54.6)
Male	2497 (48.9)	132 321 (45.4)	134 818 (45.4)
BMI (kg/m^2), mean (SD)	31.11 (5.43)	27.26 (4.63)	27.32 (4.67)
Townsend index (mean (SD))	−0.39 (3.45)	−1.42 (3.00)	−1.40 (3.01)
Ethnicity, *n* (%)			
White	4760 (93.2)	274 551 (94.2)	279 311 (94.1)
Others	349 (6.8)	17 057 (5.8)	17 406 (5.9)
Physical activity, *n* (%)			
Low	1260 (24.7)	53 930 (18.5)	55 190 (18.6)
Moderate	2062 (40.4)	118 674 (40.7)	120 736 (40.7)
High	1787 (35.0)	119 004 (40.8)	120 791 (40.7)
Annual household income, *n* (%)			
<£18 000	1767 (34.6)	65 095 (22.3)	66 862 (22.5)
£18 000-30 999	1400 (27.4)	74 975 (25.7)	76 375 (25.7)
£31 000-51 999	1109 (21.7)	76 429 (26.2)	77 538 (26.1)
£52 000-100 000	691 (13.5)	59 287 (20.3)	59 978 (20.2)
≥£100 000	142 (2.8)	15 822 (5.4)	15 964 (5.4)
Education qualification, *n* (%)			
<high school	1110 (21.7)	96 010 (32.9)	97 120 (32.7)
≥high school	3999 (78.3)	195 598 (67.1)	199 597 (67.3)
Smoking status, *n* (%)			
Never	2282 (44.7)	163 772 (56.2)	166 054 (56.0)
Former	2089 (40.9)	99 939 (34.3)	102 028 (34.4)
Current	738 (14.4)	27 897 (9.6)	28 635 (9.7)
Drinking status, *n* (%)			
Never	308 (6.0)	12 502 (4.3)	12 810 (4.3)
Former	350 (6.9)	9481 (3.3)	9831 (3.3)
Current	4451 (87.1)	269 625 (92.5)	274 076 (92.4)
$PM_{2.5}$ (μg/m^{-3}), P_{50} (P_{25}, P_{75})	10.1 (9.49, 10.8)	9.92 (9.27, 10.6)	9.93 (9.28, 10.6)
Biological ages, mean (SD)			
KDM biological age	58.07 (11.43)	52.75 (10.86)	53.42 (11.26)
KDM biological age acceleration	0.54 (11.76)	−3.90 (10.69)	−3.71 (10.97)
PhenoAge	54.55 (10.23)	50.50 (9.82)	51.31 (10.14)
PhenoAge acceleration	−2.99 (6.40)	−6.15 (5.29)	−5.82 (5.60)

Abbreviations: BMI, body mass index; KDM, Klemera–Doubal method; *n*/*N*, number; NAFLD, non-alcoholic fatty liver disease; $PM_{2.5}$, particulate matter with aerodynamic diameter <2.5 μm.

Results

The general characteristics of the study participants are summarized in Table 1. The mean age of the 296 917 participants at baseline was 56.67 years (SD: 8.06 years) and 54.6% were females. During a median of 11.9 years of follow-up, a total of 5109 cases of NAFLD were identified. Compared with participants without NAFLD, those with NAFLD were older; less educated; have higher Townsend deprivation index; more likely to be females, current smokers, previous drinkers; and less likely to take physical activity.

The main effects of biological aging and long-term ambient $PM_{2.5}$ exposure on NAFLD are depicted in Table 2. For KDM-biological age, the HRs of NAFLD were 1.49 (95% CI, 1.38-1.62) and 2.44 (95% CI, 2.25-2.65) in the moderate and high group compared with the low group. The HRs of PhenoAge-biological age were 1.49 (95% CI, 1.37-1.62) and 2.47 (95% CI, 2.28-2.67) in moderate and high group compared with the low group. For the effect of ambient $PM_{2.5}$, the HRs of NAFLD were 1.14 (95% CI, 1.06-1.22) and 1.16 (95% CI, 1.08-1.25) in moderate and high $PM_{2.5}$ exposure compared with the low group.

The combined effects of $PM_{2.5}$ and biological age on NAFLD are described in Table 3 and Figures S2, S3. The participants with high biological age and high $PM_{2.5}$ exposure exhibited the highest risk of incident NAFLD. On an additive scale, there was a positive interaction between biological age (high and low levels) and $PM_{2.5}$ exposure (high and low levels) on the risk of NAFLD. For individuals with low biological age and low levels of $PM_{2.5}$ exposure, the RERI was 0.13, suggesting that the 0.13 relative excess risk was due to additive interactions. However, no multiplicative proportions were found (P = .923). Tables 4 and 5 show the results of subgroup analysis. Higher biological age was associated with a higher risk of incident NAFLD in each $PM_{2.5}$ stratum, and a higher level of $PM_{2.5}$ exposure was associated with a higher risk of incident NAFLD in each biological age stratum.

The results of sensitivity analyses were generally robust after excluding the participants who developed NAFLD in the first 2 years of follow-up (Table S2), excluding those with cardiovascular disease or cancer at baseline (Table S3), and restricting the analysis with male participants (Table S4).

Discussion

To the best of our knowledge, this large-scale prospective cohort study was the first one to evaluate both the independent and

Table 2. Associations of biological age and long-term $PM_{2.5}$ exposure with risk of NAFLD incidence.

	Model 1		Model 2		Model 3	
	HR (95 % CI)	P	HR (95 % CI)	P	HR (95 % CI)	P
KDM						
Low biological age	Ref		Ref		Ref	
Moderate biological age	1.67 (1.54-1.81)	<.001	1.59 (1.47-1.72)	<.001	1.49 (1.38-1.62)	<.001
High biological age	3.24 (2.99-3.52)	<.001	2.79 (2.58-3.03)	<.001	2.44 (2.25-2.65)	<.001
Per SD increase	1.48 (1.46-1.51)	<.001	1.44 (1.41-1.47)	<.001	1.47 (1.43-1.52)	<.001
PhenoAge						
Low biological age	Ref		Ref		Ref	
Moderate biological age	1.69 (1.56-1.84)	<.001	1.59 (1.46-1.72)	<.001	1.49 (1.37-1.62)	<.001
High biological age	3.28 (3.04-3.54)	<.001	2.73 (2.52-2.94)	<.001	2.47 (2.28-2.67)	<.001
Per SD increase	1.52 (1.50-1.55)	<.001	1.45 (1.42-1.48)	<.001	1.38 (1.35-1.41)	<.001
$PM_{2.5}$ levels						
Low $PM_{2.5}$	Ref		Ref		Ref	
Moderate $PM_{2.5}$	1.31 (1.22-1.41)	<.001	1.15 (1.07-1.24)	<.001	1.14 (1.06-1.22)	<.001
High-$PM_{2.5}$	1.61 (1.50-1.72)	<.001	1.17 (1.09-1.26)	<.001	1.16 (1.08-1.25)	<.001
Per SD increasement	1.22 (1.19-1.25)	<.001	1.06 (1.03-1.09)	<.001	1.07 (1.04-1.10)	<.001

Abbreviations: KDM, Klemera–Doubal method; $PM_{2.5}$, particulate matter with aerodynamic diameter <2.5 μm.
Model 1 was adjusted for age and sex; Model 2 was adjusted for age, sex, ethnicity, physical activity, income, education, smoking status, drinking status, and Townsend index; Model 3 further adjusts for cardiovascular disease and cancer, further mutually adjusted for biological age (effect estimation of $PM_{2.5}$) or $PM_{2.5}$ (effect estimation of biological age).

jointed effects of $PM_{2.5}$ exposure and biological aging on the risk of incident NAFLD. Our results showed that both long-term $PM_{2.5}$ exposure and higher biological age were significantly associated with a higher risk of NAFLD incidence. On the additive scale, it showed a synergistic effect between biological age and $PM_{2.5}$ exposure, and the presence of both increases the risk of NAFLD. Therefore, ambient $PM_{2.5}$ and biological age were identified as major preventable risk factors for NAFLD.

Several epidemiologic studies have reported the link of $PM_{2.5}$ exposure with NAFLD, supporting the notion that air pollutants may contribute to the development of NAFLD. A cross-sectional study among 90 086 Chinese adults revealed that $PM_{2.5}$ was all significantly associated with increased odds of NAFLD.[6,7] A dynamic cohort study of 17 106 patients showed a significant positive association between $PM_{2.5}$ and NAFLD in the Chinese population.[12] Furthermore, as a major advanced liver disease for NAFLD, cirrhosis may be also associated with air pollution.[24] Markevych et al. found a significantly positive association between $PM_{2.5}$ and Gamma glutamyl transferase (GGT).[7]

No previous epidemiologic studies explored the relationship between biological aging and NAFLD. One animal study suggested that cellular senescence is a driver of hepatic steatosis and that the elimination of senescent cells may be a novel therapeutic strategy to reduce steatosis.[25] In the liver, aging can lead to functional and structural damage, as well as metabolic abnormalities.[26] It is reported that aging affects multiple processes during hepatic lipid metabolism, which may result in age-related liver steatosis.[27] This study firstly confirmed the previous animal study using epidemiologic study design and demonstrated that biological aging is associated with higher risk of NAFLD.

Our findings that simultaneous exposure to high levels of both biological age and $PM_{2.5}$ may intensify their individual effects on NAFLD are novel. $PM_{2.5}$ control and management of biological aging are essential for reducing risk of NAFLD. The mechanisms underlying the potential interaction between biological and $PM_{2.5}$ are currently unclear. Previous studies suggested that exposure to ambient air pollutants can disrupt lipid metabolism, impair insulin signaling, and induce chronic low-grade inflammation, thus promoting the development and progression of NAFLD.[13] There was also evidence suggesting that age-associated oxidative stress inhibits activation of progenitor liver cells, thus causing further depletion of hepatocytes and liver mass.[25,28] In addition,

Table 3. Combined effects of biological age, long-term $PM_{2.5}$ exposure, and risk of NAFLD.

Biological levels	HR (95% CI)			RERI		$P_{interaction}$
	High $PM_{2.5}$	Moderate $PM_{2.5}$	Low $PM_{2.5}$	Moderate $PM_{2.5}$	Low $PM_{2.5}$	
KDM						.411
High	Ref	0.99 (0.90-1.09)	0.87 (0.79-0.96)			
Moderate	**0.62 (0.55-0.68)**	**0.61 (0.55-0.68)**	**0.52 (0.46-0.59)**	0.00 (−0.11 to 0.12)	0.04 (−0.04 to 0.15)	
Low	**0.43 (0.39-0.50)**	**0.38 (0.33-0.43)**	**0.36 (0.31-0.41)**	−0.05 (−0.16 to 0.06)	0.05 (−0.05 to 0.16)	
PhenoAge						.923
High	Ref	0.95 (0.87-1.04)	0.84 (0.76-0.93)			
Moderate	**0.57 (0.52-0.63)**	**0.59 (0.53-0.66)**	**0.53 (0.47-0.60)**	0.05 (−0.06 to 0.16)	0.08 (−0.02 to 0.18)	
Low	**0.42 (0.37-0.47)**	**0.38 (0.33-0.43)**	**0.33 (0.28-0.38)**	−0.01 (−0.11 to 0.10)	**0.13 (0.02-0.23)**	

Abbreviations: KDM, Klemera–Doubal method; NAFLD, non-alcoholic fatty liver disease; $PM_{2.5}$, particulate matter with aerodynamic diameter <2.5 μm; RERI, relative excess risks due to interaction.
The results were fully adjusted for age, sex, ethnicity, physical activity, income, education, smoking status, drinking status, Townsend index, cardiovascular disease, and cancer. The estimates of RERI were calculated based on the reference group with high level of $PM_{2.5}$ exposure and high level of biological age.
Bolded text indicates statistically significant results (P<0.001).

Table 4. Subgroup analyses on the association of NAFLD with biological age stratified by the categories of $PM_{2.5}$.

Stratified by $PM_{2.5}$	Low $PM_{2.5}$		Moderate $PM_{2.5}$		High $PM_{2.5}$	
	HR	P	HR	P	HR	P
KDM						
Low biological age	Ref		Ref		Ref	
Moderate biological age	1.47 (1.26-1.71)	<.001	1.61 (1.40-1.85)	<.001	1.43 (1.26-1.62)	<.001
High biological age	2.39 (2.04-2.80)	<.001	2.60 (2.25-3.01)	<.001	2.38 (2.09-2.71)	<.001
PhenoAge						
Low biological age	Ref		Ref		Ref	
Moderate biological age	1.64 (1.40-1.92)	<.001	1.59 (1.37-1.84)	<.001	1.44 (1.26-1.64)	<.001
High biological age	2.47 (2.12-2.87)	<.001	2.49 (2.17-2.86)	<.001	2.51 (2.22-2.83)	<.001

Abbreviations: KDM, Klemera–Doubal method; NAFLD, non-alcoholic fatty liver disease; $PM_{2.5}$, particulate matter with aerodynamic diameter <2.5 μm.
The results were adjusted by age, sex, ethnicity, physical activity, income, education, smoking status, drinking status, Townsend index, cardiovascular disease, and cancer.

air pollutants and aging alter the gut microbiota composition. Disruption of the gut microbiota can lead to increased intestinal permeability, bacterial translocation, and subsequent liver inflammation and steatosis.[29-31]

There are several strengths in the study including the prospective study design. First, the relatively long follow-up duration, large sample size, and a wide range of covariates allowed for robust statistical analyses. Second this study firstly explored the joint effect of biological aging and $PM_{2.5}$ on the risk of NAFLD. Third, the study design utilized a longitudinal approach, which allowed the temporal relationship between exposure to air pollutants and NAFLD to be examined. In addition, the UK Biobank adopted a more precise measurement method to estimate the exposure level of ambient $PM_{2.5}$. Several potential limitations should be acknowledged. First, the observational study design make it difficult to get causal conclusion. Second, since the UK Biobank only collected main characteristics at baseline, it is difficult for us to consider the changes in biological aging, $PM_{2.5}$ and other covariates over time. Third, the UK Biobank cohort exhibited relatively low levels of $PM_{2.5}$ exposure, necessitating caution when extrapolating our findings to populations in regions with higher $PM_{2.5}$ exposure levels. Fourth, the participants included in this study were more educated, and had slightly healthier behaviors than the original population. This selection should not affect the conclusion, as we investigated the association rather than prevalence estimate in this study. Moreover, a series of subgroup analyses and sensitivity analyses, which took into account these variables, yielded similar results, demonstrating the robustness of the association. Finally, the data were collected between 2006 and 2010. Since then, advances in technology, policy, and demographic shifts may have influenced the findings. Nevertheless, the core biological mechanisms and risk factors for NAFLD remain relevant, and the UK Biobank's large, diverse cohort offers valuable long-term insights. Future research using more recent data is needed to assess the continued applicability of these results.

Conclusion

In conclusion, based on a large cohort study, this study found that both long-term $PM_{2.5}$ exposure and higher biological age were associated with an increased risk of NAFLD incidence. Moreover, it seems that simultaneous exposure to high levels of $PM_{2.5}$ and biological age enhances their individual effects.

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Table 5. Subgroup analyses on the association of NAFLD with $PM_{2.5}$ exposure stratified by the categories of biological age.

	Low biological age		Moderate biological age		High biological age	
	HR	P	HR	P	HR	P
Stratified by KDM						
Low $PM_{2.5}$	Ref		Ref		Ref	
Moderate $PM_{2.5}$	1.06 (0.90-1.24)	.499	1.18 (1.03-1.34)	.015	1.16 (1.04-1.28)	.006
High $PM_{2.5}$	1.19 (1.01-1.40)	.036	1.18 (1.03-1.36)	.020	1.17 (1.05-1.30)	.004
Stratified by PhenoAge						
Low $PM_{2.5}$	Ref		Ref		Ref	
Moderate $PM_{2.5}$	1.16 (0.98-1.38)	.094	1.10 (0.97-1.26)	.146	1.15 (1.04-1.28)	.006
High $PM_{2.5}$	1.34 (1.13-1.60)	.001	1.08 (0.94-1.24)	.274	1.18 (1.06-1.31)	.002

Abbreviations: KDM, Klemera–Doubal method; NAFLD, non-alcoholic fatty liver disease; $PM_{2.5}$, particulate matter with aerodynamic diameter <2.5 μm.
The results were adjusted by age, sex, ethnicity, physical activity, income, education, smoking status, drinking status, Townsend index, cardiovascular disease, and cancer.

Supplementary material

Supplementary material is available at the *American Journal of Epidemiology* online.

Funding

None declared.

Conflict of interest

The authors declare no conflicts of interest.

Data availability

The data used in this study are available from the UK Biobank (https://www.ukbiobank.ac.uk/) upon registration and approval. Access to the data is subject to approval by the UK Biobank Research Ethics Committee.

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