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Long-term effect of intermediate particulate matter ($PM_{1-2.5}$) on incident asthma among middle-aged and elderly adults: A national population-based longitudinal study

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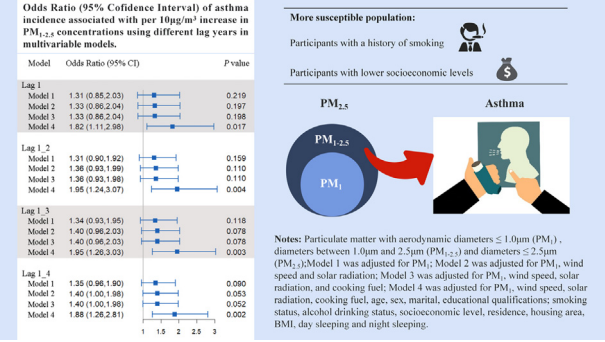
HIGHLIGHTS

- A nationwide longitudinal study of Chinese adults aged ≥45 years from 2011 to 2018
- We studied long-term effect of intermediate particulate matter ($PM_{1-2.5}$) on asthma.
- $PM_{1-2.5}$ was positively associated with incident asthma in middle-aged and elderly.
- Higher risk of asthma was observed in smokers and those at low socioeconomic level.
- Nonlinear exposure-response curve was observed between $PM_{1-2.5}$ and incident asthma.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: There is insufficient evidence about the long-term effects of intermediate particulate matter ($PM_{1-2.5}$) on asthma development in adults aged 45 years and above. This study aimed to investigate the relationship between long-term exposure to $PM_{1-2.5}$ and the incidence of asthma in adults aged 45 years and above.

Methods: A cohort study based on the China Health and Retirement Longitudinal Study (CHARLS) database was conducted to investigate the long-term effects of $PM_{1-2.5}$ on self-reported asthma incidence in adults aged 45 years and above in China from 2011 to 2018. The PM concentrations were estimated using a high-resolution (1 km^2) satellite-based spatiotemporal model. A covariate-adjusted generalized linear mixed model was used to analyze the relationship between long-term exposure to $PM_{1-2.5}$ and the incidence of asthma. Effect modifications and sensitivity analysis were conducted.

Results: After a 7-year follow-up, 103 (1.61 %) of the 6400 participants developed asthma. Each 10 μg/m^3 increment in the 1-, 2-, 3-, and 4-year moving average concentrations of $PM_{1-2.5}$ corresponded to a 1.82 [95 % confidence interval (CI):1.11–2.98], 1.95 (95 % CI: 1.24–3.07), 1.95 (95 % CI: 1.26–3.03) and 1.88 (95 % CI: 1.26–2.81) fold risk for incident asthma, respectively. A significant multiplicative interaction was observed between socioeconomic level and long-term exposure to $PM_{1-2.5}$. Stratified analysis showed that smokers and those with lower socioeconomic levels

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were at higher risk of incident asthma related to $PM_{1–2.5}$. Restricted cubic splines showed an increasing trend in asthma incidence with increasing $PM_{1–2.5}$. Sensitivity analyses showed that our model was robust.
Conclusion: Long-term exposure to $PM_{1–2.5}$ was positively associated with incident asthma in middle-aged and elderly individuals. Participants with a history of smoking and lower socioeconomic levels had a higher risk. More studies are warranted warrant to establish an accurate reference value of $PM_{1–2.5}$ to mitigate the growing asthma burden.

1. Introduction

Chronic respiratory disease remains one of the leading causes of death worldwide (Somayaji and Chalmers, 2022; Stern et al., 2020), among which asthma affected an estimated 262 million people in 2019 and caused 455,000 deaths (Collaborators, 2020a). Meanwhile, asthma has become one of the major public health problems in China (Brusselle and Ko, 2019). To reduce the prevalence and disease burden of asthma, it is essential to identify modifiable factors of asthma to guide the development of preventative programs.

Ambient air pollutants are modifiable risk factors for asthma. The Global Burden of Disease Study found that the morbidity and mortality caused by ambient particulate pollution have continued to increase (Collaborators, 2020b). Several studies have reported a positive association between short-term or long-term exposure to $PM_{2.5}$ (particles with aerodynamic diameters ≤ 2.5 μm) and asthma in adults (Fishe et al., 2022; Lam et al., 2021; Lee et al., 2021a; Liu et al., 2021a; Liu et al., 2021b; Renzi et al., 2022).

Fine particulate matter causes oxidative stress through deposition in the respiratory tract, which leads to an inflammatory airway response and impairs lung function (Ding et al., 2021; Lee et al., 2021b; Manojkumar et al., 2019; Wang et al., 2022b; Zhao et al., 2020a; Zheng et al., 2022). Geller MD et al. found correlations between PM_1 (particles with aerodynamic diameters ≤ 1 μm) and intermodal PM ($PM_{1–2.5}$) and found that PM_1 may grow into $PM_{1–2.5}$ via complex processes, including stagnation of aerosols in high relative humidity conditions followed by advection during daytime hour (Geller et al., 2004). Additionally, $PM_{1–2.5}$ has the same origin as $PM_{2.5–10}$ (particles with aerodynamic diameters between 2.5 μm and 10 μm) and its potential contribution to health effects should not be considered part of $PM_{2.5}$ (Geller et al., 2004).

Chemical compositions of $PM_{1–2.5}$ mainly include nitrate, sulfate, organic carbon, and metals (Geller et al., 2004). According to previous study, there were 41 % haze days in Shanghai from year 2008 to 2010 (Zhou et al., 2014). On clear days, ammonium was the most abundant in $PM_{1–2.5}$ while sulfate was the most abundant ion in PM_1 among sulfate, nitrate and ammonium (Qiao et al., 2016). On serious haze days, the concentration of nitrate caught up with and ultimately surpassed sulfate and ammonium in $PM_{1–2.5}$ (Qiao et al., 2016). Previously, we published a systematic review and meta-analysis, which showed that asthma was positively associated with long-term exposure to PM_1 (Hu et al., 2022a). However, it is unknown whether long-term exposure to intermediate particulate matter ($PM_{1–2.5}$) affects asthma development in adults aged 45 years and above in China after adjusting for PM_1.

In this study, we aimed to gain insight into the long-term effect of $PM_{1–2.5}$ on incident asthma in middle-aged and elderly adults. A retrospective longitudinal study was conducted to examine the relationship between long-term exposure to ambient $PM_{1–2.5}$ and asthma in middle-aged and elderly adults based on the China Health and Retirement Longitudinal Study.

2. Materials and methods

2.1. Study population

The China Health and Retirement Longitudinal Study (CHARLS) is a nationally representative project of aging with four stages of sampling, including county (district), village (residence), household and individual levels. PPS (probability proportional to size) sampling was used at the county (district)-village (residence) level. A corresponding number of samples were randomly selected from each sample village/community, and one household member aged >45 years was randomly selected as the primary respondent in each household. The baseline survey was conducted in 2011, with follow-up every 2–3 years, and currently has collected four waves of data (2011, 2013, 2015 and 2018), covering 150 district-level units and 450 village-level units (Zhao et al., 2020c).

This study used data from the baseline survey of 2011 to Waves 4 (2018) of CHARLS (http://charls.pku.edu.cn/). A total of 19,816 participants were examined in Wave 4 (2018), with a response rate of 83.84 %. We included all respondents aged 45 years or older and excluded those with missing data and participants who had been diagnosed with asthma in 2011. Finally, we included 6400 participants in the final analysis (Fig. S1).

The CHARLS study was approved by The Biomedical Ethics Committee of Peking University (IRB00001052–11015), and all participants provided written informed consent.

2.2. Outcome assessment

The outcome of asthma was defined by self-report in the CHARLS study. Trained researchers administered questionnaires through face-to-face interviews, and new incident asthma was confirmed based on the following question: “Have you been diagnosed with asthma by a doctor?”

2.3. Exposure assessment

In this study, annual average concentrations of air pollutants were calculated as long-term air pollutant exposure levels and assigned according to the corresponding geocodes (longitude and latitude) of an individual's home address. We used particulate matter data (PM_1 and $PM_{2.5}$), gaseous pollutant data [nitrogen dioxide (NO_2), sulfur dioxide (SO_2), carbon monoxide (CO), and ozone (O_3)], and meteorological factor data (wind speed and solar radiation). According to previous studies, the average $PM_{1–2.5}$ 1 to 4 years before 2018 was used as an exposure metric to assess the long-term effects of $PM_{1–2.5}$ due to data availability (Lee et al., 2021a; Liu et al., 2021b).

The data were obtained from the CHAP dataset (https://weijing-rs.github.io/product.html). The space-time extremely randomized trees (STET) model was used to estimate PM_1 concentrations at a 1 km spatial resolution across mainland China. Ground-level O_3 concentrations were estimated from solar radiation intensity and surface temperature using extended ensemble learning of the STET model, combining ground-based observations, remote sensing products, atmospheric reanalysis, and emission inventories (Wei et al., 2022). The concentrations of $PM_{2.5}$, PM_{10}, NO_2, SO_2, and CO were generated from big data (e.g., ground-based measurements, satellite remote sensing products, atmospheric reanalysis, and model simulations) using artificial intelligence by considering the spatiotemporal heterogeneity of air pollution (Wei et al., 2021).

$PM_{1–2.5}$ concentrations were calculated by subtracting the concentrations of PM_1 from $PM_{2.5}$. $PM_{2.5–10}$ concentrations were calculated by subtracting the concentrations of $PM_{2.5}$ from PM_{10}. Tenfold cross-validation showed that the R^2 (root-mean-square error) for annual predictions of PM_1, $PM_{2.5}$, NO_2, SO_2, CO and O_3 were 77 % (14.6 μg/m^3), 88 % (16.52 μg/m^3), 72 % (9.97 μg/m^3), 84 % (10.07 μg/m^3), 80 % (0.29 μg/m^3) and 87 % (17.10 μg/m^3), respectively (Chen et al., 2018a; Chen et al., 2018b; Chen et al., 2018c).

2.4. Covariates

Based on the previous literature (Ai et al., 2019; Beasley et al., 2015; Chan et al., 2019; Hu et al., 2022b; Song et al., 2022), to estimate the

independent effect of $PM_{1-2.5}$ on incident asthma, four kinds of covariates were adjusted, including a) meteorological factors: wind speed (m/s) and solar radiation (w/m^2); b) lifestyle factors: body mass index (BMI: <18.5 kg/m^2, 18.5–23.9 kg/m^2, 24–27.9 kg/m^2, ≥28 kg/m^2), alcohol drinking status (never, ever or current drinker), smoking status (never, ever or current smoker), residence (rural or urban), housing area (m^2), and socioeconomic level [average and better (very high/relatively high/average), lower (relatively poor/poor)]; c) dietary habits: cooking fuel (clean or solid), day sleeping (no nap or have a nap), and night sleeping [sleep debt (<6 h) and adequate sleep (≥6 h)]; d) and demographic characteristics: age (years), sex, marital status (singlehood/widowed/divorced or married), and educational qualifications (primary school and below, junior high school and higher).

2.5. Statistical analysis

Generalized linear mixed models (GLMMs) were used to assess the independent effect of particulate matter on incident asthma (Yang et al., 2019). The detailed information on the GLMM is described in the supplementary materials (Supplemental methods).

We calculated the average concentrations of PM_1, $PM_{1-2.5}$, and $PM_{2.5}$ for 1 to 4 years prior to 2018 to explore the long-term effects. To avoid multicollinearity among variables, a variance inflation factor (VIFs<10) metric was tested. With $PM_{1-2.5}$ as the independent variable, Model 1 was adjusted for PM_1; Model 2 was adjusted for PM_1 and meteorological factors (wind speed and solar radiation); Model 3 was adjusted for PM_1, meteorological factors (wind speed and solar radiation) and indoor air pollution (cooking fuel); Model 4 was adjusted for PM_1, meteorological factors (wind speed and solar radiation), indoor air pollution (cooking fuel) and individual characteristics (including age, sex, marital status, BMI, alcohol drinking status, smoking status, residence, housing area, socioeconomic level, educational qualifications; day sleeping, night sleeping).

Restricted cubic splines at the 5th, 35th, 65th and 95th percentiles were used to portray the relationship between the concentration of $PM_{1-2.5}$ and incident asthma, and the model fit better with knots of 4 (i.e., degrees of freedom of 3) according to the value of the C-index (the larger, the better) (Table S1), which was consistent with previous studies (Durrleman and

Table 1
Baseline characteristics of participants included in the study (n = 6400).

Covariables	Total	Incident asthma		*P*
		No	Yes	
Age, years: Median (IQR)	57 (13)	57 (13)	59 (10)	**0.012**
Sex: n (%)				0.635
Male	3219 (50.30)	3155 (50.10)	64 (62.14)	
Female	3181 (49.70)	3142 (49.90)	39 (37.86)	
Marital status: n (%)				**<0.001**
Single/widowed/divorced	592 (9.25)	582 (9.24)	10 (9.71)	
Married	5808 (90.75)	5715 (90.76)	93 (90.29)	
BMI (kg/m^2): n (%)				**<0.001**
<18.5	303 (4.73)	293 (4.65)	10 (9.71)	
18.5–23.9	2833 (44.27)	2784 (44.21)	49 (47.57)	
24–27.9	1533 (23.95)	1521 (24.15)	12 (11.65)	
≥28	552 (8.63)	542 (8.61)	10 (9.71)	
NA	1179 (18.42)	1157 (18.36)	22 (21.36)	
Alcohol drinking status: n (%)				**<0.001**
Never	4164 (65.06)	4105 (65.19)	59 (57.28)	
Ever or current drinker	2231 (34.86)	2187 (34.73)	44 (42.72)	
NA	5 (0.08)	5 (0.08)	–	
Smoking status: n (%)				**<0.001**
Never	3784 (59.13)	3737 (59.35)	47 (45.63)	
Ever or current smoker	2615 (40.86)	2559 (40.64)	56 (54.37)	
NA	1 (0.01)	1 (0.01)	–	
Cooking fuel: n (%)				**<0.001**
Clean	2954 (46.16)	2902 (46.09)	52 (50.49)	
Solid	3446 (53.84)	3395 (53.91)	51 (49.51)	
Residence: n (%)				**<0.001**
Rural	5168 (80.75)	5086 (80.77)	82 (79.61)	
Urban	1230 (19.22)	1209 (19.20)	21 (20.39)	
NA	2 (0.03)	2 (0.03)	–	
Housing area (m^2): Median (IQR)	100 (68)	100 (68)	90 (70)	0.134
Socioeconomic level: n (%)				**<0.001**
Very high	17 (0.27)	16 (0.25)	1 (0.97)	
Relatively high	163 (2.55)	161 (2.56)	2 (1.94)	
Average	3333 (52.08)	3290 (52.25)	43 (41.75)	
Relatively poor	1841 (28.77)	1807 (28.70)	34 (33.01)	
Poor	615 (9.61)	600 (9.53)	15 (14.56)	
NA	431 (6.72)	423 (6.71)	8 (7.77)	
Education qualifications: n (%)				**<0.001**
Primary school and below	1569 (24.52)	1540 (24.46)	29 (28.16)	
Junior high school and higher	4824 (75.38)	4750 (75.43)	74 (71.84)	
NA	7 (0.10)	7 (0.11)	–	
Day sleeping (min): n (%)				0.540
No nap	2716 (42.44)	2671 (42.42)	45 (43.69)	
Have a nap	3271 (51.11)	3220 (51.14)	51 (49.51)	
NA	413 (6.45)	406 (6.44)	7 (6.80)	
Night sleeping (h): n (%)				**0.005**
Sleep debt <6	4010 (62.66)	3950 (62.73)	60 (58.25)	
Adequate sleep ≥ 6	1947 (30.42)	1914 (30.40)	33 (32.04)	
NA	443 (6.92)	433 (6.87)	10 (9.71)	

Notes: Cooking fuel, fuel used in cooking as an indicator of indoor pollution; IQR, interquartile range; NA, not available. The bolded *P* value < 0.05.

Simon, 1989; Lee et al., 2018; Malloy et al., 2009). Since there were no specific limit values for $PM_{1-2.5}$, we used the median values of $PM_{1-2.5}$, 10 μg/m^3 and 5 μg/m^3 as reference values to plot the exposure-response curves for $PM_{1-2.5}$. The limiting values of 10 μg/m^3 and 5 μg/m^3 are derived from the World Health Organization (WHO) in the Air Quality Guidelines (AQG) for the annual average $PM_{2.5}$, with a target value of 10 μg/m^3 in 2005 and revised to 5 μg/m^3 in 2021 (Carvalho, 2021).

In addition, to determine potential interactions, we examined the multiplicative interactions of $PM_{1-2.5}$ with age, sex, alcohol drinking status, smoking status, cooking fuel, residence, socioeconomic level, and educational qualifications. Effect modification was analyzed with categorical variables with the median as the basis for the classification of $PM_{1-2.5}$ (Liu et al., 2022).

Various sensitivity analyses were conducted to assess the robustness of the associations between long-term exposures to $PM_{1-2.5}$ and incident asthma, including 1) Model 4 was additionally adjusted for SO_2, CO, and O_3 separately; 2) Model 4 was additionally adjusted for chronic lung disease; 3) Participants were excluded who developed asthma from 2011 to 2013 to avoid potential reverse causality; 4) Model 9 was additionally adjusted for time-varying covariates using generalized estimating equations (GEE) with a logit link; 5) We estimated the relative risk (RR) using GLMM with a Poisson distribution in the longitudinal analysis; 6) Model 4 was additionally adjusted for temperature and relative humidity which were potential risk factors for asthma; 7) we added a sensitivity analysis using the minimally adjusted model, determined by a directed acyclic graph (DAG).

All statistical analyses were performed using R (version 4.0.1) software with the packages "lme4" and "gee", and $P < 0.05$ was considered statistically significant. The long-term effect was presented as the odds ratio (OR) and 95 % confidence interval (CI) for incident asthma per 10 μg/m^3 increment in concentrations of $PM_{1-2.5}$.

3. Results

3.1. Baseline characteristics

In our study, 6, 400 participants were included in the analyses (Supplementary Fig. S1). After a follow-up of 7 years, 103 (1.61 %) individuals developed asthma (Table 1). The median age at baseline was 57 (IQR = 13). Participants with asthma were more likely to be male, have a history of smoking, and have lower educational qualifications than those without asthma.

Table 2 shows the distribution of the average concentration levels of air pollutants and meteorological factors in different lag years. Overall, the annual average concentrations of $PM_{2.5}$ were above the World Health Organization (WHO) regulations throughout the study period. PM_1, $PM_{1-2.5}$, $PM_{2.5}$, PM_{10}, NO_2, SO_2 and O_3 showed moderate to high correlations with each other. Their spearman correlation coefficients were distributed

Table 2
Characteristics of distribution of air pollutants and meteorological factors.

Lag years	Pollutants	Summary statistics							
		Mean	SD	Min	P_{25}	Median	P_{75}	P_{95}	Max
Lag 1	PM_1 (μg/m^3)	30.34	14.38	0.01	23.91	30.03	38.60	48.22	104.04
	$PM_{1-2.5}$ (μg/m^3)	16.60	6.47	1.99	11.66	15.86	21.64	25.98	27.66
	$PM_{2.5}$ (μg/m^3)	46.94	18.68	3.73	35.15	43.51	61.40	71.78	119.65
	PM_{10} (μg/m^3)	81.66	30.75	13.84	59.50	77.96	109.37	126.74	133.64
	SRA (w/m^2)	42.10	24.24	1.45	22.00	42.54	56.89	86.59	131.31
	WIN (m/s)	1.04	0.28	0.55	0.84	1.02	1.18	1.56	2.11
	SO_2 (μg/m^3)	23.45	18.62	17.58	0.19	14.55	17.58	26.30	45.49
	CO (μg/m^3)	8.99	23.65	1.04	0.59	0.88	1.04	1.35	52.45
	NO_2 (μg/m^3)	31.35	15.78	29.53	3.01	22.11	29.53	37.63	42.42
	O_3 (μg/m^3)	88.17	25.59	93.21	1.11	82.81	93.21	107.47	110.92
Lag 1–2	PM_1 (μg/m^3)	30.31	14.21	1.09	24.73	29.82	37.60	48.56	104.45
	$PM_{1-2.5}$ (μg/m^3)	17.51	7.42	2.70	11.79	17.19	24.38	28.33	30.22
	$PM_{2.5}$ (μg/m^3)	47.82	19.21	5.08	34.66	44.71	63.39	76.36	119.15
	PM_{10} (μg/m^3)	82.39	31.85	14.32	58.91	79.14	111.64	132.87	140.41
	SRA (w/m^2)	41.89	24.32	1.44	21.85	42.02	56.31	86.99	131.86
	WIN (m/s)	1.03	0.27	0.56	0.86	1.00	1.15	1.53	2.16
	SO_2 (μg/m^3)	25.52	18.57	19.76	0.18	15.83	19.76	30.26	49.50
	CO (μg/m^3)	9.03	23.63	1.06	0.67	0.92	1.06	1.48	52.42
	NO_2 (μg/m^3)	31.03	15.89	29.71	3.52	21.64	29.71	36.56	43.17
	O_3 (μg/m^3)	84.51	24.62	90.84	3.36	79.87	90.84	99.81	106.52
Lag 1–3	PM_1 (μg/m^3)	30.77	14.12	1.71	25.30	30.88	38.26	50.07	103.82
	$PM_{1-2.5}$ (μg/m^3)	18.67	8.08	2.31	11.77	18.40	26.07	31.40	35.39
	$PM_{2.5}$ (μg/m^3)	49.44	19.91	5.17	36.19	47.94	64.22	78.77	118.50
	PM_{10} (μg/m^3)	84.37	32.82	14.16	61.73	80.93	113.35	136.49	146.14
	SRA (w/m^2)	42.00	24.33	1.44	21.95	42.16	56.73	86.80	131.73
	WIN (m/s)	1.11	0.27	0.64	0.92	1.10	1.21	1.58	2.33
	SO_2 (μg/m^3)	27.38	18.38	21.66	0.95	17.07	21.66	34.42	50.45
	CO (μg/m^3)	9.06	23.61	1.09	0.69	0.92	1.09	1.53	52.40
	NO_2 (μg/m^3)	30.78	15.93	29.35	3.50	21.64	29.35	36.63	43.15
	O_3 (μg/m^3)	81.48	23.90	88.60	3.94	77.94	88.60	95.70	101.49
Lag 1–4	PM_1 (μg/m^3)	33.29	14.24	1.77	27.65	33.05	41.57	52.32	101.05
	$PM_{1-2.5}$ (μg/m^3)	19.01	8.49	4.92	11.93	17.84	26.71	32.60	36.99
	$PM_{2.5}$ (μg/m^3)	52.30	20.30	7.16	39.12	50.99	66.00	82.40	116.74
	PM_{10} (μg/m^3)	88.82	33.69	16.61	66.20	85.98	115.13	137.68	151.79
	SRA (w/m^2)	42.94	24.75	1.46	22.44	43.33	57.60	87.81	134.00
	WIN (m/s)	1.08	0.28	0.55	0.89	1.08	1.20	1.67	2.35
	SO_2 (μg/m^3)	30.11	18.16	24.48	4.64	19.47	24.48	39.17	54.32
	CO (μg/m^3)	9.08	23.59	1.14	0.78	0.97	1.14	1.57	52.36
	NO_2 (μg/m^3)	31.35	15.80	28.58	3.69	22.35	28.58	37.34	43.35
	O_3 (μg/m^3)	80.16	23.12	85.49	3.50	78.65	85.49	93.36	100.40

Notes: Min, minimum; Max, maximum; PM_1, particulate matter with aerodynamic diameters ≤ 1 μm; $PM_{1-2.5}$, particles with aerodynamic diameters between 1.0 μm and 2.5 μm; $PM_{2.5}$, particles with aerodynamic diameters ≤ 2.5 μm; PM_{10}, particles with aerodynamic diameters ≤ 10 μm; SRA, solar radiation; WIN, wind speed; SO_2, sulfur dioxide; CO, carbon monoxide; NO_2, nitrogen dioxide; O_3, Ozone; SD, standard deviation; P_{25}, 25th percentile; P_{75}, 75th percentile.

Table 3
Spearman correlation coefficients for air pollutants and meteorological factors.

	PM_1	$PM_{1-2.5}$	$PM_{2.5}$	PM_{10}	SO_2	CO	NO_2	O_3	WIN	SRA
PM_1	1.000									
$PM_{1-2.5}$	**0.502**	1.000								
$PM_{2.5}$	**0.919**	**0.783**	1.000							
PM_{10}	**0.883**	**0.740**	**0.946**	1.000						
SO_2	**0.613**	**0.461**	**0.626**	**0.617**	1.000					
CO	**0.147**	**0.218**	**0.192**	**0.189**	**0.547**	1.000				
NO_2	**0.812**	**0.632**	**0.841**	**0.798**	**0.666**	**0.244**	1.000			
O_3	**0.442**	**0.381**	**0.470**	**0.487**	**0.127**	**−0.203**	**0.488**	1.000		
WIN	**0.095**	0.005	**0.072**	**0.110**	**0.252**	**0.235**	**0.084**	**−0.059**	1.000	
SRA	**0.254**	**0.135**	**0.210**	**0.216**	**0.357**	**0.281**	**0.288**	**0.089**	**0.405**	1.000

Note: PM_1, particulate matter with an aerodynamic diameter ≤ 1.0 μm; $PM_{1-2.5}$, particles with aerodynamic diameters between 1 μm and 2.5 μm; $PM_{2.5}$, particulate matter with an aerodynamic diameter ≤ 2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter ≤ 10 μm; SO_2, sulfur dioxide; CO, carbon monoxide; NO_2, nitrogen dioxide; O_3, Ozone; WIN, wind speed; SRA, solar radiation; The bolded *P* value <0.05.

from 0.40 to 0.95, and O_3 was negatively correlated with CO and wind speed (Table 3).

3.2. The association between $PM_{1-2.5}$ and incident asthma

The associations with different lag years between long term exposure to $PM_{1-2.5}$ and incident asthma are shown in Fig. 1. In Model 1, incident asthma was not significantly associated with each 10 μg/m^3 increase in the 1-, 2-, 3-, and 4-year moving average concentrations of $PM_{1-2.5}$. In Model 2 and Model 3, the association was still not statistically significant, with a maximum effect size of 1.40 (95 % CI: 1.00–1.98) at 4 years of $PM_{2.5}$ exposure. In Model 4, incident asthma was positively and significantly associated with $PM_{1-2.5}$ exposure [lag 1-year: OR = 1.82 (95 % CI: 1.11–2.98), lag 1_2 year: OR = 1.95 (95 % CI: 1.24–3.07), lag 1_3 year: OR = 1.95 (95 % CI: 1.26–3.03) and lag 1_4 year: 1.88 (95 % CI: 1.26–2.81)].

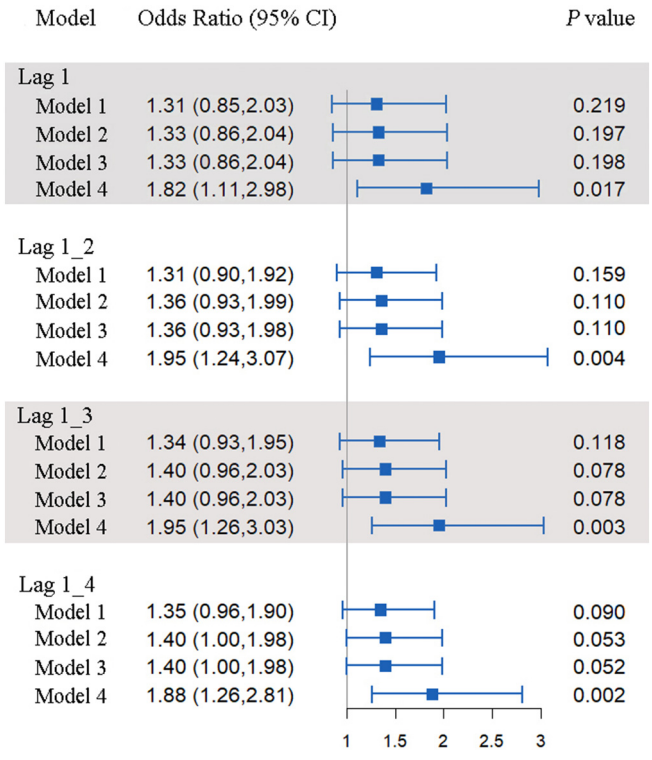

Fig. 1. OR (95 % CI) of asthma incidence associated with per 10 μg/m^3 increase in $PM_{1-2.5}$ concentrations using different lag years in multivariable models. Abbreviations: OR, odds ratio; CI, confidence interval; Model 1, adjusted for PM_1; Model 2 was adjusted for PM_1, meteorological factors (wind speed and solar radiation); Model 3 was adjusted for PM_1, meteorological factors (wind speed and solar radiation) and indoor air pollution (cooking fuel); Model 4 was adjusted for PM_1, meteorological factors (wind speed and solar radiation), indoor air pollution (cooking fuel) and individual characteristics (including age, sex, marital status, BMI, alcohol drinking status, smoking status, residence, housing area, socioeconomic level, educational qualifications; day sleeping, night sleeping).

3.3. Exposure-response curve between $PM_{1-2.5}$ exposure and incident asthma

Restricted cubic splines with 4 knots were used to portray the exposure-response curve between $PM_{1-2.5}$ exposure and incident asthma for different time window moving averages (Fig. 2). As shown in Fig. 2, the nonlinear exposure-response relationship tended to be stronger as the moving lag years increased. Compared with the AQG 2005 standard of the WHO, the exposure-response relationship curve under the AQG 2021 standard showed an upward shift. Evidence was found for the long-term effects of $PM_{1-2.5}$ on the incidence of asthma.

3.4. Interaction analysis and stratified analyses

Table 3 shows the multiplicative interaction effect of the association between the asthma incidence and the 1-, 2-, 3-, and 4-year moving average concentrations of $PM_{1-2.5}$. Significant interactions were observed between the socioeconomic level and long-term exposure to $PM_{1-2.5}$ with different lag years ($P_{lag1\text{-}y}$ = 0.013, P_{lag1_2y} = 0.022, P_{lag1_3y} = 0.022, P_{lag1_4y} = 0.019), and the socioeconomic level significantly alleviated the effect of $PM_{1-2.5}$ on the development of asthma (Table 4). Table 5 shows the results of the effect modification for socioeconomic level. With low PM, high socioeconomic level as a reference, low socioeconomic level and high PM exposure showed high risk (OR = 2.70, 95 % CI: 1.26, 5.78). Fig. S2 presents the statistical significance of the stratified analysis for the association between asthma incidence and each 10 μg/m^3 increase in the 1-, 2-, 3-, and 4-year moving average concentrations of $PM_{1-2.5}$. Compared to participants with higher socioeconomic levels, the impact of $PM_{1-2.5}$ on asthma was greater for those with lower socioeconomic levels [(OR = 3.65, 95 % CI: 2.04–6.52) vs. (OR = 1.10, 95 % CI: 0.62–1.95), Z = −2.882, *P* = 0.004] in lag 1_4 year stratified analyses. Overall, with the increase in the lag time, the results gradually become significant.

In addition, although the *P* of interaction terms was not statistically significant, we found that participants with a history of smoking had a higher risk than those who never smoked [1.95 (95 % CI: 1.26–3.03) vs. 1.88 (95 % CI: 1.26–2.81), Z = -2.442, *P* = 0.015]; men had a slightly higher risk than women [(OR = 2.12, 95 % CI: 1.3–3.44) vs. (OR = 1.65, 95 % CI: 0.95–2.87), Z = 0.672, *P* = 0.502]; participants who used solid fuels had a higher risk than those who used clean fuels [(OR = 2.64, 95 % CI: 1.49–4.66) vs. (OR = 1.57, 95 % CI: 0.89–2.75), Z = −1.274, *P* = 0.203]; and participants with lower educational qualifications had slightly higher risk [(OR = 2.30, 95 % CI: 1.01–5.24) vs. (OR = 1.81, 95 % CI: 1.20–2.74), Z = 0.504, *P* = 0.614].

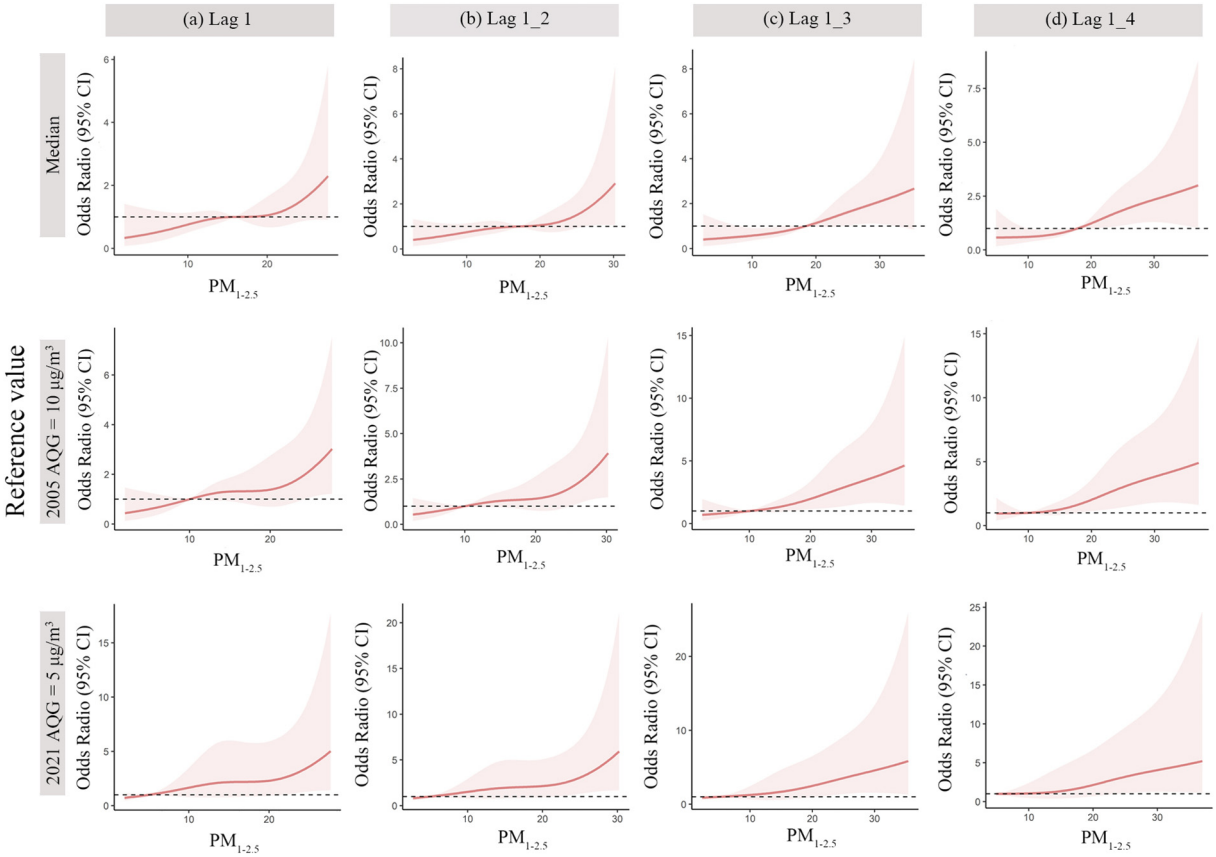

Fig. 2. Restricted natural cubic splines with 4 knots of the association between different moving averages of $PM_{1-2.5}$ and asthma incidence. Notes: (a) showed lag 1, (b) showed lag 1_2, (c) showed lag 1_3, (d) showed lag 1_4; $PM_{1-2.5}$, particulate matters with aerodynamic diameters between 1.0 μm and 2.5 μm. The median of $PM_{1-2.5}$ in lag 1, −2, −3, −4 years respectively were 15.86 μg/m^3, 17.19 μg/m^3, 18.40 μg/m^3, and 17.84 μg/m^3.

Table 4
The interaction effect of the association between asthma incidence and 1-, 2-, 3-, and 4-year moving average concentrations of $PM_{1-2.5}$ based on GLMM.

Effect modifier	Lag 1	Lag 1_2	Lag 1_3	Lag 1_4
Age				
Estimate	0.0013	0.0010	0.0005	0.0002
$P_{interact}$	0.633	0.716	0.834	0.934
Sex				
Estimate	0.0266	0.0088	0.0119	0.0142
$P_{interact}$	0.472	0.786	0.684	0.604
Alcohol drinking status				
Estimate	−0.0236	−0.0214	−0.0192	−0.0281
$P_{interact}$	0.228	0.202	0.229	0.058
Smoking status				
Estimate	−0.0146	−0.0038	−0.0024	−0.0032
$P_{interact}$	0.459	0.822	0.877	0.830
Cooking fuel				
Estimate	0.0348	0.0446	0.0358	0.0256
$P_{interact}$	0.356	0.183	0.240	0.367
Residence				
Estimate	−0.0374	−0.0286	−0.0308	−0.0388
$P_{interact}$	0.513	0.608	0.630	0.336
Socioeconomic level				
Estimate	**0.0624**	**0.0516**	**0.0436**	**0.0179**
$P_{interact}$	**0.013**	**0.022**	**0.022**	**0.019**
Educational qualifications				
Estimate	−0.0197	−0.0241	−0.0106	−0.0177
$P_{interact}$	0.640	0.510	0.742	0.558

Note: Bolded *P*-Value <0.05. $PM_{1-2.5}$, particles with aerodynamic diameters between 1.0 μm and 2.5 μm.

3.5. Sensitivity analysis

Similar results of the sensitivity analysis are shown in Table S4 for OR (95 % CI) in incident asthma per 10 μg/m^3 increment in $PM_{1-2.5}$ exposure. After additional adjustments for gaseous pollutants (SO_2, CO, O_3) and the history of chronic lung diseases, the results remained robust. The associations between risk factors and asthma did not change substantially when we excluded participants who developed asthma from 2011 to 2013 (Table S5). $PM_{1-2.5}$ still behaved as a risk factor after using the GEE model adjusted for time-varying covariates (Table S6). The results of the RR values calculated using the Poisson-linked GLMM model are similar to the results of the main model (Table S7). The effect size of $PM_{1-2.5}$ was much larger after including temperature and humidity as risk factors for

Table 5
Association between 4-year moving average of $PM_{1-2.5}$ (per 10 μg/m^3 increase) on incident asthma based on GLMM.

Socioeconomic level	$PM_{1-2.5}$	OR (95 % CI)
Average and better	<17.84 μg/m^3	Ref.
	≥17.84 μg/m^3	0.93 (0.37, 2.34)
Lower	<17.84 μg/m^3	1.61 (0.36, 7.25)
	≥17.84 μg/m^3	**2.70 (1.26, 5.78)**

Note. The bolded estimates correspond to *P*-value <0.05. $PM_{1-2.5}$, particulate matters with aerodynamic diameters between 1.0 μm and 2.5 μm; OR, odds ratio; CI, confidence interval; Covariates included PM_1, meteorological factors (wind speed and solar radiation), indoor air pollution (cooking fuel), and individual characteristics (including age, sex, marital status, BMI, alcohol drinking status, smoking status, cooking fuel, residence, housing area, educational qualifications, day sleep, and night sleep).

asthma (Table S8). The results of the sensitivity analysis remain consistent with our main findings based on the minimally adjusted model using a directed acyclic graph (Table S9). The minimally adjusted model was adjusted for PM_1, wind speed, solar radiation, age, sex, marital status, residence, socioeconomic level, and educational qualifications, selected by the directed acyclic graph (Fig. S3).

4. Discussion

This study investigated the association between long-term exposure to $PM_{1–2.5}$ and incident asthma in middle-aged and elderly individuals based on a national cohort study. We observed an increased risk of incident asthma in middle-aged and elderly adults associated with long-term exposure to $PM_{1–2.5}$ with different lag structures. Of these, three-year average $PM_{1–2.5}$ concentrations had the largest effect on the risk of incident asthma, and participants with a history of smoking and lower socioeconomic levels were at higher risk. Sensitivity analyses showed that our results were robust.

The 7-year incidence of asthma was 1.61 % in our study, which is lower than the annual incidence of 0.5 % (approximately 3.5 % for 7 years) among adults in Sweden (Rönmark et al., 1997), or the prevalence of 4.2 % reported among Chinese adults aged 20 years or older in a national cross-sectional survey (Huang et al., 2019). The difference may be due to the differences study design and the distributions of age, sex, and race. In addition, the outcome of asthma was based on self-reports in CHARLS, which may lead to underestimates of asthma incidence.

In this study, we found that $PM_{1–2.5}$ showed a significant positive association with asthma incidence among middle-aged and elderly adults, which could be related to the distribution of pollutant particle size in the human body and its chemical composition. Manojkumar and collegues reported that the deposition fraction of $PM_{2.5}$ and PM_1 is same in the tracheobronchial region but differs in the head and pulmonary regions, indicating that the deposition of $PM_{1–2.5}$ may differ from PM_1 in the head and pulmonary regions (Manojkumar et al., 2019).

Airway inflammation and oxidative stress had been found to play a role in the association between $PM_{2.5}$ and asthma (Ghozikali et al., 2022; Havet et al., 2019). Exposure to organic aerosols in $PM_{1–2.5}$ and PM_1 had a significant effect on the granulocyte macrophage colony-stimulating factor release (Lakhdar et al., 2022). On the chemical components, $PM_{1–2.5}$ is to some extent a mixture of anthropogenic activities and natural aerosols. Compared with PM_1, $PM_{1–2.5}$ has more organic matter, nitrate, dust, and sea salt, and less carbon (Ramgolam et al., 2009). In China, Qiao et al. found that $PM_{2.5}$ was dominated by PM_1 on clean days, and the contribution of $PM_{1–2.5}$ to $PM_{2.5}$ increased on haze days (account for 40 % of all natural days) (Qiao et al., 2016). When haze pollution happened, organic carbon, elemental carbon, and primary organic carbon accumulated faster in $PM_{1–2.5}$ than in PM_1 (Qiao et al., 2016).

There are other pathogenic mechanisms of $PM_{2.5}$. A Canadian population-based cohort study of 800,000 adults in Toronto found that chronic exposure to iron and copper in $PM_{2.5}$ was positively associated with respiratory diseases including asthma (Zhang et al., 2021). $PM_{2.5}$ and O_3 also have an effect on the composition of oropharyngeal microbes (Zhao et al., 2020b), suggesting that oropharyngeal microbes may also contribute to asthma status. CO and $PM_{2.5}$ have been associated with asthma hospitalization (Ma et al., 2020). The cytotoxicity of fine particulate matter may increase the contractility of sensitive human bronchial smooth muscle cells (Zheng et al., 2021).

We observed an increased risk of incident asthma in elderly adults associated with long-term exposure to $PM_{1–2.5}$. However, no the association was found for the short-term exposure(Zhang et al., 2020; Zhu et al., 2021). There is a lack of studies on $PM_{1–2.5}$ exposure and asthma, so we discussed them with studies related to $PM_{2.5}$. In the field of epidemiological studies, there is no conclusive evidence on how $PM_{2.5}$ exposure affects asthma. Similarly, Lee et al. found that long-term $PM_{2.5}$ exposure was associated with asthma incidence in middle-aged and elderly individuals (Lee et al., 2021a). Another multicountry study concluded that long-term exposure to $PM_{2.5}$ may be a significant risk factor for asthma (Ai et al., 2019). Recently, Keirsbulck. et al. reported that $PM_{2.5}$ exposure was a trigger for exacerbations of asthma (Keirsbulck et al., 2022). However, the findings of studies in Canada and New Zealand did not support a positive association between $PM_{2.5}$ exposure and asthma incidence (Hales et al., 2021; Shin et al., 2021), which may be related to the low level of both their population density and their air pollution.

Stratified analysis showed that individuals with a history of smoking were more susceptible to $PM_{2.5}$ related asthma than nonsmokers, which is consistent with a previous study (Huang et al., 2019). As markers of damage reflecting systemic oxidative stress, plasma fluorescent oxidation product levels are much lower in never smokers than in smokers (Havet et al., 2019; Huang et al., 2019). Evidence for the effect of socioeconomic level on asthma has been inconclusive. Consistent with previous findings, we concluded that a low socioeconomic level is a risk factor for asthma (Guo et al., 2021; Renzi et al., 2022; Safiri et al., 2022). However, several studies have shown that the risk of asthma is higher in urban cities than in rural areas (Wang et al., 2021). Wang DY et al. indicated that people with low socioeconomic status were more likely to be physically inactive and to smoke regularly (Wang et al., 2022a). The effect of socioeconomic level on asthma may occur through the level of exposure to air pollution. Jbaily et al. found that a low-income population was consistently exposed to higher $PM_{2.5}$ levels than a higher-income population, and the gap in exposure between them increased over time (Jbaily et al., 2022). However, in China, exposure levels are higher in urban areas than in rural areas (Lee et al., 2021b), so further studies are warranted to analyze this issue. In addition, we found that men and solid fuel users and those with low educational qualifications were more susceptible; however, no statistically significant difference was observed among the subgroups in this study.

Several studies have reported a linear relationship exposure response curve relationship between asthma incidence and $PM_{2.5}$ (Lee et al., 2021a; Liu et al., 2021b); however, to the best of our knowledge, there is no such report on $PM_{1–2.5}$. In this study, we found an S-shaped nonlinear relationship at lag1 and lag1–2 years and a J-shaped relationship at lag1–3 and lag1–4 between $PM_{1–2.5}$ and asthma. The OR of asthma morbidity tended to increase with increasing concentrations of $PM_{1–2.5}$ regardless of the reference value (median value of $PM_{1–2.5}$, 10 $\mu g/m^3$ or 5 $\mu g/m^3$). Additional studies are warrant to establish an accurate reference value of $PM_{1–2.5}$ to mitigate the increasing incidence of asthma, not limited to $PM_{2.5}$ and PM_1.

Our study has several strengths. First, we used a longitudinal study design with a nationwide representative sample of middle-aged and elderly people. Second, indoor air pollution has recently attracted much attention due to the expansion of modern lifestyles characterized by intensive urbanization and more time spent indoors (Chatkin et al., 2022; Paterson et al., 2021). We adjusted the model using the fuel used for cooking as an indicator of indoor air pollution to control for the effect of indoor air pollution exposure on the model. Third, we conducted a dual-pollutant model analysis of PM_1 and $PM_{1–2.5}$ to explore the effect of $PM_{1–2.5}$ in $PM_{2.5}$ on asthma onset. A multipollutant model sensitivity analysis was also performed to confirm the robustness of the model.

Our study also has some limitations. First, despite the high resolution (1 km^2), individual exposure to air pollution may be biased due to unevenly distributed emission sources, dilution, and physicochemical transformations. Second, information on physical activity and occupational exposure were not included, and further study is warranted. Third, the incidence of asthma in CHARLS was based on questionnaires that were self-reported, which may lead to misclassification. Four, average $PM_{1–2.5}$ prior 1 to 4 years before 2018 was calculated as exposure metrics based on the data availability, and PM data were not available before 2013.

5. Conclusion

Long-term exposure to $PM_{1–2.5}$ was positively associated with incident asthma in middle-aged and elderly individuals. Participants with a history of smoking and lower socioeconomic levels had a higher risk. Additional

studies are warrant to establish an accurate reference value of $PM_{1–2.5}$, not limited to $PM_{2.5}$ and PM_1, to mitigate the increasing incidence of asthma. More studies are warranted warrant to establish an accurate reference value of $PM_{1–2.5}$ to mitigate the growing asthma burden.

Abbreviations

$PM_{1–2.5}$	intermediate particulate matter
CHARLS	the China Health and Retirement Longitudinal Study
95 % CI	95 % confidence interval
$PM_{2.5}$	fine particulate matter with an aerodynamic diameter < 2.5 μm
PM_1	particulate matter with an aerodynamic diameter < 1.0 μm
$PM_{2.5–10}$	particles with aerodynamic diameters between 2.5 μm and 10 μm
PM_{10}	inhalable particulate matter with an aerodynamic diameter < 10 μm
PPS	probability proportional to size
NO_2	nitrogen dioxide
SO_2	sulfur dioxide
CO	carbon monoxide
O_3	ozone
STET	space-time extremely randomized trees
WIN	wind speed
SRA	solar radiation
GLMM	Generalized linear mixed model
VIF	variance inflation factor
WHO	World Health Organization
AQG	Air Quality Guidelines
GEE	generalized estimating eqs.
RR	relative risk
DAG	directed acyclic graph
OR	odds ratio
CI	confidence interval
IQR	interquartile range
SD	standard deviation

CRediT authorship contribution statement

Shuting Li: Conceptualization, Methodology, Data curation, Formal analysis, Software, Writing - Original Draft, Writing- Reviewing and Editing, Visualization. **Jing Wei:** Conceptualization, resources, Supervision, Writing- Reviewing and Editing. **Yaoyu Hu:** Conceptualization, Methodology, Visualization, Software. **Yuhong Liu:** Conceptualization, Data curation. **Meiling Hu:** Methodology, Software. **Yadi Shi:** Methodology. **Yongxi Xue:** Data curation. **Mengmeng Liu:** Data curation. **Wenhan Xie**: Methodology. **Xiuhua Guo:** Writing- Reviewing and Editing, Supervision, Resources. **Xiangtong Liu:** Conceptualization, Methodology, Data curation, Funding acquisition, Supervision, Writing- Reviewing and Editing. All authors were involved with the critical revision of the manuscript and approved the final version.

Data availability

The authors do not have permission to share data.

Declaration of competing interest

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

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Availability of data and materials

The data can be accessed from the China Health and Retirement Longitudinal Study (CHARLS) (http://charls.pku.edu.cn/) with permission via direct request. The CHAP dataset is available at https://weijing-rs.github.io/product.html.

Ethics approval

Ethics approval for the CHARLS project was obtained from the Ethics Review Committee of Peking University (IRB00001052–11015).

Consent for publication

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2022.160204.

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