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Joint association of PM_{2.5} and AIP with advanced Cardiovascular-Kidney-Metabolic syndrome in middle-aged and older Chinese adults: a national cohort study

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Abstract:

Background: The joint association of exogenous ambient pollutant (PM_{2.5}) and endogenous metabolic marker (Atherogenic Index of Plasma, AIP) with advanced CKM remains unclear.

Methods: Data from the China Health and Retirement Longitudinal Study (CHARLS) spanning 2011 and 2015 were used. Participants were categorized based on the median values of the PM_{2.5} or/and AIP. Multivariable logistic regression models were employed to explore the independent and joint associations of PM_{2.5} and AIP with advanced CKM (stages 3-4). Interaction analysis, subgroup analysis, and sensitivity analysis were performed to verify the robustness of the findings.

Results: Elevated AIP was strongly associated with an increased risk of advanced CKM. Combined exposure to high AIP and PM_{2.5} significantly increased the risk of advanced CKM, while PM_{2.5} alone showed no positive association. No significant additive or multiplicative interaction was observed between PM_{2.5} and AIP. The core associations remained robust across subgroups. Sensitivity analyses confirmed the robust of the findings.

Conclusion: Elevated AIP was strongly associated with advanced CKM risk in middle-aged and older Chinese adults. Although PM_{2.5} exposure alone was not independently associated with advanced CKM, concurrent exposure to elevated AIP

and PM_{2.5} was linked to a higher disease burden. These findings underscore the importance of integrating metabolic risk stratification with environmental exposure assessment for precision prevention of advanced CKM.

Keywords

Cardiovascular-kidney-metabolic syndrome; particulate matter with an aerodynamic diameter of 2.5 micrometers; Atherogenic Index of Plasma; CHARLS

Introduction

Cardiovascular-Kidney-Metabolic (CKM) syndrome, a multi-organ synergistic injury disease characterized by cardiovascular dysfunction, chronic kidney disease (CKD), and metabolic abnormalities, involves cross-regulation of multiple pathways including oxidative stress, inflammatory response, and vascular endothelial dysfunction[1, 2]. It has emerged as a major public health crisis requiring urgent global attention. Globally, the prevalence of CKM exceeds 25%, with a higher incidence in middle-aged and older adults, accompanied by extremely high disability and mortality rates [3]. In China, the accelerating aging demographic shift (≥ 45 years old accounting for $>30\%$ of the population) combined with the epidemic of metabolic risk factors has further aggravated the burden of CKM—compared with isolated cardiovascular disease or kidney disease, CKM patients have a 2- to 3-fold increased the risk of death from all causes and cardiovascular outcomes[4-6]. Notably, CKM exhibits distinct progressive characteristics: interventions in early stages (Stages 0-2) can significantly reduce the risk of progression to advanced stages (Stages 3-4) and adverse outcomes[7], while patients with advanced CKM face substantially elevated mortality risks [2]. Therefore, identifying modifiable risk factors and their combined effects is crucial for formulating

precise staged prevention and control strategies and alleviating the population disease burden.

Fine particulate matter (PM_{2.5}, particulate matter with an aerodynamic diameter of ≤ 2.5 micrometers) is a globally recognized environmental pollutant. Long-term PM_{2.5} exposure contributes to the pathogenesis of hypertension, insulin resistance, and kidney injury through inducing systemic inflammation, oxidative stress, and vascular endothelial damage [8, 9]—all of which are core pathological components of CKM. Previous studies based on the China Health and Retirement Longitudinal Study (CHARLS) have confirmed that PM_{2.5} exposure is closely associated with the incidence and progression of CKM in Chinese middle-aged and older adults [10]. However, existing studies have obvious limitations: most focus on the independent effects of PM_{2.5} without exploring its combined role with metabolic biomarkers, and few analyze the specific associations with different CKM stages (early incidence vs. advanced progression)[2]. Notably, as a high PM_{2.5} exposure burden country, the annual average PM_{2.5} concentration in some regions of China reached 54.4 $\mu\text{g}/\text{m}^3$ during 2011-2015[2], far exceeding the safe threshold recommended by the World Health Organization (WHO) (5 $\mu\text{g}/\text{m}^3$)[11]. Clarifying the synergistic impact of PM_{2.5} and metabolic factors is particularly important for the staged prevention and control of CKM in the Chinese population.

The Atherogenic Index of Plasma (AIP), calculated as $\log_{10}(\text{triglycerides}/\text{high-density lipoprotein cholesterol})$, is a core biomarker reflecting lipid metabolism dysregulation and atherosclerotic susceptibility[12, 13]. Unlike traditional lipid

parameters (e.g., total cholesterol, triglycerides), AIP integrates the balance between pro-atherogenic and anti-atherogenic lipids, exhibiting superior predictive efficacy for cardiometabolic diseases[14]. Existing evidence has confirmed that elevated AIP is directly associated with increased risks of chronic kidney disease and cardiovascular events[15], and its mechanisms may be closely linked to vascular endothelial damage, plaque formation, and insulin resistance[16, 17]. However, the combined effect of AIP and environmental pollutants (e.g., PM_{2.5}) in the incidence and staged progression of CKM has not been explored. Especially in the Chinese population with unique lipid profiles (e.g., high prevalence of hypertriglyceridemia) and environmental exposure characteristic[18], whether AIP can modify PM_{2.5}-related CKM risk and progression risk remains unclear.

Despite growing research on CKM risk factors, several critical gaps persist: First, most studies focus on single exposures (either environmental or metabolic) or combinations of endogenous factors (e.g., triglyceride glucose(TyG) index and body roundness index) [19], while the joint effect of exogenous environmental pollutants (PM_{2.5}) and endogenous metabolic markers (AIP) on CKM—especially on different stages (early incidence and advanced progression)—has not been systematically reported; Second, evidence on the association between PM_{2.5} and CKM is mostly derived from Western cohorts [20, 21], lacking targeted data from large-scale, nationally representative Chinese cohorts with long-term follow-up, and failing to fully consider differences in exposure characteristics and metabolic phenotypes of the Chinese population; Third, few studies have systematically evaluated subgroup

differences (e.g., age, gender, urban/rural residence) in the association between dual exposures and CKM, which is a prerequisite for precision prevention; Fourth, existing studies have not clarified the mode of action (independent effect vs. synergistic effect) of PM_{2.5} and AIP on CKM, and their robustness has rarely been validated through comprehensive sensitivity analyses, limiting the reliability of causal inferences[22].

To address these gaps, this prospective cohort study was conducted using data from the CHARLS 2011–2015, focusing on middle-aged and older adults. The primary objectives were: (1) to investigate the independent and joint associations of PM_{2.5} exposure and AIP with CKM incidence (early stages) and progression to advanced stages; (2) to explore effect modification by demographic (age, gender) and socioeconomic (urban/rural residence) factors; (3) to validate the robustness of the findings through multiple sensitivity analyses. We hypothesized that higher PM_{2.5} exposure and elevated AIP would synergistically increase the risk of CKM incidence and progression to advanced stages, and this association would vary across different subgroups. The findings of this study aim to provide evidence-based support for the staged precision prevention and control of CKM in Chinese populations, particularly highlighting the integrated management of environmental and metabolic risk factors.

Methods

Study design and population

This analysis was conducted using data from the CHARLS, a continuing prospective cohort that investigates health status and socioeconomic circumstances

among Chinese individuals aged 45 years and older.[23]. Employing a multistage stratified probability sampling method, the 2011 baseline survey enrolled 17,708 participants from 450 urban and rural communities across 150 counties/districts in 28 provinces of China, ensuring a nationally representative sample. After baseline, follow-up investigations were conducted biennially or triennially. The study protocol complied with the Declaration of Helsinki and received ethical approval from the Institutional Review Board of Peking University Health Science Center (IRB00001052-11015); written informed consent was obtained from all participants.

A total of 17,708 participants from the baseline survey were initially included. Subsequently, 13,813 participants were excluded based on the following criteria: unavailable PM_{2.5} data (n=5087) and AIP data (n=5247); diagnosis of CKM at baseline (n=290); lost to follow-up (n=3,179). Following the screening process, 3,902 participants remained and were incorporated into the final analyses. A comprehensive overview of the participant selection process is provided in Figure 1.

Fig.1 Workflow of participant recruitment and screening

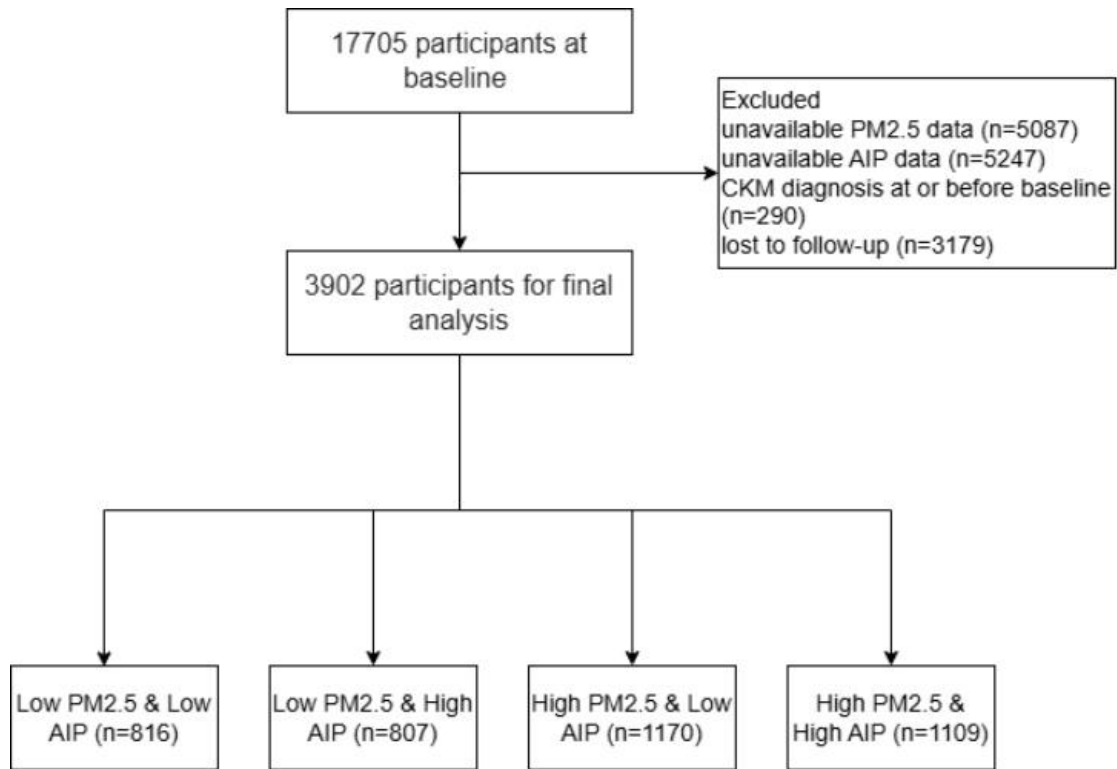


Fig.1 Abbreviations:PM2.5: fine particulate matter; AIP: Atherogenic Index of Plasma; CKM: Cardiovascular-Kidney-Metabolic

syndrome

Assessment of PM2.5 Exposure

PM2.5 exposure data in this study were derived from satellite remote sensing inverted environmental monitoring data matched to the CHARLS cohort. Based on the geographic coordinates (latitude and longitude) of participants' residential addresses at baseline, we linked to the annual average PM2.5 concentration data of the corresponding region. This data was obtained through satellite aerosol optical depth inversion combined with ground monitoring station calibration, featuring good spatial representativeness and accuracy[8, 24] .

Quality control of PM2.5 concentration data strictly followed environmental epidemiology standards. After excluding outliers (data beyond 3 standard deviations), the annual average PM2.5 exposure level for each participant was calculated.

Participants were divided into low PM_{2.5} group ($\leq$ median) and high PM_{2.5} group ($>$ median) using the median of PM_{2.5} exposure data in the CHARLS cohort as the cut-off value [25].

AIP Measurement and Calculation

The AIP was calculated based on the detection results of triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C) in fasting blood samples.

The process of blood sample collection and detection was as follows: Participants fasted for at least 8 hours before venous blood was collected by professional medical staff. Samples were transported to the CHARLS collaborating certified laboratory (Clinical Laboratory of Capital Medical University) under 4°C cold chain conditions for detection. TG and HDL-C were measured using the enzymatic colorimetric method with an automatic biochemical analyzer (Beckman Coulter AU5800) [13, 26]. The laboratory was certified by the National Center for Clinical Laboratories. Internal quality control samples were used for full-process quality control during detection. The intra-assay coefficient of variation (CV) for TG and HDL-C detection was $<2\%$, and the inter-assay CV was $<3\%$, ensuring the reliability of test results[14, 27].

The calculation formula of AIP referred to the international standard: $AIP = \log_{10}[TG(mg/dL)/HDL - C(mg/dL)]$ [12,13]. Similarly, participants were divided into low AIP group ($\leq$ median) and high AIP group ($>$ median) using the median of AIP distribution in the CHARLS cohort as the cut-off value [12, 28].

Assessment of CKM syndrome stages

CKM syndrome stages were defined in accordance with the Presidential Advisory Statement on CKM syndrome issued by the American Heart Association (AHA)[28], classified into five stages (0–4), with the core definition referring to the coexistence of subclinical or clinical cardiovascular disease (CVD), chronic kidney disease (CKD), and metabolic disorders (detailed in Supplementary Table S1); stages 3–4 were classified as advanced CKM according to the AHA definition[7].

Specifically, stage 0 was characterized by no identifiable CKM risk factors such as overweight (BMI ≥ 23 kg/m²), dyslipidemia, or prediabetes, and no evidence of CKD/CVD; stage 1 included participants with overweight/abdominal obesity (BMI ≥ 23 kg/m² or waist circumference $\geq 90/80$ cm [men/women]) or dysfunctional adipose tissue, without other metabolic risk factors or CKD; stage 2 comprised individuals with metabolic risk factors (hypertriglyceridemia ≥ 135 mg/dL, hypertension, metabolic syndrome, or diabetes) or moderate-to-high-risk CKD; stage 3 included participants with subclinical CVD, very-high-risk CKD, or high predicted 10-year CVD risk, where CKD was determined using the Kidney Disease Improving Global Outcomes (KDIGO) 2013 classification system[28], and the 10-year CVD risk was estimated using the China-PAR (Prediction for Atherosclerotic Cardiovascular Disease Risk in China) equations specifically developed and validated for Chinese populations due to population-specific characteristics[29]; metabolic risk factors (hypertriglyceridemia ≥ 135 mg/dL, hypertension, metabolic syndrome, or diabetes) or moderate-to-high-risk CKD; stage 3 included participants with subclinical CVD, very-high-risk CKD, or high predicted 10-year CVD risk, where CKD was determined using the Kidney

Disease Improving Global Outcomes (KDIGO) 2013 classification system[28], and the 10-year CVD risk was estimated using the China-PAR (Prediction for Atherosclerotic Cardiovascular Disease Risk in China) equations specifically developed and validated for Chinese populations due to population-specific characteristics[29]; stage 4 was characterized by the existence of clinical CVD, including heart failure, atrial fibrillation, coronary heart disease, and stroke.

Covariates

A structured questionnaire was administered by well-trained interviewers to systematically collect participant information. The data encompassed sociodemographic variables (age, sex, education, and marital status), lifestyle behaviors (smoking and drinking), and anthropometric measures, including body mass index (BMI); biochemical and clinical-related indicators (depression, glycosylated hemoglobin A1c [HbA1c], and C-reactive protein (CRP))[5, 30-33]. The BMI was calculated using the formula: $\text{BMI (kg/m}^2\text{)} = \text{body mass (kg)} / \text{height (m)}^2$ [34]. The depression was assessed by a Patient Health Questionnaire-9 (PHQ-9)[35].

Statistical Analysis

The Shapiro-Wilk test and Levene's test were used to evaluate the normality of distributions and homogeneity of variance for continuous variables, respectively. Continuous variables with normal distributions were expressed as mean $\pm$ standard deviation (mean $\pm$ SD), while those with skewed distributions were presented as median (interquartile range, IQR). Categorical variables were summarized as frequency (percentage, %). Intergroup comparisons were performed using independent samples t-

test or Kruskal-Wallis rank sum test for continuous variables, and χ^2 test for categorical variables.

Referring to previous literature [3, 10, 36], participants were divided into four groups based on the median values of PM_{2.5} and AIP in the cohort: Low PM_{2.5} and Low AIP, Low PM_{2.5} and High AIP, High PM_{2.5} and Low AIP, and High PM_{2.5} and High AIP. Differences in baseline characteristics among the four groups were compared. Complete case analysis was adopted for missing data handling. Participants with missing PM_{2.5} or AIP data were excluded, and a total of 3902 participants were included in the final analysis.

Multivariable logistic regression models were used to explore the independent and joint associations of PM_{2.5} and AIP with advanced CKM (stages 3-4), with effect sizes expressed as odds ratio (OR) and 95% confidence interval (95%CI). Three progressively adjusted models were constructed: Model 1 (unadjusted), Model 2 (adjusted for sociodemographic factors), and Model 3 (fully adjusted for lifestyle, anthropometric, and clinical biochemical factors). For independent effect analysis, "Low PM_{2.5}" and "Low AIP" were set as reference groups, respectively; for joint effect analysis, "Low PM_{2.5} and Low AIP" was defined as the reference group.

Additive and multiplicative interaction models were used to test the interaction between PM_{2.5} and AIP: Multiplicative interaction was determined by including a product term ("PM_{2.5} group $\times$ AIP group") in the fully adjusted model, with significance judged by likelihood ratio test. Additive interaction was assessed using relative excess risk due to interaction (RERI), attributable proportion (AP), and synergy

index (SI). The presence of additive interaction was judged by whether the 95%CI included 0 (for RERI and AP) or 1 (for SI).

Subgroup analyses were performed stratified by sex, education level, smoking status, residential area, BMI group, marital status, and depression status. The fully adjusted model was repeated in each subgroup, and interaction effects (P for interaction) were tested by including a product term ("combined exposure $\times$ stratification variable") to assess heterogeneity.

Sensitivity analyses were conducted to verify the robustness of main findings: ① redefining exposure groups using the 75th percentile as the cut-off; ② excluding extreme outliers ($\pm 3SD$); ③ omitting individual covariates one by one; ④ replacing the quasibinomial model with a binomial distribution model.

All statistical analyses were performed using R software (version 4.3.0) with a two-sided significance level set at $\alpha=0.05$. In accordance with the STROBE statement, the statistical analysis process was as follows:

Results

Baseline characteristics of participants

A total of 3902 participants (54.79% female) were included in this study, with a mean age of 58.88 ± 8.94 years. They were stratified into four subgroups based on PM_{2.5} and AIP levels: Low PM_{2.5} and Low AIP (n=816), Low PM_{2.5} and High AIP (n=807), High PM_{2.5} and Low AIP (n=1170), and High PM_{2.5} and High AIP (n=1109), with baseline characteristics summarized in Table 1. Statistically significant differences were

observed in most key indicators among the four subgroups (all $P<0.05$), including core exposure variables (PM2.5, AIP), outcome-related indicators (CKM prevalence, BMI group, HbA_{1c}), and covariates (age, sex, residential area, drinking status), while no significant differences were found in the distribution of CRP, marital status, education level, and smoking status ($P>0.05$). Independent association analysis showed that compared with low PM2.5 exposure, high PM2.5 was negatively associated with CKM risk (fully adjusted model: OR=0.79, 95%CI: 0.67~0.93, $P=0.005$); compared with low AIP, high AIP significantly increased CKM risk (fully adjusted model: OR=2.00, 95%CI: 1.68~2.37, $P<0.001$), and both associations remained robust after stepwise covariate adjustment.

Table 1 Baseline characteristics of participants

variable	Total (n=3902)	Low PM2.5 and High AIP (n=807)	Low PM2.5 and Low AIP (n=816)	High PM2.5 and High AIP (n=1109)	High PM2.5 and Low AIP (n=1170)	p.value
Age	58.88 ± 8.94	58.44 ± 8.83	59.41 ± 9.36	58.35 ± 8.52	59.32 ± 9.07	<0.01
Sex						0.02
Female	2138(54.79)	458(56.75)	416(50.98)	636(57.35)	628(53.68)	
Male	1764(45.21)	349(43.25)	400(49.02)	473(42.65)	542(46.32)	
Residential_area						<0.0001
Rural	2471(63.33)	492(60.97)	562(68.87)	651(58.70)	766(65.47)	
Urban	1431(36.67)	315(39.03)	254(31.13)	458(41.30)	404(34.53)	
Marital_status						0.28
Married or living with a partner	3489(89.42)	724(89.71)	719(88.11)	1006(90.71)	1040(88.89)	

Not_married	413(10.58)	83(10.29)	97(11.89)	103(9.29)	130(11.11)	
Education						0.10
College and above	63(1.62)	22(2.73)	13(1.59)	10(0.90)	18(1.54)	
Elementary school or below	2647(67.89)	536(66.50)	558(68.38)	750(67.69)	803(68.69)	
Secondary school	1189(30.49)	248(30.77)	245(30.02)	348(31.41)	348(29.77)	
Smoking						0.08
Ever/current smoke	1510(38.71)	301(37.30)	348(42.65)	421(37.96)	440(37.64)	
Never smoke	2391(61.29)	506(62.70)	468(57.35)	688(62.04)	729(62.36)	
Drinking						<0.01
No	2599(66.61)	556(68.90)	508(62.25)	776(69.97)	759(64.87)	
Yes	1303(33.39)	251(31.10)	308(37.75)	333(30.03)	411(35.13)	
BMI group						<0.0001
Normal (18.5 to <25)	2052(59.74)	373(55.42)	506(70.38)	466(47.36)	707(66.76)	
Obese (30 or greater)	192(5.59)	46(6.84)	19(2.64)	83(8.43)	44(4.15)	
Overweight (25 to <30)	1012(29.46)	234(34.77)	114(15.86)	420(42.68)	244(23.04)	
Underweight (<18.5)	179(5.21)	20(2.97)	80(11.13)	15(1.52)	64(6.04)	
HbA1c	5.31 ± 0.85	5.37 ± 0.91	5.21 ± 0.68	5.45 ± 1.05	5.20 ± 0.66	<0.0001
PM2.5	61.75 ± 17.65	43.54 ± 7.72	44.74 ± 7.31	74.25 ± 11.09	74.31 ± 10.40	<0.0001
AIP	0.02 ± 0.34	0.30 ± 0.27	-0.24 ± 0.17	0.27 ± 0.23	-0.24 ± 0.17	<0.0001
CPR	2.57 ± 6.32	2.57 ± 4.67	2.59 ± 6.98	2.61 ± 5.46	2.51 ± 7.47	0.99
Depression_2						0.02
depression	1382(36.93)	300(38.56)	318(40.61)	358(33.74)	406(36.25)	
normal	2360(63.07)	478(61.44)	465(59.39)	703(66.26)	714(63.75)	
ckm_group						<0.0001
0	1698(43.52)	283(35.07)	391(47.92)	415(37.42)	609(52.05)	
1	2204(56.48)	524(64.93)	425(52.08)	694(62.58)	561(47.95)	

Values are presented as mean ± standard deviation (SD), median (interquartile range, IQR), or n (%)

Abbreviations: BMI: body mass index; HbA1c: Hemoglobin A1c; PM2.5: particulate matter with an aerodynamic diameter of 2.5 micrometers; AIP: Atherogenic Index of Plasma; CRP: C-reactive protein; CKM: cardiovascular-kidney-metabolic syndrome

Association of PM2.5 and AIP with the risk of advanced CKM

Table 2 showed significant associations between combined PM2.5 and AIP exposure and the advanced CKM risk. In Model 1, the risk of advanced CKM was significantly elevated in "Low PM2.5 and High AIP" group (OR=2.10, 95%CI: 1.82~2.42, P<0.001) and "High PM2.5 and High AIP" group (OR=1.79, 95%CI: 1.55~2.07, P<0.001), while no significant association was observed in "High PM2.5 and Low AIP" group (OR=0.91, 95%CI: 0.79~1.05, P=0.186). In Model 2, the two high AIP-related groups exhibited a further increase in the risk of advanced CKM, and the core association pattern remained consistent. In Model 3, the associations remained stable and significant: OR=2.97 (95%CI: 2.53~3.49, P<0.001) for "Low PM2.5 and High AIP" group, OR=2.35 (95%CI: 2.01~2.75, P<0.001) for "High PM2.5 and High AIP" group, with only slight attenuation of OR values. Based on the analysis of the individual associations of PM2.5 and AIP with advanced CKM, AIP showed an independent and strong association with advanced CKM, while PM2.5 exposure alone showed no significant association (see Supplementary Tables S1 and S2).

Table 2 Association of PM2.5 and AIP with the risk of advanced CKM

Characteristic	Model 1			Model 2			Model 3		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Low PM2.5 and Low AIP	—	—		—	—		—	—	
Low PM2.5 and High AIP	2.10	1.91, 2.32	<0.001	3.12	2.78, 3.50	<0.001	2.93	2.58, 3.32	<0.001
High PM2.5 and Low AIP	0.88	0.80, 0.97	0.008	0.85	0.76, 0.95	0.005	0.84	0.75, 0.95	0.007
High PM2.5 and High AIP	1.78	1.62, 1.96	<0.001	2.54	2.27, 2.84	<0.001	2.32	2.05, 2.63	<0.001

Abbreviations: CI = Confidence Interval, OR = Odds Ratio

Model 1 (Unadjusted): No covariates were adjusted for; the reference group was "Low PM2.5 and Low AIP".

Model 2 (Sociodemographic and lifestyle-adjusted): Adjusted for Model 1 plus age, sex, residential area, marital status, education

level; the reference group was "Low PM2.5 and Low AIP".

Model 3 (Fully adjusted): Adjusted for Model 2 plus smoking status, and drinking status , BMI group, glycosylated hemoglobin A1c (HbA1c), C-reactive protein (CRP), and depression status; the reference group was "Low PM2.5 and Low AIP".

Abbreviations:PM2.5: particulate matter with an aerodynamic diameter of 2.5 micrometers; AIP: Atherogenic Index of Plasma

Interaction between PM2.5 and AIP

After full adjustment for potential confounders, no statistically significant additive or multiplicative interaction was observed between PM_{2.5} and AIP with respect to the risk of advanced CKM (Table 3). Among additive interaction indices, the 95% confidence intervals (CIs) of relative excess risk due to interaction (RERI), attributable proportion (AP), and synergy index (SI) all included 0; the 95% CI of the multiplicative interaction odds ratio (OR) included 1. These results indicate that the effects of PM2.5 and AIP on advanced CKM are independent, without synergistic or antagonistic interactions. Consistent findings were observed in the unadjusted model and the model adjusted only for sociodemographic factors, further supporting the absence of statistically significant interaction effects.

Table 3 Interaction between PM2.5 and AIP on the risk of advanced CKM syndrome

				Model 1
Interactive indices	Model 1	Model 2	Model 3	
Additive effect				
RERI	-0.1 (-0.8-0.59)	-0.16 (-0.88-0.57)	-0.16 (-0.85-0.52)	
AP	-0.05 (-0.4-0.29)	-0.07 (-0.43-0.28)	-0.1 (-0.5-0.31)	
SI	0.91 (-0.21-2.02)	0.87 (-0.2-1.94)	0.81 (-0.43-2.04)	
Multiplicative effect	1.06 (0.79-1.42)	1.02 (0.76-1.37)	1.02 (0.74-1.42)	

(Unadjusted): No covariates were adjusted for; the reference group was "Low PM2.5 and Low AIP".

Model 2 (Sociodemographic and lifestyle-adjusted): Adjusted for Model 1 plus age, sex, residential area, marital status, education

level; the reference group was "Low PM2.5 and Low AIP".

Model 3 (Fully adjusted): Adjusted for Model 2 plus smoking status, and drinking status, BMI group, glycosylated hemoglobin A1c (HbA1c), C-reactive protein (CRP), and depression status; the reference group was "Low PM2.5 and Low AIP".

Abbreviations: AP: proportion attributable to interaction; PM2.5: particulate matter with an aerodynamic diameter of 2.5 micrometers; AIP: Atherogenic Index of Plasma; RERI: relative excess risk due to interaction; SI: synergy index

Subgroup analysis

Subgroup analyses assessed the association between PM_{2.5} and AIP co-exposure and advanced CKM risk across subgroups. Findings were consistent with the main results in most subgroups, with no significant heterogeneity (all P for interaction >0.05). The "High PM_{2.5} and Low AIP" combination showed no significant association with advanced CKM across the examined subgroups, further supporting the consistent association of high AIP with advanced CKM risk across these populations (Table 4).

Table 4 Subgroup analyses for the association of combined PM2.5 and AIP exposure with risk of advanced CKM syndrome

character	Low PM2.5 + Low AIP	Low PM2.5 + High AIP	p	High PM2.5 + High AIP	p	High PM2.5 + Low AIP	p
Sex							
			<0.000		<0.00		
Female	ref	2.19(1.56,3.09)	1	1.75(1.270,2.428)	1	0.84(0.615,1.165)	0.305
Male	ref	1.89(1.250,2.879)	0.003	1.53(1.047,2.244)	0.028	0.82(0.582,1.157)	0.262
Education							
Secondary							
school	ref	1.99(1.258,3.170)	0.003	1.54(1.002,2.374)	0.049	0.73(0.481,1.117)	0.148
College and above	ref	0.69(0.051, 8.859)	0.772	3.43(0.198,121.965)	0.424	0.91(0.073, 10.811)	0.941
Elementary							
school or below	ref	2.04(1.481,2.817)	1	1.67(1.243,2.254)	1	0.84(0.638,1.114)	0.232
Smoking							
			<0.000		<0.00		
Never smoke	ref	2.22(1.610,3.080)	1	1.76(1.300,2.394)	1	0.86(0.645,1.166)	0.344
Ever/current							
smoke	ref	1.76(1.121,2.782)	0.015	1.43(0.951,2.180)	0.085	0.77(0.532,1.134)	0.193

Residential_ar							
ea							
Urban	ref	1.69(1.074,2.669)	0.024	1.71(1.120,2.625)	0.013	0.82(0.547,1.250)	0.368
			<0.000				
Rural	ref	2.16(1.566,2.988)	1	1.49(1.108,2.017)	0.009	0.77(0.589,1.027)	0.076
BMI_group							
Normal(18.5			<0.000		<0.00		
to <25)	ref	2.50(1.798,3.503)	1	1.77(1.303,2.429)	1	0.91(0.688,1.204)	0.509
Overweight(2							
5 to <30)	ref	1.24(0.727,2.124)	0.423	1.09(0.665,1.787)	0.725	0.54(0.323,0.926)	0.025
Obese(30 or							
greater)	ref	0.69(0.151,2.943)	0.624	1.30(0.324,4.932)	0.695	0.34(0.078,1.407)	0.148
Underweight(							
<18.5)	ref	1.79(0.581,5.759)	0.314	0.74(0.202,2.715)	0.652	0.91(0.400,2.058)	0.813
Marital_statu							
s							
Married			<0.000		<0.00		
or living with							
a partner	ref	1.95(1.488,2.574)	1	1.56(1.218,2.022)	1	0.78(0.614,0.997)	0.047
Not_married	ref	2.94(1.211, 7.412)	0.019	2.23(0.920, 5.541)	0.079	1.00(0.470, 2.135)	0.993
Depression_2							
			<0.000				
depression	ref	2.47(1.642,3.738)	1	1.57(1.069,2.327)	0.022	0.84(0.580,1.204)	0.336
normal	ref	1.75(1.252,2.475)	0.001	1.64(1.202,2.246)	0.002	0.80(0.593,1.074)	0.137

Abbreviations:PM2.5: particulate matter with an aerodynamic diameter of 2.5 micrometers; AIP Atherogenic Index of Plasma;

Sensitivity analyses

Table 5 Several sensitivity analyses were conducted to assess the robustness of the main findings (Table 5). After redefining exposure by 75th percentile grouping, excluding potential outliers of PM2.5 or AIP, omitting individual covariates one by one, and replacing the original quasibinomial model with a binomial distribution model, the association between "High PM2.5 and High AIP" and CKM remained consistent with

the main analysis (all $P < 0.001$). The "Low PM2.5 and High AIP" group still showed a significant association ($P < 0.001$), while the "High PM2.5 and Low AIP" group had no significant association ($P = 0.072 \sim 0.11$), confirming that the core conclusions were not affected by exposure definition, outliers, covariate adjustment, or model settings. Sensitivity analyses are presented in Supplementary Tables S3–S6.

Table 5 S3: Logistic Regression Results (75th Percentile Grouping)

Exposure Group	OR (95% CI)	95% CI	p-value
pm25_aip_code_factor_75			
Low PM2.5 and Low AIP	—	—	
Low PM2.5 and High AIP	1.95	1.55, 2.45	<0.001
High PM2.5 and Low AIP	1.19	0.96, 1.48	0.11
High PM2.5 and High AIP	1.98	1.37, 2.90	<0.001

Abbreviations: CI = Confidence Interval, OR = Odds Ratio

PM2.5: particulate matter with an aerodynamic diameter of 2.5 micrometers; AIP: Atherogenic Index of Plasma

S4: Logistic Regression Results (Outlier Exclusion)

Exposure Group	OR (95% CI)	95% CI	p-value
pm25_aip_code_factor_en_original			
Low PM2.5 and Low AIP	—	—	
Low PM2.5 and High AIP	1.97	1.51, 2.57	<0.001
High PM2.5 and Low AIP	0.81	0.64, 1.02	0.076
High PM2.5 and High AIP	1.61	1.26, 2.05	<0.001

Abbreviations: CI = Confidence Interval, OR = Odds Ratio

PM2.5: particulate matter with an aerodynamic diameter of 2.5 micrometers; AIP: Atherogenic Index of Plasma

S5: OR for High PM2.5 and High AIP Group After Covariate Omission

Removed Covariate	OR	95% CI (Lower)	95% CI (Upper)
Original Model	1.60	1.25	2.05
Age	1.46	1.17	1.83
Sex	1.60	1.25	2.04
Marital_status	1.60	1.25	2.04
Education	1.60	1.25	2.04
Smoking	1.59	1.25	2.02
Drinking	1.60	1.26	2.05
BMI_group	1.99	1.59	2.49
Depression_2	1.56	1.23	1.99
HbA1c	1.73	1.36	2.20

Abbreviations: CI = Confidence Interval, OR = Odds Ratio

BMI: body mass index; HbA1c: Hemoglobin A1c; PM2.5: particulate matter with an aerodynamic diameter of 2.5 micrometers;

AIP: Atherogenic Index of Plasma; CRP: C-reactive protein; CKM: cardiovascular-kidney-metabolic syndrome

S6: Logistic Regression Results (Binomial Distribution; Original: Quasibinomial)

Exposure Group	OR (95% CI)	95% CI	p-value
pm25_aip_code_factor_en_origina			

Low PM2.5 and Low AIP	—	—	
Low PM2.5 and High AIP	2.00	1.54,2.59	<0.001
High PM2.5 and Low AIP	0.81	0.64,1.02	0.072
High PM2.5 and High AIP	1.60	1.26,2.04	<0.001

Abbreviations: CI = Confidence Interval, OR = Odds Ratio

Sensitivity analysis of the combined effect of the PM2.5 and AIP level on CKM risk. (S3) Logistic Regression Results (75th Percentile Grouping) (S4) Logistic Regression Results (Outlier Exclusion) (S5) OR for High PM2.5 and High AIP Group After Covariate Omission (S6) Logistic Regression Results (Binomial Distribution; Original: Quasibinomial)

Discussion

We observed that in a representative sample of 3902 individuals, high AIP was significantly associated with an elevated risk of advanced CKM, while PM_{2.5} alone shows no positive association. Combined exposure to elevated AIP and PM_{2.5} further increased the risk of this disease, whereas no significant interaction was observed between PM_{2.5} and AIP with respect to the risk of advanced CKM. In addition, both subgroup and sensitivity analyses consistently supported the primary study findings.

First, PM_{2.5} exposure alone was not significantly associated with advanced CKM, which differs from most studies focusing on early-stage cardiorenal diseases or single-organ disorders but aligns with the pathological characteristics of advanced multi-organ injury. Li et al.'s study based on the CHARLS cohort found a positive correlation between PM_{2.5} exposure and the incidence risk of CKM stages 0-3 (early to middle stages)[10], while this study focused on populations with advanced CKM (stages 3-4). The core difference lies in the irreversibility of target organ damage: patients with

advanced CKM already have definite clinical cardiovascular lesions (e.g., coronary heart disease, heart failure) or very high-risk chronic kidney disease. At this stage, AIP-mediated lipid metabolism disorders have become the core endogenous factor driving disease progression[37], and their pathological effects are far greater than the extrinsic damage caused by PM_{2.5}, leading to the "masking" of PM_{2.5}'s independent effect. Rajagopalan et al.'s study also confirmed that in populations with metabolic disorders (e.g., obesity, dyslipidemia), the contribution of environmental pollutants to cardiometabolic diseases is significantly lower than that of metabolic factors themselves[37], which is consistent with the "metabolism-dominated, pollution-superimposed" model in this study.

Second, potential differences in lifestyle and socioeconomic factors among the high PM_{2.5} exposure group may partially explain this negative association. On one hand, regions with high PM_{2.5} exposure (e.g., areas with an average concentration of 74 $\mu\text{g}/\text{m}^3$ in this study) are mostly industrialized or densely populated areas, where residents may significantly reduce outdoor activities and extend indoor time due to frequent smog[38]. Sufficient indoor rest can reduce cardiac load caused by excessive physical activity and avoid superimposed exposure to other outdoor pollutants (e.g., traffic exhaust, industrial waste gas), indirectly lowering the risk of cardiorenal injury[39]. This finding may partly reflect residual confounding related to socioeconomic characteristics, exposure patterns, or unmeasured behavioral factors. On the other hand, regions with high PM_{2.5} exposure are often accompanied by higher urbanization and economic development levels[4]. Residents in these areas generally

have better economic conditions, enabling them to access higher-quality medical resources (e.g., regular cardiorenal function monitoring, timely intervention for metabolic abnormalities) and possess stronger health awareness (e.g., adherence to medication, dietary control)[40]. These "health advantages" brought by socioeconomic factors may further weaken the independent association of PM2.5, resulting in a slight negative correlation in statistics. Opejin et al.'s 2024 study also pointed out that ignoring confounding factors such as indoor-outdoor exposure differences and socioeconomic status may lead to misjudgment of the association between PM2.5 and diseases[38], providing a supplementary explanation for the results of this study.

Mechanistically, the effects of high AIP and PM2.5 on advanced CKM are mediated through parallel pathways without synergistic or antagonistic interactions, a pattern consistent with the latest research consensus on metabolic-environmental interactions[41]. As a core indicator reflecting the balance between triglycerides and high-density lipoprotein cholesterol, elevated AIP promotes atherosclerotic plaque formation by activating the NLRP3 inflammasome pathway (mediated by lipid metabolic disorders) and exacerbates renal microvascular endothelial injury by impairing the activity of endothelial nitric oxide synthase (eNOS) and reducing nitric oxide (NO) bioavailability.[42-44], a process highly consistent with the core pathological axis of "lipid deposition-inflammation activation-target organ damage" in advanced CKM[45]. In contrast, PM2.5 exposure has been reported to induce systemic oxidative stress through inhalation, and the polycyclic aromatic hydrocarbons, heavy metals and other components it carries can induce chronic inflammation via the

TLR4/NF- κ B pathway[46]. However, in individuals with advanced CKM, AIP-related metabolic abnormalities may represent an important pathway associated with advanced CKM progression, and the additive effect of environmental pollutants is relatively limited, which explains the non-significant independent effect of PM_{2.5}. [47, 48]

The clinical and public health value of this study lies in the operability of precise prevention and control. Clinically, AIP detection is convenient and low-cost, requiring no complex equipment, and can be quickly integrated into the CKM risk screening process for middle-aged and older adults, especially suitable for primary medical institutions. For high-AIP individuals with baseline CKM stage 2, targeted intensification of lipid metabolism intervention (such as lifestyle modification combined with individualized statin therapy) may help reduce the likelihood of progression to advanced stages[47, 49]. The "metabolic-environmental" dual-dimensional risk stratification system constructed by combining regional PM_{2.5} monitoring data may complement existing CKM risk assessment by incorporating environmental exposure information[36], providing a new tool for clinical development of individualized prevention and control plans. At the public health level, promoting interventions such as clean fuel replacement and indoor air purification for high-AIP populations in high-pollution regions of northern China can form a synergistic effect with metabolic interventions, potentially contributing to reductions in the population burden of advanced CKM[40]. Considering that the prevalence of advanced CKM in Chinese middle-aged and older adults is significantly higher than that in Western populations[1, 50], and they face the dual pressure of metabolic disorders and

environmental exposure, the "dual-target strategy" proposed in this study has clear population applicability and public health priority.

Several limitations should be acknowledged. First, as a prospective cohort study, although we adjusted for multiple covariates, including sociodemographic factors, lifestyle factors, and clinical biochemical indicators, residual confounding from unmeasured factors (e.g., dietary patterns, physical activity intensity, and genetic susceptibility loci) may still exist, limiting the ability to draw definitive causal inferences, which is an inherent limitation of observational studies[51]; second, PM_{2.5} exposure was estimated based on baseline regional monitoring data and may not fully capture individual-level dynamic exposure variations, such as residential mobility and differences in indoor protective behaviors, potentially leading to exposure misclassification. Future studies incorporating personal exposure monitoring approaches, such as wearable monitoring devices, may improve exposure assessment accuracy[38]; third, AIP categorization was based on the cohort median rather than established China-specific clinical thresholds, which may limit direct clinical interpretation. Future outcome-oriented multicenter studies are needed to determine clinically meaningful cut-off values[52]; fourth, the study population was limited to middle-aged and older Chinese adults, and the generalizability of our findings to younger populations or other ethnic groups requires further validation. Finally, CKM staging was derived from available clinical and questionnaire-based information in CHARLS, and potential misclassification of disease stages cannot be completely excluded.

Future research should focus on addressing existing limitations and deepening mechanistic analysis. It is recommended to adopt a Mendelian randomization design to clarify the causal effects of PM_{2.5} and AIP on advanced CKM, avoiding residual confounding[53]; combine multi-omics technologies such as metabolomics and transcriptomics to explore key pathways co-regulated by the two (such as the lipid metabolism-oxidative stress cross pathway)[54]; conduct intervention studies based on clinical thresholds of AIP to verify its practical value in CKM risk stratification; simultaneously expand to different CKM subtypes (such as ischemic heart disease-dominant and chronic kidney disease-dominant) to explore subtype-specific "environmental-metabolic" interaction modes[39, 55]. In addition, for comorbid populations of CKM and metabolic-associated steatotic liver disease (MASLD), the risk superposition effect of dual factors can be further revealed to provide new perspectives for comorbidity management.

Conclusion

In summary, this nationally representative cohort study demonstrated that elevated AIP was strongly associated with an increased risk of advanced CKM, whereas PM_{2.5} exposure alone was not independently associated with advanced CKM. Although individuals with concomitantly high AIP and PM_{2.5} exposure showed a higher prevalence of advanced CKM, no statistically significant interaction was observed between the two factors. These findings suggest that AIP may represent an important metabolic marker associated with advanced CKM risk, while the association between PM_{2.5} exposure and advanced CKM may be more complex and potentially influenced

by exposure patterns and other contextual factors. Further studies are warranted to clarify the underlying mechanisms and causal relationships between these exposures and CKM progression.

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Abbreviations

AIP:

Atherogenic Index of Plasma

BMI

Body mass index

CHARLS

China Health and Retirement Longitudinal Study

CI

Confidence interval

CKM:

Cardiovascular-Kidney-Metabolic syndrome

CRP

C-reactive protein

CVD

Cardiovascular diseases

HbA1c

Glycosylated hemoglobin A1c

PM2.5

particulate matter with an aerodynamic diameter of 2.5 micrometers

RERI

Relative excess risk due to interaction

SBP

Systolic blood pressure

SD

Standard deviation

SI

Synergy index

Author contributions

Yijie Lin QianLv: investigation, writing-original draft, methodology, writing-review and editing.

Xiaofeng Zhang Weili Li: writing-review, editing, investigation, and formal analysis.

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Clinical Trial Registration

Not applicable

Availability of data and materials

The datasets analyzed during the current study are available from the China Health and Retirement Longitudinal Study (CHARLS) repository (<http://charls.pku.edu.cn/>) upon reasonable request and with permission from the CHARLS project team. The PM_{2.5} exposure data used in this study were obtained from satellite-based environmental monitoring datasets and linked to CHARLS participants according to residential geographic information. Due to data access policies of the CHARLS project and restrictions on participant confidentiality, the individual-level datasets are not publicly available from the authors but can be obtained through application to the CHARLS research team.

Declarations

Competing interests

The authors declare that there are no competing conflicts of interest.

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