

Associations of average sleep duration and cumulative AIP with cardiometabolic multimorbidity risk in middle-aged and older Chinese adults: a CHARLS longitudinal study

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Abstract

Objective

To investigate the relationship between the Atherogenic Index of Plasma (AIP) and sleep duration on the risk of developing cardiometabolic multimorbidity (CMM) in middle-aged and older Chinese adults, we utilized data from the China Health and Retirement Longitudinal Study (CHARLS).

Methods

Middle-aged and older participants without chronic metabolic diseases (CMM) at baseline were selected from the CHARLS database. Both the atherogenic index of plasma (AIP) and sleep duration were categorized into four distinct groups, resulting in 16 combined subgroups. Utilizing the group with the lowest AIP and average sleep duration as the reference, multivariable Cox regression models were employed to investigate the associations between average sleep duration, cumulative average AIP, and the incidence of CMM.

Results

A total of 3,422 participants was included in the study, of whom 520 (15.20%) developed new-onset CMM. Multivariable Cox regression analysis indicated that, after full adjustment for age, sex, residence, marital status, education, smoking, drinking, hypertension, and dyslipidemia, each 1-unit increase in cumulative average sleep duration was associated with a 9.1% reduction in the risk of CMM (HR = 0.909, 95% CI: 0.857–0.964, $P = 0.001$). In contrast, each 1-unit increase in cumulative average AIP corresponded to a 68.1% increase in risk (HR = 1.681, 95% CI: 1.236–2.286, $P < 0.001$). Interaction subgroup analyses revealed that longer sleep duration significantly decreased CMM risk only among individuals with low AIP levels, with the most pronounced protective effect observed in the sleep-Q3 combined with AIP-Q1 subgroup (HR = 0.538, 95% CI: 0.336–0.862).

Conclusion

Cumulative average sleep duration and AIP serve as independent determinants of new-onset CMM in middle-aged and older populations, operating through distinct pathogenic pathways. A joint assessment of these factors may improve risk prediction. In individuals with a lower atherosclerotic burden, adequate sleep provides additional cardiovascular benefits, indicating that clinical prevention strategies should encompass both lipid metabolism and sleep health management.

1 Introduction

Cardiometabolic multimorbidity (CMM) is defined as the coexistence of two or more cardiometabolic conditions, including diabetes, ischemic stroke, and heart disease^[1]. In China, around 22.0% of middle-aged and elderly individuals are impacted by CMM, with rates rising significantly from 20.6% in the 45–55 age group to 42.7% in those aged 65 and older^[2]. The prevalence further increases to 51.8% among individuals aged 75 and above^[3]. These figures underscore a pressing and escalating public health concern. CMM is not merely a summation of coexisting diseases; it constitutes a complex syndrome driven by interconnected pathophysiological pathways, including insulin resistance, chronic low-grade inflammation, oxidative stress, and endothelial dysfunction^[4, 5]. The burden of CMM varies significantly by sex and region, with higher prevalence rates observed in women and a notable provincial disparity ranging from 10.2% to 47.9%^[6]. Compared to single cardiometabolic conditions, CMM substantially increases all-cause mortality, cardiovascular events, and functional decline, while imposing exponentially greater demands on healthcare systems^[7]. Consequently, identifying modifiable risk factors for CMM and implementing early interventions is essential for reducing disease burden and enhancing healthy life expectancy in China's aging population.

Although smoking cessation, moderate alcohol consumption, a balanced diet, and regular physical activity are well-established protective measures against cardiovascular disease^[8], sleep health has only recently been acknowledged as a critical determinant of metabolic and cardiovascular well-being^[9]. In addition to its restorative function, sleep is essential for regulating glucose and lipid metabolism, inflammatory responses, and autonomic balance. Evidence from the China Health and Retirement Longitudinal Study (CHARLS) has demonstrated longitudinal associations between sleep duration and blood lipid profiles. In particular, sleep duration was associated with HDL-C over time, while triglyceride levels were associated with subsequent sleep duration, suggesting a potentially bidirectional relationship between sleep and lipid metabolism among middle-aged and older Chinese adults^[10]. This evolving understanding is evident in the 2022 update of the American Heart Association's "Life's Essential 8," which formally incorporates sleep duration as a core cardiovascular health metric alongside diet, physical activity, and smoking^[11].

The Atherogenic Index of Plasma (AIP), introduced by Dobiášová and Frohlich in 2001^[12], serves as a composite marker for lipid-related atherogenic risk. It is calculated as the log-transformed molar ratio of triglycerides to high-density lipoprotein cholesterol^[13], providing a practical alternative to complex lipoprotein subfraction profiling. AIP exhibits a strong correlation with small dense low-density lipoprotein cholesterol^[14] and has undergone extensive validation for risk stratification in atherosclerosis, coronary heart disease, ischemic stroke, and metabolic syndrome^[15–18]. Recent longitudinal studies indicate that single baseline AIP values may underestimate cumulative lipid burden. For example, the English Longitudinal Study of Ageing found that a persistently high AIP trajectory over 12 years was associated with a 33% increased risk of cardiovascular disease (HR = 1.33, 95% CI: 1.02–1.74) compared to a low-stable trajectory^[19]. Similar findings associate cumulative AIP exposure with ischemic stroke risk^[20], suggesting that sustained elevated AIP levels may significantly drive the

progression of cardiometabolic diseases. Accumulating evidence suggests that sleep and atherogenic lipid abnormalities may represent complementary pathways linking lifestyle-related exposures to cardiometabolic multimorbidity. Inadequate sleep can adversely affect glucose homeostasis, autonomic nervous system activity, hypothalamic–pituitary–adrenal axis function, and systemic inflammation, thereby promoting insulin resistance and endothelial dysfunction^[21, 22]. In parallel, an elevated AIP, which integrates circulating triglyceride and high-density lipoprotein cholesterol concentrations, reflects an atherogenic metabolic profile and is related to lipoprotein particle size and cholesterol esterification. More recent longitudinal evidence and meta-analyses have further demonstrated positive associations between elevated AIP and cardiovascular events, cardiovascular mortality, and cardiometabolic multimorbidity^[23–25].

Both AIP and sleep are essential components of the AHA's Life's Essential 8 framework and are interconnected in their influence on cardiometabolic homeostasis. Mechanistically, short sleep duration (less than 6 hours per day) activates the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system, leading to increased release of cortisol and catecholamines. This hormonal response contributes to insulin resistance, glucose intolerance, and dyslipidemia^[26]. Sleep restriction elevates pro-inflammatory markers, including interleukin-6 and C-reactive protein, thereby exacerbating low-grade systemic inflammation. Short sleep duration is linked to increased risks of hypertension and heart failure, while both short and long sleep durations are associated with atrial fibrillation and coronary heart disease. The effects of long sleep are partially confounded by factors such as depression, medication use, sedentary behavior, and socioeconomic status^[27, 28]. A meta-analysis estimated that individuals who sleep less than 6 hours per day face 48% and 15% higher risks of coronary heart disease and stroke, respectively, whereas those who sleep more than 9 hours per day face 38% and 65% higher risks^[29]. Additionally, data from the China Health and Retirement Longitudinal Study (CHARLS) indicate a synergistic interaction: metabolic syndrome in conjunction with short sleep is associated with a 3.73-fold increase in cardiovascular risk (95% CI: 2.95–4.71)^[30].

Importantly, the relationship between sleep and cardiometabolic health may not be adequately characterized by sleep duration alone. The American Heart Association incorporated sleep duration into the Life's Essential 8 framework in 2022, recognizing sleep as a core component of cardiovascular health^[31]. More recently, the AHA emphasized that sleep health is multidimensional, encompassing duration, continuity, timing, regularity, daytime functioning, sleep architecture, and the absence of sleep disorders^[32]. Nevertheless, sleep duration remains one of the most consistently available longitudinal sleep indicators in large population-based cohorts such as CHARLS. Therefore, evaluating cumulative average sleep duration may offer a more robust assessment of habitual sleep exposure over time compared with a single baseline measure, as it accounts for within-person variability and attenuates random variation. Consistent with this perspective, a large longitudinal study based on CHARLS identified distinct sleep-duration trajectories and found that a persistently short sleep pattern was associated with increased risks of stroke, dyslipidemia, and diabetes among middle-aged and older Chinese adults^[33]. More recently, a 10-year prospective cohort study further reported associations

between sleep duration and long-term changes in several anthropometric and atherogenic indices, suggesting that habitual sleep duration may also be related to long-term metabolic and atherogenic profiles^[34]. Nevertheless, evidence integrating longitudinal sleep exposure with cumulative atherogenic lipid burden remains limited. Existing studies have primarily examined sleep trajectories in relation to individual cardiometabolic diseases or sleep duration in relation to selected lipid and atherogenic indices. Whether cumulative sleep exposure and cumulative AIP burden jointly contribute to the development of cardiometabolic multimorbidity remains insufficiently understood, particularly among middle-aged and older Chinese adults. Therefore, using longitudinal CHARLS data, the present study aimed to investigate the independent and joint associations of cumulative average sleep duration and cumulative average AIP with incident CMM.

CHARLS is a nationally representative longitudinal cohort study conducted by Peking University, encompassing 150 counties across 28 provinces in China. Since its baseline in 2011, biennial follow-ups have been performed through at least five waves, yielding robust data for the investigation of long-term exposures and chronic disease outcomes^[35]. Utilizing CHARLS data, the present study seeks to prospectively assess the independent and interactive effects of cumulative AIP exposure and longitudinal sleep duration patterns on the incidence of CMM. This research aims to enhance early risk identification, stratification, and targeted prevention strategies for CMM among middle-aged and older Chinese adults.

2 Methods

2.1 Study Population

Data were obtained from the CHARLS, a nationally representative longitudinal cohort study. Blood samples were collected during the 2011 and 2015 survey waves. For the current analysis, we integrated data from three survey waves (2011, 2013, and 2015) and utilized the 2018 wave as the follow-up endpoint to identify incident cases of CMM. Participants were included if they met the following criteria: (i) aged ≥ 45 years; (ii) had complete data on AIP and sleep duration throughout the 2011–2015 period and were free of CMM at baseline; (iii) had no missing data on key demographic variables (sex, age, education, residence, and marital status); and (iv) were not lost to follow-up between 2011 and 2015. The participant flow diagram is illustrated in Fig. 1.

2.2 Measurements

2.2.1 Demographic and Clinical Characteristics

Structured questionnaires were utilized to gather data on demographic characteristics, including sex, age, marital status, education, and residence. Additionally, information was collected regarding lifestyle behaviors such as smoking and alcohol consumption, medical history encompassing hypertension and dyslipidemia, and the use of medications, specifically lipid-lowering and antihypertensive agents.

Smoking status was categorized into three groups: never, former, and current. This classification was based on responses to two questions: (1) "Have you ever smoked?" and (2) "Do you currently smoke?" Similarly, alcohol consumption was classified into three categories: never, former, and current, based on responses to the following questions: (1) "Have you ever consumed alcohol?" and (2) "Have you consumed alcohol in the past year?" Blood samples were collected by trained personnel from the Chinese Center for Disease Control and Prevention (CDC), then centrifuged and stored at -20°C in local CDC laboratories. The samples were transported to the Beijing CDC within two weeks and subsequently stored at -80°C . Laboratory testing was conducted at the You'anmen Clinical Laboratory Center of Capital Medical University.

2.2.2 Cumulative Average AIP

The AIP was calculated as: $\text{AIP} = \log_{10}(\text{TG}/\text{HDL-C})^{[13]}$, where TG and HDL-C are expressed in mg/dL. Cumulative average AIP was computed as: $(\text{AIP_Wave1} + \text{AIP_Wave3}) / 2 \times (2015 - 2012)$. Participants were then divided into quartiles: Q1 (≤ 0.140), Q2 ($0.140-0.326$), Q3 ($0.326-0.545$), and Q4 (≥ 0.545).

2.2.3 Sleep Duration

Cumulative average sleep duration was calculated as the mean of self-reported sleep duration across Waves 1, 2, and 3. Participants were divided into quartiles: Q1 (≤ 5.5 h), Q2 ($5.5-6.5$ h), Q3 ($6.5-7.3$ h), and Q4 (≥ 7.3 h).

2.2.4 Cardiometabolic Multimorbidity (CMM)

CMM was defined as the coexistence of at least two of the following three conditions: Heart disease: assessed by asking, "Have you ever been diagnosed by a doctor with coronary heart disease, arrhythmia, heart failure, or other heart diseases?" and "Are you currently receiving any treatment (Chinese medicine/Western medicine/other/none) for heart disease?" Stroke: assessed by asking, "Have you ever been diagnosed by a doctor with stroke?" and "Are you currently receiving any treatment (Chinese medicine/Western medicine/other/none) for stroke?" Diabetes: assessed by asking, "Have you ever been diagnosed by a doctor with diabetes?" and "Are you currently receiving any treatment (Chinese medicine/Western medicine/other/none) for diabetes?"

2.3 Statistical Analysis

All statistical analyses were performed using R version 4.5.0. Baseline characteristics and between-group comparisons were conducted on the original dataset. Continuous variables are presented as mean $\pm$ standard deviation (SD) and were compared using one-way analysis of variance (ANOVA). Cox proportional hazards regression models were used to estimate the association between cumulative AIP and incident CMM, with effect sizes expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). The observation period began at baseline and ended at the Wave 4 survey or the occurrence of incident CMM, whichever came first. A total of 520 incident CMM cases were recorded. Subgroup analyses were performed stratified by age (45–60, 60–75, and ≥ 75 years), sex, smoking status (never, former, current), alcohol consumption (never, former, current), dyslipidemia, and hypertension.

Interaction effects were assessed using likelihood ratio tests. A two-sided $P < 0.05$ was considered statistically significant.

3 Results

3.1 Baseline Characteristics

A total of 3,422 participants were included in the final analysis. During follow-up, 520 incident CMM cases were identified, yielding an incidence density of 15.20%. The majority of participants had primary education or below, and approximately 85% were married. Between-group comparisons revealed statistically significant differences in age, sex, education, alcohol consumption, hypertension, dyslipidemia, and sleep duration across AIP quartiles (all $P < 0.05$), while smoking status ($P = 0.2$) and marital status ($P = 0.6$) did not differ significantly. The prevalence of hypertension and dyslipidemia increased progressively with higher AIP levels (both P for trend < 0.001). When stratified by sleep duration quartiles, significant differences were also observed in age, sex, education, smoking, alcohol consumption, hypertension, dyslipidemia, and AIP (all $P < 0.05$). These findings indicate baseline imbalance across exposure groups, therefore, all subsequent regression analyses were adjusted for these confounding factors.

3.2 Joint Effects of Cumulative Average AIP and Sleep Duration on CMM

To visually present the joint effects of cumulative average AIP and sleep duration on CMM, we constructed a heatmap of HRs for 16 subgroups using multivariable Cox regression models, with the AIP-Q1 and sleep-Q1 group as the reference ($HR = 1$). The heatmap is presented in Fig. 2. At the lowest AIP level (Q1), CMM risk decreased significantly with increasing sleep duration, with sleep-Q3 ($HR = 0.45$, $P < 0.05$) and sleep-Q4 ($HR = 0.49$, $P < 0.05$) showing significant protective effects. Within the AIP-Q2 stratum, sleep-Q2 ($HR = 0.49$, $P < 0.05$) and sleep-Q3 ($HR = 0.56$, $P < 0.05$) also exhibited significant protective effects. However, when AIP levels rose to Q3 and Q4, all HRs approached 1.0 (range: 0.74–1.10) and none reached statistical significance.

3.3 Survival Curves and Log-rank Tests

3.3.1 Survival Differences by Cumulative Average Sleep Quartiles

Kaplan–Meier curves were plotted to compare CMM-free survival across cumulative average sleep quartiles, with differences assessed by Log-rank tests. The Log-rank test showed significant differences in survival distributions across the four groups ($\chi^2 = 18.6$, $P = 0.00033$). The survival curves (Fig. 3) demonstrated that the sleep-Q1 group (shortest sleep) consistently had the lowest survival probability throughout follow-up, while the sleep-Q3 and Q4 groups maintained higher survival probabilities.

3.3.2 Survival Differences by Cumulative Average AIP Quartiles

Similarly, survival differences across cumulative average AIP quartiles were assessed using Kaplan–Meier curves and Log-rank tests. The Log-rank test indicated highly significant differences across the four groups ($\chi^2 = 26.1$, $P < 0.0001$). The survival curves (Fig. 4) showed a stepwise decline in survival probability with increasing AIP levels, with the AIP-Q4 group consistently exhibiting the lowest survival probability and the AIP-Q1 group maintaining the highest, confirming a dose–response relationship between cumulative average AIP and CMM risk.

3.3.3 Combined Effects of Cumulative Average AIP and Sleep on CMM

To further investigate the joint association of sleep duration and AIP with CMM risk, participants were cross-classified into 16 subgroups according to cumulative average sleep duration quartiles and cumulative average AIP quartiles, followed by the generation of Kaplan–Meier survival curves (Fig. 5). The Log-rank test demonstrated significant differences in survival distributions across the 16 groups ($P < 0.0001$). The survival curves showed clear clustering patterns: participants in the AIP-Q1 combined with sleep-Q3/Q4 groups maintained the highest survival probabilities throughout follow-up, while those in the AIP-Q4 combined with sleep-Q1 group experienced the steepest decline in survival.

3.4 Cox Regression Analysis

3.4.1 Sleep and AIP as Continuous Variables

To quantify the independent effects of cumulative average sleep duration and cumulative average AIP on CMM incidence, we constructed three progressively adjusted Cox proportional hazards regression models, as shown in Table 2. Model 1 (unadjusted) : Each 1-hour increase in cumulative sleep was associated with a 10.1% reduction in CMM risk (HR = 0.899, 95% CI: 0.848–0.953, $P < 0.001$). Model 2 (adjusted for age, residence, marital status, and education) and Model 3 (further adjusted for smoking, alcohol consumption, hypertension, and dyslipidemia) yielded HRs of 0.909 (95% CI: 0.857–0.963, $P = 0.001$) and 0.909 (95% CI: 0.857–0.964, $P = 0.001$), respectively, indicating stable effects. For AIP, each 1-unit increase in cumulative average AIP was associated with a 108.1% increase in CMM risk in Model 1 (HR = 2.081, 95% CI: 1.548–2.797, $P < 0.001$). The HR increased to 2.164 (95% CI: 1.612–2.906, $P < 0.001$) in Model 2 and was 1.681 (95% CI: 1.236–2.286, $P < 0.001$) in Model 3.

Table 1
Baseline characteristics of participants stratified by AIP and sleep duration

Characteristic	Overall N = 3,422 ¹	Q1 N = 856 ¹	Q2 N = 855 ¹	Q3 N = 855 ¹	Q4 N = 856 ¹	P
Age						0.009
45–60	1,547 (45%)	346 (40%)	379 (44%)	410 (48%)	412 (48%)	
60–75	1,616 (47%)	443 (52%)	402 (47%)	381 (45%)	390 (46%)	
≥ 75	259 (7.6%)	67 (7.8%)	74 (8.7%)	64 (7.5%)	54 (6.3%)	
Gender						< 0.001
Female	1,797 (53%)	396 (46%)	472 (55%)	457 (53%)	472 (55%)	
Male	1,625 (47%)	460 (54%)	383 (45%)	398 (47%)	384 (45%)	
Education						0.027
College or above	82 (2.4%)	18 (2.1%)	19 (2.2%)	19 (2.2%)	26 (3.0%)	
Elementary school or below	2,329 (68%)	601 (70%)	612 (72%)	556 (65%)	560 (65%)	
Middle school	1,011 (30%)	237 (28%)	224 (26%)	280 (33%)	270 (32%)	
Smoke						0.2
Current Smoker	1,001 (29%)	271 (32%)	237 (28%)	248 (29%)	245 (29%)	
Former Smoker	494 (14%)	137 (16%)	114 (13%)	116 (14%)	127 (15%)	
Never Smoked	1,927 (56%)	448 (52%)	504 (59%)	491 (57%)	484 (57%)	
Drink						< 0.001
Current Drinker	1,246 (36%)	370 (43%)	311 (36%)	291 (34%)	274 (32%)	
Former Drinker	362 (11%)	80 (9.3%)	95 (11%)	104 (12%)	83 (9.7%)	
Note Q1, Q2, Q3, and Q4: number of subjects remaining after each quartile of the atherogenic index of plasma (AIP); no subjects remain after Q4.						

Characteristic	Overall	Q1	Q2	Q3	Q4	P
	N = 3,422 ¹	N = 856 ¹	N = 855 ¹	N = 855 ¹	N = 856 ¹	
Never Drinker	1,814 (53%)	406 (47%)	449 (53%)	460 (54%)	499 (58%)	
Marriage						0.6
No	529 (15%)	135 (16%)	141 (16%)	133 (16%)	120 (14%)	
Yes	2,893 (85%)	721 (84%)	714 (84%)	722 (84%)	736 (86%)	
Hypertension						< 0.001
No	2,558 (75%)	706 (82%)	661 (77%)	628 (73%)	563 (66%)	
Yes	864 (25%)	150 (18%)	194 (23%)	227 (27%)	293 (34%)	
Dyslipidemia						< 0.001
No	3,095 (90%)	821 (96%)	795 (93%)	745 (87%)	734 (86%)	
Yes	327 (9.6%)	35 (4.1%)	60 (7.0%)	110 (13%)	122 (14%)	
cumavsleep						0.3
≤ 5.5h	873 (26%)	225 (26%)	230 (27%)	233 (27%)	185 (22%)	
5.5-6.5h	853 (25%)	214 (25%)	213 (25%)	210 (25%)	216 (25%)	
6.5-7.3h	914 (27%)	226 (26%)	230 (27%)	218 (25%)	240 (28%)	
≥ 7.3h	782 (23%)	191 (22%)	182 (21%)	194 (23%)	215 (25%)	
CMM						< 0.001
No	2,902 (85%)	760 (89%)	744 (87%)	708 (83%)	690 (81%)	
Yes	520 (15%)	96 (11%)	111 (13%)	147 (17%)	166 (19%)	
Note Q1, Q2, Q3, and Q4: number of subjects remaining after each quartile of the atherogenic index of plasma (AIP); no subjects remain after Q4.						

Table 2

Joint Cox regression analysis of cumulative average sleep duration and cumulative average AIP with CMM risk

Variable	Model 1 (Unadjusted)	Model 2 (Adjusted for demographics)	Model 3 (Adjusted)
Cumulative mean sleep duration (continuous variable)	HR = 0.899 (0.848 ~ 0.953), $P < 0.001$	HR = 0.909 (0.857 ~ 0.963), $P = 0.001$	HR = 0.909 (0.857 ~ 0.964), $P = 0.001$
Cumulative average AIP (continuous variable)	HR = 2.081 (1.548 ~ 2.797), $P < 0.001$	HR = 2.164 (1.612 ~ 2.906), $P < 0.001$	HR = 1.681 (1.236 ~ 2.286), $P < 0.001$
Note HRs and 95% CIs were estimated using Cox proportional hazards regression models. Model 1: unadjusted model; Model 2: adjusted for demographic characteristics; Model 3: fully adjusted model. Cumulative average sleep duration and AIP were entered as continuous variables. CMM, cardiometabolic multimorbidity; AIP, Atherogenic Index of Plasma; HR, hazard ratio; CI, confidence interval.			

3.4.2 Joint Cox Regression Analysis of Sleep and AIP

When cumulative sleep and cumulative AIP were simultaneously included in the Cox regression model with mutual adjustment (Table 2), the fully adjusted HR for sleep was 0.909 (95% CI: 0.857–0.964, $P = 0.001$) and for AIP was 1.681 (95% CI: 1.236–2.286, $P < 0.001$), consistent with the estimates from separate models. This confirms the absence of antagonistic or mediating effects between the two factors, indicating that both are independent determinants of CMM incidence. The protective effect of sleep on CMM does not appear to operate through the AIP pathway, and the AIP-associated CMM risk is not significantly modified by sleep status.

3.5 Subgroup Analyses and Interaction Effects

3.5.1 Identification of Protective Subgroups

Using the 16 sleep–AIP interaction subgroups in multivariable Cox regression analysis (with sleep-Q1 and AIP-Q1 as reference, adjusted for all covariates), we identified subgroups with $HR < 1$ and $P < 0.05$. Significant protective effects of longer sleep duration were observed exclusively among participants in the lowest AIP quartile (Q1). Specifically, the sleep-Q3 & AIP-Q1 (HR = 0.538, 95% CI: 0.336–0.862, $P = 0.010$), sleep-Q2 & AIP-Q1 (HR = 0.581, 95% CI: 0.371–0.910, $P = 0.018$), and sleep-Q4 & AIP-Q1 (HR = 0.595, 95% CI: 0.366–0.967, $P = 0.036$) subgroups all showed significantly reduced CMM risk, with the sleep-Q3 (6.5–7.3 h) combined with AIP-Q1 exhibiting the strongest protective effect.

3.5.2 Interaction Testing

To assess whether sleep and AIP exert synergistic or antagonistic effects, a sleep $\times$ AIP product interaction term was introduced into the Cox regression model. The likelihood ratio test showed no significant improvement in model fit after including the interaction term ($P = 0.165$), and the interaction

coefficient did not reach statistical significance. Stratified analyses further revealed heterogeneity in the sleep effect across AIP strata, but no consistent statistical interaction was identified.

3.6 Model Predictive Performance

Time-dependent ROC analysis (Fig. 6) showed that the basic confounding model (adjusted for age, sex, residence, marital status, education, smoking, alcohol consumption, hypertension, and dyslipidemia) achieved an AUC of 0.641. Adding cumulative average sleep and cumulative average AIP sequentially improved the AUC, with the joint model reaching 0.659 ($P = 0.045$ vs. basic model). Similarly, the C-index increased from 0.6232 in the basic model to 0.6284 after adding sleep, 0.6365 after adding AIP, and reached 0.6432 in the fully adjusted joint model (Table 3).

Table 3
ANOVA likelihood ratio test results and C-index for each model

Model	Sleep duration c^2	Sleep duration P value	AIP c^2	AIPP value	C_index
basic confounding model					0.6232
sleep duration categories added	14.4917	0.0023			0.6284
AIP categories added			14.3781	0.0024	0.6365
combined sleep duration and AIP categories	14.5648	0.0022	14.4509	0.0024	0.6432
Note Likelihood ratio tests were performed to evaluate the incremental contribution of sleep duration categories and the Atherogenic Index of Plasma (AIP) categories to the prediction model. c^2 statistics and corresponding P values represent the improvement in model fit after adding each variable. The C-index indicates the discriminatory ability of each model, with higher values representing better predictive performance. The basic confounding model was adjusted for baseline covariates. Sleep duration categories and AIP categories were sequentially added to assess their independent and combined predictive effects on cardiometabolic multimorbidity (CMM) risk.					

4 Discussion

This study utilized the CHARLS database to analyze 3,422 middle-aged and older adults (≥ 45 years) in order to investigate the associations between cumulative average sleep duration, cumulative average AIP, and the risk of incident CMM. These findings indicate that each 1-hour increase in cumulative average sleep duration correlates with a 9.1% reduction in CMM risk (HR = 0.909, 95% CI: 0.857–0.964). Conversely, each 1-unit increase in cumulative average AIP is associated with a 68.1% increase in CMM risk (HR = 1.681, 95% CI: 1.236–2.286). Although no significant statistical interaction was detected, the joint model enhanced the C-index from 0.6232 to 0.6432. Importantly, the protective effect of sleep was predominantly observed in participants within the lowest AIP quartile, with minimal to no protective effect noted at higher AIP levels. This finding that cumulative average AIP serves as a risk factor for

CMM is consistent with previous studies^[36–38]. Additionally, data from the Korea National Health and Nutrition Examination Survey indicated a correlation between obstructive sleep apnea risk and elevated AIP, particularly among individuals with diabetes^[39]. The proportional hazards assumption was satisfied for both sleep ($P = 0.216$) and AIP ($P = 0.378$), thereby reinforcing the robustness of the model. By capturing long-term exposure to atherogenic lipid profiles, cumulative average AIP may provide a more accurate assessment of the impact of chronic lipid abnormalities on CMM risk than a single baseline measurement.

The present findings are also supported by emerging evidence linking AIP to multimorbidity rather than isolated cardiovascular outcomes. A recent nationwide prospective cohort study based on CHARLS demonstrated that higher AIP was associated with progressively greater risks of single, dual, and triple cardio-renal-metabolic multimorbidity. Each 1-standard-deviation increase in AIP was associated with 17%, 31%, and 57% higher risks of single, dual, and triple CRM disease, respectively, and higher AIP also predicted transitions from single to dual and from dual to triple disease states^[23]. These findings suggest that AIP may reflect a broader systemic metabolic vulnerability rather than merely an isolated marker of coronary atherosclerosis. In parallel, a 2026 dose–response meta-analysis of 24 cohort studies reported linear associations between AIP and both cardiovascular morbidity and mortality, further supporting the epidemiological relevance of sustained AIP elevation^[24]. Another meta-analysis of longitudinal studies likewise found higher AIP to be associated with major adverse cardiovascular events, coronary heart disease, and cardiovascular mortality^[25]. Collectively, these studies strengthen the interpretation of the findings and suggest that cumulative AIP may be informative for identifying individuals exposed to a persistent adverse lipid-metabolic environment.

The inverse association between cumulative average sleep duration and incident CMM was estimated to correspond to an approximate 9% reduction in risk per additional hour of sleep. In a 22-year follow-up of the Study of Women's Health Across the Nation, Thurston et al.^[40] reported that static short sleep did not significantly elevate CMM risk; however, a progressive decline in sleep duration during the menopausal transition was linked to an increased risk of CMM. This observation resonates with the study design, which utilizes averaged sleep duration across multiple waves to minimize measurement error and capture long-term sleep patterns. These results should also be considered in the context of the increasingly multidimensional understanding of sleep health. Recent evidence from a large prospective Chinese cohort showed that sleep duration and insomnia were associated with cardiometabolic disease onset, multimorbidity, and mortality, supporting the relevance of habitual sleep characteristics to long-term cardiometabolic outcomes^[41]. Similarly, a CHARLS-based longitudinal study identified distinct sleep-duration trajectories and found that persistent short sleep was associated with increased risks of stroke, dyslipidemia, and diabetes [2024 sleep trajectory study]. Our findings extend this evidence by focusing on incident CMM and by jointly considering cumulative average sleep duration and cumulative AIP exposure^[33]. In addition, a 2026 study using CHARLS and SHARE reported that longer-term sleep patterns and better sleep quality were associated with lower risks of cardio-renal-metabolic multimorbidity, while poor sleep quality was associated with increased risk^[42]. These findings are

broadly consistent with the observation that cumulative average sleep duration was inversely associated with incident CMM. However, the use of sleep duration alone captures only one dimension of sleep health. The 2025 AHA scientific statement emphasizes that sleep duration, regularity, timing, continuity, daytime functioning, sleep architecture, and sleep disorders may all contribute to cardiometabolic health^[32]. Because CHARLS provides repeated information on sleep duration but relatively limited longitudinal information on several other dimensions of sleep health, the findings should therefore be interpreted as evidence concerning habitual sleep duration rather than overall sleep health. The present data further indicate that sleep and AIP function through relatively independent pathways in the development of CMM. Both the heatmap (Fig. 2) and subgroup analyses (Table 2) revealed that the protective effect of longer sleep was evident only among participants in the lowest AIP quartile, with the combination of sleep-Q3 and AIP-Q1 exhibiting the most significant risk reduction (HR = 0.538). This suggests that the cardioprotective effect of sleep is contingent upon a lower baseline atherogenic burden, when lipid metabolism is already severely disrupted, adjustments in sleep alone may be inadequate to alter the risk trajectory.

Chronic sleep deprivation mechanistically activates the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis, resulting in sustained elevations of cortisol. This hormonal increase subsequently induces insulin resistance and endothelial injury, thereby promoting atherosclerosis^[43]. The Atherogenic Index of Plasma (AIP), a composite measure of triglycerides (TG) to high-density lipoprotein cholesterol (HDL-C), encapsulates much of this metabolic information. Consequently, when AIP levels are elevated, the marginal protective effect of sleep—considered an upstream behavioral factor—is limited. Yu et al. ^[44] employed two-step Mendelian randomization to demonstrate that HDL-C mediated 4.5%–10.8% and TG mediated 7.2%–15.1% of the associations between insomnia and cardiovascular diseases. In contrast, Hallab et al. ^[45] reported that hypertriglyceridemia, rather than hypercholesterolemia, was independently associated with sleep disturbances, indicating a 29% increased risk after adjusting for body mass index (BMI), cognitive function, and depression^[46]. This may elucidate the modest effect of sleep on cumulative AIP observed in the study. AIP encompasses both TG and HDL-C pathways, which do not entirely coincide with sleep-related pathways, thereby offering epidemiological support for the diminished protective effect of sleep in the context of elevated AIP. Jin et al. ^[23], utilizing CHARLS data, confirmed that AIP independently predicts cardio-renal-metabolic multimorbidity. Specifically, each 1-SD increase in AIP correlates with a 17% and 31% increase in the risks of single and dual/triple CRM multimorbidity, respectively, demonstrating significant predictive effects on diabetes and stroke. Mechanistically, AIP integrates insulin resistance, inflammation, and endothelial injury—all of which are downstream consequences of sleep disruption—further elucidating why the marginal protective effect of sleep is significantly reduced at high AIP levels. The improvement in C-index (from 0.6232 to 0.6432) and AUC (from 0.641 to 0.659), both statistically significant, indicates that the combination of sleep and AIP enhances risk prediction compared to either factor alone.

From a prevention perspective, the present findings suggest that sleep management and lipid-metabolic management may be complementary rather than interchangeable strategies. Adequate sleep may be particularly relevant before substantial atherogenic dyslipidemia develops, whereas individuals with elevated AIP may require a broader approach addressing triglyceride metabolism, HDL-related abnormalities, body weight, physical activity, diet, and glycemic control in addition to sleep health. The modest but statistically significant improvement in discrimination after adding sleep and AIP to the conventional risk model further suggests that these readily obtainable factors may provide incremental information for population-level risk stratification, although the improvement in AUC and C-index should not be interpreted as evidence of clinical utility without external validation.

Several mechanisms may explain why the association between longer sleep duration and CMM risk was more apparent among individuals with lower AIP levels. First, sleep duration and atherogenic dyslipidemia may influence overlapping metabolic pathways, including insulin resistance, autonomic imbalance, systemic inflammation, and endothelial dysfunction. When the underlying atherogenic burden is relatively low, improvements in sleep duration may exert measurable metabolic and vascular benefits, thereby reducing the probability of progression toward multiple cardiometabolic diseases. In contrast, among individuals with persistently elevated AIP, substantial triglyceride-rich lipoprotein abnormalities and low HDL-C may represent a more advanced metabolic state in which the incremental benefit attributable to sleep duration is relatively small. Second, elevated AIP may identify individuals with a broader metabolic phenotype characterized by insulin resistance and chronic low-grade inflammation. Once this metabolic burden is established, modification of a single behavioral factor such as sleep duration may be insufficient to substantially alter the overall disease trajectory. This interpretation is also compatible with evidence that AIP predicts the onset and progression of multimorbidity across multiple cardiometabolic disease states ^[23, 47].

Importantly, the absence of a statistically significant multiplicative interaction should be distinguished from the heterogeneous associations observed across AIP strata. In the present study, the sleep × AIP interaction term did not significantly improve model fit ($P = 0.165$), whereas stratified analyses suggested that the magnitude of the sleep association differed according to AIP level. This pattern may indicate effect heterogeneity without sufficient statistical evidence for formal interaction. Therefore, these subgroup findings should be interpreted as hypothesis-generating rather than as definitive evidence that AIP modifies the causal effect of sleep on CMM.

5 Limitations

Several limitations should be acknowledged. First, as an observational cohort study, residual confounding and reverse causality cannot be entirely excluded. Although we adjusted for multiple confounders in Cox regression models without evidence of multicollinearity, unmeasured or inadequately measured confounders may remain. Second, CMM outcomes were based on self-reported physician diagnoses, which may introduce information bias. Third, the study population was restricted to Chinese adults aged ≥ 45 years, limiting generalizability to other populations. Future studies with larger and more

diverse samples and more comprehensive data collection are needed to further validate the predictive value of average sleep and cumulative AIP for CMM.

6 Conclusions

This study confirms that both cumulative average sleep duration and cumulative average AIP are independent determinants of incident CMM in middle-aged and older Chinese adults. These two factors operate through largely independent pathways, and their combined assessment improves CMM risk prediction. Notably, the cardioprotective effect of sleep is significant only among individuals with low AIP levels and essentially disappears at higher AIP levels, suggesting that clinical prevention strategies should address both lipid metabolism and sleep health concurrently.

Declarations

Conflict of Interest

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

Ethical Approval

The CHARLS study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Peking University (IRB00001052-11015). All participants provided written informed consent before enrollment. The present study utilized publicly available, anonymized CHARLS data and involved secondary data analysis; thus, no additional ethics approval was required.

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Author Contribution

F: Conceptualization, data curation, formal analysis, methodology, validation, formal analysis, investigation, data curation, writing-original draft, and writing-review & editing, software, validation, data curation. Z: Formal analysis, supervision, methodology, software, resources. H. and L.: Data curation,

methodology. J. and G.: Methodology, validation. Yi Zheng*:Supervision, project administration. Huarong Wang*: Supervision, project administration. Li Duan*: Supervision, project administration, formal analysis, funding acquisition. All authors reviewed the manuscript.

Data Availability

The CHARLS data used in this study are available from the China Health and Retirement Longitudinal Study (CHARLS) database and can be accessed through the official CHARLS website:
<https://charls.pku.edu.cn/>

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Figures

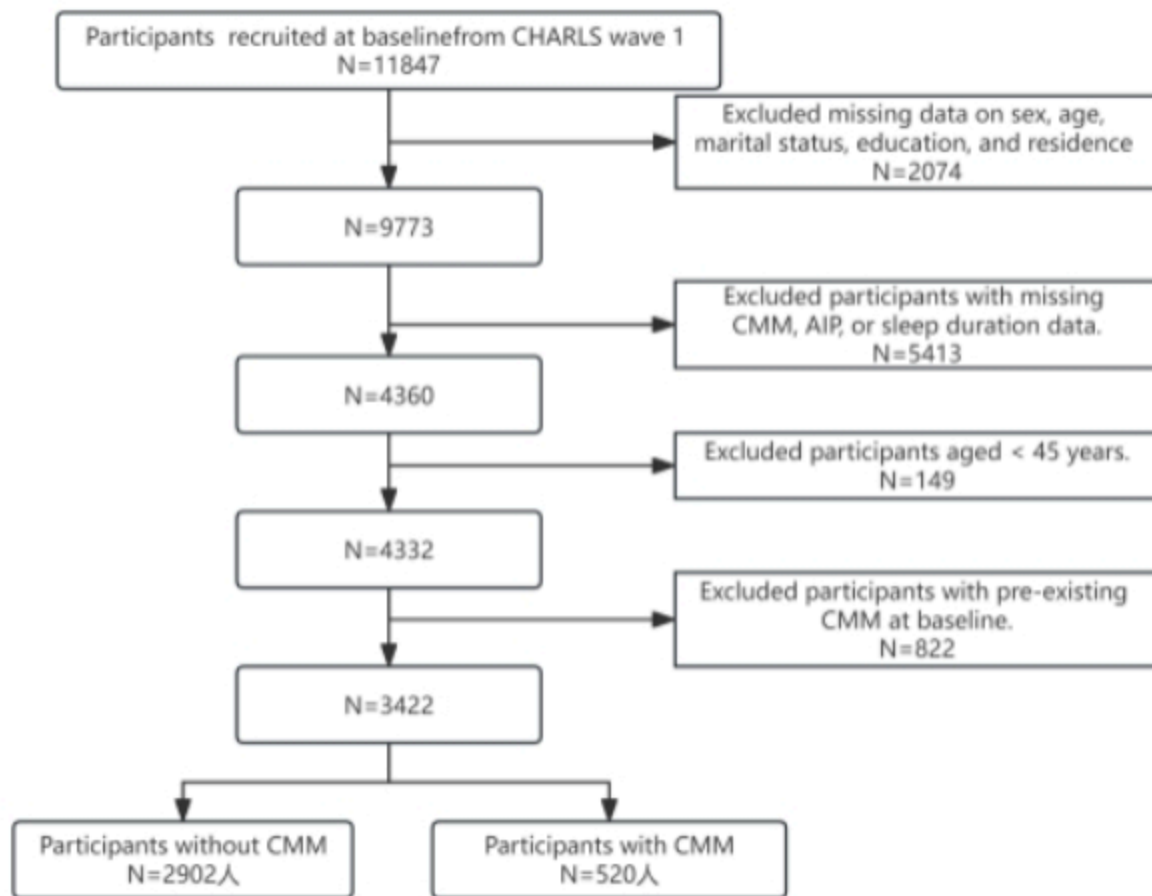


Figure 1

Flowchart of participant enrollment and exclusion criteria in the study

Adjusted HR for CMM by AIP and Sleep Duration



Figure 2

Heatmap of adjusted hazard ratios for incident cardiometabolic multimorbidity according to joint categories of cumulative average AIP and sleep duration.

Note The heatmap presents adjusted hazard ratios (HRs) for incident cardiometabolic multimorbidity (CMM) across combinations of cumulative average atherogenic index of plasma (AIP) quartiles and cumulative average sleep duration quartiles. The lowest AIP quartile combined with the lowest sleep duration quartile (Q1–Q1) was used as the reference group (HR = 1.00). HRs were estimated using multivariable Cox proportional hazards regression models adjusted for age, residential area, marital status, education level, sex, smoking status, alcohol consumption, hypertension, and dyslipidemia. The numbers within each cell represent HRs. Statistical significance is indicated by $P < 0.05$, $P < 0.01$, and $P < 0.001$.

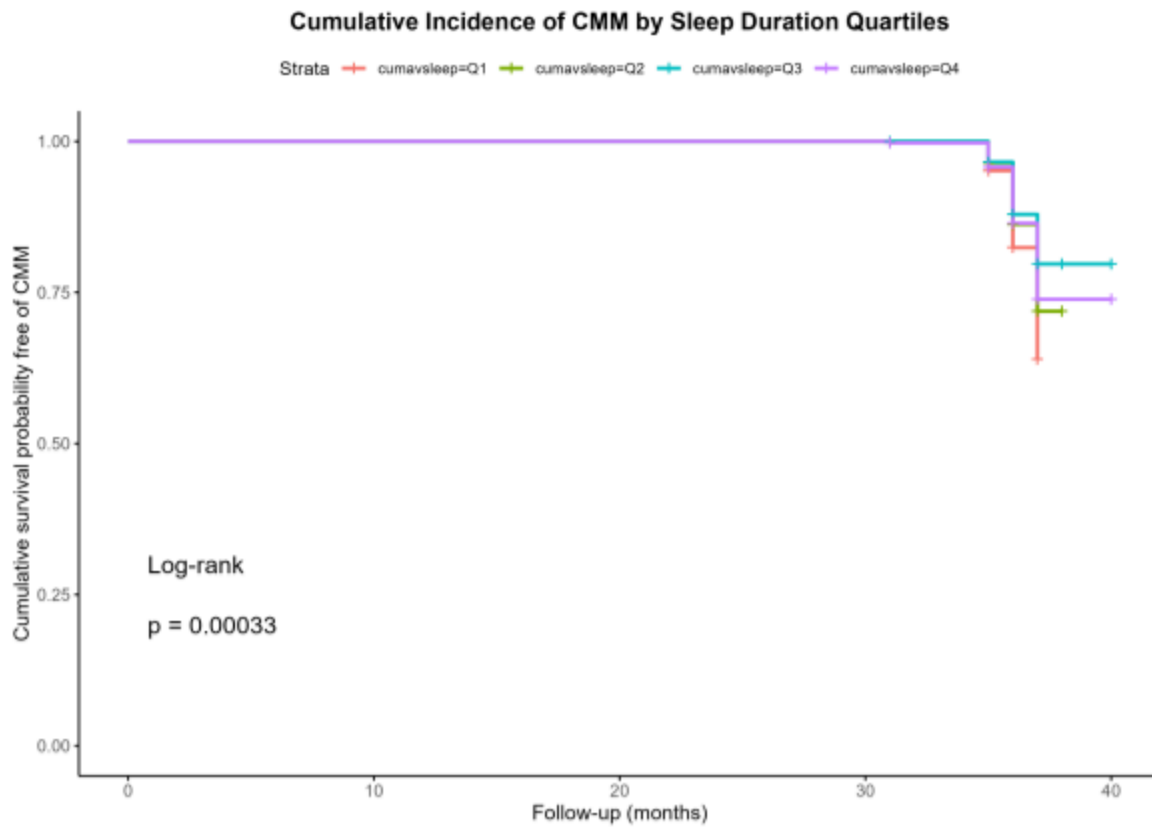


Figure 3

Kaplan–Meier survival curves for the probability of remaining free from cardiometabolic multimorbidity according to quartiles of cumulative average sleep duration.

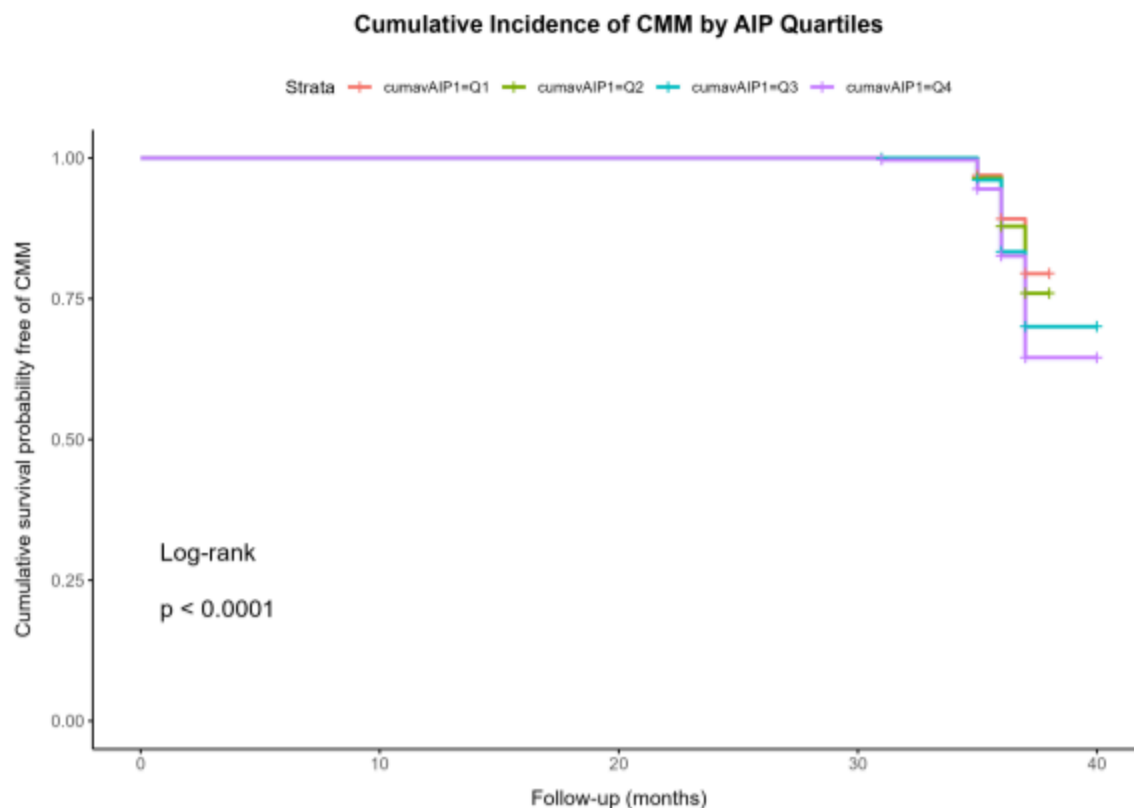


Figure 4

Kaplan–Meier survival curves for the probability of remaining free from cardiometabolic multimorbidity according to quartiles of cumulative average atherogenic index of plasma (AIP).

Note Figure 3 shows survival curves stratified by quartiles of cumulative average sleep duration. Figure 4 shows survival curves stratified by quartiles of cumulative average atherogenic index of plasma (AIP). Figure 5 shows survival curves according to the combined categories of AIP and sleep duration. Q1–Q4 indicate increasing quartiles of sleep duration or AIP. The log-rank test was used to compare differences among groups.

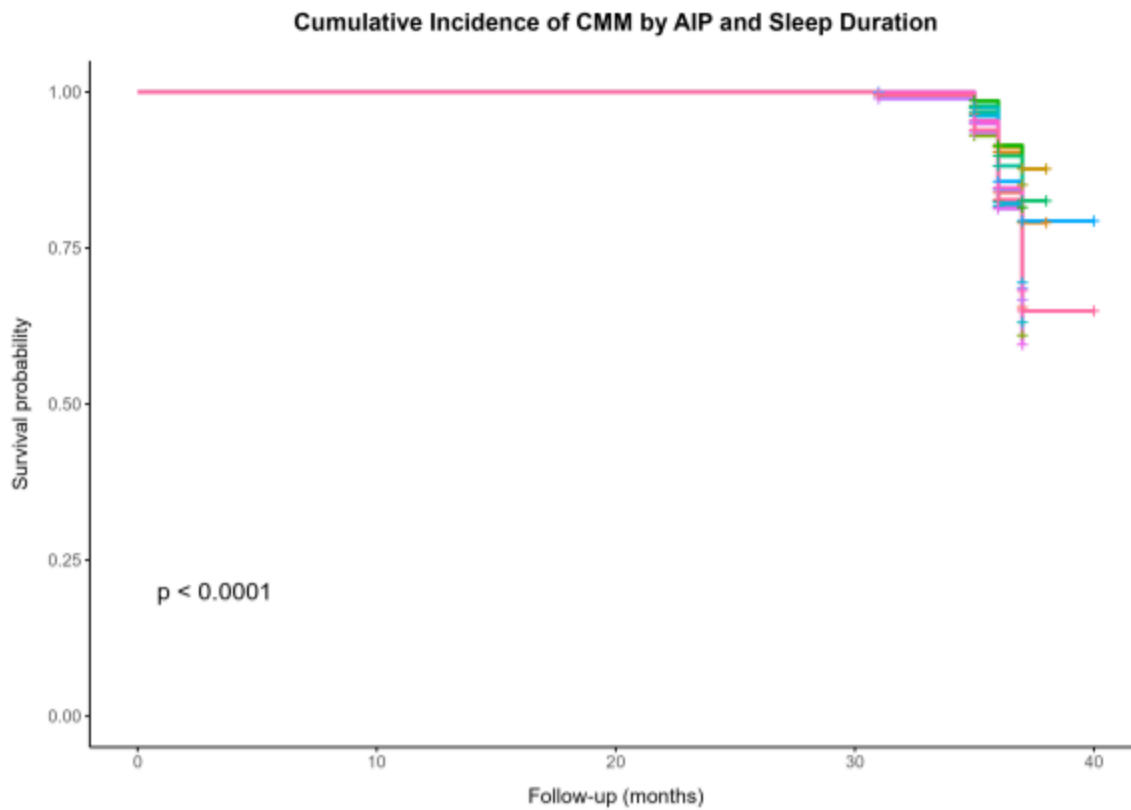


Figure 5

Kaplan–Meier survival curves for the probability of remaining free from cardiometabolic multimorbidity according to joint categories of cumulative average AIP and sleep duration.

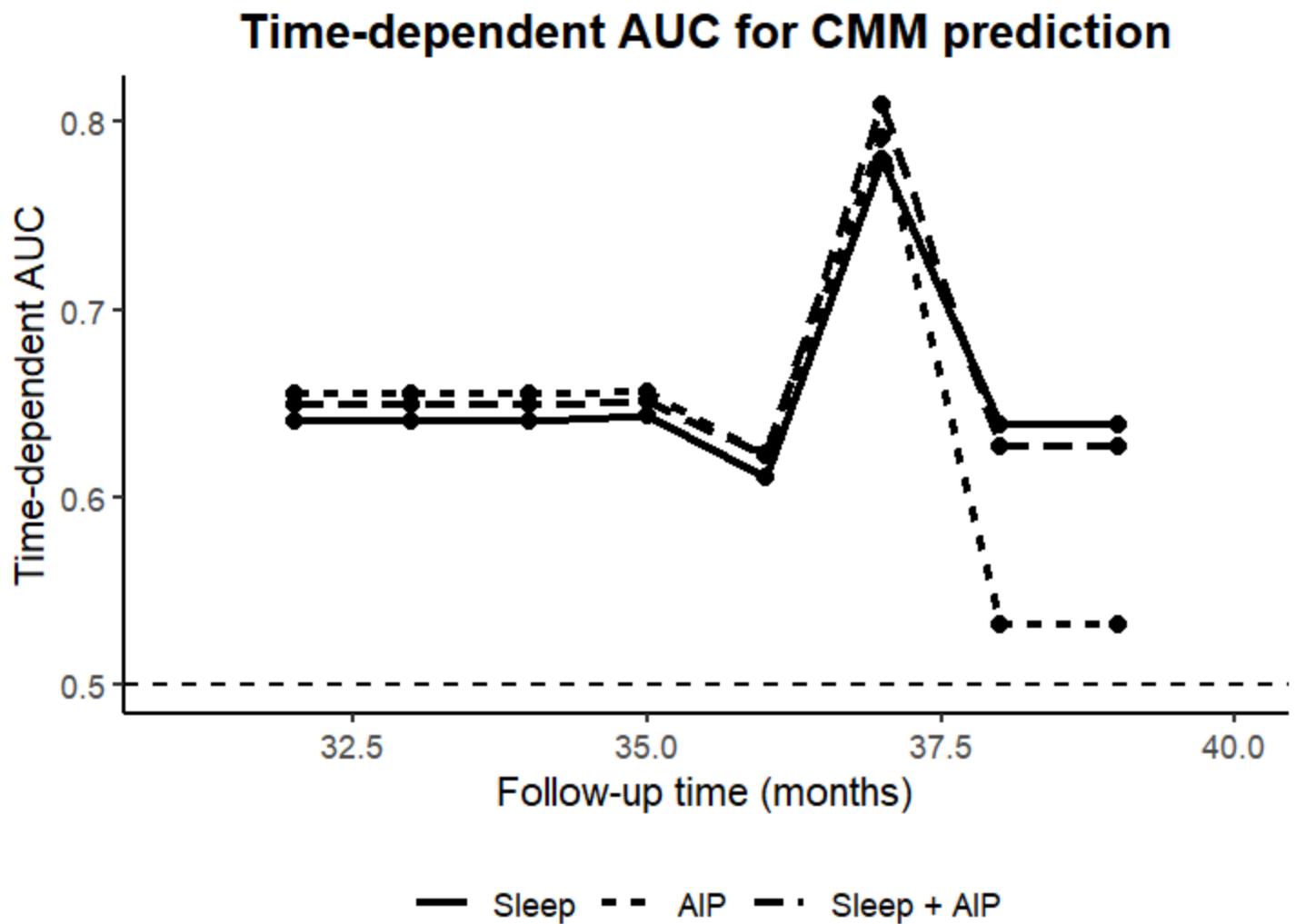


Figure 6

Time-dependent area under the curve (AUC) of Cox models for predicting incident cardiometabolic multimorbidity (CMM).

Note Time-dependent AUCs were estimated for models including cumulative average sleep duration, cumulative average atherogenic index of plasma (AIP), and their combination, adjusted for age, residence, marital status, education, sex, smoking status, alcohol consumption, hypertension, and dyslipidemia. Higher AUC values indicate better discrimination ability.