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Joint associations of cumulative uric acid-to-HDL cholesterol ratio and cumulative depressive symptom burden with incident cardiometabolic multimorbidity: a landmark analysis of CHARLS

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Abstract

Background

Cardiometabolic multimorbidity (CMM) is a growing health concern in ageing populations. Although the uric acid-to-high-density lipoprotein cholesterol ratio (UHR) and depressive symptoms have each been associated with cardiometabolic risk, their cumulative joint associations remain unclear. Whether depressive symptom burden modifies the UHR–CMM association also warrants investigation.

Methods

We conducted a prospective landmark analysis in the China Health and Retirement Longitudinal Study (CHARLS). UHR and depressive symptoms were assessed in 2011 and 2015. Cumulative UHR (cuUHR) and cumulative depressive symptom burden (cuCESD) were calculated as the mean of the two measurements multiplied by the 4-year interval. Participants with CMM by the 2015 landmark were excluded. Cox models assessed individual and joint associations with incident CMM and estimated standardized 3-year absolute risks. Effect modification was examined on multiplicative and additive scales, with spline models allowing a nonlinear cuUHR association.

Results

Among 5,617 participants, 1,030 developed CMM. In adjusted models, each standard deviation increase in cuUHR was associated with a hazard ratio (HR) of 1.198 (95% confidence interval [CI] 1.142–1.258). Each 5-score-year increase in cuCESD was associated with an HR of 1.059 (95% CI 1.045–1.074). Compared with participants with low levels of both exposures, those with high levels of both had the highest hazard (HR 2.550, 95% CI 2.063–3.152). Their standardized 3-year risk was 15.21% (95% CI 13.62%–16.92%), compared with 6.30% (95% CI 5.17%–7.46%) in the low/low group. The continuous multiplicative interaction indicated a weaker relative cuUHR–CMM association at higher cuCESD (interaction HR 0.989, 95% CI 0.981–0.998; likelihood-ratio P = 0.006). Evidence for this interaction weakened after adjustment for baseline cardiometabolic disease burden. Additive-interaction estimates were not statistically significant.

Conclusions

Higher cuUHR and cuCESD were individually and jointly associated with incident CMM. In the primary model, the relative cuUHR–CMM association was weaker at higher depressive symptom burden, while the high/high group had the highest estimated absolute risk. These findings warrant replication and evaluation of the prognostic value of repeated metabolic and depressive symptom assessments.

1. Background

Cardiometabolic multimorbidity (CMM), generally defined as the coexistence of multiple cardiometabolic conditions, is an important clinical and public health concern in ageing populations. Accumulating cardiometabolic diseases is associated with greater mortality and shorter life expectancy than a single condition alone(1, 2). Cardiometabolic disease patterns have also been associated with disability, while studies of multimorbidity more broadly report greater medication burden and health-care use(3–5). Identifying modifiable factors associated with progression from zero or one cardiometabolic disease to multimorbidity is therefore relevant to prevention(6).

Serum uric acid reflects purine metabolism and has been linked to oxidative stress, endothelial dysfunction, and metabolic disturbances relevant to insulin resistance and cardiovascular disease(7, 8). HDL particles participate in cholesterol efflux and have anti-inflammatory functions, although HDL cholesterol (HDL-C) concentration does not directly measure these functions(9, 10). The uric acid-to-HDL cholesterol ratio (UHR) combines these two biomarker concentrations and has been studied as a composite marker of cardiometabolic risk. A nationwide CHARLS study reported that higher UHR was associated with incident CMM, with evidence of a nonlinear association(11). This finding raises the question of whether UHR assessed repeatedly before follow-up is associated with subsequent CMM.

Depressive symptoms are another potentially modifiable factor associated with cardiometabolic health. Proposed pathways include hypothalamic-pituitary-adrenal and sympathetic activation, low-grade inflammation, sleep disturbance, adverse health behaviors, and poorer adherence to care(12, 13). Longitudinal CHARLS analyses have reported associations of depression and greater depressive symptom severity with higher CMM risk(14). Other work has examined the joint associations of depression and lipid-related metabolic dysfunction with CMM(15). It remains unclear whether cumulative depressive symptom burden modifies the association between cumulative UHR and subsequent CMM.

Studies that evaluate metabolic and psychological exposures separately, at a single time point, or as binary co-exposures may not capture repeated exposure or effect modification across the continuous exposure distribution. Research on cumulative LDL cholesterol provides a precedent for examining exposure history in relation to subsequent cardiovascular outcomes(16). A landmark framework uses measurements obtained before the risk period to separate exposure assessment from subsequent outcome ascertainment and clarify temporal ordering(17).

Using repeated CHARLS assessments, we examined cuUHR and cumulative depressive symptom burden during 2011–2015 in relation to incident CMM after the 2015 landmark. We assessed whether both cumulative exposures were associated with higher CMM risk after covariate adjustment. We also examined whether participants with dual high exposure had the greatest absolute risk and adjusted hazard, and whether depressive symptom burden modified the cuUHR–CMM association. Continuous interaction, conditional estimates, and quartile-stratified analyses described relative effect modification, while standardized absolute risks and additive interaction characterized joint risk.

2. Methods

2.1 Study design and population

CHARLS is an ongoing, nationally representative longitudinal study of middle-aged and older adults in China, initiated in 2011 using a multistage probability sampling strategy. Detailed cohort design and sampling procedures have been reported previously(18). The present analysis used 2011 as the cohort baseline and 2015 as the landmark separating cumulative exposure assessment from outcome follow-up. Measurements obtained in 2011 and 2015 were used to construct cumulative metabolic and depressive symptom exposures. Incident CMM was then assessed after the 2015 landmark.

The participant-selection process is shown in Fig. 1. Among 17,705 baseline records, 5,510 participants were excluded before or at the 2015 landmark because of missing baseline CMM status or post-2015 outcome/follow-up information (n = 444), prevalent CMM at baseline (n = 1,766), missing CMM status in 2015 (n = 1,931), CMM by the 2015 landmark (n = 1,075), or absence of valid post-2015 risk time (n = 294). Of 12,195 participants eligible at the 2015 landmark, 6,578 were further excluded because uric acid or HDL-C measurements were missing in 2011 or 2015 (n = 6,292) or CES-D scores were unavailable in 2011 or 2015 (n = 286). The final analytic cohort comprised 5,617 participants, of whom 1,030 developed incident CMM.

CHARLS was approved by the Institutional Review Board of Peking University (IRB00001052-11015 for the household survey and anthropometric assessments; IRB00001052-11014 for biomarker collection), and all participants provided written informed consent. The present analysis used de-identified publicly available CHARLS data.

2.2 Assessment of UHR and cumulative UHR

Uric acid and HDL-C were measured in blood samples collected according to CHARLS protocols(18). UHR was calculated separately for 2011 and 2015 as uric acid (mg/dL) divided by HDL-C (mg/dL). To represent exposure over the 4-year interval, cuUHR was calculated using the trapezoidal area-under-the-curve approximation: cuUHR = $(UHR_{2011} + UHR_{2015}) / 2 \times 4$ years, expressed in ratio-years. This calculation integrated the two measurements over a common pre-landmark interval. Because the interval was identical for all participants, differences in cuUHR reflected differences in the two-wave mean UHR. For continuous Cox models, cuUHR was standardized using its sample standard deviation (SD) and analyzed per 1-SD increase. The SD was 0.1533 ratio-years in the analytic cohort.

For the joint-exposure analysis, cuUHR was dichotomized at the sample median (0.356078). These categories facilitated comparisons between exposure groups and were not treated as clinical diagnostic thresholds.

2.3 Depressive symptoms and cumulative depressive symptom burden

Depressive symptoms were assessed in 2011 and 2015 using the 10-item Center for Epidemiologic Studies Depression Scale (CES-D-10), a commonly used instrument in CHARLS and older Chinese populations(19, 20). Higher scores indicate greater depressive symptom severity.

Cumulative depressive symptom burden (cuCESD) was calculated analogously to cuUHR as cuCESD = $(\text{CES-D}_{2011} + \text{CES-D}_{2015}) / 2 \times 4$ years and expressed in score-years. In the continuous interaction analysis, cuCESD was centered at its sample mean and scaled per 5-score-year increase. For the four-group joint analysis, cuCESD was dichotomized at the sample median of 28 score-years. Quartiles and selected percentiles of cuCESD were used to characterize effect modification without relying on a single binary threshold.

2.4 Definition of cardiometabolic multimorbidity and follow-up

CMM was defined as the coexistence of at least two cardiometabolic diseases among hypertension, diabetes, heart disease, and stroke. At each included CHARLS wave, disease status was derived from the corresponding disease indicators in the analytic dataset. The number of qualifying conditions was summed for each participant at each wave. Participants with two or more qualifying cardiometabolic diseases at the 2011 baseline or by the 2015 landmark were excluded from the post-landmark risk set.

For the landmark analysis, follow-up began at the 2015 assessment. Incident CMM was defined as the first post-2015 observation of at least two qualifying cardiometabolic diseases. Follow-up time was calculated from the 2015 landmark to the first observed CMM event. Participants who remained free of CMM were censored at their last available follow-up with evaluable outcome information. This design separated the 2011–2015 cumulative exposure window from subsequent CMM ascertainment.

2.5 Covariates

Covariates were selected based on demographic, socioeconomic, and behavioral relevance and defined using information from the 2011 cohort baseline. The primary adjustment set included age, sex, education, marital status, residence (urban/rural), and current smoking status. Education was grouped into low, middle, and high categories using the original CHARLS coding, and marital status was categorized as married versus other. The primary models did not additionally adjust for individual cardiometabolic diseases used to construct the outcome. Because pre-existing disease could affect both exposure levels and progression to CMM, baseline cardiometabolic disease burden in 2011 (0 versus 1 condition) was examined in sensitivity analyses.

2.6 Statistical analysis

Approximately normally distributed continuous variables were summarized as means (standard deviations) and compared using independent-samples Student’s t-tests. Skewed continuous variables were summarized as medians [25th, 75th percentiles] and compared using Wilcoxon rank-sum tests. Categorical variables were summarized as counts (percentages) and compared using Pearson’s chi-

square tests. Comparisons were made between participants with and without incident CMM after the 2015 landmark. Table 1 presents 2011 baseline characteristics together with cumulative exposures constructed from the 2011 and 2015 measurements. Descriptive summaries used available observations for each variable. Missing values in variables used only for descriptive characterization did not result in additional participant exclusions. The primary Cox-model covariates were complete for all 5,617 participants in the analytic cohort. Cox proportional hazards regression estimated hazard ratios (HRs) and 95% confidence intervals (CIs)(21). Model 1 was unadjusted; Model 2 adjusted for age and sex. Model 3 additionally adjusted for education, marital status, residence, and current smoking. All three models included 5,617 participants and 1,030 incident CMM events.

Table 1

Baseline characteristics and cumulative exposures by incident cardiometabolic multimorbidity status

Characteristic	Level	Overall (N = 5617)	No incident CMM (N = 4587)	Incident CMM (N = 1030)	P value
Age, years		57.60 (8.93)	57.28 (9.02)	59.03 (8.36)	< 0.001
Sex					0.002
	Male	2593 (46.2%)	2163 (47.2%)	430 (41.7%)	
	Female	3024 (53.8%)	2424 (52.8%)	600 (58.3%)	
Education					0.010
	Low	2605 (46.4%)	2084 (45.4%)	521 (50.6%)	
	Middle	2493 (44.4%)	2068 (45.1%)	425 (41.3%)	
	High	519 (9.2%)	435 (9.5%)	84 (8.2%)	
Marital status					0.088
	Married	4874 (86.8%)	3997 (87.1%)	877 (85.1%)	
	Other	743 (13.2%)	590 (12.9%)	153 (14.9%)	
Residence					0.054
	Urban	1850 (32.9%)	1537 (33.5%)	313 (30.4%)	
	Rural	3767 (67.1%)	3050 (66.5%)	717 (69.6%)	
Current smoking					< 0.001

Note. Data are presented as mean (SD), median [25th, 75th percentiles], or n (%). Groups were compared using Student's t-tests, Wilcoxon rank-sum tests, or Pearson's chi-square tests, respectively. Characteristics were assessed in 2011; cumulative exposures cover 2011–2015. cuUHR and cuCESD are expressed in ratio-years and score-years, respectively. Disease burden denotes the number of cardiometabolic diseases present in 2011. Analyses used available observations for each variable.

Abbreviations: BMI, body mass index; CES-D, Center for Epidemiologic Studies Depression Scale; CMM, cardiometabolic multimorbidity; CRP, C-reactive protein; cuCESD, cumulative depressive symptom burden; cuUHR, cumulative uric acid-to-HDL cholesterol ratio; HDL-C, high-density lipoprotein cholesterol; SD, standard deviation; UHR, uric acid-to-HDL cholesterol ratio.

Characteristic	Level	Overall (N = 5617)	No incident CMM (N = 4587)	Incident CMM (N = 1030)	P value
	No	3869 (68.9%)	3111 (67.8%)	758 (73.6%)	
	Yes	1748 (31.1%)	1476 (32.2%)	272 (26.4%)	
Ever drinking					0.088
	No	3423 (61.0%)	2772 (60.5%)	651 (63.3%)	
	Yes	2190 (39.0%)	1813 (39.5%)	377 (36.7%)	
BMI, kg/m²		23.30 (3.69)	23.04 (3.62)	24.44 (3.79)	< 0.001
Waist circumference, cm		84.43 (9.60)	83.62 (9.36)	88.03 (9.80)	< 0.001
Systolic blood pressure, mmHg		127.38 (20.14)	125.55 (19.61)	135.44 (20.46)	< 0.001
Diastolic blood pressure, mmHg		74.68 (11.83)	73.79 (11.62)	78.60 (11.97)	< 0.001
Uric acid, mg/dL		4.20 [3.50, 5.04]	4.19 [3.49, 5.02]	4.28 [3.51, 5.12]	0.078
HDL-C, mg/dL		51.64 (15.39)	52.22 (15.53)	49.06 (14.48)	< 0.001
Fasting blood glucose, mg/dL		101.52 [93.96, 110.70]	100.89 [93.60, 109.44]	104.85 [95.76, 116.82]	< 0.001
High-sensitivity CRP, mg/L		0.93 [0.52, 1.94]	0.88 [0.50, 1.83]	1.21 [0.64, 2.38]	< 0.001
Baseline CES-D score		7.00 [3.00, 12.00]	7.00 [3.00, 11.00]	8.00 [4.25, 14.00]	< 0.001

Note. Data are presented as mean (SD), median [25th, 75th percentiles], or n (%). Groups were compared using Student's t-tests, Wilcoxon rank-sum tests, or Pearson's chi-square tests, respectively. Characteristics were assessed in 2011; cumulative exposures cover 2011–2015. cuUHR and cuCESD are expressed in ratio-years and score-years, respectively. Disease burden denotes the number of cardiometabolic diseases present in 2011. Analyses used available observations for each variable.

Abbreviations: BMI, body mass index; CES-D, Center for Epidemiologic Studies Depression Scale; CMM, cardiometabolic multimorbidity; CRP, C-reactive protein; cuCESD, cumulative depressive symptom burden; cuUHR, cumulative uric acid-to-HDL cholesterol ratio; HDL-C, high-density lipoprotein cholesterol; SD, standard deviation; UHR, uric acid-to-HDL cholesterol ratio.

Characteristic	Level	Overall (N = 5617)	No incident CMM (N = 4587)	Incident CMM (N = 1030)	P value
Baseline UHR		0.08 [0.06, 0.11]	0.08 [0.06, 0.11]	0.09 [0.07, 0.12]	< 0.001
Cumulative UHR (cuUHR)		0.36 [0.28, 0.46]	0.35 [0.28, 0.45]	0.37 [0.30, 0.49]	< 0.001
Cumulative CES-D burden (cuCESD)		28.00 [16.00, 46.00]	28.00 [16.00, 44.00]	34.00 [18.50, 52.00]	< 0.001
Baseline cardiometabolic disease burden					< 0.001
	0 diseases	4246 (75.6%)	3694 (80.5%)	552 (53.6%)	
	1 disease	1371 (24.4%)	893 (19.5%)	478 (46.4%)	

Note. Data are presented as mean (SD), median [25th, 75th percentiles], or n (%). Groups were compared using Student's t-tests, Wilcoxon rank-sum tests, or Pearson's chi-square tests, respectively. Characteristics were assessed in 2011; cumulative exposures cover 2011–2015. cuUHR and cuCESD are expressed in ratio-years and score-years, respectively. Disease burden denotes the number of cardiometabolic diseases present in 2011. Analyses used available observations for each variable.

Abbreviations: BMI, body mass index; CES-D, Center for Epidemiologic Studies Depression Scale; CMM, cardiometabolic multimorbidity; CRP, C-reactive protein; cuCESD, cumulative depressive symptom burden; cuUHR, cumulative uric acid-to-HDL cholesterol ratio; HDL-C, high-density lipoprotein cholesterol; SD, standard deviation; UHR, uric acid-to-HDL cholesterol ratio.

First, we examined UHR in 2011 and 2015, cuUHR, CES-D scores in 2011 and 2015, and cuCESD in relation to incident CMM. UHR-based exposures were modeled per 1-SD increase, CES-D scores per 5-point increase, and cuCESD per 5-score-year increase. Restricted cubic spline Cox models with four knots assessed each association's shape, using the sample median of the corresponding exposure as the reference. Spline models used the Model 3 adjustment set(22).

Second, joint associations were evaluated by cross-classifying participants using the sample median cutoffs for cuUHR and cuCESD. This yielded low/low, high-cuUHR/low-cuCESD, low-cuUHR/high-cuCESD, and high/high groups. Values below each cutoff were classified as low, and values at or above it as high. The low/low group served as the reference. An exploratory ordinal joint-exposure score counted the number of high-exposure domains: 0 for low/low, 1 for either single-high group, and 2 for high/high. Separate Cox models estimated the association per one-domain increase using the Model 1–3 adjustment sets. Standardized 3-year absolute risks were estimated for the four groups from the fully adjusted Cox model to complement the HRs.

Third, we assessed continuous multiplicative effect modification by including a product term between standardized cuUHR and centered cuCESD scaled per 5 score-years(23). Likelihood-ratio tests compared models with and without this term. Main-effect coefficients in interaction models represented conditional associations at the mean level of the other exposure. We estimated conditional cuUHR associations (simple slopes) at the 10th, 25th, 50th, 75th, and 90th percentiles of cuCESD. We also estimated cuUHR associations within cuCESD quartiles and tested heterogeneity across quartiles (Supplementary Table S1). Additional analyses adjusted for baseline cardiometabolic disease burden and stratified by that burden (Supplementary Table S2).

Given evidence of nonlinearity in the cuUHR association, we also fitted a model with a 3-degree-of-freedom natural cubic spline for standardized cuUHR and its interaction with cuCESD. The fit was compared with the corresponding spline model without interaction using a likelihood-ratio test and the Akaike information criterion (AIC; Supplementary Table S3). This test assessed the spline interaction terms jointly; it did not compare spline interaction with a linear product-term model. A two-dimensional response surface displayed model-based standardized 3-year CMM risk across cuUHR and cuCESD values. Predictions were restricted to the 2.5th–97.5th percentiles of each exposure to reduce extrapolation into sparse extremes.

We assessed proportional hazards for the fully adjusted continuous interaction model using Schoenfeld residuals (Supplementary Table S4)(24). Multicollinearity was evaluated using variance inflation factors (VIFs; Supplementary Table S5), and alternative 40th-, 50th-, and 67th-percentile dichotomization cutoffs were examined (Supplementary Table S6). Additive interaction was evaluated on the standardized 3-year risk scale using the interaction contrast, relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP), and synergy index (S). Their 95% CIs were obtained from 2,000 participant-level bootstrap resamples (Supplementary Table S7)(23, 25). Included and excluded landmark-eligible participants were compared using standardized mean differences (SMDs; Supplementary Table S8). Tests were two-sided, with $P < 0.05$ considered statistically significant. Effect estimates and CIs were also considered when interpreting exploratory interaction and sensitivity analyses. All statistical analyses were performed using IBM SPSS Statistics (version 27.0), EmpowerStats (version 5.2), and R (version 4.5.2).

3. Results

3.1 2011 baseline and pre-landmark exposure characteristics

Among the 5,617 participants, mean age at the 2011 baseline was 57.60 years (SD 8.93), and 53.8% were women. After the 2015 landmark, 1,030 participants developed incident CMM (Table 1). These participants were older at baseline (59.03 versus 57.28 years) and more often female (58.3% versus 52.8%). They also had higher body mass index, waist circumference, systolic and diastolic blood pressure, fasting glucose, and high-sensitivity C-reactive protein. Baseline CES-D score, baseline UHR,

cuUHR, and cuCESD were higher, while HDL-C was lower, among participants who subsequently developed CMM. Baseline uric acid alone did not differ significantly between groups ($P = 0.078$).

Baseline cardiometabolic disease burden differed by outcome status. One condition was present in 2011 in 46.4% of participants who developed CMM, compared with 19.5% of those who did not ($P < 0.001$). Median cuUHR was 0.36 [0.28, 0.46] overall and 0.37 [0.30, 0.49] among incident cases. Median cuCESD was 28 [16, 46] overall and 34 [18.5, 52] among incident cases.

3.2 Associations of cumulative UHR and depressive symptom burden with incident CMM

All six exposure measures were positively associated with incident CMM in the fully adjusted models (Table 2). Each 1-SD increase in cuUHR was associated with a 19.8% higher hazard (HR 1.198, 95% CI 1.142–1.258; $P < 0.001$). Each 5-score-year increase in cuCESD was associated with a 5.9% higher hazard (HR 1.059, 95% CI 1.045–1.074; $P < 0.001$). Positive associations were also observed for UHR and CES-D scores measured separately in 2011 and 2015.

Table 2
Associations of time-specific and cumulative exposures with incident cardiometabolic multimorbidity

Exposure	Model 1 HR (95% CI)	P value	Model 2 HR (95% CI)	P value	Model 3 HR (95% CI)	P value
UHR 2011, per 1-SD increase	1.126 (1.080–1.174)	< 0.001	1.154 (1.107–1.203)	< 0.001	1.154 (1.108–1.202)	< 0.001
UHR 2015, per 1-SD increase	1.141 (1.078–1.207)	< 0.001	1.193 (1.125–1.265)	< 0.001	1.198 (1.129–1.271)	< 0.001
cuUHR, per 1-SD increase	1.151 (1.096–1.208)	< 0.001	1.197 (1.139–1.257)	< 0.001	1.198 (1.142–1.258)	< 0.001
CES-D 2011, per 5-point increase	1.179 (1.126–1.234)	< 0.001	1.157 (1.104–1.213)	< 0.001	1.158 (1.104–1.215)	< 0.001
CES-D 2015, per 5-point increase	1.211 (1.158–1.265)	< 0.001	1.198 (1.146–1.253)	< 0.001	1.203 (1.149–1.259)	< 0.001
cuCESD, per 5-score-year increase	1.062 (1.048–1.076)	< 0.001	1.058 (1.044–1.072)	< 0.001	1.059 (1.045–1.074)	< 0.001

Note. Separate Cox models were fitted for each exposure. Model 1 was unadjusted; Model 2 adjusted for age and sex; Model 3 additionally adjusted for education, marital status, residence, and current smoking. Covariates were assessed in 2011. Exposure increments are specified in the row labels. All models included 5617 participants and 1030 incident CMM events after the 2015 landmark.

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CMM, cardiometabolic multimorbidity; cuCESD, cumulative depressive symptom burden; cuUHR, cumulative uric acid-to-HDL cholesterol ratio; HR, hazard ratio; SD, standard deviation; UHR, uric acid-to-HDL cholesterol ratio.

Restricted cubic spline analyses showed overall positive associations for both cumulative exposures (Fig. 2). There was evidence of nonlinearity for cuUHR (*P* for overall association < 0.001; *P* for nonlinearity = 0.034). For cuCESD, the overall association was significant, with no clear evidence of departure from linearity (*P* for overall association < 0.001; *P* for nonlinearity = 0.239).

3.3 Joint associations and absolute risk

Crude CMM event proportions were 10.46%, 17.25%, 20.47%, and 23.92% in the low/low, high-cuUHR/low-cuCESD, low-cuUHR/high-cuCESD, and high/high groups, respectively (Table 3). Relative to low/low, the fully adjusted HR was 1.833 (95% CI 1.471–2.283) for high cuUHR/low cuCESD and 2.020 (95% CI 1.638–2.490) for low cuUHR/high cuCESD. The high/high group had the largest HR (2.550, 95% CI 2.063–3.152). In a separate exploratory Cox model, each one-domain increase in the ordinal joint-exposure score was associated with a 52.2% higher hazard after full adjustment (HR 1.522, 95% CI 1.385–1.673; $P < 0.001$).

Table 3
Joint associations of cumulative UHR and depressive symptom burden with incident cardiometabolic multimorbidity

Joint exposure group	N	Events	Event proportion, %	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Low cuUHR + Low cuCESD	1157	121	10.46	1.000 (Reference)	1.000 (Reference)	1.000 (Reference)
High cuUHR + Low cuCESD	1513	261	17.25	1.734 (1.397–2.151)	1.840 (1.478–2.292)	1.833 (1.471–2.283)
Low cuUHR + High cuCESD	1651	338	20.47	2.093 (1.701–2.577)	2.029 (1.648–2.499)	2.020 (1.638–2.490)
High cuUHR + High cuCESD	1296	310	23.92	2.528 (2.049–3.120)	2.538 (2.055–3.135)	2.550 (2.063–3.152)
Ordinal joint-exposure score, per one-domain increase				1.516 (1.380–1.664)	1.517 (1.381–1.666)	1.522 (1.385–1.673)

Note. Median cutoffs were 0.356078 ratio-years for cuUHR and 28 score-years for cuCESD; values below each cutoff were classified as low and values at or above it as high. Event proportions equal events/N × 100%. Cox Model 1 was unadjusted; Model 2 adjusted for age and sex; Model 3 additionally adjusted for education, marital status, residence, and current smoking. The ordinal score counted high-exposure domains: 0 for low/low, 1 for either single-high group, and 2 for high/high. Separate Cox models estimated HRs per one-domain increase. All non-reference comparisons and score associations had P < 0.001.

Abbreviations: CI, confidence interval; CMM, cardiometabolic multimorbidity; cuCESD, cumulative depressive symptom burden; cuUHR, cumulative uric acid-to-HDL cholesterol ratio; HR, hazard ratio.

Standardized 3-year risks followed the same ordering (Supplementary Table S7). Estimated risk was 6.30% (95% CI 5.17%–7.46%) for low/low and 11.24% (9.83%–12.75%) for high cuUHR/low cuCESD. It

was 12.25% (10.96%–13.66%) for low cuUHR/high cuCESD and 15.21% (13.62%–16.92%) for high/high exposure.

3.4 Effect modification by cumulative depressive symptom burden

The continuous interaction model indicated effect modification of the relative cuUHR–CMM association by depressive symptom burden (Table 4). The fully adjusted product-term HR was 0.989 (95% CI 0.981–0.998; Wald *P* = 0.011), with likelihood-ratio *P* = 0.006. This estimate indicated a weaker relative cuUHR association at higher cuCESD levels.

Table 4
Continuous multiplicative interaction between cumulative UHR and cumulative depressive symptom burden

Variable	Model 1 HR (95% CI)	P value	Model 2 HR (95% CI)	P value	Model 3 HR (95% CI)	P value
cuUHR, per 1-SD increase	1.209 (1.146–1.275)	< 0.001	1.242 (1.175–1.313)	< 0.001	1.244 (1.176–1.314)	< 0.001
cuCESD, per 5-score-year increase	1.068 (1.054–1.082)	< 0.001	1.062 (1.047–1.076)	< 0.001	1.062 (1.048–1.077)	< 0.001
cuUHR x cuCESD	0.990 (0.981–0.998)	0.016	0.989 (0.981–0.998)	0.016	0.989 (0.981–0.998)	0.011
P for interaction (LRT)	-	0.009	-	0.008	-	0.006

Note. Cox models included mean-centered cuUHR and cuCESD, scaled per 1 SD (0.1533 ratio-years) and 5 score-years, respectively, and their product term. Main-effect HRs are conditional on the other exposure's mean. Model 1 was unadjusted; Model 2 adjusted for age and sex; Model 3 additionally adjusted for education, marital status, residence, and current smoking. Coefficient P values are from Wald tests; the final row reports likelihood ratio tests comparing models with and without the product term. N = 5617; events = 1030.

Abbreviations: CI, confidence interval; CMM, cardiometabolic multimorbidity; cuCESD, cumulative depressive symptom burden; cuUHR, cumulative uric acid-to-HDL cholesterol ratio; HR, hazard ratio; LRT, likelihood ratio test; SD, standard deviation.

Conditional estimates from this interaction model quantified the pattern (Fig. 3). At the 10th percentile of cuCESD (8.0 score-years), the HR per 1-SD increase in cuUHR was 1.312 (95% CI 1.211–1.423). Corresponding HRs were 1.289 (1.201–1.384) at the 25th percentile, 1.256 (1.184–1.332) at the median,

and 1.207 (1.146–1.271) at the 75th percentile. At the 90th percentile, the HR was 1.162 (1.093–1.235). All five CIs excluded unity.

Quartile-stratified estimates showed a broadly similar pattern (Supplementary Table S1). The HR per 1-SD higher cuUHR was 1.329 (95% CI 1.187–1.487) in cuCESD Q1 and 1.334 (1.171–1.519) in Q2. Estimates were lower in Q3 (HR 1.200, 95% CI 1.078–1.336) and Q4 (HR 1.125, 95% CI 1.035–1.223), with *P* for interaction = 0.020. The pattern was not strictly monotonic, as the Q1 and Q2 estimates were similar.

3.5 Joint response surface and sensitivity analyses

Adding interaction terms between a 3-df natural spline for cuUHR and cuCESD improved fit relative to the spline model without interaction (likelihood-ratio chi-square = 17.975, df = 3, $P < 0.001$). AIC decreased from 17,364.577 to 17,352.602 (Supplementary Table S3). This was a joint test of the spline interaction terms, distinct from the linear product-term test in Table 4. The response surface showed the highest model-based standardized 3-year risks in the region with both high cuUHR and high cuCESD. The cuUHR risk gradient varied across the cuCESD distribution (Fig. 4).

No statistically significant departure from additivity was detected (Supplementary Table S7). The interaction contrast was − 0.020 (95% CI − 0.046 to 0.006), and RERI was − 0.315 (− 0.794 to 0.093). AP was − 0.130 (− 0.321 to 0.039), and S was 0.818 (0.638–1.080). All CIs included their corresponding null values, leaving uncertainty about the magnitude and direction of additive interaction.

With additional adjustment for baseline cardiometabolic disease burden, the continuous interaction estimate moved closer to unity, and its CI included the null (HR 0.992, 95% CI 0.982–1.002; likelihood-ratio *P* = 0.079; Supplementary Table S2). Disease-burden-stratified estimates were also below unity but were not statistically significant. Binary interaction estimates were significant with the 40th-percentile and median cutoffs, but not with the 67th-percentile cutoff (Supplementary Table S6). The binary results therefore depended on the dichotomization threshold.

The global Schoenfeld test provided no evidence against proportional hazards for the fully adjusted interaction model (*P* = 0.959). All reported VIFs were below 2.0 (Supplementary Tables S4–S5). Most observed baseline characteristics had small SMDs in comparisons of included and excluded landmark-eligible participants. Potentially meaningful differences were present for uric acid and selected education and marital-status categories. Biomarker missingness was common among excluded participants, limiting what available-case comparisons could establish about selection bias (Supplementary Table S8).

4. Discussion

In this prospective landmark analysis, higher cuUHR and greater depressive symptom burden during 2011–2015 were each associated with subsequent CMM after covariate adjustment. Participants with dual high exposure had the highest event proportion, adjusted HR, and standardized 3-year absolute risk.

The continuous interaction model indicated a weaker relative cuUHR association at higher cuCESD levels, with a broadly similar pattern in quartile-stratified estimates. However, interaction evidence weakened after adjustment for baseline cardiometabolic disease burden. The findings distinguish the level of joint absolute risk from variation in the relative cuUHR association.

Earlier CHARLS research associated higher UHR with incident CMM and reported a nonlinear exposure-response relationship(11). Other longitudinal work linked depression and depressive symptom severity to CMM(14). A multicohort study using CHARLS and ELSA examined depression and lipid metabolic dysfunction, including the atherogenic index of plasma and remnant cholesterol(15). These exposures were individually and jointly associated with incident CMM. Cross-sectional work in adults with depressive symptoms also examined metabolic risk indices, without establishing temporal ordering(26). We extended this line of research by deriving both exposures from repeated pre-landmark assessments and examining continuous effect modification. Conditional estimates, stratified analyses, and absolute risks clarified how a weaker relative cuUHR association at higher depressive burden could coexist with the highest joint absolute risk.

Uric acid and HDL provide a plausible biological context for the cuUHR association. Experimental studies show that uric acid can impair endothelial function and promote oxidative stress when its pro-oxidant effects predominate(7, 8). These processes are relevant to vascular inflammation and insulin resistance. HDL supports cholesterol efflux and has anti-inflammatory functions; prospective studies have associated these functional measures with cardiovascular events independently of HDL-C concentration(9, 10). UHR combines two relevant biomarker concentrations, but does not directly measure oxidative stress or HDL function. The descriptive differences in UHR and cuUHR, alongside a nonsignificant difference in uric acid alone, do not establish the ratio's added value over its components.

The depressive symptom association is consistent with several proposed psychobiological pathways. Studies in patients with coronary disease associated depression with higher cortisol levels and reduced heart-rate variability, supporting the relevance of neuroendocrine and autonomic pathways(27, 28). Prospective evidence also linked depressive symptoms to subsequent inflammatory change(29). Sleep, physical activity, smoking, diet, adherence, and health-care engagement provide other plausible pathways. Behavioral factors, particularly inactivity, accounted for part of the depression–cardiovascular association in the Heart and Soul Study(12, 13). We did not directly test these mechanisms. Repeated assessment captured symptoms at two points, but could not establish persistent depressive symptoms throughout the interval.

The product-term HR below unity described attenuation of the proportional increase in CMM hazard associated with a fixed cuUHR increment at higher cuCESD levels. It did not imply that greater depressive burden was protective. The standardized 3-year risk remained more than twice as high in the high/high group as in low/low (15.21% versus 6.30%). UHR and depressive symptoms may involve overlapping inflammatory, neuroendocrine, metabolic, or behavioral pathways, although we did not measure such overlap. Relative measures also depend on the risk distribution and model scale, so the

interaction coefficient cannot identify a biological mechanism(23). The weaker interaction after adjustment for baseline disease burden suggests that pre-existing disease may partly shape the observed pattern.

Multiplicative and additive interaction address different questions, and evidence on one scale need not imply evidence on the other(23, 25). The primary model provided evidence of multiplicative effect modification, while risk-based additive-interaction estimates remained inconclusive. Their bootstrap CIs did not rule out additive interaction. The absolute-risk estimates provided a separate description of near-term disease occurrence, with the greatest estimated risk among participants with dual high exposure.

Uric acid and HDL-C are routinely available laboratory measures, and brief depressive symptom instruments can be used in clinical and community settings. Repeated assessment of both domains merits evaluation for CMM risk stratification. However, we did not compare discrimination, calibration, or clinical decision-making against models based on single measurements or conventional risk factors. The prognostic value of integrating metabolic and mental-health assessment therefore remains to be established.

The analysis drew on a large national longitudinal cohort. Strengths included repeated pre-landmark exposure measurements, separation of exposure assessment from outcome follow-up, and analyses of both relative associations and absolute risk. Conditional estimates and quartile stratification helped describe effect modification, but shared data and related models did not provide independent replication. Sensitivity analyses addressed baseline disease burden, cutoff choice, model assumptions, and selection associated with requiring complete repeated exposure measurements.

The observational design precludes causal inference, and residual or unmeasured confounding remains possible. CMM ascertainment relied partly on survey-based disease indicators and may be affected by recall or differences in diagnostic access. Cumulative exposure was approximated from two measurements over four years. With a common interval, these measures were proportional to the two-wave averages and could not capture short-term fluctuations or detailed trajectories. CES-D-10 assessed depressive symptoms rather than a clinical diagnosis of major depressive disorder(19, 20). Requiring repeated biomarker and symptom measurements excluded many eligible participants and may have introduced selection bias. The final cohort should not be assumed to retain the source cohort's national representativeness; similarities among participants with available measurements do not exclude selection bias(30). The interaction also weakened after adjustment for baseline disease burden, indicating sensitivity to model specification. Median cutoffs were sample-specific and cannot be interpreted as clinical thresholds. Finally, the response surface showed point estimates without uncertainty at every exposure combination. External replication and validation are needed before using it to inform clinical decisions.

5. Conclusions

Higher cuUHR and cumulative depressive symptom burden were individually and jointly associated with incident CMM in this CHARLS landmark cohort. Dual high exposure was associated with the highest estimated absolute risk and adjusted HR. In the primary model, the relative cuUHR association weakened at higher depressive burden, but interaction evidence diminished after adjustment for baseline disease burden. These findings warrant replication and assessment of whether repeated metabolic and depressive symptom measurements add prognostic value beyond established risk factors.

Abbreviations

AIC
Akaike information criterion
AP
Attributable proportion due to interaction
CES-D
Center for Epidemiologic Studies Depression Scale
CES-D-10
10-item Center for Epidemiologic Studies Depression Scale
CHARLS
China Health and Retirement Longitudinal Study
CI
Confidence interval
CMM
Cardiometabolic multimorbidity
cuCESD
Cumulative depressive symptom burden
cuUHR
Cumulative uric acid-to-high-density lipoprotein cholesterol ratio
ELSA
English Longitudinal Study of Ageing
HDL
High-density lipoprotein
HDL-C
High-density lipoprotein cholesterol
HR
Hazard ratio
LDL
Low-density lipoprotein
RERI
Relative excess risk due to interaction
S

Synergy index
SD
Standard deviation
SMD
Standardized mean difference
UHR
Uric acid-to-high-density lipoprotein cholesterol ratio
VIF
Variance inflation factor

Declarations

Ethics approval and consent to participate:

The CHARLS protocol was approved by the Institutional Review Board of Peking University (IRB00001052-11015 for the household survey and IRB00001052-11014 for biomarker collection). Written informed consent was obtained from all participants.

Consent for publication:

Not applicable.

Competing interests:

The authors declare no competing interests.

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Author Contribution

Haowei Li and Jiabing He contributed equally to this work. They conceived and designed the study, curated the data, performed the statistical analyses, interpreted the results, and drafted the manuscript. Yuan Gao contributed to data preparation, statistical analysis, and interpretation of the results. Lili Zhang and Jiangting Luo contributed to data checking, literature review, and critical revision of the manuscript. Jia Liu contributed to interpretation of the findings and critical revision of the manuscript. Jingjing Wang contributed to study conception and design, supervised the research, provided methodological guidance,

and critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

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Data Availability

The data analyzed in this study were obtained from the China Health and Retirement Longitudinal Study (CHARLS). Access can be requested through the official CHARLS website (https://charls.pku.edu.cn/) and requires user registration, acceptance of the data use agreement, and approval by the CHARLS team. Redistribution of individual-level data by the authors is not permitted under the CHARLS data use agreement.

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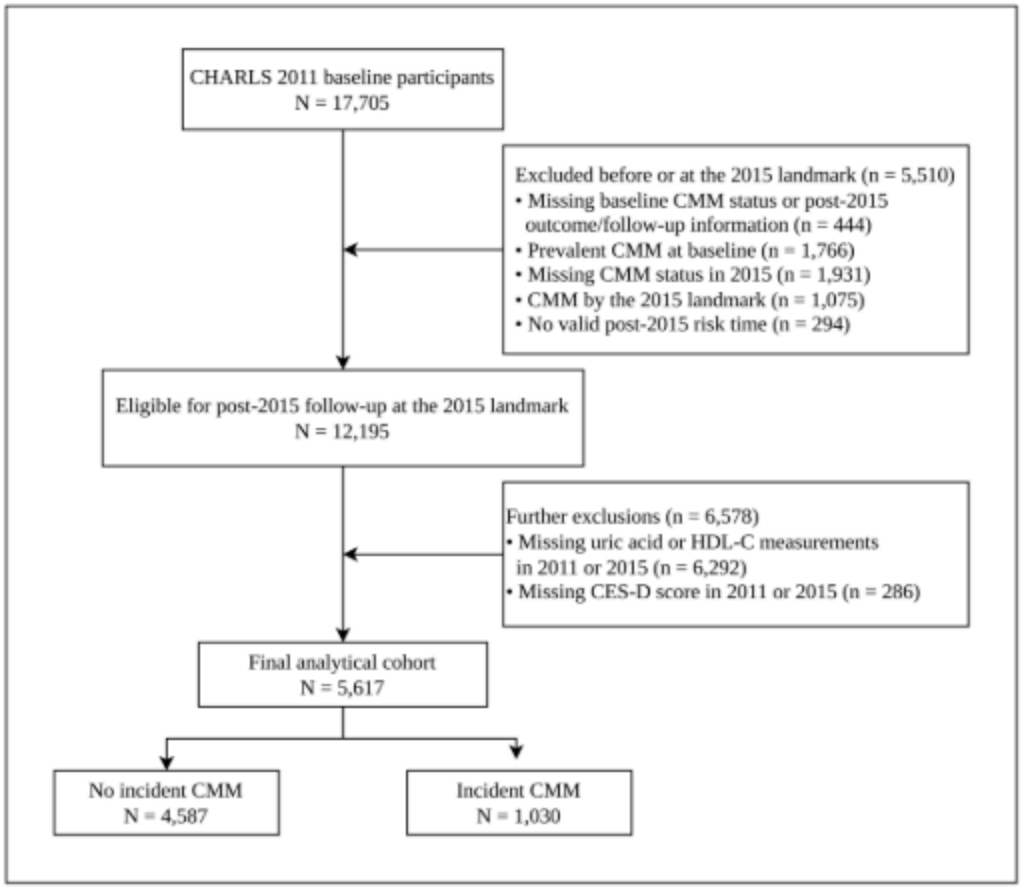
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Figures

Figure 1. Flowchart of participant selection



Note. Exposure assessment used measurements from 2011 and 2015, with outcome follow-up beginning at the 2015 landmark. The final cohort included 5,617 participants without CMM by the landmark, of whom 1,030 subsequently developed CMM.
Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; CHARLS, China Health and Retirement Longitudinal Study; CMM, cardiometabolic multimorbidity; HDL-C, high-density lipoprotein cholesterol.

Figure 1

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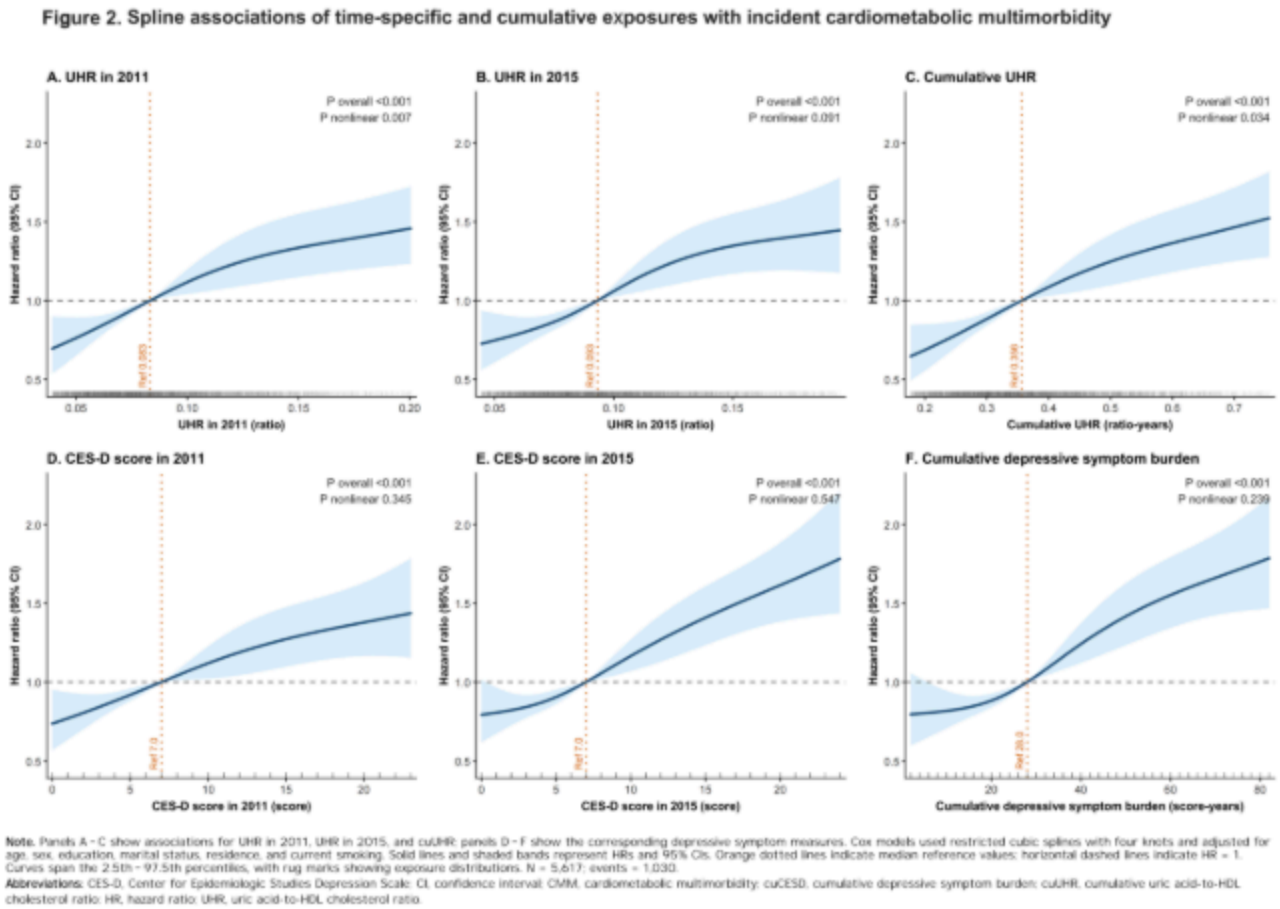
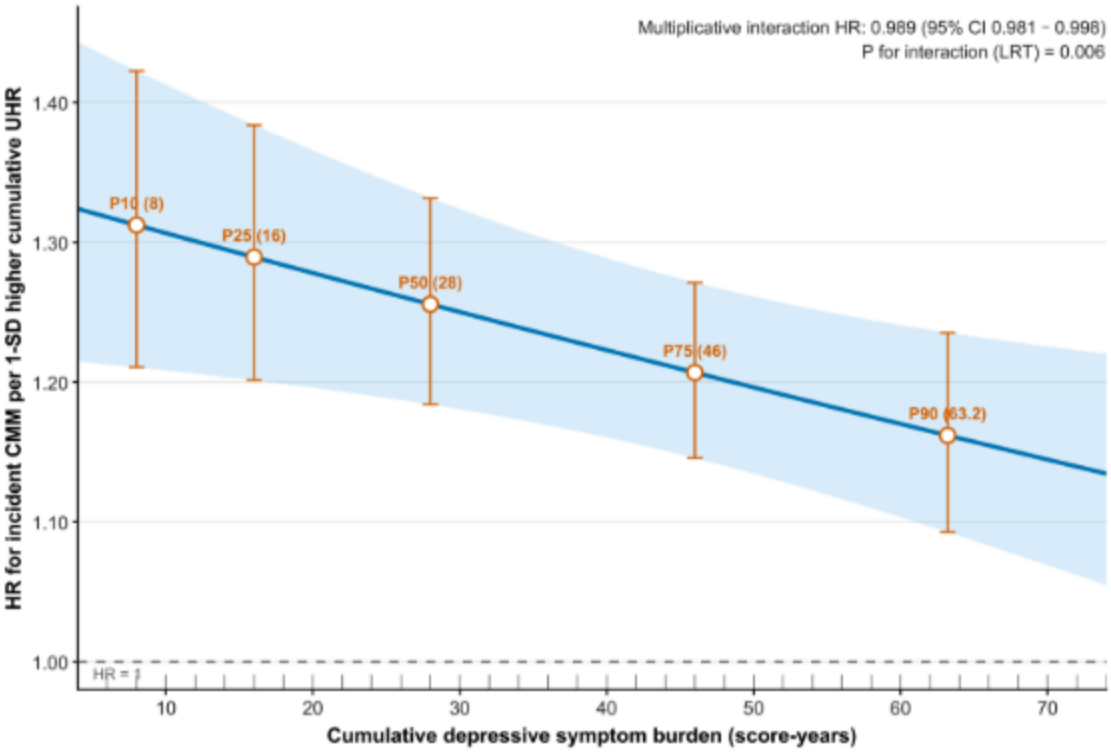


Figure 2

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Figure 3. Conditional association of cumulative UHR with cardiometabolic multimorbidity across cumulative depressive symptom burden



Note. Conditional HRs per 1-SD increase in cuUHR (0.1533 ratio-years) were estimated from a Cox model including both exposures, their interaction, and adjustment for age, sex, education, marital status, residence, and current smoking. cuCESD was scaled per 5 score-years. The line and shaded band show HRs and 95% CIs across the 5th – 95th percentiles of cuCESD; orange points and error bars indicate selected percentiles. Rug marks show the cuCESD distribution. The interaction P value is from a likelihood ratio test. N = 5,617; events = 1,030.

Abbreviations: CI, confidence interval; CMM, cardiometabolic multimorbidity; cuCESD, cumulative depressive symptom burden; cuUHR, cumulative uric acid-to-HDL cholesterol ratio; HR, hazard ratio; SD, standard deviation.

Figure 3

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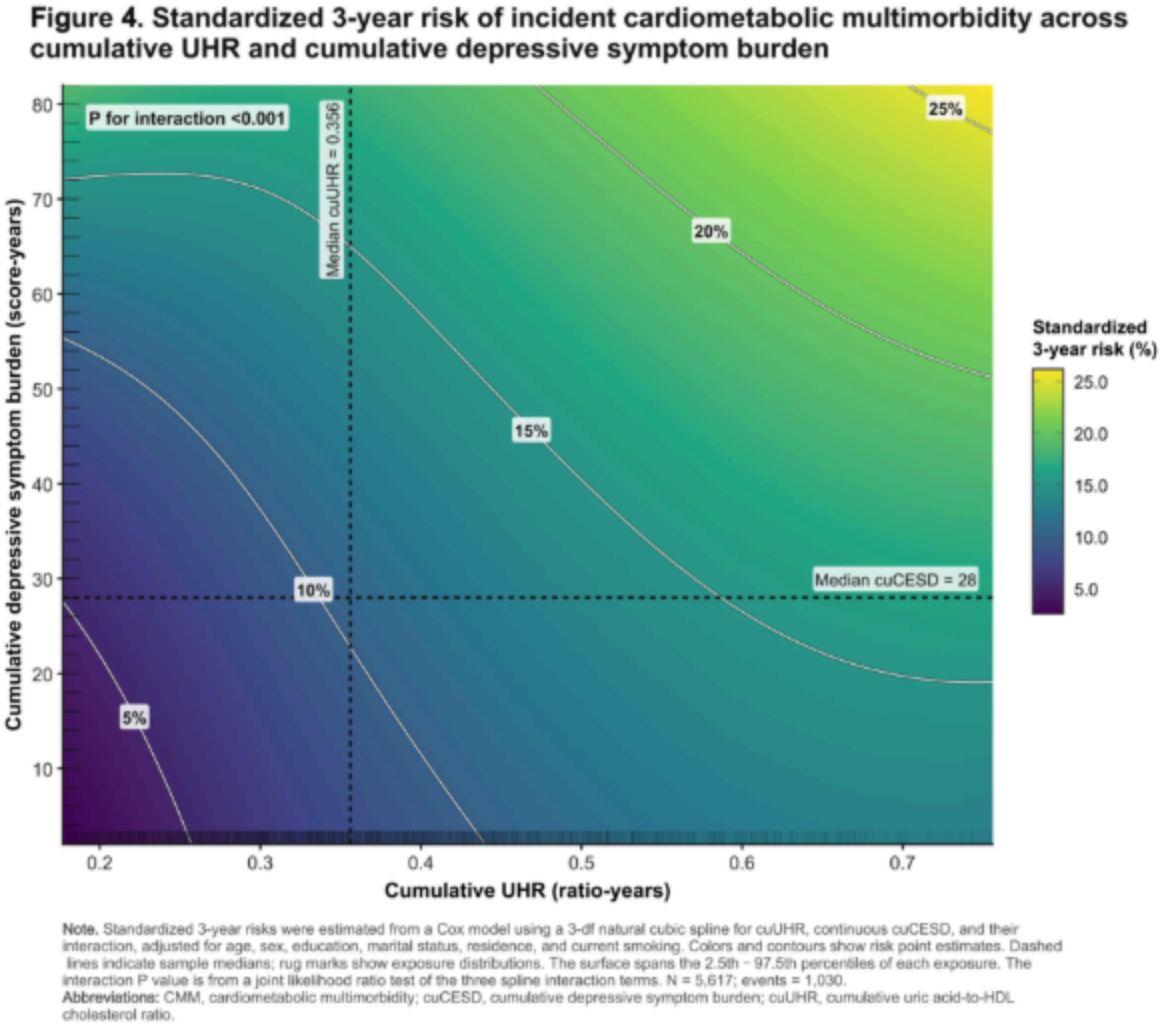


Figure 4

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