Additional file 1

Supplementary Tables and Figures

Sleep deterioration, CKM-related vulnerability, and incident cardiovascular disease in middle-aged and older adults: a longitudinal landmark cohort study

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Contents

Supplementary Table S1. Sensitivity analyses for the joint phenotype.

Sensitivity analysis	Outcome	Estimate type	Estimate (95% CI)	*P*-value	Participants, n	Events	Notes
Excluding 2020	Incident CVD through 2018	RR	2.03 (1.66–2.49)	<0.001	8228	860	
Sleep decrease ≥2 h	Incident CVD through 2020	RR	2.22 (1.83–2.69)	<0.001	8228	1368	
Incident short sleep <6 h	Incident CVD through 2020	RR	1.88 (1.51–2.33)	<0.001	8228	1368	
Persistent short sleep <6 h	Incident CVD through 2020	RR	1.72 (1.39–2.12)	<0.001	8228	1368	
CKM count ≥1	Incident CVD through 2020	RR	2.24 (1.89–2.65)	<0.001	8228	1368	
Expanded CKM without CKD	Incident CVD through 2020	RR	2.06 (1.75–2.43)	<0.001	6832	1177	
Expanded CKM with eGFR-only CKD	Incident CVD through 2020	RR	2.04 (1.73–2.41)	<0.001	6830	1177	eGFR-only CKD proxy.
TyG-WHtR high	Incident CVD through 2020	RR	1.49 (1.23–1.80)	<0.001	6891	1198	Biomarker/body-measurement subsample.
eGFR-only CKD proxy	Incident CVD through 2020	RR	1.29 (0.89–1.88)	0.185	7149	1243	eGFR-only CKD proxy.
Physical activity adjusted	Incident CVD through 2020	RR	2.33 (1.83–2.98)	<0.001	3110	491	Sample size reduced; sensitivity only.
Excluding zero sleep	Incident CVD through 2020	RR	1.99 (1.70–2.32)	<0.001	8210	1364	
Person-period discrete-time	Interval incident CVD	RR	2.07 (1.76–2.43)	<0.001	14897	1368	
Logistic OR alternative	Incident CVD through 2020	OR	2.38 (1.94–2.92)	<0.001	8228	1368	Odds ratio, not risk ratio; estimate shown for the both conditions group.

Notes: The displayed result is the both conditions group for each sensitivity analysis. Logistic sensitivity estimates are ORs, not RRs. TyG-WHtR and eGFR-only CKD analyses are sensitivity analyses only.

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; OR, odds ratio; RR, risk ratio; TyG-WHtR, triglyceride-glucose index multiplied by waist-to-height ratio.

Supplementary Table S2. Follow-up retention by joint phenotype.

Joint phenotype	Eligible before follow-up	Followed in 2018 or 2020	Lost without CVD follow-up	Follow-up, %	Loss, %
Neither condition	4439	4226	213	95.2	4.8
Sleep deterioration only	2088	1972	116	94.4	5.6
CKM vulnerability only	1489	1408	81	94.6	5.4
Both conditions	686	653	33	95.2	4.8

Notes: Follow-up retention was assessed among participants who were CVD-free through 2015 and had a primary joint phenotype.

Abbreviations: CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease.

Supplementary Table S3. Inverse probability of censoring weighted sensitivity analysis.

Joint phenotype	n	Events	IPCW RR (95% CI)	*P*-value
Sleep deterioration only	8228	1368	1.13 (0.98–1.29)	0.082
CKM vulnerability only	8228	1368	1.74 (1.54–1.96)	<0.001
Both conditions	8228	1368	1.98 (1.70–2.31)	<0.001

Notes: The IPCW model used a logistic follow-up model conditional on joint phenotype and Model 3 covariates; weights were truncated at the 1st and 99th percentiles.

Abbreviations: CI, confidence interval; IPCW, inverse probability of censoring weighting; RR, risk ratio.

Supplementary Table S4. Survey-weighted sensitivity analyses.

Weighting approach	n	Sleep deterioration only RR (95% CI)	CKM vulnerability only RR (95% CI)	Both conditions RR (95% CI)
2015 individual weight, community-clustered	8155	1.11 (0.94–1.32)	1.73 (1.49–2.00)	1.86 (1.52–2.27)
2015 biomarker weight, community-clustered	8155	1.11 (0.91–1.36)	1.69 (1.42–2.00)	1.77 (1.41–2.22)
2013 longitudinal individual weight	7093	1.19 (0.99–1.43)	1.81 (1.55–2.11)	1.75 (1.42–2.15)

Notes: Weights were normalized to mean 1. Community-clustered sandwich variance was used when community identifiers were available.

Abbreviations: CI, confidence interval; CKM, cardiovascular-kidney-metabolic; RR, risk ratio.

Supplementary Table S5. Sensitivity analyses incorporating death and Exit-module outcomes.

Outcome extension	n	Events	Sleep deterioration only RR (95% CI)	CKM vulnerability only RR (95% CI)	Both conditions RR (95% CI)
CVD or Exit all-cause death	8234	1387	1.12 (0.98–1.29)	1.74 (1.55–1.96)	1.98 (1.70–2.31)
CVD or Exit heart/stroke proxy	8233	1411	1.10 (0.96–1.25)	1.70 (1.51–1.91)	1.95 (1.68–2.27)

Notes: Death and Exit-module extensions are supplementary only because timing and cause information are less precise than interview-wave self-reported CVD outcomes.

Abbreviations: CI, confidence interval; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; RR, risk ratio.

Supplementary Table S6. Sensitivity analyses using alternative sleep deterioration definitions.

Sleep definition	Operational rule	Exposed n	Exposed, %	Both conditions RR (95% CI)	*P*-value
Primary sleep deterioration ≥1 h	sleep15 - sleep13 ≤ -1	3193	31.9	1.99 (1.70–2.32)	<0.001
Sleep decrease ≥2 h	sleep15 - sleep13 ≤ -2	1528	15.2	2.22 (1.83–2.69)	<0.001
Incident short sleep <6 h	sleep13 ≥6 and sleep15 <6	1289	12.9	1.88 (1.51–2.33)	<0.001
Persistent short sleep <6 h	sleep13 <6 and sleep15 <6	1694	16.9	1.72 (1.39–2.12)	<0.001

Notes: Each row reports the both conditions group under the corresponding sleep definition and the primary CKM vulnerability definition.

Abbreviations: CI, confidence interval; CKM, cardiovascular-kidney-metabolic; RR, risk ratio.

Supplementary Table S7. Multiple-imputation sensitivity analysis.

Exposure group	Imputations	n	Events	RR (95% CI)	*P*-value
Sleep deterioration only	5	8259	1375	1.13 (0.99–1.30)	0.078
CKM vulnerability only	5	8259	1375	1.74 (1.54–1.96)	<0.001
Both conditions	5	8259	1375	2.00 (1.71–2.33)	<0.001

Notes: Multiple imputation used the primary Model 3 covariate set and was conducted as a sensitivity analysis for missing covariate information. Results should be interpreted against the primary complete-case model.

Abbreviations: CI, confidence interval; CKM, cardiovascular-kidney-metabolic; RR, risk ratio.

Supplementary Table S8. Additional prediction analyses.

Model	Apparent AUC	10-fold CV AUC	10-fold CV Brier	Delta AUC vs base	IDI	Continuous NRI
Base model	0.599	0.579	0.1376	Reference	Reference	Reference
Base + sleep deterioration	0.601	0.581	0.1376	0.002	0.001	0.040
Base + CKM vulnerability	0.635	0.619	0.1357	0.040	0.015	0.308
Base + joint phenotype	0.636	0.620	0.1356	0.041	0.015	0.306

Notes: Prediction metrics are exploratory and are intended to assess incremental risk stratification, not to establish a clinical prediction model.

Abbreviations: AUC, area under the receiver operating characteristic curve; CKM, cardiovascular-kidney-metabolic; CV, cross-validated; IDI, integrated discrimination improvement; NRI, net reclassification improvement.

Supplementary Table S9. Subgroup analyses.

Subgroup domain	Subgroup level	n	Events	Both conditions RR (95% CI)	*P*-value
Age	<65 years	5620	810	2.48 (2.05–3.01)	<0.001
Age	≥65 years	2608	558	1.46 (1.14–1.88)	0.003
Sex	Male	3945	610	2.13 (1.65–2.75)	<0.001
Sex	Female	4283	758	1.89 (1.56–2.30)	<0.001
Baseline sleep duration	≥6 h	5670	875	2.16 (1.81–2.59)	<0.001
Baseline sleep duration	<6 h	2558	493	1.58 (1.14–2.21)	0.007
Hukou category	1	6849	1129	2.07 (1.75–2.45)	<0.001
Hukou category	2	1286	224	1.78 (1.19–2.65)	0.005
Hukou category	3	89	14	1.05 (0.24–4.52)	0.950
Hukou category	4	4	1	Not estimable	Not estimable

Notes: Rows report the both conditions group within each subgroup. Very small strata were retained for transparency but should not be interpreted as evidence for absence or presence of heterogeneity.

Abbreviations: CI, confidence interval; CKM, cardiovascular-kidney-metabolic; RR, risk ratio.

Supplementary Table S10. Additional descriptive biomarker analyses across joint phenotypes.

Biomarker	Neither condition	Sleep deterioration only	CKM vulnerability only	Both conditions	Difference: both conditions vs neither condition
BMI, kg/m2	22.76 ± 3.25	22.73 ± 3.18	26.65 ± 3.28	26.34 ± 2.97	3.58
Waist circumference, cm	83.02 ± 9.32	82.80 ± 9.10	95.09 ± 7.60	94.55 ± 7.14	11.52
Systolic blood pressure, mmHg	122.71 ± 17.27	123.66 ± 17.96	141.24 ± 19.78	142.59 ± 19.84	19.87
Diastolic blood pressure, mmHg	72.80 ± 10.25	72.98 ± 10.35	82.38 ± 12.30	82.59 ± 12.37	9.78
Triglycerides	129.43 ± 82.82	128.84 ± 82.41	174.19 ± 102.52	169.74 ± 100.84	40.31
HDL cholesterol	52.55 ± 11.88	53.64 ± 12.26	48.30 ± 10.01	49.08 ± 10.40	-3.47
Glucose	98.08 ± 25.25	97.97 ± 22.77	113.37 ± 42.50	113.55 ± 45.95	15.47
eGFR	94.61 ± 15.20	94.78 ± 14.72	93.61 ± 15.55	92.68 ± 16.88	-1.93
TyG-WHtR	4.52 ± 0.69	4.52 ± 0.67	5.41 ± 0.64	5.42 ± 0.64	0.90

Notes: Values are mean ± SD among participants with non-missing biomarker measurements. This table is descriptive and should not be interpreted as mediation evidence.

Abbreviations: CKM, cardiovascular-kidney-metabolic; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; SD, standard deviation; TyG-WHtR, triglyceride-glucose waist-to-height ratio.

Supplementary Table S11. E-value and lag sensitivity analyses.

Analysis	n	Events	RR (95% CI)	*P*-value	E-value	E-value for CI limit
Primary both conditions	8228	1368	1.99 (1.70–2.32)	<0.001	3.39	2.80
CKM vulnerability only	8228	1368	1.74 (1.54–1.96)	<0.001	2.88	2.46
Sleep deterioration alone	9986	1668	1.15 (1.04–1.27)	0.005	1.56	1.25
2018-only CVD sensitivity	8228	860	2.03 (1.66–2.49)	<0.001	3.48	2.70
Sleep decrease ≥2 h sensitivity	8228	1368	2.22 (1.83–2.69)	<0.001	3.87	3.07
Incident short sleep <6 h sensitivity	8228	1368	1.88 (1.51–2.33)	<0.001	3.16	2.40
Lag sensitivity excluding 2018 early CVD events	6926	508	2.14 (1.62–2.81)	<0.001	3.69	2.63

Notes: E-values quantify the minimum unmeasured-confounding strength, on the risk-ratio scale, needed to move the point estimate or confidence-limit estimate to the null. The lag sensitivity excludes participants with incident CVD by 2018 and evaluates later CVD reported by 2020.

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; RR, risk ratio.

Supplementary Table S12. External cohort transferability analyses using sleep-symptom proxies.

Cohort	Sleep proxy	n	Events	Sleep-proxy only RR (95% CI)	CKM vulnerability only RR (95% CI)	Both proxies RR (95% CI)
HRS	Restless sleep, binary CESD proxy	4774	1167	1.21 (1.00–1.46)	1.53 (1.37–1.70)	1.55 (1.23–1.95)
ELSA	Trouble falling asleep, ordinal symptom proxy	4768	725	0.97 (0.79–1.19)	1.30 (1.10–1.54)	1.51 (1.14–1.99)
KLoSA	Restless sleep, ordinal CESD proxy	7049	721	0.88 (0.72–1.07)	1.59 (1.31–1.92)	1.82 (1.41–2.36)
MHAS	Feeling rested on waking, ordinal symptom proxy	7716	534	0.95 (0.73–1.25)	1.67 (1.39–2.01)	1.63 (1.22–2.19)
SHARE	Medication for sleep problems, binary proxy	24278	3072	1.14 (0.94–1.38)	1.52 (1.41–1.63)	1.50 (1.12–2.00)

Notes: These analyses used cohort-specific sleep-symptom proxies because repeated sleep-duration measures were not available in this analysis. They are exploratory external cohort transferability checks and are not equivalent to the CHARLS sleep-deterioration exposure.

Abbreviations: CHARLS, China Health and Retirement Longitudinal Study; CI, confidence interval; CKM, cardiovascular-kidney-metabolic; RR, risk ratio.

Supplementary Table S13. External cohort transferability analyses using repeated sleep-duration measures.

Cohort	Repeated sleep source	Model n	Events	Event rate, %	Sleep loss, %	CKM vulnerability, %	Sleep deterioration only RR (95% CI)	CKM vulnerability only RR (95% CI)	Both conditions RR (95% CI)	Both conditions *P*-value	Direction
HRS 2012–2016	Derived from paired sleep/wake times	2317	205	8.8	24.6	34.1	1.23 (0.81–1.85)	1.24 (0.91–1.69)	1.55 (1.00–2.39)	0.049	Positive direction
HRS 2014–2018	Derived from paired sleep/wake times	2216	99	4.5	25.2	36.0	0.78 (0.38–1.63)	1.54 (1.00–2.39)	1.62 (0.83–3.15)	0.155	Positive direction
ELSA	Derived from paired sleep/wake times	4290	61	1.4	21.2	20.8	1.11 (0.55–2.24)	1.65 (0.89–3.04)	2.02 (0.76–5.40)	0.161	Positive direction
SHARE	Reported/derived sleep duration	1090	62	5.7	27.6	33.1	0.55 (0.26–1.16)	1.12 (0.64–1.94)	0.63 (0.22–1.79)	0.388	Directionally discordant

Notes: Events and event rates are unweighted counts and proportions within the same complete-case model sample shown in the Model n column. These repeated sleep-duration analyses are exploratory external cohort transferability checks and are distinct from the sleep-symptom proxy analyses in Supplementary Table S12. Results varied across cohorts, with directionally discordant estimates in SHARE.

Abbreviations: CI, confidence interval; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; ELSA, English Longitudinal Study of Ageing; HRS, Health and Retirement Study; RR, risk ratio; SHARE, Survey of Health, Ageing and Retirement in Europe.

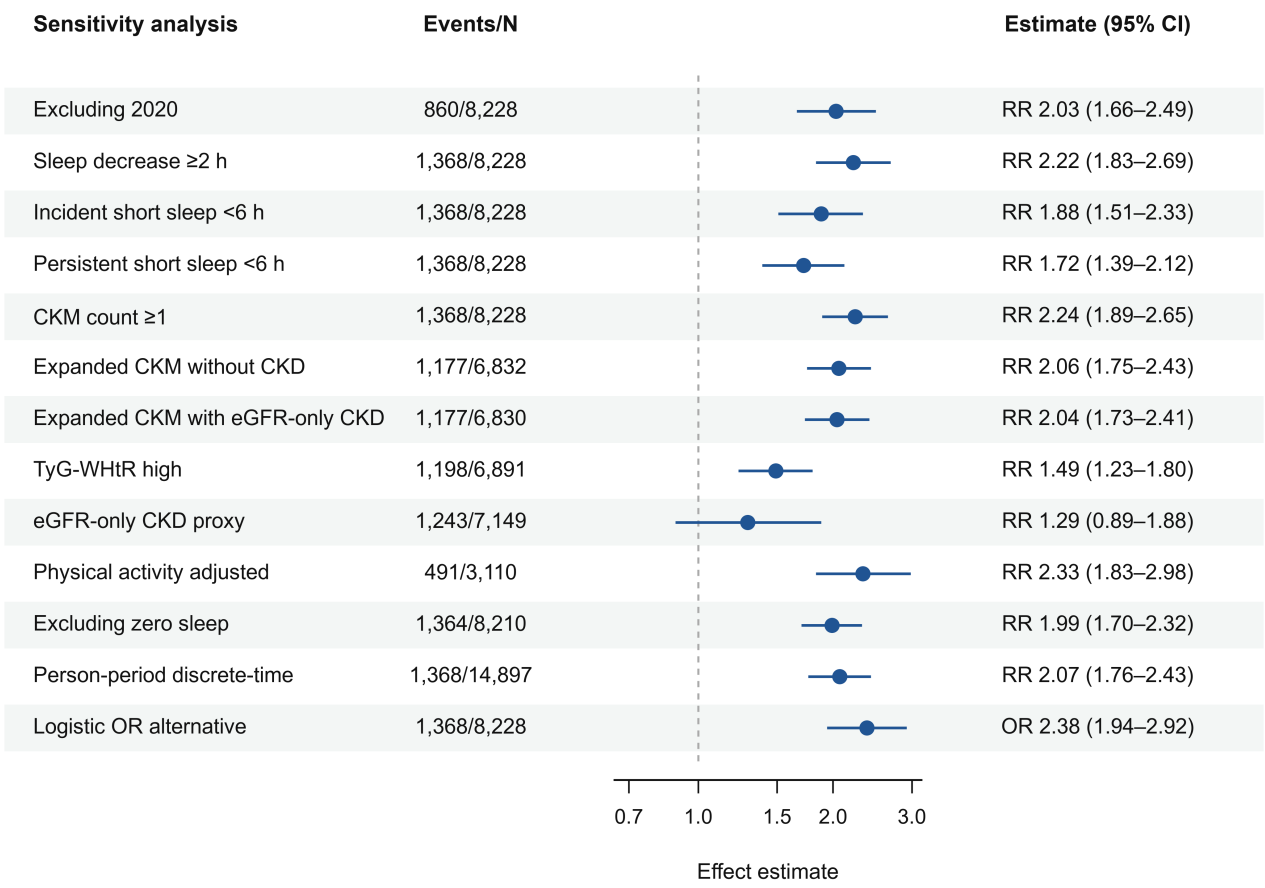
Supplementary Table S14. Secondary cardiovascular outcome analyses.

Outcome	Joint phenotype	Model n	Events	Adjusted RR (95% CI)	*P*-value
Incident heart disease	Sleep deterioration only	8228	988	1.20 (1.02–1.42)	0.024
	CKM vulnerability only	8228	988	1.65 (1.42–1.91)	<0.001
	Both conditions	8228	988	1.82 (1.50–2.21)	<0.001
Incident stroke	Sleep deterioration only	8228	495	0.97 (0.76–1.25)	0.837
	CKM vulnerability only	8228	495	2.02 (1.64–2.50)	<0.001
	Both conditions	8228	495	2.41 (1.86–3.12)	<0.001

Notes: Model 3 adjusted for age, sex, education, hukou/urban-rural status, marital status, smoking, drinking, and baseline nighttime sleep duration. The reference group was the neither-condition group. Secondary outcomes are supportive and were not retained in the main manuscript tables.

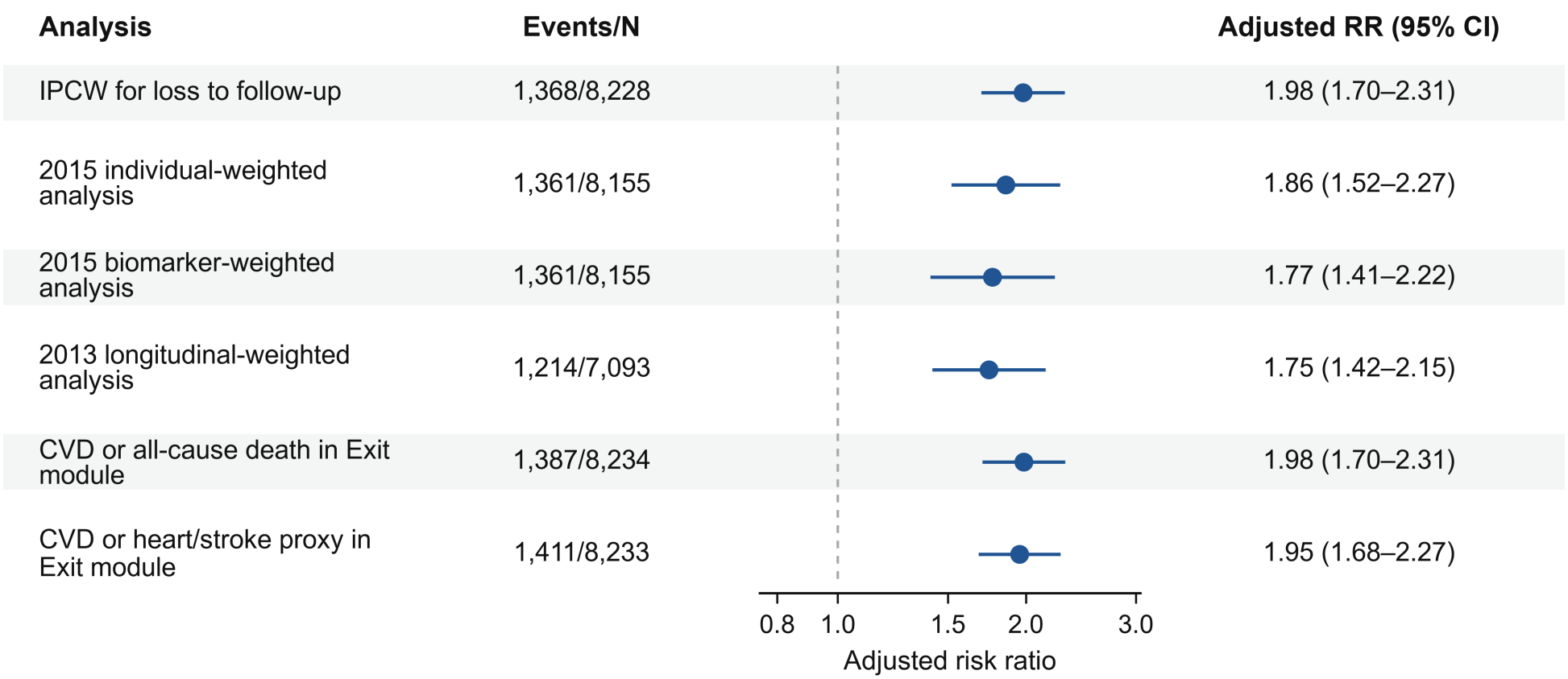
Abbreviations: CI, confidence interval; CKM, cardiovascular-kidney-metabolic; RR, risk ratio.

Supplementary Figure S1. Sensitivity analyses for the joint sleep deterioration-CKM vulnerability phenotype.



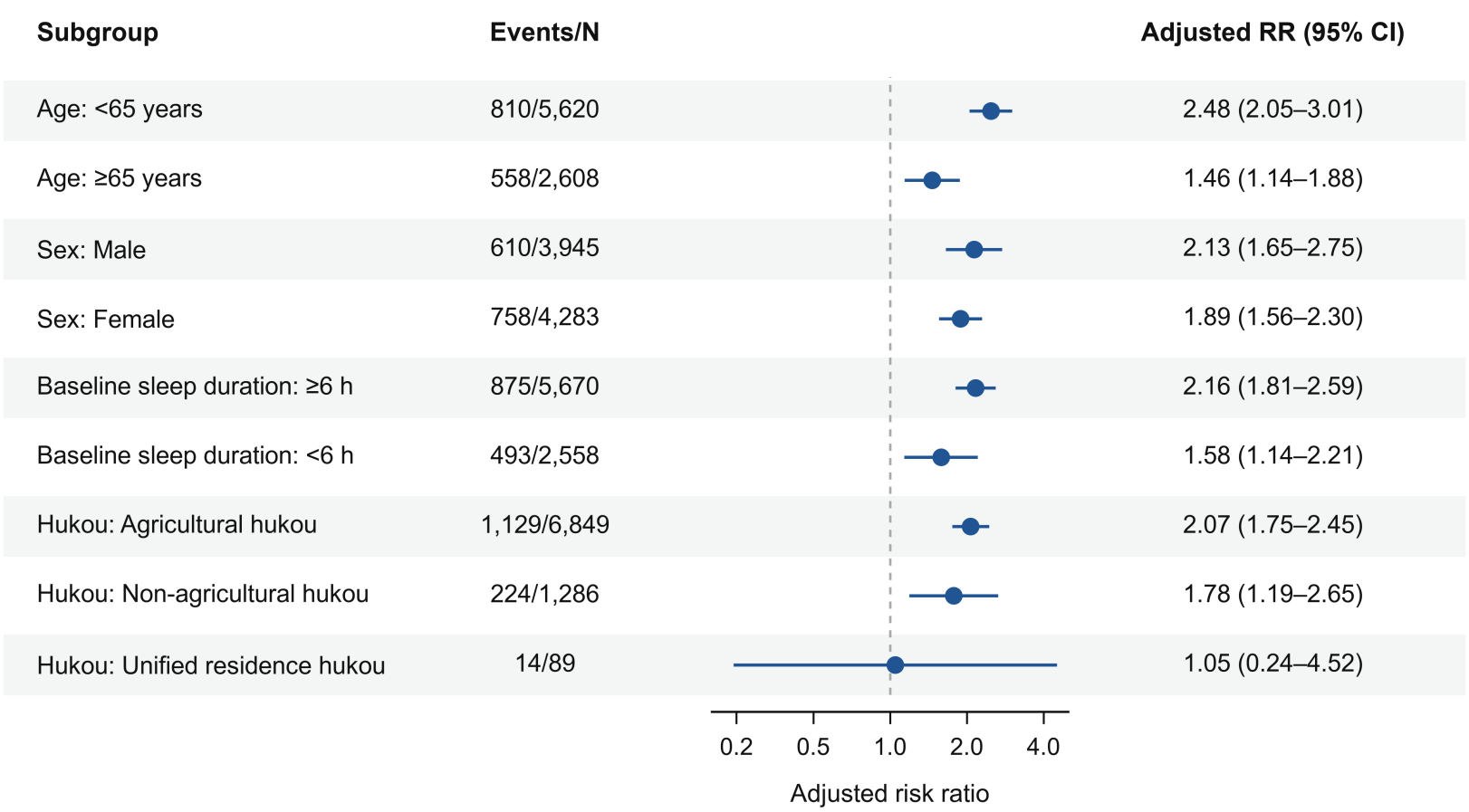
Legend: Circles indicate effect estimates and horizontal lines indicate 95% confidence intervals (CIs) for the both-conditions group compared with the neither-condition group. Estimates are risk ratios (RRs), except for the logistic-regression sensitivity analysis, which is reported as an odds ratio (OR). Events/N are unweighted counts from the corresponding model-specific analytic samples. The vertical dashed line indicates the null value of 1.0. CKM denotes cardiovascular-kidney-metabolic; OR, odds ratio; RR, risk ratio.

Supplementary Figure S2. Additional sensitivity analyses for the joint phenotype and incident cardiovascular disease.



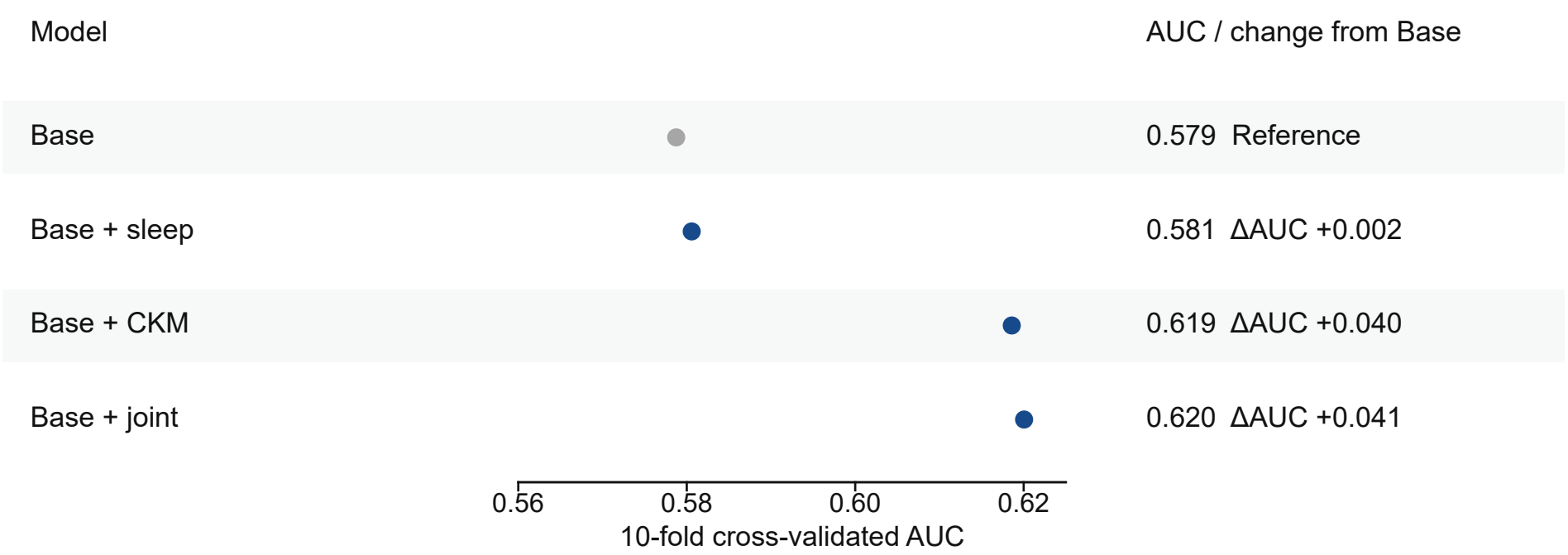
Legend: Circles indicate adjusted RRs and horizontal lines indicate 95% CIs for the both-conditions group compared with the neither-condition group. Analyses include inverse probability-of-censoring weighting, survey-weighted sensitivity analyses, and outcome extensions using death or Exit-module information. Events/N are unweighted counts from the corresponding analytic samples. The vertical dashed line indicates the null value of 1.0. CVD denotes cardiovascular disease; RR, risk ratio.

Supplementary Figure S3. Subgroup analyses of the joint phenotype and incident cardiovascular disease.



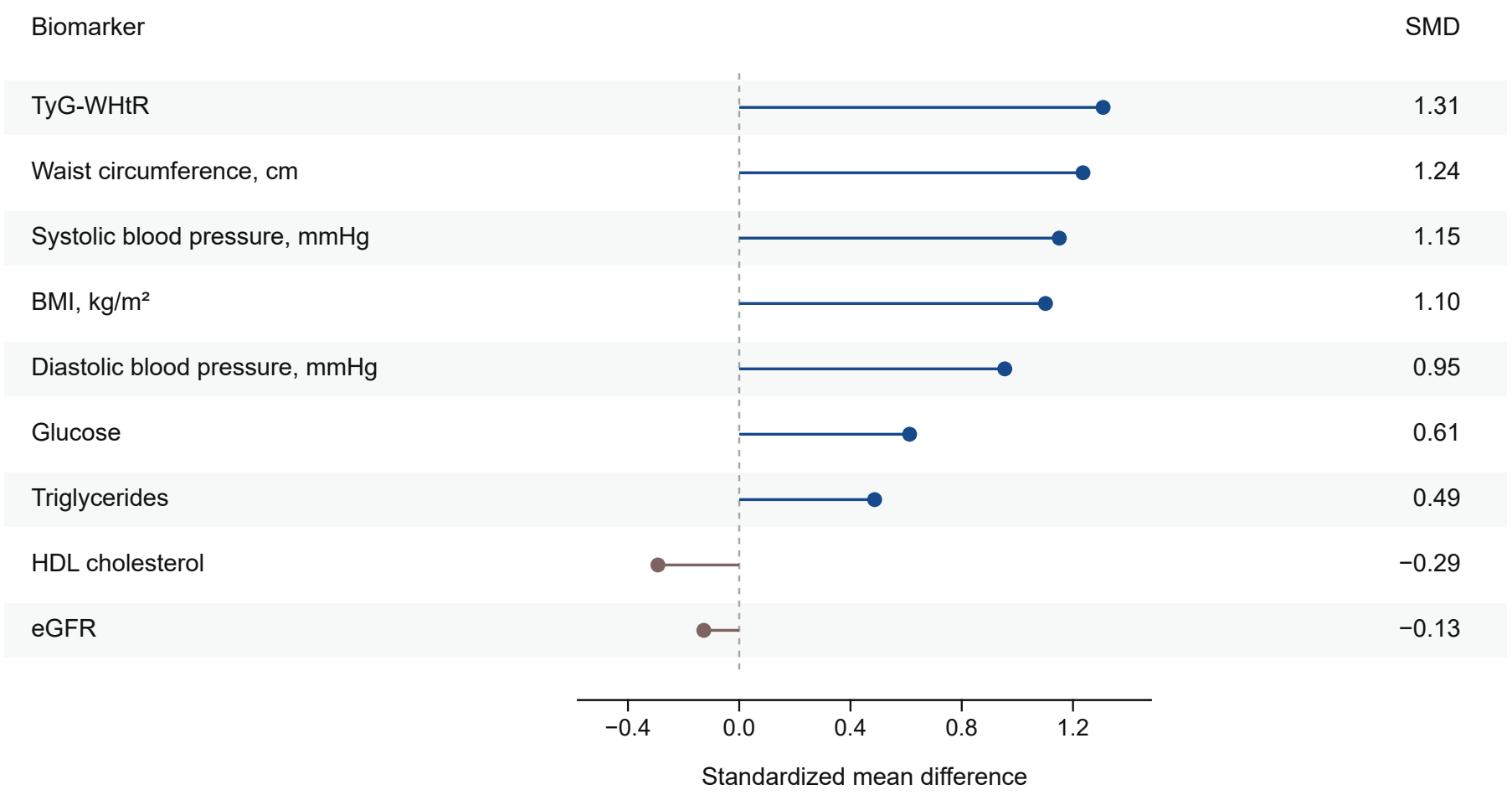
Legend: Circles indicate subgroup-specific adjusted RRs and horizontal lines indicate 95% CIs for the both-conditions group compared with the neither-condition group. Events/N are unweighted subgroup counts from the Model 3 complete-case sample. Formal P values for interaction were not available in the locked subgroup outputs and therefore are not displayed; subgroup-specific association P values were not relabeled as interaction tests. CVD denotes cardiovascular disease; RR, risk ratio.

Supplementary Figure S4. Additional prediction analyses.



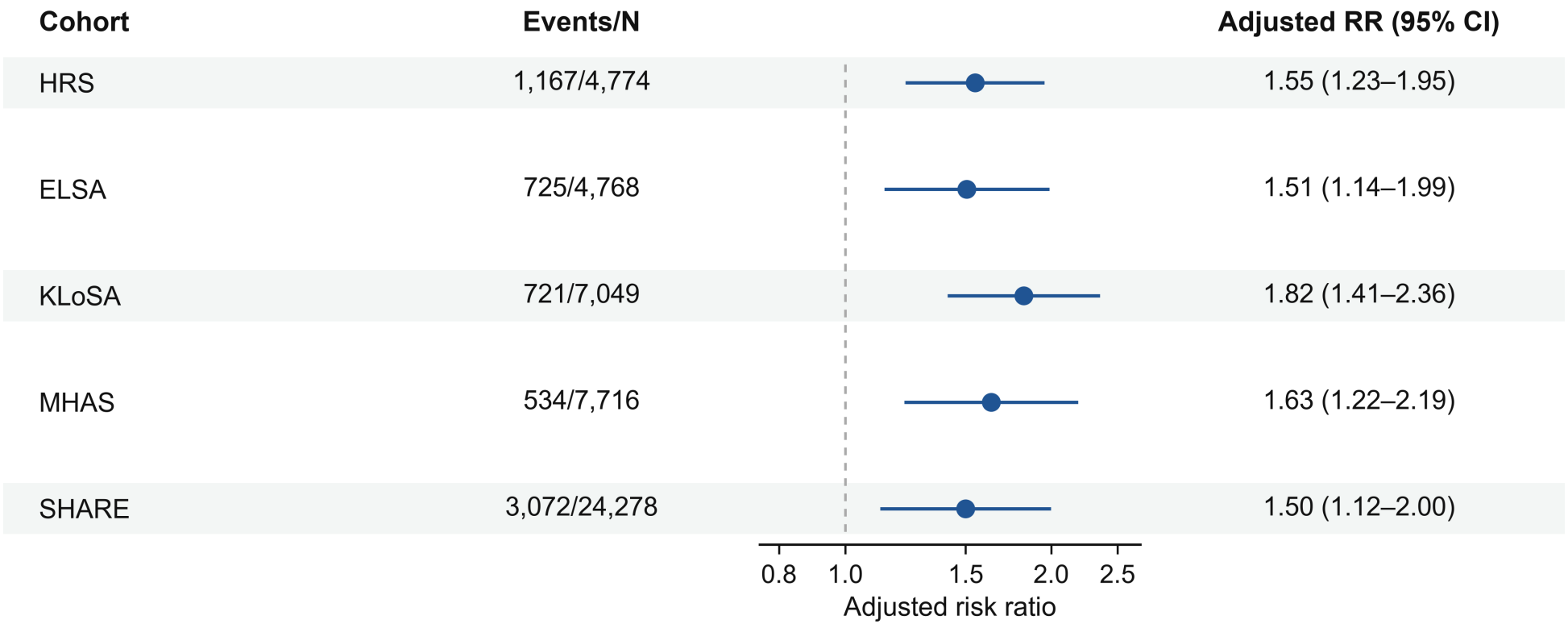
Legend: Points show the 10-fold cross-validated area under the receiver operating characteristic curve (AUC) for the four prediction models. AUC values and changes in AUC relative to the Base model are shown directly. Confidence intervals are not shown. This was an exploratory prediction analysis. CKM denotes cardiovascular-kidney-metabolic.

Supplementary Figure S5. Additional descriptive biomarker analyses.



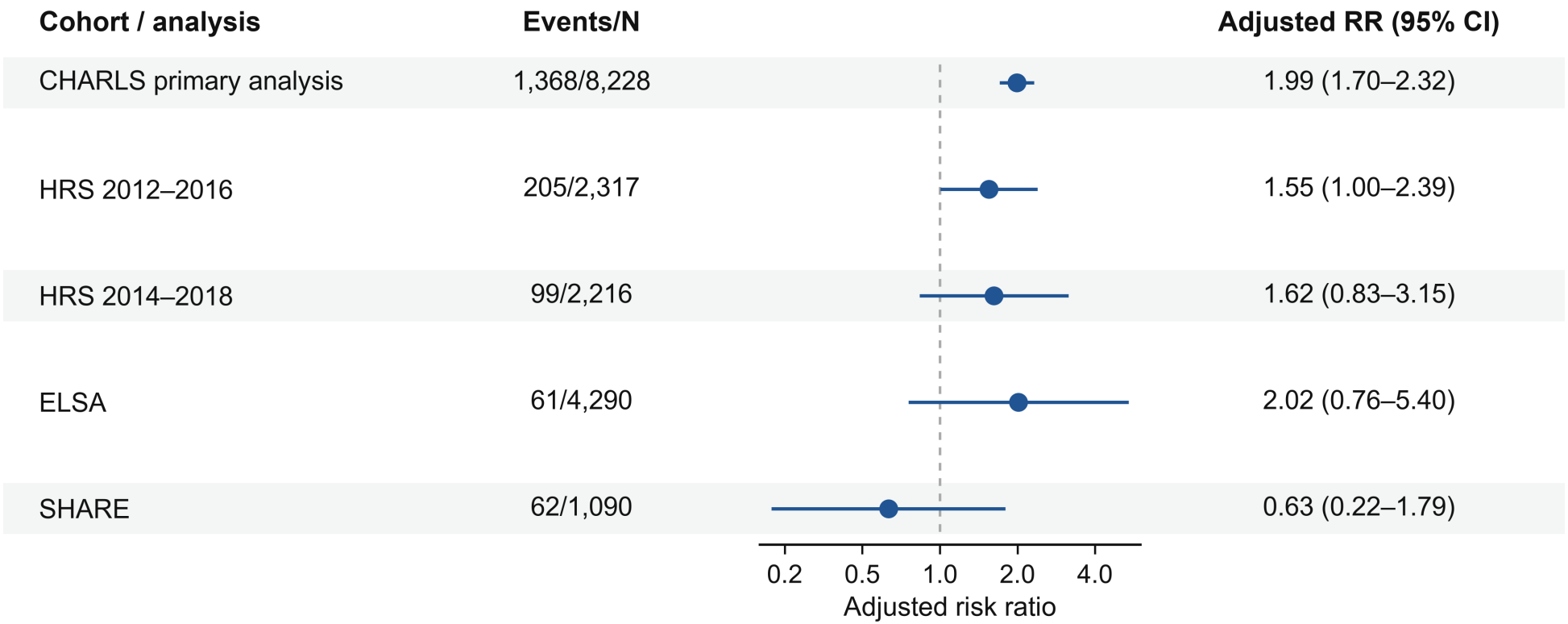
Legend: Points show standardized mean differences comparing the both-conditions group with the neither-condition group; thin lines extend from the null value of 0. Biomarkers are ordered by the absolute magnitude of the standardized mean difference. Positive values indicate higher levels in the both-conditions group and negative values indicate lower levels. Confidence intervals and P values are not shown. These analyses are descriptive and not evidence of mediation. BMI denotes body mass index; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; TyG-WHtR, triglyceride-glucose-waist-to-height ratio.

Supplementary Figure S6. External cohort transferability analyses using sleep-symptom proxies.



Legend: Circles indicate adjusted RRs and horizontal lines indicate 95% CIs for the joint sleep-proxy deterioration and CKM-vulnerability group compared with the cohort-specific reference group. Events/N are unweighted counts from each complete-case model sample. These exploratory external analyses used cohort-specific symptom proxies and are not equivalent to the CHARLS repeated sleep-duration exposure. The vertical dashed line indicates the null value of 1.0. CKM denotes cardiovascular-kidney-metabolic; RR, risk ratio.

Supplementary Figure S7. Repeated sleep-duration external cohort transferability analyses.



Legend: Circles indicate adjusted RRs and horizontal lines indicate 95% CIs for the both-conditions group compared with the neither-condition group in CHARLS and the corresponding repeated-sleep groups in HRS, ELSA, and SHARE. Events/N are unweighted counts from each complete-case model sample. These analyses were exploratory transferability checks and showed cohort heterogeneity. The vertical dashed line indicates the null value of 1.0. CHARLS denotes China Health and Retirement Longitudinal Study; CI, confidence interval; ELSA, English Longitudinal Study of Ageing; HRS, Health and Retirement Study; RR, risk ratio; SHARE, Survey of Health, Ageing and Retirement in Europe.