

Supplementary Information

Multidomain vulnerability burden and incident cardiovascular disease among middle-aged and older adults: evidence from three longitudinal ageing cohorts

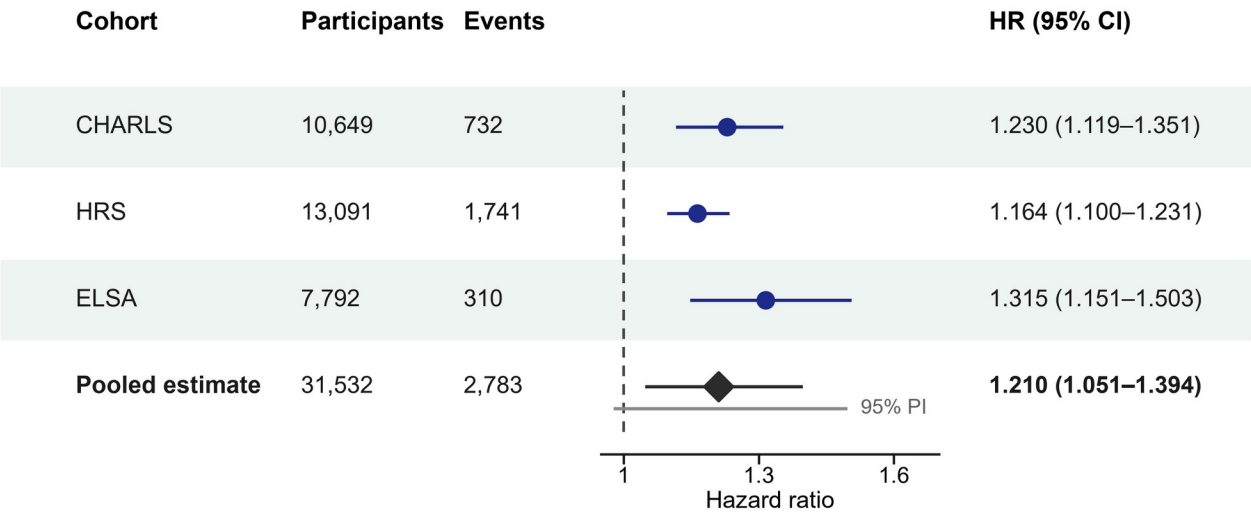
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Supplementary Figure S1



Supplementary Figure S1. Association of multidomain vulnerability burden with incident stroke. Cohort-specific hazard ratios were estimated using adjusted Cox models including age, sex, hypertension, diabetes, current smoking, and body mass index (BMI). The pooled estimate used random-effects meta-analysis with restricted maximum likelihood and Hartung-Knapp adjustment. The grey horizontal line indicates the 95% prediction interval, which crossed 1.

Alt text: Supplementary forest plot showing cohort-specific and pooled hazard ratios for incident stroke per one additional vulnerability domain across CHARLS, HRS and ELSA, with confidence intervals and a 95% prediction interval that crosses 1.

Supplementary Table S1. Cohort-specific variable definitions.

Item	Definition	Notes
Baseline wave	CHARLS wave 1 (2011); HRS wave 5 (2000); ELSA wave 4 (2008)	Fixed before analysis
Eligibility	Age ≥50 years; baseline heart disease=0 and stroke=0	Baseline CVD missing excluded
Exposure	Multidomain vulnerability burden, range 0–3	ADL/IADL limitation, mobility limitation, elevated depressive symptoms
ADL/IADL limitation	CHARLS: adlab_c, iadl; HRS: adl6a, iadl5a; ELSA: adltot6, iadltot2_e	Any observed difficulty=1; complete observed normal items=0; partial missing without positive=missing
Main mobility limitation	CHARLS: walk100a; HRS: walk1a, walksa, walkra; ELSA: walk100a, walkra	Same complete-required missing rule for multi-item domains
Strict mobility sensitivity	CHARLS: walk100a; HRS: walk1a; ELSA: walk100a	Single-item definition
Elevated depressive symptoms	CHARLS CES-D-10 ≥10; HRS/ELSA CES-D-8 ≥4	Harmonised participant-wave variables
Incident overall CVD	First new report of heart disease or stroke	Any explicit component positive defines CVD positive
Incident stroke	First new report of stroke	Prespecified secondary outcome
Event time	Midpoint between last negative and first positive wave	First positive survey date used only as sensitivity analysis

Notes: Multi-item functional domains were coded as present if any observed item indicated difficulty, absent only when all prespecified items were observed and normal, and missing when no positive item was observed but at least one prespecified item was missing. Definitions used harmonised participant-wave variables. Event time was assigned to the midpoint between the last negative and first positive survey waves.

Abbreviations: ADL, activities of daily living; CES-D, Center for Epidemiologic Studies Depression Scale; CHARLS, China Health and Retirement Longitudinal Study; CVD, cardiovascular disease; ELSA, English Longitudinal Study of Ageing; HRS, Health and Retirement Study; IADL, instrumental activities of daily living.

Supplementary Table S2. Baseline characteristics according to observed vulnerability burden among participants with complete data for all three vulnerability domains.

Panel	Characteristic	Vulnerability burden 0	Vulnerability burden 1	Vulnerability burden ≥2	P-value
CHARLS	Sample size	4,977	2,911	1,297	
CHARLS	Age, years	60.5 ± 7.5	62.0 ± 8.1	63.4 ± 8.2	<0.001
CHARLS	Male sex	2,854 (57.3)	1,313 (45.1)	511 (39.4)	<0.001
CHARLS	Hypertension	1,054 (21.2)	745 (25.7)	322 (25.0)	<0.001
CHARLS	Diabetes	225 (4.5)	168 (5.8)	65 (5.1)	0.045
CHARLS	Current smoking	1,785 (35.9)	923 (31.7)	369 (28.5)	<0.001
CHARLS	BMI, kg/m ²	23.4 ± 3.9	22.9 ± 3.9	22.3 ± 3.5	<0.001
CHARLS	ADL/IADL limitation	0 (0.0)	981 (33.7)	1,279 (98.6)	—
CHARLS	Mobility limitation	0 (0.0)	17 (0.6)	131 (10.1)	—
CHARLS	Elevated depressive symptoms	0 (0.0)	1,913 (65.7)	1,265 (97.5)	—
CHARLS	Follow-up duration, years	7.2 ± 2.6	6.9 ± 2.7	6.7 ± 2.7	<0.001
CHARLS	Incident CVD events	1,047 (21.0)	770 (26.5)	398 (30.7)	<0.001
CHARLS	Incident stroke events	303 (6.1)	216 (7.4)	110 (8.5)	0.003
HRS	Sample size	8,155	2,206	1,538	
HRS	Age, years	64.5 ± 8.6	67.0 ± 9.8	67.9 ± 10.6	<0.001
HRS	Male sex	3,310 (40.6)	725 (32.9)	385 (25.0)	<0.001
HRS	Hypertension	3,000 (36.8)	999 (45.3)	800 (52.0)	<0.001
HRS	Diabetes	740 (9.1)	283 (12.8)	317 (20.6)	<0.001
HRS	Current smoking	1,181 (14.5)	373 (16.9)	293 (19.1)	<0.001
HRS	BMI, kg/m ²	26.7 ± 4.6	27.7 ± 5.6	29.2 ± 7.0	<0.001
HRS	ADL/IADL limitation	0 (0.0)	445 (20.2)	1,293 (84.1)	—
HRS	Mobility limitation	0 (0.0)	1,016 (46.1)	1,420 (92.3)	—
HRS	Elevated depressive symptoms	0 (0.0)	745 (33.8)	825 (53.6)	—

Panel	Characteristic	Vulnerability burden 0	Vulnerability burden 1	Vulnerability burden ≥2	P-value
HRS	Follow-up duration, years	12.4 ± 6.4	10.5 ± 6.4	8.9 ± 6.1	<0.001
HRS	Incident CVD events	2,894 (35.5)	880 (39.9)	669 (43.5)	<0.001
HRS	Incident stroke events	1,004 (12.3)	316 (14.3)	242 (15.7)	<0.001
ELSA	Sample size	5,303	1,471	787	
ELSA	Age, years	63.1 ± 8.2	66.5 ± 9.9	67.2 ± 10.6	<0.001
ELSA	Male sex	2,512 (47.4)	544 (37.0)	275 (34.9)	<0.001
ELSA	Hypertension	1,708 (32.2)	644 (43.8)	382 (48.5)	<0.001
ELSA	Diabetes	315 (5.9)	167 (11.4)	111 (14.1)	<0.001
ELSA	Current smoking	642 (12.2)	220 (15.0)	183 (23.5)	<0.001
ELSA	BMI, kg/m ²	27.8 ± 4.7	28.9 ± 5.7	30.8 ± 7.0	<0.001
ELSA	ADL/IADL limitation	0 (0.0)	910 (61.9)	765 (97.2)	—
ELSA	Mobility limitation	0 (0.0)	64 (4.4)	541 (68.7)	—
ELSA	Elevated depressive symptoms	0 (0.0)	497 (33.8)	473 (60.1)	—
ELSA	Follow-up duration, years	7.9 ± 2.9	7.2 ± 3.2	6.3 ± 3.3	<0.001
ELSA	Incident CVD events	912 (17.2)	354 (24.1)	217 (27.6)	<0.001
ELSA	Incident stroke events	168 (3.2)	77 (5.2)	55 (7.0)	<0.001

Notes: ADL/IADL limitation, mobility limitation, and elevated depressive symptoms constitute the vulnerability-burden definition; between-group tests were therefore not performed for these three component domains.

Abbreviations: ADL, activities of daily living; BMI, body mass index; CHARLS, China Health and Retirement Longitudinal Study; CVD, cardiovascular disease; ELSA, English Longitudinal Study of Ageing; HRS, Health and Retirement Study; IADL, instrumental activities of daily living.

Supplementary Table S3. Missing data and MICE settings.

Panel A. MICE settings

Cohort	Analysis	Number of imputations	Maximum iterations	Logged events
CHARLS	Primary analysis	20	20	0
CHARLS	Strict mobility sensitivity analysis	20	20	0
HRS	Primary analysis	20	20	0
HRS	Strict mobility sensitivity analysis	20	20	0
ELSA	Primary analysis	20	20	0
ELSA	Strict mobility sensitivity analysis	20	20	0

Panel B. Missingness of main baseline analysis variables

Cohort	Variable	Missing n	Total n	Missing %
CHARLS	ADL/IADL limitation	119	10,652	1.1
CHARLS	Body mass index	2,069	10,652	19.4
CHARLS	Current smoking	366	10,652	3.4
CHARLS	Diabetes	75	10,652	0.7
CHARLS	Elevated depressive symptoms	796	10,652	7.5
CHARLS	Hypertension	42	10,652	0.4
CHARLS	Mobility limitation	660	10,652	6.2
HRS	ADL/IADL limitation	10	13,091	0.1
HRS	Body mass index	211	13,091	1.6
HRS	Current smoking	2	13,091	<0.1
HRS	Diabetes	0	13,091	0.0
HRS	Elevated depressive symptoms	1,002	13,091	7.7
HRS	Hypertension	0	13,091	0.0
HRS	Mobility limitation	229	13,091	1.7

Cohort	Variable	Missing n	Total n	Missing %
ELSA	ADL/IADL limitation	1	7,792	<0.1
ELSA	Body mass index	1,557	7,792	20.0
ELSA	Current smoking	128	7,792	1.6
ELSA	Diabetes	0	7,792	0.0
ELSA	Elevated depressive symptoms	231	7,792	3.0
ELSA	Hypertension	0	7,792	0.0
ELSA	Mobility limitation	1	7,792	<0.1

Notes: Panel A summarizes the prespecified multiple-imputation settings. Panel B summarizes missingness in the main baseline analysis variables. Logged events were zero for all six MICE objects.

Abbreviations: ADL, activities of daily living; CHARLS, China Health and Retirement Longitudinal Study; ELSA, English Longitudinal Study of Ageing; HRS, Health and Retirement Study; IADL, instrumental activities of daily living; MICE, multiple imputation by chained equations.

Supplementary Table S4. Sample inclusion and exclusion flow.

Cohort	Fixed baseline wave	Step	Participants	Notes
CHARLS	1	Fixed baseline wave participants	17,708	
CHARLS	1	Age ≥50 years	13,680	
CHARLS	1	Free of baseline cardiovascular disease	11,330	Baseline CVD missing remains excluded
CHARLS	1	No history of cardiovascular disease before baseline	11,330	Prior heart disease=1 or stroke=1 at any earlier wave excludes the participant
CHARLS	1	Valid post-baseline follow-up	10,652	
HRS	5	Fixed baseline wave participants	19,578	
HRS	5	Age ≥50 years	19,021	
HRS	5	Free of baseline cardiovascular disease	14,038	Baseline CVD missing remains excluded
HRS	5	No history of cardiovascular disease before baseline	14,038	Prior heart disease=1 or stroke=1 at any earlier wave excludes the participant
HRS	5	Valid post-baseline follow-up	13,091	
ELSA	4	Fixed baseline wave participants	11,050	
ELSA	4	Age ≥50 years	10,749	
ELSA	4	Free of baseline cardiovascular disease	8,667	Baseline CVD missing remains excluded
ELSA	4	No history of cardiovascular disease before baseline	8,667	Prior heart disease=1 or stroke=1 at any earlier wave excludes the participant
ELSA	4	Valid post-baseline follow-up	7,792	

Notes: Participants with missing baseline cardiovascular disease status were excluded. Participants with any explicit heart disease or stroke before baseline were permanently excluded. Valid follow-up required at least one post-baseline wave with an informative cardiovascular disease assessment.

Abbreviations: CHARLS, China Health and Retirement Longitudinal Study; CVD, cardiovascular disease; ELSA, English Longitudinal Study of Ageing; HRS, Health and Retirement Study.

Supplementary Table S5. Complete-case association results.

Cohort	Analysis	Exposure	HR	95% CI	P-value
CHARLS	Complete-case analysis	Per one additional vulnerability domain	1.217	1.147–1.291	<0.001
HRS	Complete-case analysis	Per one additional vulnerability domain	1.175	1.133–1.218	<0.001
ELSA	Complete-case analysis	Per one additional vulnerability domain	1.238	1.151–1.331	<0.001

Notes: Hazard ratios are from complete-case adjusted Cox models including age, sex, hypertension, diabetes, current smoking, and body mass index.

Abbreviations: CHARLS, China Health and Retirement Longitudinal Study; CI, confidence interval; ELSA, English Longitudinal Study of Ageing; HR, hazard ratio; HRS, Health and Retirement Study.

Supplementary Table S6. Sensitivity analysis excluding cardiovascular events occurring within the first 2 years of follow-up.

Cohort	Analysis	Exposure	HR	95% CI	P-value
CHARLS	Excluding events within the first 2 years	Per one additional vulnerability domain	1.252	1.186–1.322	<0.001
HRS	Excluding events within the first 2 years	Per one additional vulnerability domain	1.158	1.114–1.203	<0.001
ELSA	Excluding events within the first 2 years	Per one additional vulnerability domain	1.169	1.084–1.261	<0.001

Notes: Hazard ratios are from adjusted Cox models after excluding cardiovascular events occurring within the first 2 years of follow-up. Adjusted models included age, sex, hypertension, diabetes, current smoking, and body mass index.

Abbreviations: CHARLS, China Health and Retirement Longitudinal Study; CI, confidence interval; ELSA, English Longitudinal Study of Ageing; HR, hazard ratio; HRS, Health and Retirement Study.

Supplementary Table S7. Sensitivity analysis using the first positive survey date.

Cohort	Analysis	Exposure	HR	95% CI	P-value
CHARLS	First positive survey date	Per one additional vulnerability domain	1.239	1.178–1.303	<0.001
HRS	First positive survey date	Per one additional vulnerability domain	1.174	1.134–1.215	<0.001
ELSA	First positive survey date	Per one additional vulnerability domain	1.244	1.168–1.326	<0.001

Notes: Hazard ratios are from adjusted Cox models. Adjusted models included age, sex, hypertension, diabetes, current smoking, and body mass index. Event time was assigned to the date of the first positive survey rather than the midpoint of the interval between the last negative and first positive surveys.

Abbreviations: CHARLS, China Health and Retirement Longitudinal Study; CI, confidence interval; ELSA, English Longitudinal Study of Ageing; HR, hazard ratio; HRS, Health and Retirement Study.

Supplementary Table S8. Strict single-item mobility sensitivity analysis.

Cohort	Analysis	Exposure	HR	95% CI	P-value
CHARLS	Strict mobility sensitivity analysis	Per one additional vulnerability domain using the strict mobility definition	1.238	1.177–1.302	<0.001
HRS	Strict mobility sensitivity analysis	Per one additional vulnerability domain using the strict mobility definition	1.173	1.127–1.220	<0.001
ELSA	Strict mobility sensitivity analysis	Per one additional vulnerability domain using the strict mobility definition	1.248	1.171–1.331	<0.001

Notes: Hazard ratios are from adjusted Cox models using the strict single-item mobility definition. Adjusted models included age, sex, hypertension, diabetes, current smoking, and body mass index.

Abbreviations: CHARLS, China Health and Retirement Longitudinal Study; CI, confidence interval; ELSA, English Longitudinal Study of Ageing; HR, hazard ratio; HRS, Health and Retirement Study.

Supplementary Table S9A. Segmented associations within 0–5 years and after 5 years.

Cohort	Follow-up interval	Exposure	HR	95% CI	P-value
CHARLS	0–5 years	Per one additional vulnerability domain	1.237	1.148–1.332	<0.001
CHARLS	>5 years	Per one additional vulnerability domain	1.238	1.157–1.325	<0.001
HRS	0–5 years	Per one additional vulnerability domain	1.208	1.150–1.270	<0.001
HRS	>5 years	Per one additional vulnerability domain	1.142	1.089–1.198	<0.001

Cohort	Follow-up interval	Exposure	HR	95% CI	P-value
ELSA	0–5 years	Per one additional vulnerability domain	1.285	1.189–1.390	<0.001
ELSA	>5 years	Per one additional vulnerability domain	1.159	1.038–1.295	0.009

Supplementary Table S9B. Schoenfeld residual tests for proportional hazards.

Cohort	Term	χ^2	df	P-value
CHARLS	Age	0.235	1	0.628
CHARLS	Male sex	1.103	1	0.294
CHARLS	Hypertension	4.238	1	0.040
CHARLS	Diabetes	0.007	1	0.936
CHARLS	Current smoking	0.003	1	0.959
CHARLS	Body mass index	0.025	1	0.874
CHARLS	Per one additional vulnerability domain	0.029	1	0.865
CHARLS	Global test	6.538	7	0.479
HRS	Age	0.060	1	0.806
HRS	Male sex	2.818	1	0.093
HRS	Hypertension	2.490	1	0.115
HRS	Diabetes	7.259	1	0.007
HRS	Current smoking	3.078	1	0.079
HRS	Body mass index	2.954	1	0.086
HRS	Per one additional vulnerability domain	1.943	1	0.163
HRS	Global test	23.665	7	0.001
ELSA	Age	3.610	1	0.057
ELSA	Male sex	1.651	1	0.199
ELSA	Hypertension	0.991	1	0.319
ELSA	Diabetes	0.009	1	0.924
ELSA	Current smoking	1.433	1	0.231
ELSA	Body mass index	4.681	1	0.030
ELSA	Per one additional vulnerability domain	1.618	1	0.203
ELSA	Global test	14.260	7	0.047

Notes: Panel A shows segmented adjusted Cox associations within 0–5 years and after 5 years of follow-up. Panel B shows Schoenfeld residual tests for the proportional hazards assumption. Exposure-specific tests did not indicate violation of the proportional hazards assumption. Covariate-level tests suggested departures for hypertension in CHARLS, diabetes in HRS and body mass index in ELSA, although the global test was significant only in HRS and ELSA.

Abbreviations: CHARLS, China Health and Retirement Longitudinal Study; CI, confidence interval; ELSA, English Longitudinal Study of Ageing; HR, hazard ratio; HRS, Health and Retirement Study.

Supplementary Table S10. Cohort-specific and pooled stroke results.

Cohort	Participants	Events	Exposure	HR	95% CI	P-value
CHARLS	10,649	732	Per one additional vulnerability domain	1.230	1.119–1.351	<0.001
HRS	13,091	1,741	Per one additional vulnerability domain	1.164	1.100–1.231	<0.001
ELSA	7,792	310	Per one additional vulnerability domain	1.315	1.151–1.503	<0.001
Pooled estimate	31,532	2,783		1.210	1.051–1.394	

Heterogeneity: $I^2=38.4\%$; $\tau^2=0.0013$; Q-test $P=0.199$; 95% prediction interval 0.981–1.493.

Notes: Stroke was a prespecified secondary outcome. Hazard ratios are from the prespecified adjusted analyses. The 95% prediction interval was 0.981–1.493 and included 1.

Abbreviations: CHARLS, China Health and Retirement Longitudinal Study; CI, confidence interval; ELSA, English Longitudinal Study of Ageing; HR, hazard ratio; HRS, Health and Retirement Study.

Supplementary Table S11. Age-stratified associations of multidomain vulnerability burden with incident cardiovascular disease in each cohort.

Cohort	Age group	Analysis n	Events	Exposure	Adjusted HR	95% CI	P-value
CHARLS	50–64 years	7,303	1,676	Per one additional vulnerability domain	1.232	1.156–1.313	<0.001
CHARLS	65–74 years	2,375	688	Per one additional vulnerability domain	1.198	1.091–1.314	<0.001
CHARLS	≥75 years	974	207	Per one additional vulnerability domain	1.376	1.166–1.624	<0.001
HRS	50–64 years	6,754	2,230	Per one additional vulnerability domain	1.230	1.170–1.294	<0.001
HRS	65–74 years	3,856	1,627	Per one additional vulnerability domain	1.219	1.146–1.297	<0.001
HRS	≥75 years	2,481	999	Per one additional vulnerability domain	1.035	0.962–1.113	0.361
ELSA	50–64 years	4,519	677	Per one additional vulnerability domain	1.251	1.135–1.378	<0.001
ELSA	65–74 years	2,167	522	Per one additional vulnerability domain	1.279	1.144–1.430	<0.001
ELSA	≥75 years	1,106	324	Per one additional vulnerability domain	1.186	1.037–1.356	0.013

Notes: These are additional age-stratified analyses. Each age-stratum model retained continuous age adjustment within the stratum and additionally adjusted for sex, hypertension, diabetes, current smoking, and BMI. Effect differences should not be inferred solely from individual age-stratum P-values.

Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio.

Supplementary Table S12. Age-group interaction tests and age-stratified pooled associations.

Panel A. Age-group interaction tests

Cohort	Comparison	Ratio of HRs	95% CI	Interaction <i>P</i> -value	Global interaction <i>P</i> -value
CHARLS	65–74 vs 50–64 years	0.983	0.881–1.097	0.762	0.626
CHARLS	≥75 vs 50–64 years	1.075	0.906–1.277	0.407	0.626
HRS	65–74 vs 50–64 years	0.952	0.883–1.028	0.209	<0.001
HRS	≥75 vs 50–64 years	0.825	0.759–0.897	<0.001	<0.001
ELSA	65–74 vs 50–64 years	0.990	0.862–1.138	0.890	0.610
ELSA	≥75 vs 50–64 years	0.928	0.796–1.082	0.339	0.610

Panel B. Age-stratified pooled associations

Age group	Number of cohorts	Pooled HR	95% CI	I ² , %	τ ²	Q-test <i>P</i> -value	95% prediction interval
50–64 years	3	1.234	1.213–1.255	0.0	0.0000	0.957	1.213–1.255
65–74 years	3	1.224	1.145–1.308	0.0	0.0000	0.658	1.145–1.308
≥75 years	3	1.175	0.825–1.673	81.3	0.0163	0.004	0.611–2.259

Notes: Ratios of hazard ratios compare the association per one additional vulnerability domain in each older age group with that in participants aged 50–64 years. Cohort-specific interaction models included age group, vulnerability burden, their interaction, and the prespecified covariates. Age-stratified pooled estimates were obtained using random-effects meta-analysis with restricted maximum likelihood estimation and Hartung-Knapp adjustment. Because only three cohorts contributed to each age stratum, heterogeneity and prediction intervals should be interpreted cautiously. Estimates among participants aged ≥ 75 years showed substantial between-cohort heterogeneity.

Abbreviations: CI, confidence interval; ELSA, English Longitudinal Study of Ageing; HR, hazard ratio; HRS, Health and Retirement Study; REML, restricted maximum likelihood.

Supplementary Table S13. Individual and mutually adjusted associations of vulnerability domains with incident cardiovascular disease.

Cohort	Domain	Model type	Analysis n	Events	Adjusted HR	95% CI	P-value
Panel A. Individual-domain models							

Cohort	Domain	Model type	Analysis n	Events	Adjusted HR	95% CI	P-value
CHARLS	ADL/IADL limitation	Individual-domain model	10,652	2,571	1.342	1.231–1.462	<0.001
CHARLS	Mobility limitation	Individual-domain model	10,652	2,571	1.132	0.844–1.517	0.407
CHARLS	Elevated depressive symptoms	Individual-domain model	10,652	2,571	1.325	1.219–1.439	<0.001
HRS	ADL/IADL limitation	Individual-domain model	13,091	4,856	1.315	1.218–1.419	<0.001
HRS	Mobility limitation	Individual-domain model	13,091	4,856	1.342	1.251–1.440	<0.001
HRS	Elevated depressive symptoms	Individual-domain model	13,091	4,856	1.202	1.101–1.312	<0.001
ELSA	ADL/IADL limitation	Individual-domain model	7,792	1,523	1.380	1.228–1.551	<0.001
ELSA	Mobility limitation	Individual-domain model	7,792	1,523	1.566	1.336–1.835	<0.001
ELSA	Elevated depressive symptoms	Individual-domain model	7,792	1,523	1.293	1.117–1.497	<0.001
Panel B. Mutually adjusted domain model							
CHARLS	ADL/IADL limitation	Mutually adjusted domain model	10,652	2,571	1.261	1.153–1.379	<0.001
CHARLS	Mobility limitation	Mutually adjusted domain model	10,652	2,571	0.956	0.710–1.287	0.766
CHARLS	Elevated depressive symptoms	Mutually adjusted domain model	10,652	2,571	1.255	1.152–1.369	<0.001
HRS	ADL/IADL limitation	Mutually adjusted domain model	13,091	4,856	1.158	1.062–1.263	<0.001
HRS	Mobility limitation	Mutually adjusted domain model	13,091	4,856	1.244	1.148–1.348	<0.001
HRS	Elevated depressive symptoms	Mutually adjusted domain model	13,091	4,856	1.098	1.001–1.204	0.048
ELSA	ADL/IADL limitation	Mutually adjusted domain model	7,792	1,523	1.241	1.089–1.414	0.001
ELSA	Mobility limitation	Mutually adjusted domain model	7,792	1,523	1.331	1.115–1.589	0.002
ELSA	Elevated depressive symptoms	Mutually adjusted domain model	7,792	1,523	1.165	1.001–1.356	0.048

Notes: These are exploratory construct-decomposition analyses. In Panel A, each domain entered a separate model. In Panel B, the three domains entered the same model. All models adjusted for age, sex, hypertension, diabetes, current smoking, and BMI. These results should not be interpreted as showing that every domain was independently significant in every cohort.

Abbreviations: ADL, activities of daily living; BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; IADL, instrumental activities of daily living.

Supplementary Table S14. Leave-one-domain-out analyses of multidomain vulnerability burden and incident cardiovascular disease.

Excluded domain	Included domains	Cohort	Analysis n	Events	HR per one additional included vulnerability domain	95% CI	P-value	I ² , %	τ ²	Q-test P-value	95% prediction interval
ADL/IADL limitation	Mobility limitation + elevated depressive symptoms	CHARLS	10,652	2,571	1.292	1.197–1.395	<0.001				
ADL/IADL limitation	Mobility limitation + elevated depressive symptoms	HRS	13,091	4,856	1.226	1.167–1.287	<0.001				
ADL/IADL limitation	Mobility limitation + elevated depressive symptoms	ELSA	7,792	1,523	1.327	1.204–1.463	<0.001				
ADL/IADL limitation	Pooled estimate	Pooled			1.265	1.143–1.400		32.0	0.0006	0.253	1.091–1.467
Mobility limitation	ADL/IADL limitation + elevated depressive symptoms	CHARLS	10,652	2,571	1.257	1.192–1.325	<0.001				
Mobility limitation	ADL/IADL limitation + elevated depressive symptoms	HRS	13,091	4,856	1.208	1.147–1.272	<0.001				
Mobility limitation	ADL/IADL limitation + elevated depressive symptoms	ELSA	7,792	1,523	1.283	1.181–1.394	<0.001				
Mobility limitation	Pooled estimate	Pooled			1.240	1.154–1.333		1.1	0.0000	0.387	1.152–1.335
Elevated depressive symptoms	ADL/IADL limitation + mobility limitation	CHARLS	10,652	2,571	1.287	1.191–1.391	<0.001				
Elevated depressive symptoms	ADL/IADL limitation + mobility limitation	HRS	13,091	4,856	1.218	1.167–1.272	<0.001				
Elevated depressive symptoms	ADL/IADL limitation + mobility limitation	ELSA	7,792	1,523	1.302	1.202–1.410	<0.001				
Elevated depressive symptoms	Pooled estimate	Pooled			1.255	1.144–1.377		35.7	0.0006	0.238	1.089–1.447

Notes: These robustness and construct-decomposition analyses are not new instruments. Their purpose is to assess whether the main association was completely driven by any single vulnerability domain. Pooled estimates used random-effects meta-analysis with REML and Hartung-Knapp.

Abbreviations: ADL, activities of daily living; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; IADL, instrumental activities of daily living; REML, restricted maximum likelihood.

Supplementary Table S15. Associations of multidomain vulnerability burden with incident heart disease.

Cohort	Analysis n	Heart disease events	Exposure	Adjusted HR	95% CI	P-value	I ² , %	τ ²	Q-test P-value	95% prediction interval
CHARLS	10,652	2,074	Per one additional vulnerability domain	1.239	1.172–1.310	<0.001				
HRS	13,091	3,937	Per one additional vulnerability domain	1.186	1.142–1.232	<0.001				
ELSA	7,792	1,309	Per one additional vulnerability domain	1.214	1.133–1.301	<0.001				
Pooled estimate				1.206	1.138–1.277		5.8	0.0000	0.431	1.130–1.286

Notes: Incident heart disease was an additional component-outcome analysis. Heart disease and stroke were defined separately, and stroke positivity did not define heart disease positivity. Models adjusted for age, sex, hypertension, diabetes, current smoking, and BMI. Meta-analysis used REML and Hartung-Knapp.

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; REML, restricted maximum likelihood.

Supplementary Table S16. Sensitivity analyses addressing cohort-specific departures from the proportional hazards assumption.

Cohort	Covariate with PH departure	Time interaction used	PH-sensitivity reference HR	PH-sensitivity reference 95% CI	Extended Cox exposure HR	Extended Cox 95% CI	Absolute change	Relative percentage change	Time-interaction P-value
CHARLS	Hypertension	Hypertension × log(time)	1.236	1.176–1.299	1.236	1.176–1.299	-1.79×10^{-4}	−0.01	0.473
HRS	Diabetes	Diabetes × log(time)	1.173	1.134–1.215	1.173	1.133–1.214	-1.69×10^{-4}	−0.01	0.017
ELSA	BMI	BMI × log(time)	1.244	1.167–1.325	1.244	1.168–1.326	7.82×10^{-4}	0.06	0.154

Notes: Reference and extended Cox estimates in Supplementary Table S16 were derived from the full primary analytic samples (CHARLS n=10,652; HRS n=13,091; ELSA n=7,792) using 20 completed datasets generated by multiple imputation for the extension analyses and pooled with Rubin's rules. These sensitivity models were fitted specifically to evaluate cohort-specific departures from the proportional-hazards assumption and were not used as the primary multiply imputed estimates reported in Table 2. The reference model was $\text{Surv}(\text{time to incident cardiovascular disease, incident cardiovascular disease}) \sim \text{age} + \text{sex} + \text{hypertension} + \text{diabetes} + \text{current smoking} + \text{body mass index} + \text{multidomain vulnerability burden}$. The extended models added hypertension × log(time) in CHARLS, diabetes × log(time) in HRS, and body mass index × log(time) in ELSA. Within each cohort, the reference and extended models used the same participants and the same 20 imputed datasets. The reference estimates differ slightly from Table 2 because they were recomputed within the extension-analysis imputation workflow for direct comparison with the extended proportional-hazards sensitivity models.

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; PH, proportional hazards.