

Prior depressive-symptom burden, current deviation from personal history, and incident heart disease: a three-cohort longitudinal study

Wei Jiang

Anhui University of Traditional Chinese Medicine

Pan Liu

Anhui University of Traditional Chinese Medicine

Peiyang Zhou

Anhui University of Traditional Chinese Medicine

Ge Yang

Anhui University of Traditional Chinese Medicine

Yike Wei

Anhui University of Traditional Chinese Medicine

Xiaohua Dai

xin_d3980@163.com

The First Affiliated Hospital of Anhui University of Chinese Medicine

Research Article

Keywords: depressive symptoms, incident heart disease, cardiovascular epidemiology, cardiovascular risk, primary prevention, longitudinal study, multi-cohort study, repeated measures

Posted Date: August 15th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10355469/v1>

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Additional Declarations: No competing interests reported.

Abstract

Background

Depressive symptoms are associated with cardiovascular risk, but epidemiologic analyses commonly use a single baseline or current score even when repeated assessments are available. A current score may reflect long-standing symptom burden, recent departure from personal history, or both. We examined whether separating these components provides distinct information about subsequent heart-disease risk.

Methods

We used person-wave data from adults aged 50 years or older in the Health and Retirement Study (HRS), the Survey of Health, Ageing and Retirement in Europe (SHARE), and the English Longitudinal Study of Ageing (ELSA). Prior burden was defined as the mean of depressive-symptom scores before the current wave. Current deviation was defined as the current score minus that prior mean. Discrete-time survival models estimated associations with survey-reported incident heart disease at the next selected wave. HRS was the primary cohort, SHARE provided an independent EURO-D replication cohort, and ELSA provided a second CES-D-8 cohort. HRS–ELSA heterogeneity was examined on the raw CES-D-8 scale, followed by reweighting of HRS toward the measured ELSA baseline covariate distribution.

Results

The main analyses included 7,094 HRS participants with 821 events, 26,489 SHARE participants with 2,792 events, and 2,271 ELSA participants with 419 events. In HRS, both prior burden and current deviation were associated with incident heart disease, with a larger coefficient for prior burden. SHARE showed a similar ordering using EURO-D. ELSA showed no clear association for either component. HRS–ELSA heterogeneity was present for both components, and reweighting HRS to resemble ELSA on measured baseline characteristics did not materially reduce the HRS associations. HRS supporting analyses linked life-course adversity with depressive-symptom burden and incident heart disease, whereas biomarker findings were limited.

Conclusions

Repeated depressive-symptom histories contained cardiovascular risk information beyond a current score alone in HRS and SHARE, with stronger associations for accumulated prior burden than for current deviation. ELSA did not reproduce this pattern. Repeated symptom measures may improve the epidemiologic characterization of psychosocial cardiovascular risk, but cross-cohort validation is needed before they are used in risk stratification or primary-prevention settings.

1. Introduction

Cardiovascular risk assessment and primary prevention depend on identifying exposures that precede clinical disease and can be measured reliably in population studies. Depressive symptoms have been associated with incident cardiovascular disease across prospective cohorts [1, 2]. However, cardiovascular epidemiology commonly represents depressive symptoms using a single baseline score, a current score, or a binary high-symptom indicator, even when repeated assessments are available.

A single current score can conceal clinically different histories. One participant may have experienced elevated symptoms for years; another may have recently worsened from a previously low level; a third may be improving after earlier distress. These patterns may carry different information about subsequent heart-disease risk because persistent symptoms can accompany long-term behavioural, social, and cardiometabolic vulnerability, whereas recent change may also reflect short-term illness or evolving disease [3].

Trajectory studies have shown that persistent, increasing, and remitting depressive symptoms can differ in their associations with later cardiovascular outcomes [3, 4]. However, trajectory groups do not directly answer a cardiovascular epidemiology question that arises at each follow-up wave: when a current symptom score is observed, how much of its association with subsequent disease reflects accumulated prior burden, and how much reflects recent movement away from the person's own history?

We therefore separated each current depressive-symptom score into two time-ordered components. Prior burden was defined as the mean of symptom scores before the current wave. Current deviation was defined as the current score minus that prior mean. This approach keeps the exposure continuous and person-specific. It does not replace trajectory modelling; it tests whether repeated symptom history contains cardiovascular risk information that is obscured by a cross-sectional snapshot.

We applied this approach to survey-reported incident heart disease in three population-based longitudinal cohorts: the Health and Retirement Study (HRS), the Survey of Health, Ageing and Retirement in Europe (SHARE), and the English Longitudinal Study of Ageing (ELSA) [5–7]. HRS served as the primary cohort, SHARE provided an independent replication using EURO-D, and ELSA provided a second cohort using CES-D-8. This design allowed us to evaluate both reproducibility and cross-cohort heterogeneity in the temporal symptom–heart disease association.

The primary aim was to determine whether prior depressive-symptom burden and current deviation from personal history were independently associated with subsequent incident heart disease and whether prior burden showed the stronger association. A second aim was to test whether the pattern generalized

across cohort settings and persisted after accounting for measured HRS–ELSA compositional differences. In HRS, life-course adversity and selected inflammatory biomarkers were examined as supporting cardiovascular context rather than as formal mediation analyses.

2. Methods

2.1. Data sources and study design

We used repeated measures from HRS, SHARE, and ELSA, three large population-based longitudinal cohorts. HRS was treated as the primary cohort because it included repeated CES-D-8 assessments, life-course adversity information, and biomarker data [5]. SHARE was used as an independent replication cohort with EURO-D [6]. ELSA was used as a second CES-D-8 cohort and as the target for the cross-cohort reweighting analysis [7].

The main analyses used a person-wave design. Analyses were restricted to participants aged 50 years or older at the start of each risk interval. At each eligible wave, depressive-symptom history was constructed from measurements before that wave, and incident heart disease was assessed at the next selected follow-up wave. Participants entered a risk interval only when they were free of heart disease at the start of the interval and had the required symptom history, covariates, and next-wave outcome information. Follow-up stopped after the first incident heart-disease event. This structure preserved temporal ordering between the symptom-history measures and the cardiovascular outcome. The final analytic samples are reported in the Results and cohort flow diagram.

2.2. Depressive-symptom measures and exposure construction

HRS and ELSA used the eight-item Center for Epidemiologic Studies Depression scale (CES-D-8) [8]. SHARE used EURO-D [9]. Total scores were treated as repeated depressive-symptom measures, with higher scores indicating greater symptom burden.

For each eligible person-wave, prior burden was calculated as the mean of all available depressive-symptom scores before the current wave. Current deviation was calculated as the current symptom score minus that prior mean. A positive deviation indicated that the current score was higher than the participant's earlier average; a negative deviation indicated that it was lower. At least two prior symptom assessments were required before a person-wave contributed to the main dynamic analysis.

The decomposed model included prior burden and current deviation simultaneously. A separate current-snapshot model included the current depressive-symptom score as a single exposure. HRS and ELSA primary analyses used cohort-specific standard-deviation scaling. SHARE analyses used a fixed Wave-1 EURO-D standard deviation. Direct HRS–ELSA comparisons also used the raw CES-D-8 point scale.

2.3. Incident heart disease

The outcome was incident heart disease reported at the next selected follow-up wave. Participants were considered at risk only if they had no reported heart disease at the start of the interval. Incident disease was defined as newly reported heart disease at the next wave according to each cohort's harmonized or cohort-specific measure.

Because the outcome came from large longitudinal surveys rather than uniformly adjudicated cardiovascular registries, it should be interpreted as survey-reported incident heart disease [10]. Person-waves with missing next-wave heart-disease status were excluded from the primary outcome model.

2.4. Covariates

Covariate adjustment was prespecified within each cohort. All primary models included follow-up-interval fixed effects. HRS and ELSA models adjusted for life-course adversity, age, sex, education, and BMI. SHARE models adjusted for age, sex, education, BMI, hypertension, diabetes, and partnered status, with country fixed effects. Differences in adjustment sets reflected cohort design and data availability.

Covariates were included to reduce confounding by baseline demographic composition, socioeconomic position, and major cardiometabolic risk factors. The models were not designed or interpreted as causal mediation analyses.

2.5. Primary statistical analysis

Primary analyses used discrete-time survival models in person-wave format. Incident heart disease at the next selected wave was modelled among participants free of heart disease at the start of the interval. Models included interval fixed effects to allow the baseline hazard to vary across follow-up intervals. Standard errors were clustered at the participant level. Hazard ratios and 95% confidence intervals were estimated from complementary log-log models [11].

For each cohort, the current-snapshot model included the current depressive-symptom score as the exposure. The decomposed model included prior burden and current deviation simultaneously. We compared the two decomposed coefficients using a linear contrast. The cohorts were analysed separately rather than pooled because symptom instruments, survey structure, and cohort context differed.

2.6. Diagnostics, sensitivity analyses, and HRS–ELSA reweighting

We examined whether the decomposition produced problematic collinearity using the correlation between prior burden and current deviation, variance inflation factors, and condition-index diagnostics.

Sensitivity analyses tested whether findings depended on prior-history availability, early risk intervals, exposure scaling, outcome observability, country composition, or age. These analyses included complete-history or alternative-history definitions, exclusion of the first risk interval, raw CES-D-8 point-scale

analyses in HRS and ELSA, SHARE observation weighting, country-clustered standard errors, and leave-one-country-out analyses. Age-related effect modification was examined by including interactions of prior burden and current deviation with age modelled continuously per 10 years; analyses using age 65 years at the start of each risk interval as a threshold were secondary. Observation weighting followed inverse-probability weighting principles for incomplete outcome observation [12]. Cohort-specific details are provided in the supplementary tables, including Supplementary Table S6 for age-related analyses.

Because HRS and ELSA both used CES-D-8, we tested HRS–ELSA heterogeneity on the raw CES-D-8 scale using cohort-by-exposure interaction terms. We then reweighted HRS toward the measured baseline covariate distribution of ELSA. Balance was assessed using standardized mean differences, effective sample size, and empirical support diagnostics [13]. Weighted HRS estimates were compared with original HRS estimates and observed ELSA estimates. This analysis tested whether measured baseline composition could account for the HRS–ELSA difference; it was not interpreted as causal transportability.

2.7. HRS supporting analyses

Two supporting analyses were conducted in HRS. First, life-course adversity was examined as an upstream correlate of repeated depressive-symptom burden and incident heart disease. Adversity was analysed as a standardized score. Depressive-symptom burden was summarized using repeated CES-D-8 measures, including mean symptom burden, number of high-burden waves, and endpoint-state categories.

Second, IL-6, sTNFR1, and a prespecified two-marker inflammatory composite were analysed in the HRS biomarker subsample [14]. Biomarker-selection weighting was used because biomarker availability was restricted to a subset of participants. These analyses were secondary and were not designed to test mediation.

2.8. Missing data, ethics, and software

Analyses used complete data for the variables required in each model. Sample sizes therefore differed across the main dynamic analyses, HRS supporting analyses, biomarker analyses, and sensitivity analyses. SHARE outcome observability was evaluated separately because many eligible person-waves lacked next-wave outcome information.

HRS, SHARE, and ELSA are established population-based longitudinal cohorts available through public or registered-access research data repositories, with their own ethical approvals and informed-consent procedures. The present study used de-identified secondary data and did not involve new participant contact.

All analyses were conducted in R. Statistical tests were two-sided, and P values below 0.05 were considered statistically significant.

OpenAI ChatGPT was used solely to assist with debugging R code.

3. Results

3.1. Analytic cohorts

The HRS primary analysis included 7,094 participants, 17,611 person-waves, and 821 incident heart-disease events. SHARE contributed 26,489 participants, 47,295 person-waves, and 2,792 events. ELSA contributed 2,271 participants, 9,248 person-waves, and 419 events. HRS and ELSA used CES-D-8; SHARE used EURO-D (Fig. 1; Table 1).

Table 1
Cross-cohort cardiovascular epidemiology design and outcome framework

Cohort	Analytic role	Psychological measure	Historical burden	Risk intervals	Model and adjustment	Participants	Person-waves	Events	Primary finding
HRS	Primary cohort	CES-D-8	Mean of all available strictly prior CES-D assessments; minimum prior assessments = 2	2016–2018; 2018–2020; 2020–2022	Complementary log-log person-wave model with interval fixed effects and respondent-clustered robust SE; adjusted for life-course adversity, age, sex, education, and BMI	7,094	17,611	821	Both components associated; prior burden stronger
SHARE	Replication cohort	EURO-D total	Mean of all available strictly prior EURO-D assessments; minimum prior assessments = 2	W4–W5; W5–W6; W6–W8; W8–W9	Complementary log-log person-wave model with interval and country fixed effects and respondent-clustered HC0 SE; adjusted for age, sex, education, BMI, hypertension, diabetes, and partnered status	26,489	47,295	2,792	Both components associated; prior burden stronger
ELSA	Same-instrument evaluation and reweighting target	CES-D-8	Mean of all available strictly prior CES-D assessments; minimum prior assessments = 2	W4–W5; W5–W6; W6–W7; W7–W8; W8–W9; W9–W10	Complementary log-log person-wave model with interval fixed effects and respondent-clustered robust SE; adjusted for life-course adversity, age, sex, education, and BMI	2,271	9,248	419	No clear association for either component
Note: Prior burden was defined as the mean of all eligible depressive-symptom assessments strictly before the current wave; at least two prior assessments were required.									
Abbreviations: BMI, body mass index; CES-D, Center for Epidemiologic Studies Depression scale; ELSA, English Longitudinal Study of Ageing; EURO-D, European Depression scale; HRS, Health and Retirement Study; SE, standard error; SHARE, Survey of Health, Ageing and Retirement in Europe.									

3.2. Cardiovascular context of life-course adversity and depressive-symptom burden in HRS

As supporting cardiovascular context, higher life-course adversity was associated with greater depressive-symptom burden in HRS (Fig. 2). Per 1-SD higher adversity, the three-wave mean CES-D-8 burden was higher by 0.124 SD units (95% CI, 0.105–0.142; $P < 0.001$). Higher adversity was also associated with a greater number of high-burden waves from 2012 to 2016 (OR = 1.321; 95% CI, 1.251–1.395; $P < 0.001$).

Compared with stable low burden, higher adversity was associated with incident high burden by 2016 (OR = 1.255; 95% CI, 1.144–1.377; $P < 0.001$), remitted high burden (OR = 1.335; 95% CI, 1.223–1.458; $P < 0.001$), and persistent high burden (OR = 1.497; 95% CI, 1.361–1.645; $P < 0.001$). Higher adversity was also associated with incident heart disease (HR = 1.121; 95% CI, 1.053–1.194; $P < 0.001$). In repeated CES-D-8 models from 2012 to 2016, adversity was associated with higher symptom level at 2012 ($\beta = 0.130$; 95% CI, 0.109–0.152; $P < 0.001$), while the adversity-by-time term was not significant ($\beta = -0.006$ per 2 years; 95% CI, -0.017 to 0.005; $P = 0.258$).

3.3. Primary HRS decomposition analysis

In HRS, the current CES-D-8 snapshot was associated with incident heart disease (HR per cohort-specific SD = 1.185; 95% CI, 1.112–1.262; $P < 0.001$). In the decomposed model, prior burden had an HR of 1.260 (95% CI, 1.163–1.365; $P < 0.001$), and current deviation had an HR of 1.112 (95% CI, 1.026–1.206; $P = 0.010$). The coefficient for prior burden was larger than that for current deviation (β difference = 0.124; 95% CI, 0.027–0.222; $P = 0.013$) (Table 2; Fig. 3).

Table 2
Associations of current and historical depressive-symptom measures with incident heart disease across cohorts

Cohort	Analytic role	Effect unit	Participants	Person-waves	Events	Current snapshot HR (95% CI)	Current P	Historical burden HR (95% CI)	History P	Current deviation HR (95% CI)	Deviation P	History-deviation beta difference (95% CI)
HRS	Primary cohort	Per cohort-specific SD	7,094	17,611	821	1.185 (1.112–1.262)	< 0.001	1.260 (1.163–1.365)	< 0.001	1.112 (1.026–1.206)	0.010	0.124 (0.027–0.222)
SHARE	Construct-level replication	Per fixed SHARE Wave-1 EURO-D SD	26,489	47,295	2,792	1.171 (1.129–1.215)	< 0.001	1.231 (1.173–1.291)	< 0.001	1.136 (1.088–1.186)	< 0.001	0.080 (0.027–0.134)
ELSA	Same-instrument evaluation	Per cohort-specific SD	2,271	9,248	419	0.955 (0.861–1.059)	0.381	1.015 (0.885–1.164)	0.833	0.912 (0.807–1.030)	0.137	0.107 (–0.048–0.262)

Note: Current-snapshot estimates were obtained from separately specified models. Historical-burden and current-deviation estimates were obtained from the joint model containing historical burden and current deviation. HRS and ELSA effects are per cohort-specific SD; SHARE effects are per the fixed Wave-1 EURO-D SD. Effect should therefore not be interpreted as strictly exchangeable across instruments.

Abbreviations: CI, confidence interval; ELSA, English Longitudinal Study of Ageing; EURO-D, European Depression scale; HR, hazard ratio; HRS, Health and Retirement Study; SD, standard deviation; SHARE, Survey of Health, Ageing and Retirement in Europe.

3.4. Cross-cohort replication and evaluation

SHARE showed a similar pattern using EURO-D. The current EURO-D snapshot was associated with incident heart disease (HR per fixed SHARE Wave-1 EURO-D SD = 1.171; 95% CI, 1.129–1.215; $P < 0.001$). In the joint model, prior burden had an HR of 1.231 (95% CI, 1.173–1.291; $P < 0.001$), and current deviation had an HR of 1.136 (95% CI, 1.088–1.186; $P < 0.001$). Prior burden again had the larger coefficient (β difference = 0.080; 95% CI, 0.027–0.134; $P = 0.003$) (Table 2; Fig. 3).

ELSA did not show the same pattern. The current CES-D-8 snapshot was not associated with incident heart disease (HR per cohort-specific SD = 0.955; 95% CI, 0.861–1.059; $P = 0.381$). In the joint model, prior burden had an HR of 1.015 (95% CI, 0.885–1.164; $P = 0.833$), and current deviation had an HR of 0.912 (95% CI, 0.807–1.030; $P = 0.137$). The coefficient difference between prior burden and current deviation was not significant (β difference = 0.107; 95% CI, –0.048 to 0.262; $P = 0.175$).

3.5. Decomposition diagnostics and sensitivity analyses

Prior burden and current deviation were not strongly collinear (Supplementary Fig. S2). The correlation between the two components was –0.291 in HRS, –0.317 in SHARE, and –0.254 in ELSA. The VIFs for prior burden and current deviation were 1.204 and 1.101 in HRS, 1.303 and 1.140 in SHARE, and 1.139 and 1.084 in ELSA.

HRS complete-history analyses were close to the primary estimates. Prior burden had an HR of 1.262 (95% CI, 1.164–1.368; $P < 0.001$), and current deviation had an HR of 1.120 (95% CI, 1.032–1.216; $P = 0.007$). After removal of the first risk interval, prior burden remained associated with incident heart disease (HR = 1.297; 95% CI, 1.173–1.434; $P < 0.001$), while current deviation was weaker and no longer significant (HR = 1.062; 95% CI, 0.960–1.175; $P = 0.246$).

In SHARE, results were stable when history was restricted to the two most recent prior EURO-D measurements, when the number of prior measurements was added to the model, after observation weighting, and in leave-one-country-out analyses. Prior burden remained the larger component across these analyses, and all leave-one-country-out HRs remained above 1.12 for both components.

ELSA sensitivity analyses remained near the null. Complete prior-history analyses, restriction to the first three ELSA intervals, and harmonized-core models without BMI did not reveal a clear positive association for either component.

Continuous age did not clearly modify the associations in HRS or ELSA (joint interaction $P = 0.522$ and $P = 0.093$, respectively). In SHARE, the relative associations attenuated with older age: per 10-year older age, the hazard ratio was multiplied by 0.928 (95% CI, 0.886–0.971; P for interaction = 0.001) for prior burden and by 0.954 (95% CI, 0.912–0.997; P for interaction = 0.038) for current deviation (joint interaction $P = 0.002$). In analyses stratified at age 65 years, joint interaction P values were 0.552 in HRS, 0.029 in ELSA, and 0.048 in SHARE. Point estimates for both components were above 1 in both HRS and SHARE age groups; ELSA stratum-specific estimates were imprecise and did not show consistent positive associations (Supplementary Table S6).

3.6. HRS–ELSA heterogeneity and reweighting

On the common raw CES-D-8 scale, HRS and ELSA differed for both components (Fig. 4). The ELSA-minus-HRS coefficient difference was –0.115 for prior burden (95% CI, –0.211 to –0.019; $P = 0.019$) and –0.116 for current deviation (95% CI, –0.204 to –0.028; $P = 0.010$).

In original HRS models scaled per 1 CES-D-8 point, the HR was 1.132 for prior burden (95% CI, 1.085–1.182; $P < 0.001$) and 1.060 for current deviation (95% CI, 1.014–1.107; $P = 0.009$). After reweighting HRS to the measured baseline covariate distribution of ELSA, the HRs remained positive for prior burden (HR = 1.133; 95% CI, 1.060–1.202; bootstrap $P = 0.004$) and current deviation (HR = 1.066; 95% CI, 1.004–1.139; bootstrap $P = 0.040$). In observed ELSA, the corresponding HRs were 1.009 and 0.944. Weighting reduced the maximum absolute standardized mean difference from 0.481 to 0.024, with an effective sample size of 3,912 and target support coverage of 97.1%.

3.7. Secondary HRS cardiovascular biomarker analysis

In the secondary HRS biomarker sample, sTNFR1 was associated with incident heart disease after biomarker-selection weighting (HR per SD = 1.171; 95% CI, 1.023–1.342; $P = 0.022$). IL-6 and the two-marker inflammatory composite were not associated with incident heart disease. These biomarker results are reported as secondary context rather than evidence of mediation.

4. Discussion

4.1. Principal findings

Across three population-based longitudinal cohorts, separating repeated depressive-symptom measurements into prior burden and current deviation produced distinct patterns of association with incident heart disease. In HRS, both components were associated with the outcome, but prior burden had the larger coefficient. SHARE reproduced this ordering using EURO-D rather than CES-D-8. ELSA showed no clear association for either component. The principal cardiovascular epidemiology finding is therefore not a universal positive association, but a history-dominant risk pattern that was present in two cohorts and absent in a third.

The HRS–ELSA comparison was especially informative because both cohorts used CES-D-8. On the common raw-score scale, associations were stronger in HRS than in ELSA for both prior burden and current deviation. Reweighting HRS to resemble ELSA on the measured baseline variables—age, sex, education, BMI, and adversity—changed the HRS estimates little. Thus, the observed heterogeneity was not explained by the baseline variables included in the weighting model.

4.2. Cardiovascular interpretation of prior burden and current deviation

A current depressive-symptom score does not show how that score developed. The same value may represent sustained symptoms in one participant and a recent increase from a previously low level in another. For cardiovascular risk characterization, these histories may not be equivalent: accumulated burden may mark prolonged exposure to adverse behavioural, autonomic, inflammatory, metabolic, or social conditions, whereas recent deviation may be more sensitive to acute stress, intercurrent illness, or early manifestations of cardiovascular disease.

In this analysis, prior burden used each participant's earlier symptom record as the reference, while current deviation indicated whether the present score was above or below that earlier level. Across four ageing cohorts, transitions toward higher depressive-symptom levels have been associated with greater incident cardiovascular risk, whereas improvement or remission has been associated with lower risk [2]. A recent CHARLS study similarly found that moderate-stable and persistently high depressive-symptom trajectories were associated with incident cardiovascular disease [3], and HRS trajectory analyses have linked repeatedly high symptoms with subsequent stroke [4]. Our decomposition addresses a different question from trajectory classification: it separates the information carried by accumulated prior burden from the information carried by the current departure from each participant's own history. This approach is simpler than trajectory modelling and can update at each follow-up wave without assigning participants to latent trajectory groups.

In HRS and SHARE, prior burden had the larger association after current deviation was included in the same model. Current deviation was not irrelevant, but its association was smaller and was less stable in some HRS sensitivity analyses. A cautious interpretation is that repeatedly elevated symptoms may serve as a marker of more persistent cardiovascular vulnerability, whereas recent deviation may depend more strongly on the timing of measurement and short-term health changes. These observational data do not establish that either component is causal, nor do they show that reducing depressive symptoms would directly lower heart-disease risk.

4.3. Cross-cohort heterogeneity and cardiovascular generalizability

The SHARE result strengthens the reproducibility of the HRS finding. SHARE differed from HRS in geography, survey design, and symptom instrument, yet the ordering of estimates was similar: prior burden showed the stronger association, and current deviation also contributed. This supports prior depressive-symptom burden as a cardiovascular risk marker that can be examined beyond a single CES-D-8 cohort.

ELSA, however, limits generalization. It used CES-D-8, as HRS did, but its estimates were close to null. The decomposition did not appear to fail technically in ELSA: the two components were not highly collinear, variance inflation factors were low, and sensitivity analyses did not reveal a hidden positive pattern. Cross-national harmonization work has shown that CES-D symptom expression may differ across population-study settings even when related items are available [15]. Longitudinal measurement work in ELSA also emphasizes that detecting change in depressive symptoms depends on measurement assumptions that are not always examined directly [16]. A recent CHARLS–ELSA analysis of depressive symptoms and incident stroke likewise reported differences in the strength and precision of cohort-specific estimates [17].

The reweighting analysis argues against one simple explanation for the HRS–ELSA difference. After HRS was reweighted toward the measured baseline distribution of ELSA, the HRS associations persisted. This does not mean that the HRS estimates can be transported causally to ELSA. Generalizability and transportability require assumptions about target populations, effect heterogeneity, measured covariates, and unmeasured differences that are stronger than covariate balancing alone [18]. Transporting observational estimates also requires attention to biases in the source study as well as source–target

population differences [19]. The analysis shows only that the measured variables used for weighting did not account for the observed heterogeneity. Differences in symptom reporting, cardiovascular outcome ascertainment, attrition, survival into the analytic sample, health-care contact, or unmeasured clinical context may still matter. Prior HRS–ELSA work has shown that attrition and health composition can differ between the two studies [20].

Age did not provide a general explanation for the cross-cohort heterogeneity. Continuous-age interactions supported attenuation of the relative associations with older age in SHARE, but not in HRS or ELSA. Threshold-based analyses suggested age-group interaction in ELSA and SHARE; however, ELSA stratum-specific estimates were imprecise and did not show consistent positive associations, whereas point estimates for both components remained above 1 in both HRS and SHARE age groups. Thus, age-related variation appeared cohort- and specification-specific rather than a universal effect.

Taken together, the cross-cohort findings support a bounded cardiovascular interpretation. Repeated depressive-symptom history identified a history-dominant risk pattern in HRS and SHARE, but not in ELSA. This inconsistency is itself relevant to cardiovascular epidemiology: psychosocial risk markers should be validated in the intended population before they are incorporated into risk stratification or primary-prevention research.

4.4. Life-course and biomarker context for cardiovascular risk

The HRS adversity analyses place prior symptom burden within a broader cardiovascular risk environment. Higher life-course adversity was associated with greater repeated CES-D-8 burden, more high-burden waves, and greater odds of incident, remitted, or persistent high-burden states. Adversity was also associated with incident heart disease. Recent prospective work has linked adverse childhood and adulthood experiences with new-onset cardiovascular disease [21], and another cohort study reported associations among adverse childhood experiences, depressive symptoms, and later cardiovascular disease [22]. These supporting findings suggest that repeated symptom burden partly reflects longer-term social and psychological disadvantage, but they do not prove that depressive symptoms mediate an adversity–heart disease pathway.

The biomarker findings provided only limited cardiovascular context. sTNFR1 was associated with incident heart disease in the weighted HRS biomarker sample, whereas IL-6 and the two-marker inflammatory composite were not consistently associated with the outcome. Prior evidence links IL-6 and other inflammatory markers with coronary risk [23, 24], and sTNFR1 has been associated with heart-failure risk [25] and kidney-function decline [26]. The present results do not support a strong inflammatory mediation claim. The main inference therefore rests on the longitudinal symptom-history analyses rather than on the biomarker subsample.

4.5. Strengths and limitations

The study has several strengths for cardiovascular epidemiology. Exposure construction was time ordered: prior burden used only symptom measurements obtained before the current wave, and the cardiovascular outcome was assessed at the next selected wave. The person-wave design allowed symptom history to update during follow-up rather than remain fixed at baseline, while excluding participants with prevalent heart disease at the start of each risk interval.

The three-cohort structure tested the same risk-marker concept under different conditions. HRS provided the primary analysis, SHARE tested construct-level replication with another symptom instrument, and ELSA tested whether the HRS CES-D-8 pattern appeared in a separate cohort using the same instrument. The null ELSA result weakened a simple positive narrative but provided a direct test of generalizability rather than assuming that one cohort's association would transport.

Several checks reduced concern that the results were driven by a single modelling artefact. Prior burden and current deviation were not strongly collinear. SHARE estimates were stable after observation weighting, country clustering, prior-measurement adjustment, exclusion of the first risk interval, and leave-one-country-out analyses. HRS estimates were similar in complete-history and raw-score analyses. These checks support the internal robustness of the cohort-specific associations, although they do not establish causality.

The study also has important limitations. It was observational, so depressive-symptom history should be interpreted as a cardiovascular risk marker rather than a proven causal exposure or treatment target. Stronger causal interpretation would require additional assumptions or triangulation across designs with different sources of bias [27]. Depressive symptoms may reflect early physical illness, pain, sleep problems, disability, social adversity, health behaviours, medication use, or frailty. Some of these factors change over time and may be both causes and consequences of symptoms, leaving residual confounding and reverse causation possible.

The outcome was based on survey-reported or harmonized heart-disease measures rather than uniformly adjudicated cardiovascular events. This enabled large multi-cohort analyses but limited diagnostic precision and prevented subtype-specific conclusions about coronary disease, heart failure, or other cardiac conditions. Agreement between self-reported disease and medical records varies by condition; prior validation work found substantial agreement for myocardial infarction and stroke but weaker agreement for heart failure [28]. Agreement between self-reports, proxy reports, and register-based diagnoses also differs across specific cardiovascular conditions [29]. Symptom measurement differed as well: HRS and ELSA used CES-D-8, whereas SHARE used EURO-D, so the SHARE result indicates consistency of the broader construct rather than item-level equivalence.

ELSA is the main restriction on generalization, and the analyses evaluated association rather than improvement in formal cardiovascular risk prediction. We therefore cannot conclude that adding symptom history improves discrimination, calibration, or clinical decision-making beyond established risk scores. The biomarker analysis was restricted to an HRS subsample and did not provide a consistent inflammatory signal. The HRS adversity analyses also relied on recalled life-course information; prospective and retrospective adversity measures can identify overlapping but non-identical groups [30].

4.6. Conclusions

Repeated depressive-symptom history can distinguish accumulated burden from recent deviation in cardiovascular epidemiologic studies. In HRS and SHARE, both components were associated with incident heart disease, with stronger associations for prior burden; ELSA did not reproduce the pattern. These findings support repeated symptom measures as potential markers for more refined psychosocial cardiovascular risk characterization, while the cross-cohort heterogeneity shows that validation is required before clinical risk-stratification or primary-prevention use.

Abbreviations

BMI
body mass index
CES-D
Center for Epidemiologic Studies Depression Scale
CES-D-8
eight-item Center for Epidemiologic Studies Depression scale
CI
confidence interval
ELSA
English Longitudinal Study of Ageing
EURO-D
European Depression scale
HRS
Health and Retirement Study
HR
hazard ratio
IL-6
interleukin-6
IPW
inverse-probability weighting
OR
odds ratio
SD
standard deviation
SHARE
Survey of Health, Ageing and Retirement in Europe
sTNFR1
soluble tumor necrosis factor receptor 1
VIF
variance inflation factor.

Declarations

Clinical trial number: not applicable.

Ethics approval and consent to participate

The HRS was approved by the University of Michigan Health Sciences and Behavioral Sciences Institutional Review Board. SHARE was approved by the Ethics Committee of the University of Mannheim for Waves 1–4 and by the Ethics Council of the Max Planck Society for Wave 4 and the subsequent continuation of the study, with country-specific ethics review where required. ELSA obtained ethical approval for each wave from the relevant United Kingdom research ethics committee. All participants provided informed consent. The present study was a secondary analysis of de-identified data and involved no additional participant contact. All procedures in the parent cohorts were performed in accordance with relevant guidelines and regulations, including the Declaration of Helsinki.

Consent for publication

Not applicable.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Author Contribution

WJ and XD conceived the study. WJ designed the analytic strategy, curated the data, implemented and checked the analysis code, performed the statistical analyses, prepared the tables and figures, and drafted the manuscript. PL contributed to the analytic strategy, checked the methodological consistency of the analyses, interpreted the results, and critically revised the manuscript. PZ, GY, and YW contributed to data checking, literature review, verification of tables and figures, and manuscript review. XD supervised the study, contributed to interpretation of the findings, and critically revised the manuscript. All authors read and approved the final manuscript and agreed to be accountable for all aspects of the work.

Data Availability

HRS data are available to registered users through the HRS Data Portal (<https://hrsdata.isr.umich.edu/>); access to restricted or sensitive files is subject to the applicable supplemental data-use agreement. SHARE scientific-use files are available to individually registered users through the SHARE Research Data Center (<https://share-eric.eu/data/>). ELSA data are available through the UK Data Service (<https://ukdataservice.ac.uk/>) under the applicable access conditions. The authors are not permitted to redistribute the source datasets; researchers may obtain the same data directly from the named repositories.

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Figures

A Overall study architecture and cohort roles



B Rolling-window decomposition of each person-wave observation

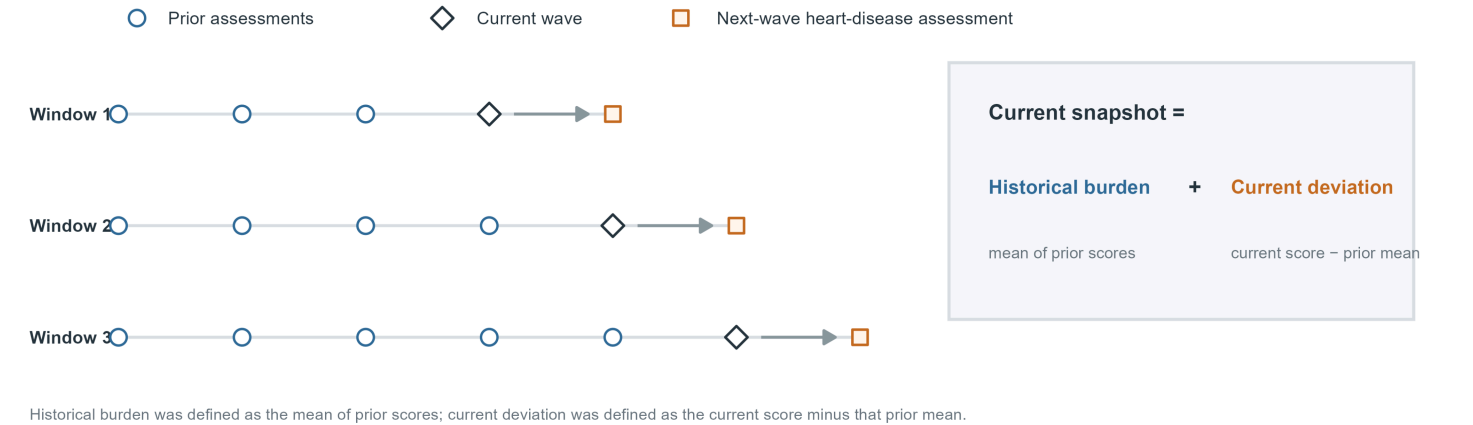
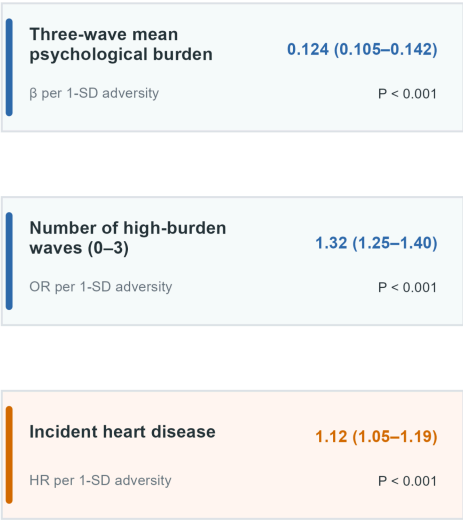


Figure 1

Study architecture and rolling-window decomposition of depressive-symptom history for incident heart disease. (A) HRS served as the primary longitudinal cohort, SHARE as the independent construct-level replication cohort using EURO-D, and ELSA as the independent same-instrument evaluation and reweighting target using CES-D-8. The HRS adversity and biomarker analyses were supporting cardiovascular-context branches. (B) For each eligible person-wave, prior burden was the mean of all eligible symptom assessments strictly before the current wave, current deviation was the current score minus that prior mean, and incident heart disease was assessed at the next selected wave. Participants could contribute multiple risk intervals until the first incident event. E, incident heart-disease events; N, participants; PW, person-waves.

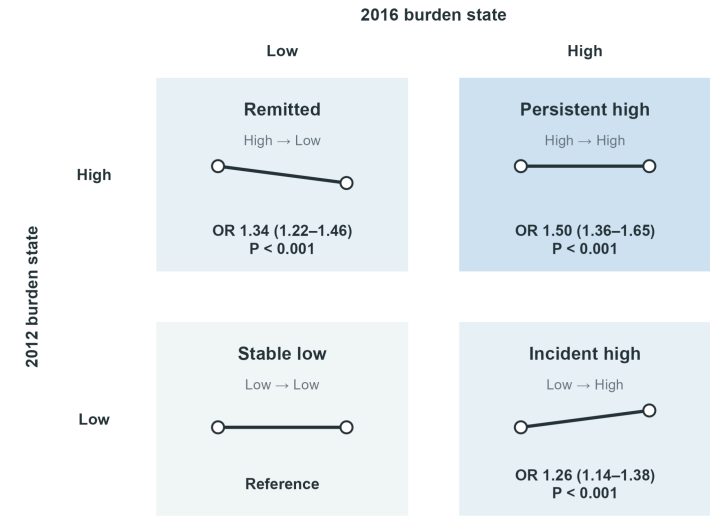
A Adversity, cumulative psychological burden, and incident heart disease

Adjusted associations per 1-SD higher life-course adversity



B Psychological-burden states, 2012–2016

Odds ratios per 1-SD higher adversity; stable low burden was the reference



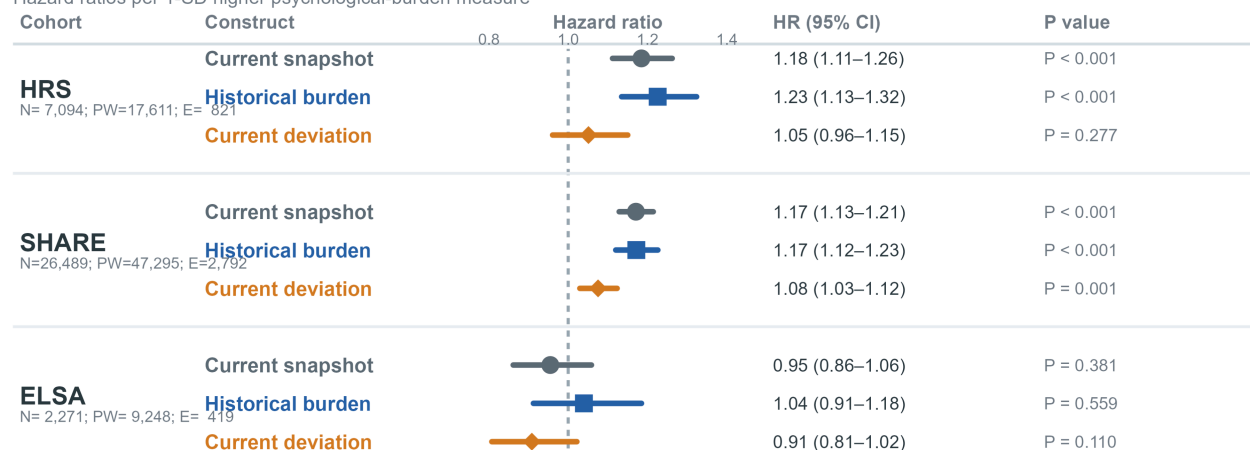
Repeated-measures model: adversity level $P < 0.001$; adversity $\times$ time $P = 0.258$.

Figure 2

Life-course adversity, depressive-symptom burden, and incident heart disease in HRS. (A) Adjusted associations per 1-SD higher life-course adversity with the three-wave mean CES-D-8 burden, the number of high-burden waves (0–3), and incident heart disease. Linear regression coefficients, ordinal odds ratios, and hazard ratios are shown as appropriate. (B) Associations between adversity and four depressive-symptom burden states defined by the prespecified high/low CES-D-8 classification in 2012 and 2016; stable low was the reference. The repeated-measures model tested the adversity main effect and adversity-by-time interaction. CI, confidence interval; HR, hazard ratio; OR, odds ratio; SD, standard deviation.

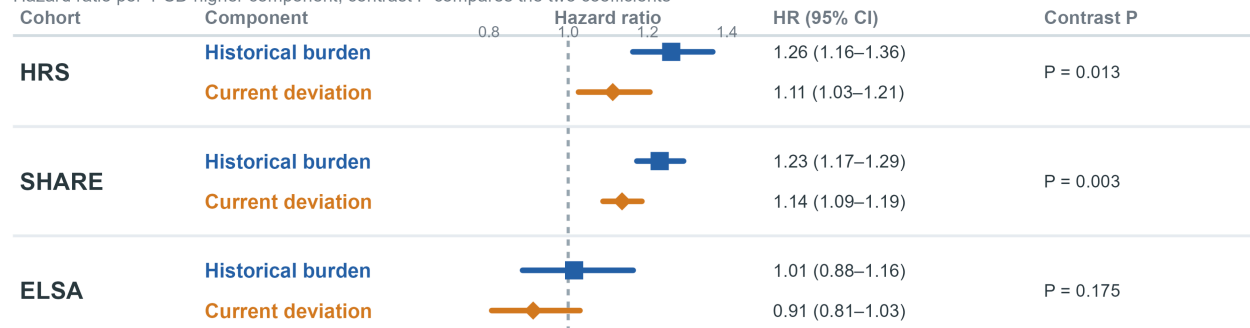
A Separate associations with incident heart disease

Hazard ratios per 1-SD higher psychological-burden measure



B Historical burden and current deviation in the same model

Hazard ratio per 1-SD higher component; contrast P compares the two coefficients

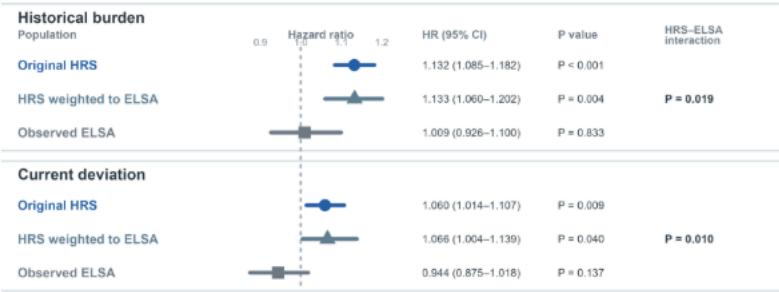


Historical burden was calculated only from assessments before the current wave.

Figure 3

Associations of depressive-symptom history components with incident heart disease across cohorts. (A) Current snapshot, prior burden, and current deviation were evaluated in separately specified models. (B) Prior burden and current deviation were entered jointly; contrast P values test equality of the two log-hazard-ratio coefficients. Estimates are per cohort-specific SD in HRS and ELSA and per fixed SHARE Wave-1 EURO-D SD in SHARE. Prior burden used only assessments strictly before the current wave. Effect magnitudes should not be interpreted as strictly exchangeable across instruments. CI, confidence interval; HR, hazard ratio; SD, standard deviation.

A Transport analysis from HRS to ELSA
Hazard ratios per 1-point higher CES-D score, observed ELSA estimates shown for comparison



B Transport diagnostics

Maximum SMD	Effective sample size	Target support	Bootstrap
0.481 → 0.024	3,912	97.1%	500/500
Before → after weighting	55.1% of source participants	ELSA targets within HRS support	Successful replicates

SMD = standardized mean difference; ESS = effective sample size.

Figure 4

Cross-cohort heterogeneity and reweighting from HRS to ELSA. (A) Prior-burden and current-deviation associations are shown per 1-point higher CES-D-8 score for original HRS, HRS reweighted to the measured baseline composition of the ELSA analytic sample, and observed ELSA. HRS–ELSA interaction P values test heterogeneity on the common raw CES-D scale. Participant-bootstrap confidence intervals and P values are shown for the reweighted HRS estimates. (B) Diagnostics summarize covariate balance, effective sample size, target support, and successful bootstrap replications. Reweighting addresses measured baseline composition only and does not establish causal transportability. ESS, effective sample size; SMD, standardized mean difference.

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