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Depressive symptom change after herpes zoster onset in adults aged 60 and older: a within-person UK Biobank cohort study

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Abstract

Background

Herpes zoster (HZ) can impair wellbeing in older adults, but diagnoses recorded after illness do not necessarily indicate sustained within-person depressive symptom worsening. We examined symptom change using repeated questionnaires linked to dated HZ records.

Methods

This UK Biobank cohort analysis included 58399 adults aged 60 or older with three complete, ordered Patient Health Questionnaire-9 (PHQ-9) assessments from 2016 to 2022–2023 and no HZ before the first assessment. 323 developed HZ between assessments. Participant fixed-effects models, response weighting, an exploratory equivalence test and paired PHQ-9 > = 10 transitions assessed change and uncertainty. The age restriction was introduced during journal adaptation after the original all-age analysis.

Results

The fixed-effects difference was − 0.252 PHQ-9 points (95% confidence interval [CI] -0.499 to -0.004). The response-weighted difference was − 0.229 (-0.494 to 0.036). Equivalence within +/-0.308 points was not established (P = 0.327). Seven participants newly crossed PHQ-9 > = 10 and 12 remitted (exact paired P = 0.359). The adjusted risk ratio was 0.91 (0.55 to 1.50). A pre-event placebo analysis showed a higher probability of PHQ-9 > = 10 before future HZ (risk difference 3.69 (0.03 to 7.35) percentage points), limiting causal interpretation.

Conclusions

HZ onset was not followed by sustained average depressive symptom worsening at the available assessments in this selected older cohort. The small negative estimate does not establish a protective effect. Acute reactions, severe complications and clinically important effects in vulnerable subgroups remain unresolved.

Background

Herpes zoster (HZ) is a painful reactivation of varicella-zoster virus, with incidence and complications increasing with age [1, 2]. Pain, sleep disruption and functional impairment can affect wellbeing during illness and recovery; prospective clinical studies describe substantial burden in older patients [3, 4]. Understanding the duration of psychological burden is relevant to follow-up after a common skin infection in later life.

A nationwide claims study reported more depression diagnoses after HZ [5]. That result concerns clinical diagnoses and health-care contact, not repeated measurements of the same person's symptoms. Conversely, mood disorders, psychological stress and elevated depressive symptom trajectories have been associated with subsequent HZ [6–8]. Stable vulnerability, changing health circumstances and illness-related clinical contact may therefore contribute to observed associations. Long questionnaire intervals can also miss acute distress followed by recovery.

We addressed three connected questions: whether depressive symptoms remain higher within the same person after HZ onset, how precisely average change can be bounded, and whether new clinically relevant screening-threshold crossings outnumber remissions. Repeated pre-event measurements help distinguish this question from cross-sectional burden or diagnoses recorded after illness. The analysis focuses on adults aged 60 and older, while retaining the original unrestricted analysis as a comparison. We did not aim to establish a causal effect or evaluate screening policy.

Methods

Design and participants

UK Biobank recruited approximately 500000 adults in the United Kingdom during 2006–2010 [9, 10]. We used the 2016 Mental Health Questionnaire (completed during July 2016-July 2017 in this cohort), a pain questionnaire containing a second PHQ-9 (January 2019-March 2020), and the 2022–2023 Mental Well-being Questionnaire (October 2022-August 2023) [11, 12], linked to the UK Biobank HZ first-occurrence record. The three direct source exports were joined using harmonized participant identifiers. Each source had one row per identifier; no joined source-cohort expansion occurred (Additional file 1, Table S2).

Eligibility required all nine PHQ-9 items at all three assessments, complete assessment dates in chronological order, derived age of at least 60 years at the first PHQ-9, and no recorded HZ before that assessment. Age at the first PHQ-9 was approximated by recruitment age plus elapsed years from recruitment to that questionnaire. It is not an exact birthday-based age. The available source cohort contained 501936 participants, of whom 93363 completed three ordered PHQ-9 assessments. Excluding 31821 younger respondents and 3143 with prior HZ left 58399 participants (Fig. 1). The fixed available sample determined precision; no sample-size target was used to select an effect.

The age60 focus was selected to match the geriatric research question during journal adaptation, after the original all-age results were known and before examining the age60 estimates. This analysis is therefore not presented as prospectively preregistered. The original all-age and age65 results are retained to show the effect of population restriction. Reporting follows STROBE and RECORD [13, 14]; completed checklists and reproducibility materials are supplied as Additional files 2–4.

Exposure and outcomes

HZ was defined using Field 130178, the UK Biobank first-occurrence date. At an assessment, post-HZ status equalled 1 when the date preceded measurement and 0 otherwise. Once positive, this history indicator remained positive. It did not indicate ongoing infection or persistent pain. The 323 participants whose HZ status changed between assessments identified the within-person exposure contrast; unexposed participants helped estimate common wave changes.

PHQ-9 items were harmonized to 0–3 and summed only when all nine were observed, giving a score from 0 to 27 [15]. Continuous score was the primary outcome. A score > = 10 was a secondary screening threshold, not a clinical diagnosis. Item fields, date definitions and adjustment variables are in Additional file 1, Table S1. We used the supplied first-occurrence phenotype rather than constructing a new clinical diagnostic algorithm, and did not validate HZ against individual medical records.

Within-person estimation and precision

The primary linear participant fixed-effects model included time-varying post-HZ status and questionnaire-wave indicators after person-mean centering. It removed measured and unmeasured participant characteristics constant over time and controlled changes common across waves. Heteroscedasticity-consistent standard errors were clustered by participant. Recruitment age, sex and other fixed baseline characteristics were absorbed by participant effects, not separately estimated. Time-varying illness, treatment and life events could remain confounded with onset.

An exploratory two-one-sided-test analysis compared the 90% confidence interval (CI) with +/-0.10 of the first-wave PHQ-9 standard deviation in the age60 cohort [16]. This standardized boundary was inherited from the earlier analysis framework, not an externally validated PHQ-9 minimal clinically important difference. We did not transfer the original all-age equivalence conclusion to the age-restricted cohort. A 95% CI was reported alongside the 90% equivalence interval.

Screening-threshold transitions

For each incident-HZ participant, the assessments bounding the onset interval supplied paired pre- and post-event PHQ-9 > = 10 status. An exact two-sided binomial test compared new crossings with remissions among discordant pairs under probability 0.5. Concordant pairs contributed to prevalence and the paired risk difference (RD), but not to this conditional test. The RD CI used the sampling variance of the within-pair difference and was not described as an exact interval.

Comparison-based models combined each incident-HZ onset interval with both intervals from participants without HZ before their final questionnaire. A linear probability model estimated adjusted RD; modified Poisson regression estimated risk ratio (RR). Parsimonious models included pre-interval PHQ-9, interval, recruitment age and sex. Supporting models additionally included ethnicity, education, income, smoking, alcohol, deprivation, body mass index, self-rated health and longstanding illness. Participant-clustered standard errors accounted for two intervals from unexposed participants. These

models did not restrict everyone to screening negative before the interval and therefore did not estimate first-ever depression incidence. The late-onset group supplied a pre-event placebo comparison during the earlier interval.

Targeted robustness checks and missingness

Four groups of checks addressed selection, timing, outcome form and model stability. Response inverse-probability weights were estimated among age60 first-PHQ-9 respondents, including those with prior HZ. The denominator logistic model included first-wave PHQ-9, prior HZ, recruitment age, sex, ethnicity, education, income, smoking, alcohol, deprivation and body mass index. An intercept-only numerator targeted this first-questionnaire source population. Predicted probabilities were clipped to 0.01–0.99 and stabilized weights truncated at the 1st/99th percentiles among three-wave responders. The same participant weight was applied across their repeated records. Effective sample size and measured balance were reported; these weights did not reconstruct the entire UK Biobank population.

Timing checks used 90- and 365-day lags and time since HZ. A prior-mental-health-history restriction used baseline indicators specified in Table S1. First-difference models independently parameterized interval score change, with separate early/late estimates. Square-root and log-transformed PHQ-9, deletion of each incident-HZ participant in turn, deterministic mutually exclusive half samples, and an age65 restriction assessed sensitivity to outcome form, influence and population definition. These are internal checks, not prediction-oriented cross-validation or external replication.

The primary model required no covariate imputation because outcomes and dates were complete and baseline covariates were absorbed by participant effects. Supporting response and binary models used missing categories for categorical covariates and median replacement with missing indicators for deprivation and body mass index. A rare missing alcohol level was replaced by the source-sample modal category to avoid unit leverage. These pragmatic approaches do not eliminate missing-data bias. MICE from earlier work addressed a different prior-HZ between-person model and was not used to impute outcomes or enlarge this incident-HZ sample. Supporting P values are exploratory and were not multiplicity-adjusted; no result was selected for significance.

Analyses ran locally in R 4.6.0. Independent matrix calculations reproduced the primary coefficient and participant-clustered covariance, and 16 automated checks verified cohort counts, transitions, weights and outputs (Table S13). OpenAI Codex assisted with code development and verification planning; analyses used locally held data and only aggregate outputs were examined in the AI-assisted workflow. No participant-level data were transmitted to the language model. Code, runtime details and validation outputs are in Additional file 4.

Results

Cohort characteristics

The 58399 participants had a mean derived age of 67.6 years at the first PHQ-9, and 55.6% were women. Incident HZ occurred between the first and pain-wave assessment in 133 participants and between the pain-wave and final assessment in 190; 58076 had no HZ before final measurement. Median intervals were approximately 2.44 and 3.74 years. First-wave PHQ-9 means were 1.92, 2.43 and 2.20 in early-HZ, late-HZ and no-HZ groups, respectively (Table 1; full characteristics in Table S3).

Table 1
Characteristics by HZ timing

Characteristic	No HZ (n = 58076)	Early HZ (n = 133)	Late HZ (n = 190)
Age at first PHQ-9, years	67.58 (4.37)	66.79 (4.31)	66.74 (4.68)
PHQ-9 at first questionnaire	2.20 (3.09)	1.92 (2.60)	2.43 (3.30)
PHQ-9 at pain questionnaire	2.40 (3.24)	2.06 (2.61)	3.04 (4.02)
PHQ-9 at final questionnaire	2.35 (3.25)	1.83 (2.53)	2.46 (3.25)
Female sex	32276 (55.6%)	80 (60.2%)	108 (56.8%)
University education	26951 (46.4%)	58 (43.6%)	106 (55.8%)
Current smoking	3186 (5.5%)	7 (5.3%)	11 (5.8%)
Body mass index, kg/m2	26.69 (4.34)	26.32 (4.18)	26.69 (4.49)
Townsend deprivation index	-1.94 (2.70)	-2.32 (2.37)	-1.75 (2.73)
Longstanding illness, yes	16125 (27.8%)	36 (27.1%)	52 (27.4%)

Continuous values are mean (standard deviation); categorical values are n (%). Age is derived at first PHQ-9; other characteristics are measured at recruitment except the questionnaire scores. Full characteristics are in Table S3.

Average symptom change and its precision

The primary difference was − 0.252 (-0.499 to -0.004) PHQ-9 points (P = 0.046), a small negative estimate rather than a sustained average increase. The 90% CI was − 0.460 to -0.044; it extended outside the +/-0.308-point boundary, so equivalence was not established (P = 0.327; Table S5). The negative estimate was not interpreted as evidence of protection.

Response weighting gave − 0.229 (-0.494 to 0.036) (P = 0.090; Table 2). Primary weighted effective sample size was 56961.7 of 58399, with weights from 0.773 to 1.564. Balance diagnostics are in Table S9. The estimate excluding prior mental-health history was − 0.189 (-0.447 to 0.069), while 90- and 365-day lags gave − 0.263 (-0.514 to -0.012) and − 0.344 (-0.620 to -0.068), respectively. These checks did not provide evidence of persistent average worsening, but several CIs included zero and do not justify causal claims.

Table 2
Primary and targeted supporting estimates

Analysis	Estimate (95% CI)	P value	Participants	HZ switchers
Age60 primary participant fixed effects	-0.252 (-0.499 to -0.004)	0.046	58399	323
IPW participant fixed-effects model	-0.229 (-0.494 to 0.036)	0.090	58399	323
Fixed effects excluding prior mental-health history	-0.189 (-0.447 to 0.069)	0.151	39664	211
Participant fixed effects with 90-day lag	-0.263 (-0.514 to -0.012)	0.040	58399	315
Participant fixed effects with 365-day lag	-0.344 (-0.620 to -0.068)	0.015	58399	275
Stacked first-difference model	-0.337 (-0.647 to -0.026)	0.034	58399	323

Effects are PHQ-9 point differences. HZ switchers identify the within-person contrast; for lagged analyses they are participants whose lagged exposure status changes. First differences use interval score changes and are not an identical parameterization of the primary model. All CIs are participant-clustered.

Screening transitions and pre-event change

Among 323 incident-HZ participants, 297 remained below PHQ-9 > = 10, 7 newly crossed the threshold, 12 remitted and 7 remained above it. Pre/post prevalence was 5.88%/4.33%. The exact test used 19 discordant pairs (P = 0.359), and paired RD was − 1.55 percentage points (95% CI -4.19 to 1.10).

Compared with 116152 no-HZ intervals, adjusted RD was − 0.48 (-2.47 to 1.50) percentage points and RR was 0.91 (0.55 to 1.50) (Table 3). Fully adjusted estimates were similarly imprecise (Table S6). In contrast, the late-onset group's pre-event placebo RD was 3.69 (0.03 to 7.35) percentage points (P = 0.048). This signal preceded HZ and limits interpretation of post-onset differences as consequences of infection.

Table 3
Screening-threshold transition analyses

Analysis	Estimate	95% CI	P value
Paired transition RD	-1.55 percentage points	-4.19 to 1.10	Not applicable
Exact paired binomial test	7 new crossings vs 12 remissions	Not applicable	0.359
Baseline-adjusted RD	-0.48 percentage points	-2.47 to 1.50	0.635
Baseline-adjusted RR	0.91	0.55 to 1.50	0.713

Paired analyses include 323 incident-HZ intervals; the exact test conditions on 19 discordant pairs. Adjusted models compare 323 incident-HZ with 116152 no-HZ intervals, including pre-interval PHQ-9, interval, recruitment age and sex. RD is in percentage points; RR is unitless. Screening status is not a clinical diagnosis.

Parameterization and estimate stability

First differences gave − 0.337 (-0.647 to -0.026). Early- and late-interval estimates differed in magnitude, with the larger negative estimate in the late interval (Table S7). Half-sample estimates were − 0.404 (-0.781 to -0.026) and − 0.123 (-0.448 to 0.201); both were negative but their precision differed. Leave-one-switcher-out estimates ranged from − 0.274 to -0.218, with maximum absolute shift 0.034 (Table S8). Transformed-score results were imprecise. The age65 estimate was − 0.185 (-0.498 to 0.129), and the unrestricted original cohort estimate was − 0.027 (-0.262 to 0.207) (Table S11). Population restriction therefore changed the point estimate; neither age-specific heterogeneity nor a protective effect was established. Figure 2 presents estimate stability.

Discussion

Principal findings and relation to earlier evidence

In this selected cohort of adults aged 60 and older, HZ onset was not followed by sustained average depressive symptom worsening at the available PHQ-9 assessments. The small negative point estimate, the weighted CI crossing zero, failure to establish equivalence, and broad binary-outcome intervals need to be considered together. In particular, the detected pre-event screening-status difference argues against interpreting the negative post-onset estimate as a protective effect of HZ.

The study addresses a different estimand from a diagnosis-based cohort reporting increased depression after HZ [5]. Diagnoses depend on symptoms but also clinical contact, recognition and treatment. Repeated questionnaires concern measured symptom burden at specific dates, while participant effects reduce stable between-person differences. The findings neither invalidate diagnosis-based associations nor explain their mechanism. Studies linking mood disorders and depressive trajectories to later HZ [6–8] also make pre-event vulnerability plausible; the current placebo result is consistent with the need to examine that temporal context, without establishing why it occurred.

The negative change could reflect chance, regression toward earlier symptom levels after a pre-event rise, time-varying health circumstances, treatment or selection. The data cannot distinguish these possibilities. We therefore retain the full CIs and original all-age comparison rather than emphasizing the borderline primary P value. The equivalence result from the unrestricted cohort does not apply to this age-restricted population, and the continuous-score analysis cannot establish equivalence of the binary screening outcome.

Clinical relevance for older adults

For geriatric dermatology, distinguishing acute distress from symptoms persisting at later routine assessments is useful. Clinical studies of active HZ and complications describe pain and impaired quality of life [3, 4]; our widely spaced questionnaires were not scheduled around rash onset or recovery. A person could experience distress and recover between measurements. This study consequently cannot support reducing mental-health assessment during acute disease, complicated recovery or persistent pain, nor does it test the benefit of screening. Clinical decisions should remain based on current presentation and needs rather than this population-average estimate alone.

Strengths and limitations

Strengths are three complete measurements using the same symptom scale, dated HZ records, a within-person contrast and transparent reporting of paired transitions and robustness checks. The binomial analysis answers whether changes in screening status favor one direction; the weighting, lag, transformation and influence checks answer different methodological questions. More tables or prediction-oriented cross-validation would not remove the design's temporal or selection limitations.

Important limitations remain. Only 323 participants identified the exposure contrast, and only 19 pairs changed threshold status. The apparent large source cohort does not replace those informative event counts. Questionnaire spacing of approximately 2–4 years misses acute changes and makes timing-specific estimates imprecise. The pre-event signal and differing interval estimates weaken a causal interpretation. Stable participant effects do not control changing illness, treatment or life events.

HZ first-occurrence records may miss community episodes or differ from biological onset. Severity, ophthalmic or neurologic involvement, postherpetic neuralgia, vaccination and antiviral treatment were not characterized in this onset analysis. PHQ-9 is a screening measure, not a diagnosis. Approximate age derivation may misclassify people near the age cutoff. Questionnaire context changed between waves, and wave indicators cannot separate every context effect from population change.

UK Biobank volunteers and repeated questionnaire responders are selected populations [17, 18]. Weighting addresses measured response selection conditional on answering the first questionnaire, not initial participation, unmeasured selection or all subsequent missingness mechanisms. Supporting missing-category and median-replacement approaches are pragmatic, not fully model-based imputations. Finally, this age restriction was introduced after the original study results were known; it was not independently registered, supporting analyses were correlated and multiplicity was not adjusted,

and no external validation was available. These constraints limit both generalizability and claims about clinically important individual effects.

Conclusions

Among selected adults aged 60 and older with three complete PHQ-9 assessments, HZ onset was not followed by sustained average symptom worsening at the available measurement times. The small negative estimate does not establish protection or equivalence. Pre-event symptom differences, sparse screening transitions and wide assessment intervals leave acute burden and outcomes in vulnerable or severely affected patients unresolved.

Abbreviations

CI: confidence interval; FE: fixed effects; HZ: herpes zoster; IPW: inverse-probability weighting; PHQ-9: Patient Health Questionnaire-9; RD: risk difference; RR: risk ratio; TOST: two one-sided tests.

Declarations

Ethics approval and consent to participate

UK Biobank operates under NHS North West-Haydock Research Ethics Committee approval 21/NW/0157. Participants provided written informed consent. This secondary analysis used UK Biobank application 206581.

Clinical trial number: not applicable.

Consent for publication

Not applicable. No identifiable individual information is reported.

Availability of data and materials

UK Biobank data are available to approved researchers through its access procedures. Participant-level data cannot be redistributed by the authors. Analysis code, runtime details, analysis decisions and aggregate validation outputs are supplied in Additional file 4. The study was not preregistered in an independent registry.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JZ: Conceptualization, methodology, formal analysis, software, validation, data curation, visualization, writing - original draft, writing - review and editing. YL: Methodology, investigation, validation, writing - review and editing. YG: Conceptualization, supervision, writing - review and editing. WM: Conceptualization, resources, supervision, project administration, writing - review and editing. All authors read and approved the final manuscript.

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Figures

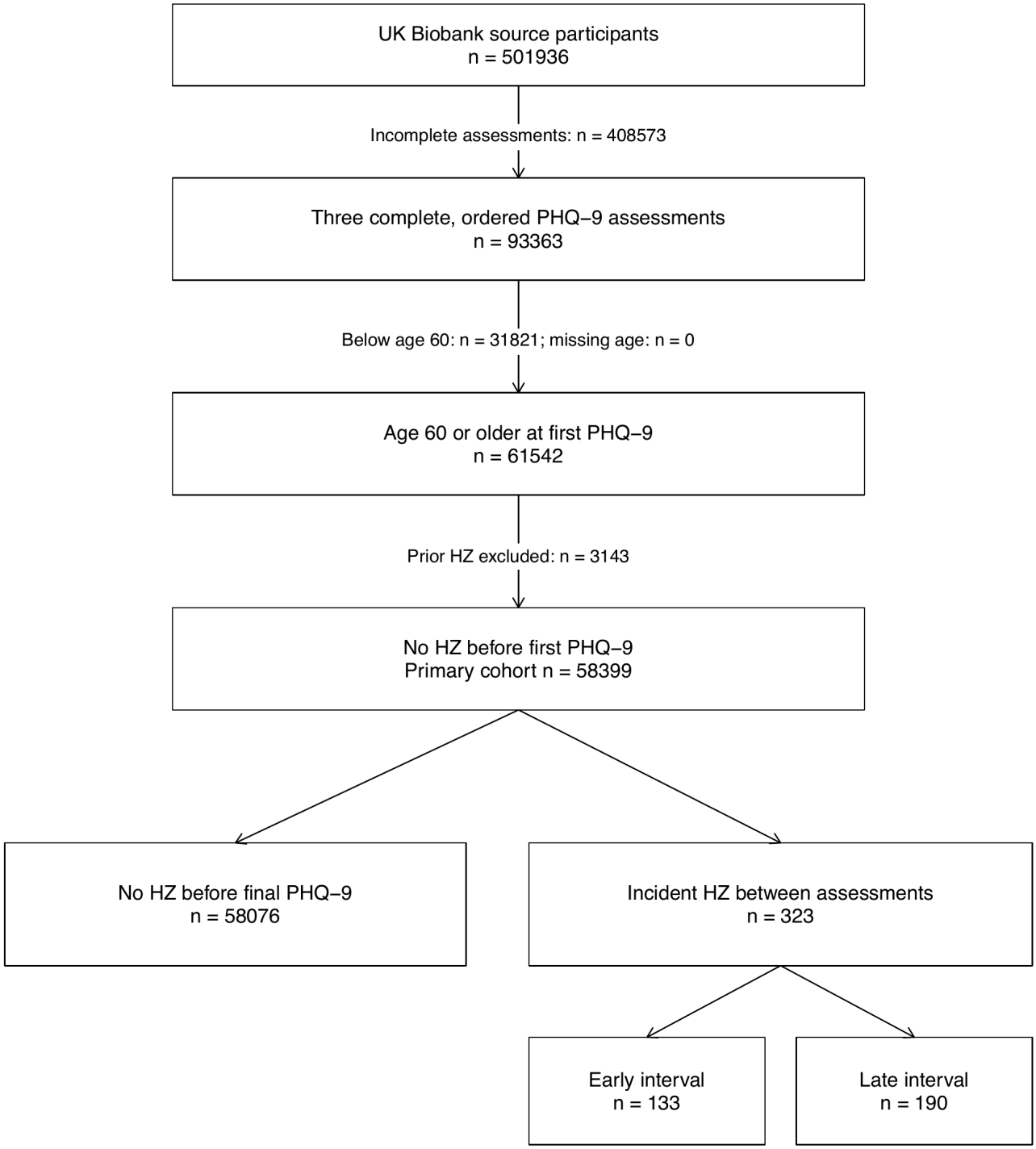


Figure 1

Cohort flow and exposure timing. The geriatric cohort required derived age >=60 at first PHQ-9, three complete and ordered questionnaires, and no earlier HZ. Early/late refer to the two questionnaire intervals. Generated from validated aggregate counts using AI-assisted plotting code (OpenAI Codex, GPT-5; OpenAI), not generative image synthesis.

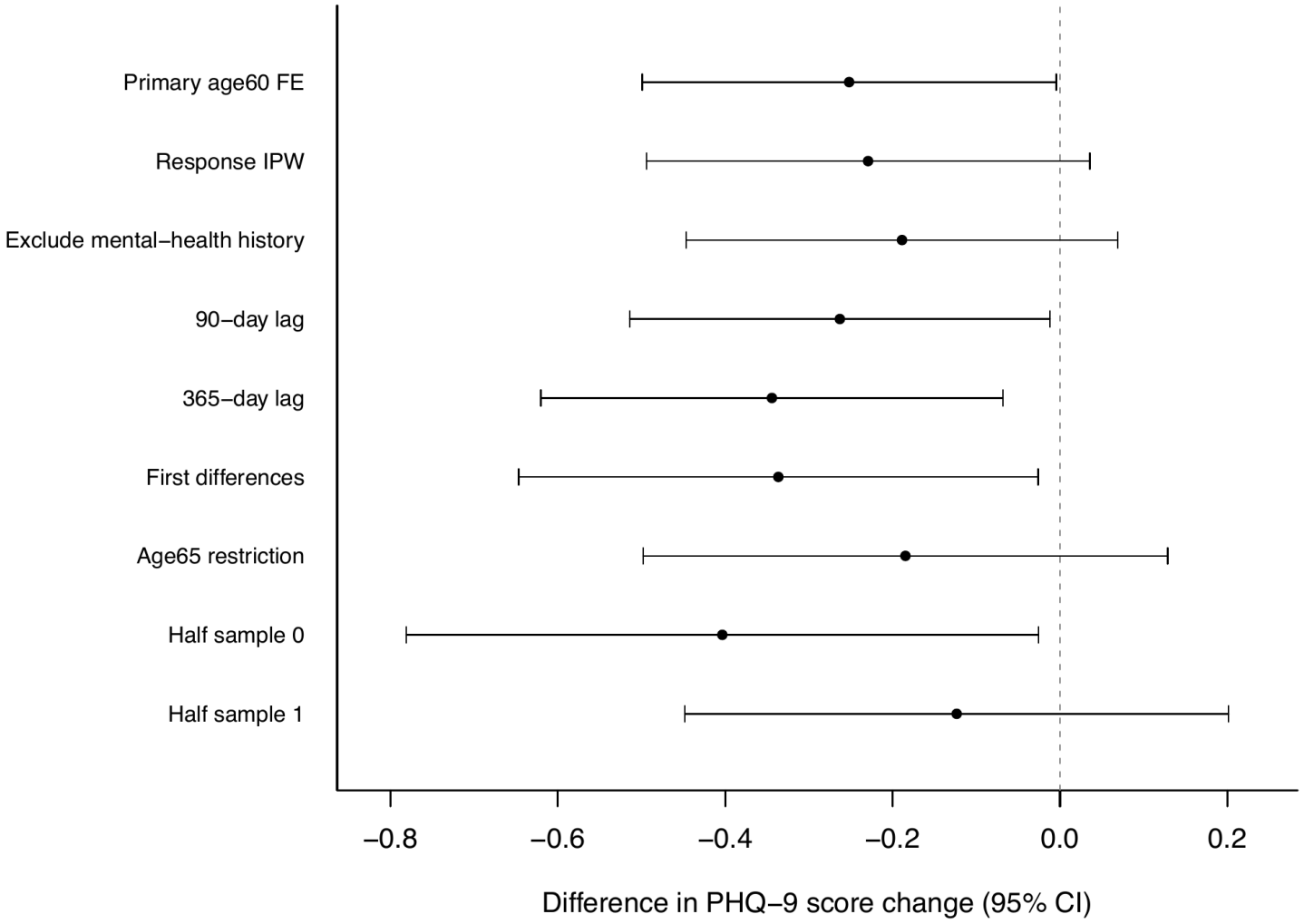


Figure 2

Stability of symptom-change estimates. Points and lines show estimates and 95% CIs in PHQ-9 points. Different restrictions and parameterizations are supporting checks, not independent replication. Generated from verified model outputs using AI-assisted plotting code (OpenAI Codex, GPT-5; OpenAI), not generative image synthesis.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- AdditionalFile1SupplementaryMaterial.docx