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Joint trajectories of the non-HDL-cholesterol to HDL-cholesterol ratio and physical activity, lipid-lowering medication, and incident cardiovascular disease: a landmark analysis in two ageing cohorts

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Research Article

Keywords: non-HDL cholesterol to HDL cholesterol ratio, physical activity, group-based trajectory, cardiovascular disease, lipid-lowering medication, cohort study, English Longitudinal Study of Ageing

Posted Date: November 18th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11544811/v1

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Additional Declarations: No competing interests reported.

Abstract

Background

The non-HDL-cholesterol to HDL-cholesterol ratio (NHHR) summarises atherogenic lipid burden and predicts cardiovascular disease (CVD), and guideline management pairs lipid-lowering medication with advice to be physically active. Published trajectory studies, however, have modelled NHHR alone (typically in untreated samples) and have not asked how physical activity shapes risk within NHHR trajectory classes. We therefore modelled the two exposures jointly and tested how lipid-lowering treatment modifies the resulting risk pattern.

Methods

We included 4,150 English Longitudinal Study of Ageing participants aged ≥ 50 with NHHR and physical activity measurements at three waves (2004, 2008, 2012). Group-based multivariate trajectory modelling identified five joint NHHR–activity classes (mean posterior assignment probability 0.85). Incident CVD was ascertained from the 2012 landmark to 2018 in Cox models with three adjustment levels; medication comparisons used inverse-probability-of-treatment weighting. The untreated-population analysis was repeated in CHARLS.

Results

Mean age was 68.3 years (SD 8.1), 55.5% of participants were women, and 577 developed CVD over 21,852 person-years. Relative to the reference class (moderate NHHR, high activity), fully adjusted hazard ratios were 1.43 (95% CI 1.03–1.97) for the high-NHHR/low-activity class and 1.51 (1.02–2.22) for the isolated-high-NHHR class, but 0.99 (0.70–1.38) for the class whose NHHR fell alongside low activity. Within treated participants, achieved NHHR did not predict events (0.88, 0.70–1.12). Comparing the two low-activity classes, which shared the highest prevalence of lipid-lowering treatment (36% each), the class whose NHHR remained high carried 67% higher risk than the class whose NHHR fell (1.67, 1.03–2.73). Achieved NHHR predicted events in untreated participants (1.29 per unit, 1.09–1.52); the untreated gradient replicated in CHARLS (1.32, 1.08–1.62).

Conclusion

Joint NHHR–activity trajectories stratify CVD risk beyond either exposure alone. Lipid-lowering treatment flattens the NHHR–risk gradient, and among the two low-activity classes that shared the highest treated prevalence, the class whose NHHR remained high faced the greatest excess. Joint trajectory assessment may refine risk stratification in treated dyslipidaemia.

Background

Lowering LDL cholesterol prevents cardiovascular events, with causal support from genetic and trial evidence [1, 2]. A substantial share of events nevertheless occurs in patients whose LDL cholesterol is already at target [3], and part of this residual risk tracks atherogenic lipid burden that a single LDL value does not capture: remnant cholesterol and other triglyceride-rich particles [3, 4]. The non-HDL-cholesterol to HDL-cholesterol ratio (NHHR) expresses that burden and its counterweight in one quantity: the numerator carries all apolipoprotein B-containing particles, and the denominator summarises the protective fraction. Higher NHHR has been associated with cardiovascular disease (CVD) in community-dwelling ageing cohorts [5], with cardiometabolic multimorbidity across two national cohorts [6], and with residual risk in patients already under treatment for atrial fibrillation or type 2 diabetes [7, 8]. Clinical guidelines accordingly pair lipid-lowering medication with lifestyle advice, of which physical activity is the component most consistently recommended to all treated patients [9, 10, 11].

What guidelines do not say is how much activity matters for a patient whose lipid values respond poorly to treatment, because the evidence base has grown along two separate lines. One way to capture such exposure is group-based trajectory modelling, which reduces repeated measurements to long-term patterns [12, 13]. Applied to NHHR, this framework suggests that where the ratio sits over years, not just at one draw, separates risk: CHARLS participants in the top tertile of baseline and cumulative NHHR had roughly 43–45% more cardiovascular events than those in the bottom tertile, and the persistently high trajectory class carried 41% excess [5]. Comparable patterns have been reported for NHHR in patient populations with peripheral artery disease or type 2 diabetes [8, 14]. These studies share two limitations. First, the trajectory window sits inside or immediately before the outcome window, so early events and prodromal lipid changes are hard to exclude [5, 14]. Second, patients on lipid-lowering medication are typically excluded (the CHARLS analysis removed 422 antihyperlipidemic users by design), which removes exactly the group in which the clinical question is most pressing [5].

Physical activity could, in principle, soften the risk attached to an adverse lipid trajectory. Active adults develop less cardiovascular disease in a dose-dependent way across prospective cohorts [15], and in ELSA itself, taking up activity in later life tracks healthier ageing [16]. Activity raises HDL cholesterol and apolipoprotein A-I, improves insulin sensitivity, and lowers triglyceride-rich particles [17, 18]. Published evidence has nevertheless developed along the same two separate lines: single-marker lipid trajectories [5, 14] on one side, and joint behavioural modelling on the other. Joint trajectory modelling, in which a biomarker and a behaviour are typed together, has been applied to activity and diet [19] but not, to our knowledge, to a lipid ratio and activity, and not in a population that includes treated patients.

We therefore modelled NHHR and physical activity jointly in the English Longitudinal Study of Ageing (ELSA), retained participants on lipid-lowering treatment, and separated the exposure window (2004–2012) from the outcome window (2012–2018) with a landmark design. We asked three questions. First, do joint NHHR–activity trajectory classes stratify incident CVD risk? Second, does the NHHR–risk relation differ between treated and untreated participants? Third, does the untreated-population risk

pattern replicate in an independent ageing cohort, CHARLS [20, 21]? Throughout, the three lipid time points and three activity time points support a trajectory reading of both exposures.

Methods

Study design and participants

ELSA is a nationally representative panel of adults aged 50 and over in England, interviewed every two years with nurse visits alternating in earlier waves [20]. We used waves 2 to 9 (2004–2018/19). Of 19,802 participants contributing at least one wave, 13,516 had at least one nurse-visit lipid measurement. We required NHHR and the physical activity items at two or more of the three exposure waves (2004, 2008, 2012), age of at least 50 years in 2012, and no self-reported doctor-diagnosed heart attack or stroke between 2004 and 2012. Lipid-lowering medication users were retained by design. The analytic cohort comprised 4,150 participants (1,144 treated, 27.6%); 1,827 had NHHR at all three exposure waves and 2,323 at exactly two (1,499 missed the 2004 nurse visit, and the remainder missed 2008 or 2012), so the trajectory model was fitted on the waves each participant had available, 10,127 observed NHHR person-waves of 12,450 possible. The baseline (2004) NHHR missingness carried into the fully adjusted models (36.1%; below) is a direct consequence of this two-wave inclusion design. The 2012 wave served as the landmark (t = 0); the exposure window was 2004–2012 and the outcome window 2012–2018 (Fig. 1, Panel A).

Both studies were approved by their original ethics committees, and all participants gave informed consent in the source studies. The present analysis used fully anonymised secondary data under the data-use agreements of ELSA and CHARLS.

Exposure assessment

Total cholesterol and HDL cholesterol were measured in fasting morning blood samples at the nurse visits in 2004, 2008, and 2012. NHHR was computed as (total cholesterol − HDL cholesterol)/HDL cholesterol in mmol/L, the definition used in prior NHHR analyses [5]; internally negative laboratory codes were treated as missing.

Physical activity at each wave was summarised with a 0–3 ordinal score following the convention used in prior ELSA work [22]: participants received the highest applicable level of 3 for vigorous activity at least once a week, 2 for moderate activity at least once a week, 1 for mild activity at least once a week, and 0 otherwise. The three-wave activity histories support the same trajectory reading as the lipid histories, and we use "joint trajectories" for the combined NHHR–activity typing throughout.

Joint trajectory modelling

We fitted group-based multivariate trajectory models with the R package gbmt [23, 24], which extends the Nagin framework [12, 13] to two simultaneous indicators. Both indicators were centred within persons before fitting. We searched two to six classes with eight random starts and up to 2,000 iterations. Standard multiple starts converged repeatedly to a suboptimal local likelihood at five classes; the reported solution initialised each five-class fit from a single split of the four-class solution and kept the best fit (log likelihood − 27,142, against − 29,668 for four classes). Additional file 1: Table S1 gives the enumeration statistics for every candidate joint-model solution; Table S2 in the same file holds the single-exposure fits and their class contrasts.

In the joint model the Bayesian information criterion dropped from 62,582 at two classes to 54,449 at six. Moving from five classes (54,641) to six bought only 192 points and carved off a class holding 8.8% of participants, so we stopped at five. Assignment quality met both rules set in advance: average posterior assignment probability (APPA) reached 0.853 overall (0.82–0.88 across classes) against a 0.70 threshold, and the smallest class held 14.3% of the cohort against a 5% floor [12]. For the primary analysis each participant took the class with the highest posterior probability (MAP); the sensitivity analyses below revisit that assignment. We named classes by level and trend rather than by rank: high NHHR with low activity (C1), moderate NHHR with high activity (C2, reference), low NHHR with high activity (C3), declining NHHR with low activity (C4), and persistently high NHHR (C5). Because the reference is simply the largest class, not a clinically defined ideal, the contrasts compare trajectory phenotypes with one another.

Outcome ascertainment

Incident CVD in the outcome window defined the endpoint: a first self-reported doctor diagnosis of heart attack or stroke at any wave from 2014 to 2018, among participants free of CVD through 2012. We counted follow-up in two-year interview cycles from the 2012 landmark. An event dated to the cycle in which it was first reported; participants who reported no event were censored at their last interview. For the 653 who did not take part after 2012 we assumed an event at six months, then stress-tested that assumption in a worst-case sensitivity analysis. Over 21,852 person-years, 577 participants developed CVD (26.4 per 1,000 person-years).

Lipid-lowering medication

A participant counted as treated if they reported current lipid-lowering medication at the 2008 or 2012 nurse visit (n = 1,144; 27.6%). Because the 2004 wave recorded no medication, treatment begun and ended before 2008 leaves no trace in this classification. Treated participants were older, carried more diabetes and hypertension, and started from higher NHHR; every crude medication contrast was therefore re-estimated after balancing these indications (below).

Covariates

All covariates came from the 2012 landmark: age, sex, education (low, intermediate, high), nurse-visit body mass index, former and current smoking, diabetes reported at any wave through 2012, and hypertension reported through 2012. Baseline (2004) NHHR also entered the fully adjusted model, so that trajectory shape could be read apart from starting level. We fitted models in three tiers: crude; age, sex, diabetes, and hypertension adjusted; and fully adjusted. In complete-case analyses, 2,215 participants (377 events) had all covariates; baseline NHHR was the largest missing item (36.1%), followed by education (7.4%) and body mass index (6.7%). Multiple imputation by chained equations (m = 10; predictive mean matching for NHHR and body mass index, multinomial logit for education; pooled by Rubin's rules) served as the primary missing-data sensitivity analysis [25].

Statistical analysis

Class–outcome associations were estimated with Cox proportional hazards models. Proportional hazards were checked with scaled Schoenfeld residuals; the global test in the fully adjusted model was not significant (P = 0.14), although body mass index showed a time-varying effect (P = 0.004). Pre-specified contrasts were: each class against C2; the two low-NHHR classes against each other (C4 against C3), which isolates the activity contrast at comparable lipid levels; and the two low-activity classes against each other (C1 against C4), which are the two classes with the highest treated share (36% each) and which differ in whether NHHR remained high despite treatment. Kaplan–Meier curves and the log-rank test described absolute risk (Additional file 1: Figure S1). All reported P values are nominal and were not adjusted for multiplicity; the class contrasts were pre-specified.

The medication analyses proceeded in three steps. First, the total association of treatment with risk was estimated before and after inverse-probability-of-treatment weighting (IPTW) [26]: a propensity score for treatment was fitted by logistic regression on age, sex, education, body mass index, diabetes, hypertension, former smoking, current smoking, and baseline NHHR in the 2,215 complete cases, with good overlap (0.08–0.89) and an effective sample size of 1,845; all nine covariates reached absolute standardised differences below 0.05 after weighting. Second, the same contrast was estimated within class C4, applying the same propensity-score weights. Third, we tested whether the NHHR–risk gradient differed by treatment status, using achieved NHHR (the 2012 value at the landmark) in treated and untreated participants separately and formally as a treatment-by-NHHR interaction.

Robustness analyses covered assignment uncertainty and alternative specifications: pseudo-class draws (20 draws with posterior probabilities and Rubin pooling) [27]; posterior-probability-weighted Cox; multiple imputation (above); exclusion of participants reporting doctor-diagnosed high cholesterol in 2004, a proxy for treatment before medication was recorded (n = 2,461); worst-case censoring, in which the 653 participants lost before 2014 were counted as events; cause-specific models for coronary heart disease (499 events) and stroke (105 events) separately; a time-varying medication status updated at each two-year cycle in the outcome window; and, because body mass index violated the proportional hazards assumption, refitting with the baseline hazard stratified by BMI quartiles and with a BMI-by-log-time interaction. To test whether joint modelling added information beyond either exposure alone, the trajectory model was also fitted to NHHR and to physical activity separately under the same

specification, and the resulting classes were entered into Cox models in the same adjustment tiers. Unmeasured confounding was quantified with E-values [28].

All analyses ran in R 4.3.2 with the survival, gbmt, mclust, and mice packages. STROBE [29] guided reporting; the completed checklist accompanies the submission.

Replication in CHARLS

We then repeated the untreated-population analysis in CHARLS, a nationally representative longitudinal survey of Chinese adults aged 45 and over [21]. From participants with NHHR at 2011 and 2015 and physical activity (MET-minutes per week, log-transformed) at both waves, we excluded those with self-reported heart disease or stroke by 2015, those younger than 45 in 2011, and NHHR values beyond three standard deviations of the pooled mean, leaving 1,075 participants (83 treated, 7.7%; 182 events over 5,119 person-years). Latent profile analysis (Gaussian mixture, VVI model, G = 2–4 by BIC; best G = 4, APPA 0.886) typed the four indicators (NHHR 2011, NHHR 2015, log activity 2011, log activity 2015) jointly. Cox models adjusted for age, sex, urban residence, education, current smoking, alcohol use, body mass index, diabetes, and hypertension at baseline, with and without baseline NHHR. The treatment-by-achieved-NHHR gradient test mirrored the ELSA analysis with the 2015 landmark and follow-up to 2020; the outcome at 2018 covered doctor-diagnosed heart disease (stroke was not asked that cycle) and was extended to stroke in 2020. Class structure and model estimates appear in Additional file 1: Tables S4–S5 and Figure S2.

Results

Cohort and joint trajectory classes

The 4,150 participants had a mean age of 68.3 years (SD 8.1) in 2012, and 55.5% were women (Table 1; Fig. 1, Panel B). Five joint NHHR–activity trajectory classes emerged over 2004–2012 (Fig. 2). C1 (15.6% of participants) combined the second-highest NHHR, drifting down from 4.76 to 4.04, with low and falling activity (1.72 to 1.36). C2, the reference class (34.2%), held moderate NHHR (4.05 to 3.54) with sustained high activity (2.48 to 2.43). C3 (20.4%) paired the lowest NHHR (2.99 to 2.54) with the highest and stable activity (2.50 to 2.53). C4 (15.5%) showed the steepest NHHR decline (3.50 to 2.78) alongside the lowest activity (1.65 to 1.25). C5 (14.3%) sat at the top of the NHHR distribution for the whole period (5.34 to 5.23) with intermediate-to-high activity (2.35 to 2.31). Treated participants concentrated in the two low-activity classes: 36.0% in C1 and 35.9% in C4, about half again the share seen elsewhere (23–24%). Diabetes and hypertension climbed the same ladder, from 5.3% and 36.5% in C2 to 13.8% and 50.9% in C1.

Cardiovascular risk across classes

Crude rates ranged from 21.7 per 1,000 person-years in C2 to 32.4 in C1 (Table 1). Six-year cumulative incidence climbed from 12.5% in C2 through 14.1% (C3), 16.6% (C4), and 17.7% (C5) to 18.5% in C1 (log-rank P = 0.003). Once fully adjusted, the two high-NHHR classes separated from the rest and the treatment-responsive class did not: C1 carried a hazard ratio (HR) of 1.43 (95% CI 1.03–1.97) and C5 1.51 (1.02–2.22), against 1.11 (0.78–1.57) for C3 and 0.99 (0.70–1.38) for C4 (Table 2; Fig. 3A). Crude estimates ran 1.51 (1.19–1.93) for C1, 1.13 (0.89–1.44) for C3, 1.39 (1.08–1.79) for C4, and 1.43 (1.11–1.84) for C5; C4's fall from a crude 1.39 to 0.99 under adjustment traces to that class's older age and heavier comorbidity, not to any reversal of direction.

Table 1
Baseline characteristics (2012 landmark) by joint trajectory class, ELSA (N = 4,150)

n (%)	**C1 high NHHR/low activity**	**C2 moderate NHHR/high activity (ref)**	**C3 low NHHR/high activity**	**C4 declining NHHR/low activity**	**C5 persistently high NHHR**
	647 (15.6)	**1,421 (34.2)**	**847 (20.4)**	**641 (15.5)**	**594 (14.3)**
Events / person-years	108 / 3,334	165 / 7,602	112 / 4,570	95 / 3,192	97 / 3,154
Crude rate /1,000 py	32.4	21.7	24.5	29.8	30.8
Age, years, mean (SD)	69.7 (8.6)	67.3 (7.4)	67.4 (7.4)	72.4 (9.2)	66.0 (7.1)
Men, %	41.7	48.1	34.0	33.1	66.3
BMI, kg/m², mean (SD)	28 (5)	28 (5)	28 (5)	28 (5)	28 (5)
Low education, %	40.2	23.8	19.3	41.9	25.1
Former smoker, %	68.3	58.7	59.4	63.2	65.2
Current smoker, %	14.8	7.2	5.7	10.6	15.2
Diabetes, %	13.8	5.3	7.6	15.0	7.1
Hypertension, %	50.9	36.5	31.4	50.2	35.9
Baseline (2004) NHHR, mean (SD)	4.76 (0.63)	4.05 (0.52)	2.99 (0.42)	3.50 (0.62)	5.34 (0.83)
Activity score (2004), mean	1.72	2.48	2.50	1.65	2.35
Lipid-lowering medication, %	36.0	24.0	24.0	35.9	23.1

Contrasts within strata

Two contrasts locate the risk more precisely. Within the two low-NHHR classes, low activity did not itself signal excess risk: C4 against C3 gave 0.77 (0.51–1.15) fully adjusted, and a complementary continuous analysis with median-split exposures gave a ratio-of-product term of borderline significance (P = 0.065), so we found no evidence that activity modifies risk within a favourable lipid trajectory. By contrast, comparing the two low-activity classes that shared the highest treated share, C1 carried 67% higher risk than C4 (1.67, 1.03–2.73) after full adjustment, including baseline NHHR (Table 2). Restricted to the 463 treated members of these two classes, the same contrast was directionally consistent but imprecise (1.45, 0.72–2.93; 63 events). Under the 20-draw pseudo-class procedure, which propagates assignment uncertainty, this class-pair contrast moved to 1.38 (0.75–2.53), retaining direction but not separation from the null. The separation did not survive single-exposure modelling. NHHR-only trajectory classes carried no risk gradient: the higher-NHHR class against the lower gave 1.01 (0.76–1.35) fully adjusted and 1.10 (0.93–1.29) before baseline NHHR entered the model. Physical-activity-only classes likewise produced no contrast beyond unity at any class number tested (estimates 0.84–1.06 for two to four classes; Additional file 1: Table S2). The excess risk therefore emerged only when the two exposures were modelled jointly, supporting the joint readout over either single-exposure summary.

Table 2
Cox proportional hazards models for incident cardiovascular disease, ELSA (landmark 2012, follow-up to 2018)

Contrast	Crude HR (95% CI)	Fully adjusted HR (95% CI)[1]
C1 vs C2	1.51 (1.19–1.93)	1.43 (1.03–1.97)
C3 vs C2	1.13 (0.89–1.44)	1.11 (0.78–1.57)
C4 vs C2	1.39 (1.08–1.79)	0.99 (0.70–1.38)
C5 vs C2	1.43 (1.11–1.84)	1.51 (1.02–2.22)
C4 vs C3 (the two low-NHHR classes)[2]	—	0.77 (0.51–1.15)
C1 vs C4 (the two low-activity classes)[2]	—	1.67 (1.03–2.73)
C1 vs C4, pseudo-class draws (20, Rubin)[2]	—	1.38 (0.75–2.53)
Medication vs no medication within C4	1.75 (1.04–2.96)[5]	1.66 (0.97–2.84)[3] / 1.40 (0.78–2.50)[4]
Time-varying medication, outcome window	—	1.11 (0.89–1.39)

[1] Fully adjusted: age, sex, education, BMI, former and current smoking, diabetes, hypertension, baseline (2004) NHHR; complete cases n = 2,215 (377 events). [2] Subgroup models fully adjusted within the stated classes. [3] Adjusted, unweighted (complete cases within C4). [4] Inverse-probability-of-treatment weighted.

[5] Estimated within the 2,215 complete cases; on the full C4 class (n = 641), the crude estimate is 1.47 (0.98–2.21).

Treatment: confounding by indication and gradient attenuation

Treated participants differed systematically from untreated ones at baseline (age 70.2 versus 67.6 years; diabetes 20.1% versus 4.6%; hypertension 60.3% versus 31.9%; baseline NHHR 4.24 versus 3.96), and medication did lower NHHR (− 1.03 versus − 0.36 units over 2004–2012). Treatment was associated with risk in crude terms (HR 1.31) but neutral after IPTW (1.07, 0.84–1.38), and the same pattern held within classes: within C4, the crude treatment contrast of 1.75 (1.04–2.96) fell to 1.40 (0.78–2.50) after weighting, and within C1, from 1.14 to 1.01. A time-varying specification of medication in the outcome window gave 1.11 (0.89–1.39) (Table 2).

The achieved-NHHR analysis separated the two treatment strata. In untreated participants, achieved NHHR predicted events per unit increase (1.29, 1.09–1.52). In treated participants it did not (0.88, 0.70–1.12), and the formal interaction was significant (interaction HR 0.75, 0.59–0.95; likelihood-ratio P = 0.013). Within the treated stratum, activity did not further modify the NHHR–risk relation (interaction P = 0.65).

Sensitivity analyses

The two high-NHHR class estimates were robust across every specification that changed the data or the estimator, while the pseudo-class draws, which propagate assignment uncertainty, retained direction but widened intervals past unity (Table 3; Additional file 1: Table S3; Fig. 3B); the C1-versus-C4 class-pair contrast behaved the same way (1.38, 0.75–2.53, against 1.67 under MAP assignment). Multiple imputation left C1 essentially unchanged (1.37, 1.04–1.80) and strengthened C5 (1.63, 1.18–2.26). Excluding participants diagnosed with high cholesterol in 2004 moved C1 to 1.39 (0.97–2.00) and left C5 significant at 1.56 (1.02–2.38). Under worst-case early censoring, every class contrast moved toward the null and none remained significant (C1 1.25, 0.97–1.61; C5 1.26, 0.93–1.71; C4 1.17, 0.92–1.50), bounding the possible effect of informative dropout. Stratifying the baseline hazard by BMI quartiles, or adding a BMI-by-log-time interaction, left the class estimates essentially unchanged (C1 1.37–1.38, C4 0.96–0.97, and C5 1.49, 1.00–2.23), and if anything slightly strengthened C5. Cause-specific models tied C5 to coronary events (1.54, 1.01–2.35) and flagged a wide, non-significant stroke estimate for C4 (1.95, 0.94–4.03). The E-value for C1 was 2.21 (lower limit 1.21), meaning an unmeasured confounder would need to be associated with both the class and the outcome by a factor of at least 2.2 to explain the estimate away; the corresponding values were 2.73 for the C1-versus-C4 contrast and 1.99 for the treatment interaction.

Table 3
Sensitivity analyses, fully adjusted hazard ratios (95% CI), ELSA

Analysis	C1	C5	C4
Main (MAP assignment, complete cases)	1.43 (1.03–1.97)	1.51 (1.02–2.22)	0.99 (0.70–1.38)
Multiple imputation (N = 4,150)	1.37 (1.04–1.80)	1.63 (1.18–2.26)	1.01
Pseudo-class draws (20, Rubin pooling)	1.27 (0.86–1.88)	1.32 (0.82–2.13)	1.03 (0.69–1.56)
Posterior-probability-weighted Cox	1.36 (0.96–1.93)	—	—
Excluding 2004-diagnosed hypercholesterolaemia (n = 2,461)	1.39 (0.97–2.00)	1.56 (1.02–2.38)	0.80 (0.54–1.19)
Worst-case early censoring (653 dropouts as events)	1.25 (0.97–1.61)	1.26 (0.93–1.71)	1.17 (0.92–1.50)
Baseline hazard stratified by BMI quartiles	1.37 (0.98–1.92)	1.49 (1.00–2.23)	0.97 (0.68–1.37)
Coronary heart disease only (499 events)	1.23 (0.86–1.76)	1.54 (1.01–2.35)	—
Stroke only (105 events)	—	—	1.95 (0.94–4.03)
E-value, point estimate (CI limit)	2.21 (1.21)	—	—
E-value, C1 vs C4 (CI limit)	2.73 (1.21)	—	—
E-value, treatment × achieved NHHR interaction (CI limit)	1.99 (1.28)	—	—

Replication in CHARLS

The CHARLS typing produced four joint classes whose ordering matched ELSA: the highest crude event rate fell in the high-NHHR class (47.9 per 1,000 person-years) and the lowest in the low-NHHR/high-activity class (25.2). Class main effects, however, did not survive adjustment: with baseline NHHR in the model, the high-NHHR class carried 1.04 (0.62–1.75), the low-NHHR/high-activity class 0.82 (0.49–1.36), and the very-low-activity class 0.88 (0.57–1.36), consistent with the limited power of 182 events and with the absorption of between-class differences by baseline NHHR when only two lipid time points are available. Treatment showed more extreme confounding by indication than in ELSA (crude HR 2.94, 2.00–4.33; 2.07, 1.31–3.30 after adjustment), reflecting that lipid-lowering medication in China in 2011 was nearly confined to very-high-risk patients. The central untreated-population finding did replicate: achieved NHHR predicted events per unit in untreated participants (1.32, 1.08–1.62) but not in the 83

treated ones (0.79, 0.42–1.48). Because the treated stratum held 31 events, we report the stratum-specific estimates and do not press the formal interaction in this cohort.

Discussion

Following 4,150 English adults aged 50 and over from a 2012 landmark, we found that joint NHHR–activity trajectories sort older adults into five phenotypes whose cardiovascular futures differ materially. Two findings carry the paper. Where a high lipid trajectory met inactivity, risk concentrated: 43% excess in the high-NHHR/low-activity class and 51% in the persistently high class, but none in the class whose NHHR fell alongside low activity once age and comorbidity were accounted for. Treatment, meanwhile, reshaped what the lipid measure itself means: achieved NHHR predicted events among the untreated but not the treated (interaction P = 0.013), and the untreated gradient of about 1.3 per unit reappeared in CHARLS almost unchanged.

Between the two low-activity phenotypes, the 1.67 contrast pushes this reading past single measurements. Activity levels in the two classes were comparably low and treated shares the highest in the cohort; what separated them was treatment response, NHHR staying high in C1 while falling in C4. Survival of the contrast after adjustment for baseline NHHR points to information in the trajectory that a single value misses, which is what motivated joint typing in the first place. A small literature has noticed something similar in treated populations, where falling lipid values bring no benefit: in a peripheral artery disease cohort, a declining NHHR trajectory offered no risk advantage (HR 1.04) [14]. Our data make the distinction sharper still. The excess belonged to the joint phenotype, poor treatment response together with inactivity; the fall in NHHR by itself bought nothing. The crude excess among treated participants, which vanished under IPTW, parallels the classical confounding-by-indication signature [30] and should discourage naive reading of medication "harm" in observational lipid data.

Against prior trajectory work, the contribution is threefold. Single-marker NHHR trajectories in CHARLS established that long-term exposure stratifies risk [5], and our untreated-population gradient confirms that signal; but that literature excluded treated patients, modelled one exposure at a time, and measured the exposure window partly inside the outcome window. Joint behavioural–biomarker typing exists for activity with diet [19] and for activity with sleep in ELSA itself [31]; NHHR has been typed against outcomes in treated atrial fibrillation and type 2 diabetes populations [8]; yet no published model, to our knowledge, types a lipid ratio and activity together or tests how treatment modifies the resulting risk pattern. The replication of the untreated gradient in a second national cohort, in a different health system with far lower treatment penetration, is the strongest external support the design can offer.

The anticipated buffering role of activity, however, was not confirmed. At comparable lipid levels, the low-activity class showed no excess against the high-activity class (0.77, 0.51–1.15), the continuous-exposure interaction did not reach significance (P = 0.065), and within treated participants activity did not modify the NHHR–risk relation (P = 0.65). This pattern makes physiological sense. Activity works largely through the lipid fraction that the ratio already captures [17, 18], so once trajectories are typed

jointly, little independent behavioural separation may remain. Read practically, the message is conservative: in this cohort activity mattered in combination with lipid response, and not as an independent buffer at any fixed lipid level.

Several limitations bound these conclusions. Outcome and medication status were self-reported, and self-reported myocardial infarction and stroke agree only moderately with adjudicated or coded records in ageing cohorts [32, 33]. Misclassification identical across classes biases toward the null; differential reporting by treatment status cannot be excluded. The analytic extract carried no mortality data, so competing risks went unmodelled. To bracket the distortion this could cause, the worst-case analysis converted all 653 early dropouts into events and still returned 1.25 (0.97–1.61). Physical activity was self-reported and coarsely graded; in ELSA it correlates only modestly with objective accelerometry [16]. Error of that kind usually attenuates exposure contrasts, which makes the class differences we observe more likely understated than inflated. The trajectory classes are empirical summaries, not validated clinical phenotypes. They require replication before any clinical use, and a five-class structure that is stable here need not be the natural partition elsewhere. Baseline NHHR was missing for 36.1% of participants in the fully adjusted models, a direct consequence of two-wave inclusion, which let participants who missed the 2004 nurse visit enter through their 2008 and 2012 measurements. Complete-case estimates and tenfold multiple imputation agreed closely; this supports, without proving, robustness to the missingness mechanism. Body mass index violated proportional hazards, and beyond medication we modelled no time-varying covariates. Finally, CHARLS replicated the untreated gradient on 182 events and had no power for the class contrasts; its 83 treated participants, with a much stronger indication profile, explain why the medication association there stayed positive even after adjustment.

What our findings isolate is a specific clinical question, not a general one. In untreated older adults, serial NHHR behaves as the lipid literature expects. The highest-risk phenotype here paired a lipid ratio that stayed high with inactivity, and a clinician can recognise it from measurements already collected in routine care. One caution attaches to that contrast: it was estimated across all members of the two low-activity classes, only about a third of whom were treated. Restricted to treated members the estimate kept its direction but lost precision (1.45, 0.72–2.93), so the treatment-specific reading stays provisional. The discriminating next test is prospective: does a joint trajectory readout at treatment initiation, re-evaluated after one year, identify poor responders whose risk is not captured by achieved LDL cholesterol or achieved NHHR alone? Randomised evidence on intensifying treatment in that group would settle whether the 1.67 contrast reflects response itself or an unmeasured substrate of it, and the E-value of 2.73 for the class contrast says such confounding would need to be strong.

Conclusions

In two national ageing cohorts, joint trajectories of the non-HDL-cholesterol to HDL-cholesterol ratio and physical activity stratified cardiovascular risk among older adults, with excess concentrated in the high-NHHR classes and, among the two low-activity classes that shared the cohort's highest treated prevalence, in the class whose ratio remained high. Lipid-lowering treatment flattened the NHHR–risk

gradient, an effect compatible with successful treatment rather than treatment failure, once confounding by indication was removed. Serial joint assessment of lipid response and activity may refine risk stratification in treated dyslipidaemia; the classes used here are empirical and require validation before clinical application.

Abbreviations

APPA: average posterior assignment probability · BMI:body mass index · CHARLS:China Health and Retirement Longitudinal Study · CHD:coronary heart disease · CI:confidence interval · CVD:cardiovascular disease · ELSA:English Longitudinal Study of Ageing · HDL-C:high-density lipoprotein cholesterol · HR:hazard ratio · IPTW:inverse-probability-of-treatment weighting · MAP:maximum a posteriori · MET:metabolic equivalent of task · MICE:multiple imputation by chained equations · NHHR:non-HDL-cholesterol to HDL-cholesterol ratio · PA:physical activity · SD:standard deviation · STROBE:Strengthening the Reporting of Observational Studies in Epidemiology

Declarations

Ethics approval and consent to participate:

ELSA and CHARLS were approved by their respective ethics committees, and all participants gave informed consent in the original studies. The present secondary analysis of fully anonymised data followed the data-use agreements of both studies.

Consent for publication:

Not applicable.

Competing interests:

The authors declare no competing interests.

Funding:

This work was supported by the Fujian Provincial Natural Science Foundation (grant number 2023J01121175). The funder had no role in study design, data analysis, or manuscript preparation.

Author Contribution

Xin Yang: conceptualisation, methodology, formal analysis, and writing—original draft. Lingfeng Yang: data curation, validation, and visualisation. Weiguo Li: supervision, funding acquisition, project administration, and writing—review and editing. All authors read and approved the final manuscript.

Acknowledgement

The authors thank the participants and research teams of the English Longitudinal Study of Ageing and the China Health and Retirement Longitudinal Study.

Data Availability

The datasets supporting the conclusions of this article are available as follows: ELSA data are archived at the UK Data Service under study number SN 5050 (https://beta.ukdataservice.ac.uk/datacatalogue/studies/study/?id=5050) and were accessed by the authors under the UK Data Service end-user licence; CHARLS data are publicly available from the CHARLS project (http://charls.charlsdata.com) after free registration. No additional data restriction applies; all analysis code is available from the corresponding author on reasonable request.

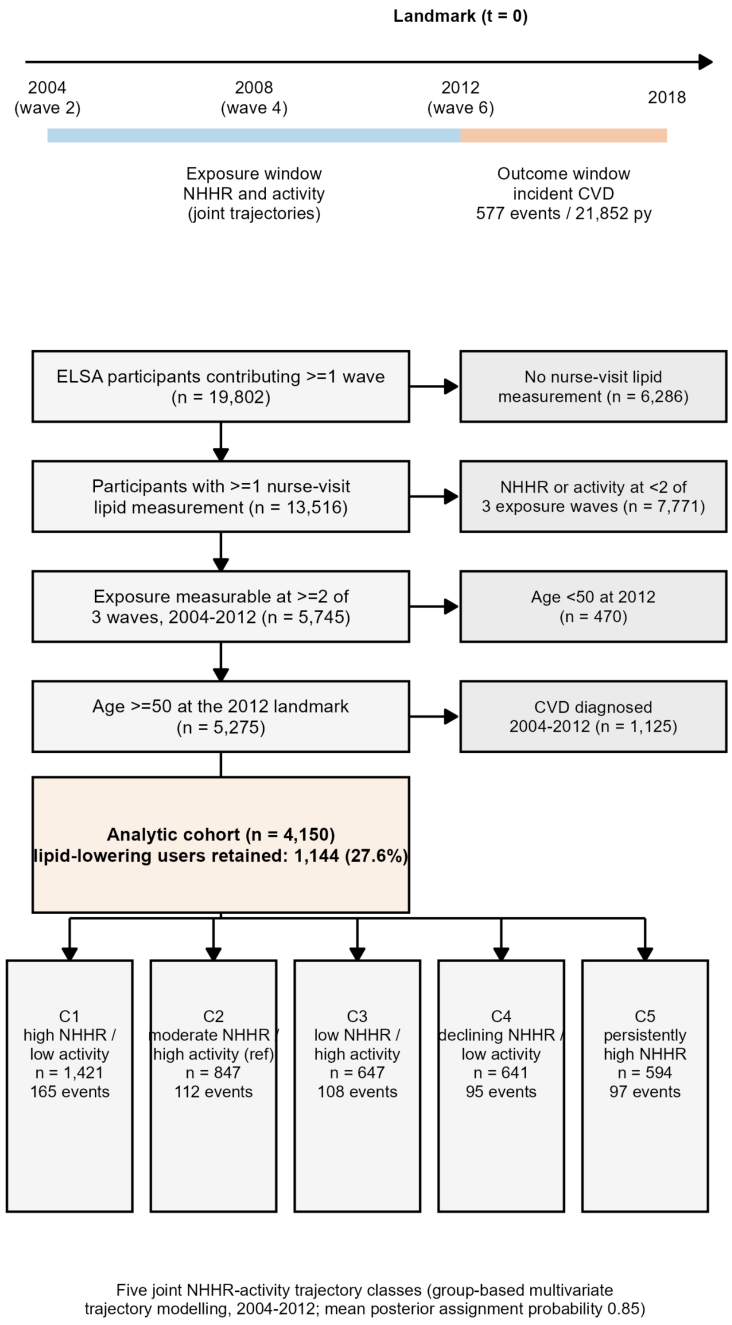
References

1. Boekholdt SM, Arsenault BJ, Mora S, et al. Association of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B levels with risk of cardiovascular events among patients treated with statins: a meta-analysis. JAMA. 2012;307(12):1302–9. 10.1001/jama.2012.366.
2. Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. Eur Heart J. 2017;38(32):2459–72. 10.1093/eurheartj/ehx144.
3. Sandesara PB, Virani SS, Fazio S, Shapiro MD. The forgotten lipids: triglycerides, remnant cholesterol, and atherosclerotic cardiovascular disease risk. Endocr Rev. 2019;40(2):537–57. 10.1210/er.2018-00184.
4. Burnett JR, Hooper AJ, Hegele RA. Remnant cholesterol and atherosclerotic cardiovascular disease risk. J Am Coll Cardiol. 2021;76(23):2736–9. 10.1016/j.jacc.2020.10.029.
5. Wang B, et al. Changes in the non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR) and cardiovascular disease: a trajectory analysis in CHARLS. Lipids Health Dis. 2025;24:112. 10.1186/s12944-025-02536-3.
6. Pan Y, Bi J, Feng L, He X. Association of a novel triglyceride-glucose and non-HDL-to-HDL cholesterol ratio (TyG-NHHR) index with cardiometabolic multimorbidity: a dual-cohort prospective study in Chinese and European adults. J Health Popul Nutr. 2026;45:128. 10.1186/s41043-026-01307-9.
7. Soler-Espejo E, Chen Y, Rivera-Caravaca JM, et al. Relation of the non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio to residual risk in anticoagulated patients with atrial fibrillation: a report from the prospective Murcia AF Project III cohort. Cardiovasc Diabetol. 2025;24:374. 10.1186/s12933-025-02927-x.

8. Liu M, Pei J, Zeng C, Xin Y. Association of non-high-density lipoprotein cholesterol/high-density lipoprotein cholesterol ratio with cardiovascular outcomes in patients with type 2 diabetes mellitus: evidence from the ACCORD cohort. Diabetes Obes Metab. 2025;27(1):300–11. 10.1111/dom.16018.
9. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(9):111–88. 10.1093/eurheartj/ehz455.
10. Bull FC, Al-Ansari SS, Biddle S, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. Br J Sports Med. 2020;54(24):1451–62. 10.1136/bjsports-2020-102955.
11. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021;42(34):3227–337. 10.1093/eurheartj/ehab484.
12. Nagin DS, Odgers CL. Group-based trajectory modeling in clinical research. Annu Rev Clin Psychol. 2010;6:109–38.
13. Nagin DS, Jones BL, Elmer J. Recent advances in group-based trajectory modeling for clinical research. Annu Rev Clin Psychol. 2024;20:285–305. 10.1146/annurev-clinpsy-081122-012416.
14. Zhang Y, Jing Z, Liu Z, et al. Baseline and longitudinal patterns of non-HDL-C to HDL-C ratio (NHHR) and major adverse cardiovascular events in peripheral artery disease. Sci Rep. 2025;15:35993. 10.1038/s41598-025-19856-0.
15. Li J, Siegrist J. Physical activity and risk of cardiovascular disease—a meta-analysis of prospective cohort studies. Int J Environ Res Public Health. 2012;9(2):391–407. 10.3390/ijerph9020391.
16. Hamer M, Lavoie KL, Bacon SL. Taking up physical activity in later life and healthy ageing: the English Longitudinal Study of Ageing. Br J Sports Med. 2014;48(3):239–43. 10.1136/bjsports-2013-092993.
17. Lin X, Zhang X, Guo J, et al. Effects of exercise training on cardiorespiratory fitness and biomarkers of cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc. 2015;4(7):e002014. 10.1161/JAHA.115.002014.
18. Smart NA, Downes D, Van der Touw T, et al. The effect of exercise training on blood lipids: a systematic review and meta-analysis. Sports Med. 2025;55(1):67–78. 10.1007/s40279-024-02115-z.
19. Aryannezhad S, Imamura F, Mok A, et al. Combined associations of physical activity, diet quality and their trajectories with incidence of diabetes and cardiovascular diseases in the EPIC-Norfolk study. Sci Rep. 2025;15:11261. 10.1038/s41598-025-93679-x.
20. Steptoe A, Breeze E, Banks J, Nazroo J. Cohort profile: the English Longitudinal Study of Ageing. Int J Epidemiol. 2013;42:1640–8.
21. Zhao Y, Hu Y, Smith JP, Strauss J, Yang G. Cohort profile: the China Health and Retirement Longitudinal Study (CHARLS). Int J Epidemiol. 2014;43:61–8.
22. Hamer M, de Oliveira C, Demakakos P. Non-exercise physical activity and survival: English Longitudinal Study of Ageing. Am J Prev Med. 2014;47(4):452–60. 10.1016/j.amepre.2014.05.044.

23. Magrini A. Assessment of agricultural sustainability in European Union countries: a group-based multivariate trajectory approach. AStA Adv Stat Anal. 2022;106(4):673–703. 10.1007/s10182-022-00437-9.
24. Nagin DS, Jones BL, Passos VL, Tremblay RE. Group-based multi-trajectory modeling. Stat Methods Med Res. 2018;27(7):2015–23. 10.1177/0962280216673085.
25. van Buuren S, Groothuis-Oudshoorn K. mice: multivariate imputation by chained equations in R. J Stat Softw. 2011;45(3):1–67. 10.18637/jss.v045.i03.
26. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivar Behav Res. 2011;46:399–424.
27. Wang CP, Hendricks Brown C, Bandeen-Roche K. Residual diagnostics for growth mixture models. J Am Stat Assoc. 2005;100(471):1054–76. 10.1198/016214505000000501.
28. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. Ann Intern Med. 2017;167:268–74.
29. von Elm E, Altman DG, Egger M, et al. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ. 2007;335(7624):806–8. 10.1136/bmj.39335.541782.AD.
30. Freemantle N, Marston L, Walters K, et al. Making inferences on treatment effects from real world data: propensity scores, confounding by indication, and effect estimators. BMJ. 2013;347:f6409. 10.1136/bmj.f6409.
31. Bloomberg M, Brocklebank L, Hamer M. Joint associations of physical activity and sleep duration with cognitive ageing: longitudinal analysis of the English Longitudinal Study of Ageing. Lancet Healthy Longev. 2023;4(7):e345–53. 10.1016/S2666-7568(23)00083-1.
32. Jamrozik E, Hyde Z, Alfonso H, et al. Validity of self-reported versus hospital-coded diagnosis of stroke: a cross-sectional and longitudinal study. Cerebrovasc Dis. 2014;37(4):256–62. 10.1159/000358583.
33. McCormick N, Lacaille D, Bhole V, et al. Validity of myocardial infarction diagnoses in administrative databases: a systematic review. PLoS ONE. 2014;9(3):e92286. 10.1371/journal.pone.0092286.

Figures



Five joint NHHR-activity trajectory classes (group-based multivariate trajectory modelling, 2004-2012; mean posterior assignment probability 0.85)

Figure 1

Study timeline and participant flow. Panel A: the exposure window (NHHR and physical activity at up to three waves, 2004–2012) is separated from the outcome window (incident cardiovascular disease, 2012–2018) by the 2012 landmark. Panel B: sequential participant flow, with exclusions itemised by reason at each step (steps do not overlap); lipid-lowering medication users were retained by design (1,144; 27.6%). The analytic cohort was typed into five joint NHHR–activity trajectory classes (mean

posterior assignment probability 0.853), with class-specific numbers of participants and events shown at the bottom. CVD, cardiovascular disease; NHHR, non-HDL-cholesterol to HDL-cholesterol ratio.

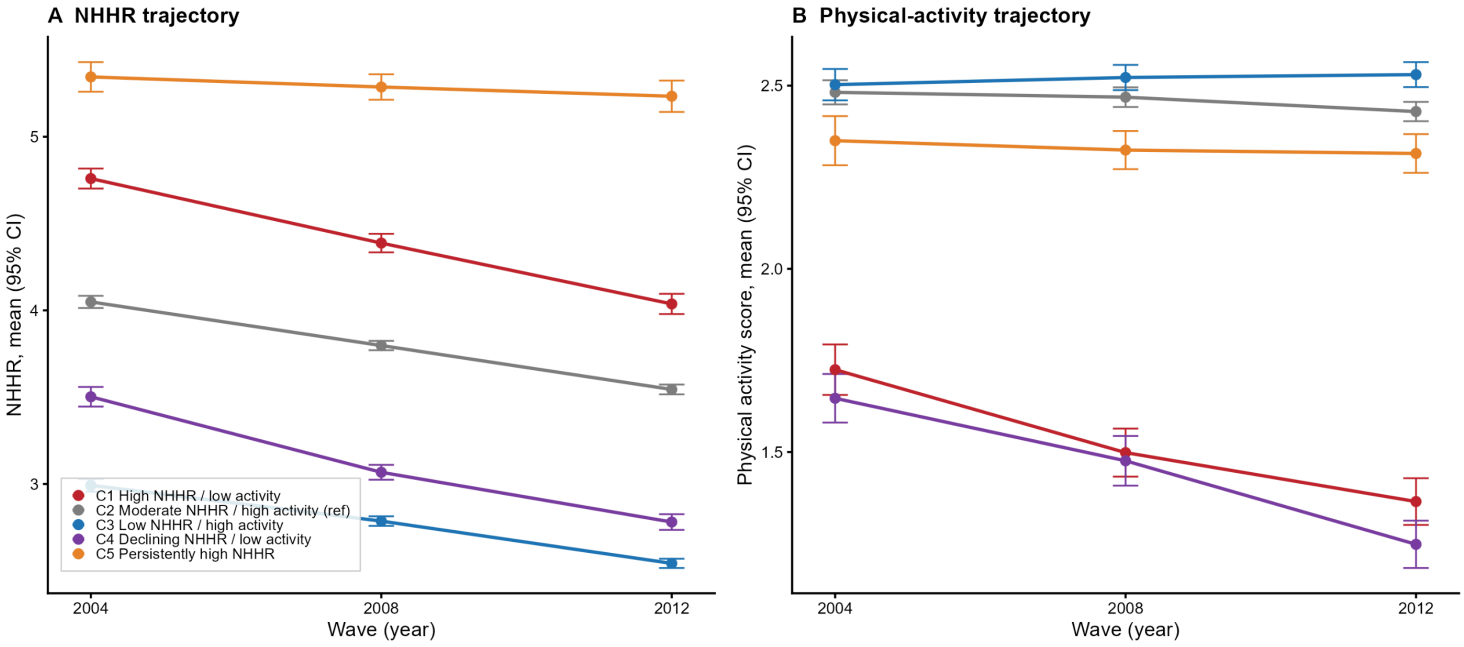


Figure 2

Joint NHHR and physical activity trajectory classes, ELSA 2004–2012. Panel A: mean NHHR by class and wave. Panel B: mean physical activity score (0–3) by class and wave. Error bars are 95% confidence intervals. C1, high NHHR with low activity; C2, moderate NHHR with high activity (reference); C3, low NHHR with high activity; C4, declining NHHR with low activity; C5, persistently high NHHR. Five classes from group-based multivariate trajectory modelling; mean posterior assignment probability 0.853.

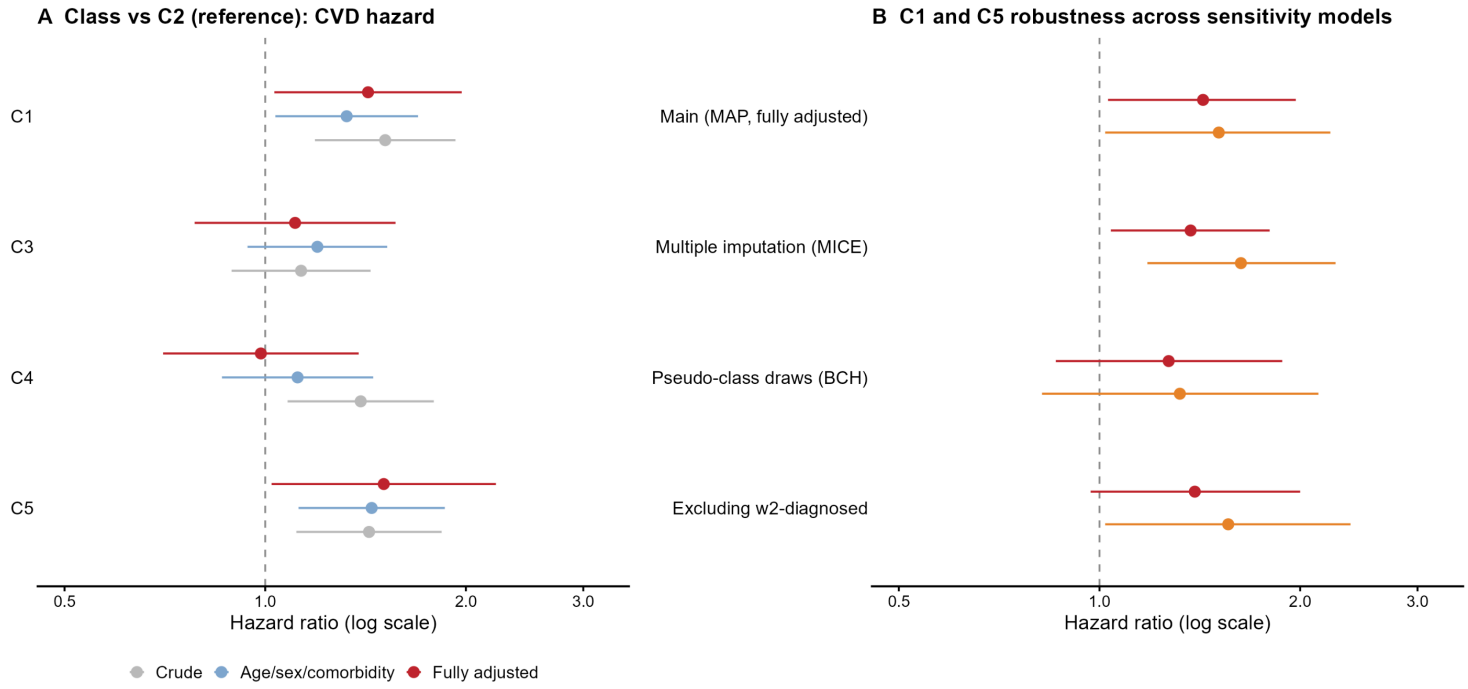


Figure 3

Hazard ratios for incident cardiovascular disease. Panel A: each class against the reference class C2 under three adjustment tiers (crude; age, sex, diabetes, hypertension; fully adjusted with education, body mass index, smoking, and baseline NHHR). Panel B: sensitivity of the C1 and C5 estimates to multiple imputation, pseudo-class draws, and exclusion of participants diagnosed with high cholesterol in 2004. Horizontal bars are 95% confidence intervals; the dashed line marks no association.

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