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Cardiovascular health and its association with dementia, Parkinson's Disease, and mortality among UK older adults

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ABSTRACT

Background: Previous research has primarily examined individual factors of cardiovascular health (CVH) and disease in PD and dementia, but no study has examined CVH measures with PD, dementia, and mortality simultaneously while accounting for potentially confounding factors.
Objectives: To examine the relationship between CVH, all-cause dementia, Parkinson's disease (PD), and mortality, focusing on associations and health transitions from a large population-based study.
Methods: We investigated these relationships using Cox Proportional Hazards and multistate parametric models with Weibull regression from the UK Biobank data (n = 269,816, Age = 50 + y individuals, ≤15y follow-up, 2006–2021).
Results: Full Cox models found poor CVH (measured with standardized reverse-coded Life's Essential 8 total score, $LE8_{zrev}$), to be associated with increased risks for all-cause dementia (Hazard Ratio (HR) = 1.14, 95 % CI: 1.11–1.18, P < 0.001) and all-cause mortality (HR = 1.31, 95 % CI: 1.29–1.33, P < 0.001). Unlike "Healthy to PD" and "Dementia→Death" transitions, PD→Death (Weibull full model: HR = 1.18, 95 % CI: 1.06–1.31, P = 0.002), Healthy→dementia (HR = 1.15, 95 % CI: 1.12–1.19, P < 0.001), and Healthy→Death (HR = 1.33, 95 % CI: 1.32–1.35, P < 0.001) exhibited a positive relationship with poor CVH.
Conclusions: Poor CVH is directly associated with an increased risk of mortality from PD, transition into Dementia, and all-cause mortality without dementia or PD occurrence. Clinicians should aggressively screen for and manage CVH risk measures to reduce the risk of poor cognitive health outcomes.

1. Introduction

Nearly 55 million people around the world are living with dementia, a progressive form of cognitive impairment, with cases projected to exceed 130 million by 2050 (Organization, 2021b). Parkinson's disease (PD), another significant public health issue, affected more than 5 million people worldwide in 2016, and it's considered among fastest growing neurological conditions worldwide (Bloem et al., 2021). These trends are largely related to increased life expectancy (Organization, 2021a), with another factor affecting them being the increased risk of developing dementia and PD in the oldest segments of the population (Bloem et al., 2021; Long et al., 2023). Together, expenditures on dementia and PD are considered costly burdens on healthcare and society as a whole (Cantarero-Prieto et al., 2020; Dahodwala et al., 2021; Kowal et al., 2013; Schaller et al., 2015). Therefore, it is necessary to understand potential mechanisms by which these conditions develop with age, to help inform prevention and reduction strategies.

Research indicates that dementia and PD share common pathological

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mechanisms, including inflammation and metabolic dysfunction. Chronic neuroinflammation, triggered by microglia activation and pro-inflammatory cytokines, contributes to neuronal damage and disease progression (Balestri et al., 2024; Batra et al., 2024; Zhang et al., 2023). Metabolic disturbances, like impaired glucose metabolism and mitochondrial dysfunction, exacerbate oxidative stress and neuronal vulnerability, linking the two diseases (Balestri et al., 2024; Batra et al., 2024; Zhang et al., 2023). This pathological commonality provides a basis for studying them jointly along with all-cause mortality as a prognostic absorbing outcome.

Importantly, previous studies have indicated an association between dementia and cardiovascular disease (CVD) and associated risk factors such as hypertension and dyslipidemia (Deckers et al., 2017; Song et al., 2021; Wolters et al., 2018). In the most recent Lancet Commission, vision loss and high LDL cholesterol have been included as modifiable risk factors for dementia, adding to the 12 risk factors reported in the 2020 Lancet Commission, which included socio-environmental factors such as lower education, social isolation, and air pollution, along with lifestyle factors such as physical inactivity, excessive consumption of alcohol and cardio-metabolic biological factors such as obesity, hypertension and diabetes (Livingston et al., 2020, 2024). Additionally, the number of people living with dementia continues to increase, along with racial and socio-economic disparities requiring prevention and reduction strategies (Beydoun et al., 2023a; Livingston et al., 2024). While associations between dementia and CVD are straightforward, associations between CVD and PD are not. CVD and PD share biological processes such as inflammatory pathways, disrupted lipid metabolism, insulin resistance, and oxidative stress (Potashkin et al., 2020). However, older adults who have PD are also at heightened risk for CVD such as stroke (Alves et al., 2020a) and coronary artery disease (Chua et al., 2022). Additionally, those with PD are at increased risk of long-term CVD mortality rates (Ke et al., 2024); similarly, CVD-related mortalities have been associated with dementia, but have decreased in the last 2 decades (Ranganathan et al., 2024).

It has been documented that PD and dementia are connected. Cognitive decline is common in PD, approximately one-quarter of individuals with PD have PD-related dementia (e Sousa et al., 2022). Cognitive decline more broadly has been associated with cardiovascular factors such as blood pressure abnormalities (Kwaśniak-Butowska et al., 2021). However, little research has simultaneously looked at various lifestyle and biological aspects of cardiovascular health (CVH) and its association with cognitive impairment, dementing illness, and outcomes of dementia including all-cause mortality, along with transitions between those health states. To this end, the American Heart Association introduced a CVH metric in 2010, focusing on health promotion at both individual and population levels. The "Life's Simple 7″ measures include factors like BMI, fasting blood glucose, cholesterol, blood pressure, physical activity, and smoking status (Beydoun et al., 2024; Hayman and Martyn-Nemeth, 2022; Lloyd-Jones et al., 2010, 2022). The "Life's Essential 8" (LE8) included sleep health in addition to these metrics and produced a more continuous measure by altering definitions of the remaining 7 metrics (Beydoun et al., 2024; Hayman and Martyn-Nemeth, 2022; Lloyd-Jones et al., 2010, 2022). A higher score on LE8 reflected better CVH (Beydoun et al., 2024; Hayman and Martyn-Nemeth, 2022; Lloyd-Jones et al., 2010, 2022).

Previous research has focused on individual factors of CVH in relation to PD and dementia risk (Justin et al., 2013; Potashkin et al., 2020). However, no research has examined the association of CVH measures with PD, dementia, and mortality, while testing transitions between them. The present study uses a nationally representative sample of older adults from the UK Biobank study to examine the associations of CVH with all-cause dementia, PD, and mortality and transitions between those health states, using a multistate approach. It is hypothesized that poor CVH is associated with greater risk and poorer prognosis of dementia and PD, along with greater mortality risk. The approach utitlized can provide a more comprehensive evaluation of CVH risk factors for dementia and mortality, and better guiding prevention practices.

2. Materials and methods

2.1. Database

The UK Biobank is a large-scale prospective study involving nearly 500,000 individuals aged 37–73 years from 2006 to 2010 in the UK. Participants were sent to 22 assessment centers in England, Scotland, or Wales to complete questionnaires and participate in face-to-face interviews(UK Biobank, 2007). The questionnaires covered various fields of interest and included input from international collaborators (UK Biobank, 2007). Several biological and physical measures were collected (UK Biobank, 2007). The initiative received ethical approval from the Northwest Multi-Centre Research Ethics Committee. Data is made available to specific institutions through an application process to the UK Biobank's access management system after completing a material transfer agreement and paying fees based on tier level of access. The UK Biobank access management team and the National Institutes of Health Institutional Review Board approved the current application (#77963), which has recently been expanded.

2.2. Mortality linkage

All UK Biobank participants had their death registries linked, following the comprehensive process described at this URL: https://biobank.ndph.ox.ac.uk/ukb/ukb/docs/DeathLinkage.pdf. The major emphasis of this study is the date of death supplied in the dataset, but the connection also includes primary and contributing causes of death that are categorized according to the ICD-10 system.

2.3. Dementia and PD outcomes

The UK Biobank used an algorithm to determine the earliest onset of dementia and PD using hospital and death registry data. Incident outcomes after baseline assessment were also based on these data. The study focused on all-cause dementia and PD, using the ICD10 code 42018 for both conditions. Participants with existing dementia or PD were excluded from the analysis. Further details on the algorithm and ICD10 codes can be found at https://biobank.ndph.ox.ac.uk/showcase/ukb/docs/alg_outcome_main.pdf.

2.4. CVH: Life's essential 8

The American Heart Association (AHA) introduced a CVH metric in 2010, which includes both population and individual-level health promotion. CVH was initially defined as seven modifiable biological and behavioral characteristics that can reduce the risk of CVD and increase longevity and quality of life. The "Life's Simple 7" (LS7) CVH measure includes factors like BMI, fasting blood glucose, cholesterol, blood pressure, physical activity, diet and smoking status. The "Life's Essential 8" (LE8) measure, which now includes sleep health, was a result of a re-evaluation of LS7. More details are provided in **Online** Supplementary Methods 1**.** For further details on computations of LE8 scores, please refer to supplementary materials of previously published work (Beydoun et al., 2023b, 2024), original sources of information (Hayman and Martyn-Nemeth, 2022; Lloyd-Jones et al., 2010, 2022) and the code used in our analysis available at https://github.com/baydounm/UKB-paper15-supplementarydata. The total score of LE8, which is the key exposure in this analysis, was z-score standardized and reverse coded by multiplying the z-score by −1 (LE8z_rev) to reflect poorer CVH with higher score (for each SD).

2.5. Covariates

Age, gender, race/ethnicity (White, Black, South Asian, and Others),

and household size were all possible sociodemographic factors. Socioeconomic status (SES) measures include household income, educational achievement, and the Townsend Deprivation Index (TDI). Baseline data on educational attainment were gathered using a touch-screen questionnaire; they were regrouped following prior research, as 1 = Intermediate, joining "O Levels/GCSEs/Equivalent" and "A/AS Levels Equivalent"; 2 = Higher level or "College/University"; 0 = Low, combining "CSEs/Equivalent," "NVQ/HND/HNC/Equivalent," and "Other professional qual." The five categories for household income before taxes were 1 = "£18,000," 2 = "£18,000-£29,999," 3 = "£30,000-£51,999," 4 = "52,000-£100,000," and 5 = ">£100,000". TDI ratings were computed at the residential postcode level on owner occupation, vehicle ownership, population levels in homes, and unemployment using national census data, with higher scores indicating greater socioeconomic disadvantage (Townsend and Beattie, 1987). Single SES summary scores were obtained by averaging z-scores of household income, educational attainment, and TDI z-score (multiplied by −1). The covariates that were selected for this study were similar to the ones selected for previous analyses (Beydoun et al., 2024) and were considered important potential confounders without being on the causal pathway between exposure (LE8 scores) and various outcomes of interest.

2.6. Study sample selection

Of the initial UK Biobank data, we included individuals who were at risk for dementia, PD, or death, and thus we excluded those who were less than 50y at baseline, given the <15y of follow-up. We also excluded individuals with incomplete key covariates and those who had prevalent PD or dementia, or whose earliest date of occurrence was prior to baseline assessment. The UK Biobank sample consisted of 502,160 participants, with 384,486 aged ≥50 years at baseline. 270,538 had available data on socio-demographic, economic, lifestyle, and biological factors. Of this group, 722 were excluded for the prevalence of dementia or PD. The final sample size was 269,816 participants who were followed up for up to 15 years for incidence of dementia, PD, and/or all-cause mortality (Fig. S1).

2.7. Statistical methods

We first characterized the sample using means and proportions and examined covariate distributions by sex, using regression models to test for sex differences across covariates. We then separately examined relationships between CVH and each of PD, dementia, and mortality. We fit Kaplan-Meier survival functions from which we obtained estimates of event-free survival probabilities for each of our three outcomes. For each outcome, we used time on the study—defined as the number of years between baseline age and age at the event or censoring (death or end of follow-up set to October 31st, 2021, in the case of dementia and PD)—as the underlying timescale. Log-rank tests were used to test differences in survival by CVH status.

To evaluate the relationships between CVH and PD, dementia, and mortality, we fit a series of Cox Proportional Hazards (PH) models with full covariate adjustment, including baseline age, sex, race/ethnicity (Non-White vs. White), household size and SES z-score. We used time on study as the underlying timescale as was calculated for the Kaplan-Meier survival functions. Schoenfeld residuals and visual inspection were used to verify the PH assumption. We then replicated these analyses in models stratified by sex and tested for differences using interaction terms in the fully adjusted Cox models. A sensitivity analysis was conducted using the Royston-Parmar flexible parametric model, with restricted cubic splines applied to baseline age, with three degrees of freedom and interaction with baseline age.

We importantly modeled health state transitions using a closed-cohort transition model containing four states to reflect disease progression and mortality: healthy (state 1; dementia- and PD-free), PD (state 2; irrespective of dementia status), dementia (state 3; irrespective of PD status), death (state 4). Transition rates between the states were modeled using fully parametric Weibull regression. Weibull regression allows for the explicit modeling of the baseline hazard function while offering greater flexibility relative to the Cox PH model. This includes, for example, the ability to accommodate non-proportional hazards and more precise estimates of the survival functions and hazard rates. Furthermore, the Weibull model's parametric framework allows for the estimation of transition probabilities and the evaluation of covariate relationships over time, allowing us to further elucidate the time-dependent processes that unfold to shape transitions between the states in our models. More importantly, a multistate model is a useful tool for modeling disease progression, capturing transitions from healthy to intermediate states like dementia or PD. It accounts for competing risks and dependencies, estimates transition probabilities, and reflects the sequential nature of events. In contrast, separate Cox models treat each event in isolation, potentially overlooking interdependencies and intermediate states' impact on overall risk profiles.

All analyses were performed in Stata 18.0 (StataCorp, College Station, TX), using "msset" function for multistate analyses, with Aalen-Johansen estimates of transition probabilities computed using the "msaj" function. For each state transition, we extracted survival probabilities with and without conditioning on covariates with corresponding 95 % confidence intervals. More details are provided in **online** supplementary methods 2.

3. Results

Table 1 displays distributions of sample characteristics of the selected 269,816 participants, before and after stratifying by sex. In this sample, women were younger than men by 0.6y, on average, while the household size was larger among men, who also had a higher SES z-score, consistently in terms of TDI, household income, and educational attainment. More importantly, LE8 total, lifestyle, and biological scores were higher among women, compared to their male counterparts. All three outcomes of interest had a greater cumulative incidence among men compared to women.

The Kaplan-Meier curves show a significant association between LE8z_rev, a reversed z-score representing poorer CVH, and an increased probability of developing all-cause dementia and all-cause mortality (Fig. 1, $P < 0.001$, log-rank test), but not for developing PD ($P > 0.05$), (Fig. 1). Based on a series of fully adjusted Cox proportional hazards models taking each of the three outcomes separately (Table 2), poor CVH (per SD of LE8z_rev) was associated with 14 % increased risk of all-cause dementia (HR = 1.14, 95 % CI: 1.11–1.18, $P < 0.001$) and 31 % increased risk of all-cause mortality (HR = 1.31, 95 % CI: 1.29–1.33, $P < 0.001$), with no detectable association with the outcome of incident PD. In addition, no heterogeneity by sex was observed when examining the interaction between LE8z_rev and sex in unstratified models. Based on models used in Table 2, SES z-score is inversely related to dementia and mortality risk with a lower risk of about 28 %–29 % per SD and thus a HR of ~0.71–0.72, $P < 0.001$. Therefore, poor CVH has similar effect on mortality risk to SES, while having a weaker association with dementia risk compared to SES.

After implementing the multistate modeling approach, we identified transitions from the health state (alive, non-dementia, non-PD) to dementia, PD, and mortality, as well as from PD to dementia, PD to death, and dementia to death. These transitions are depicted in Fig. 2, with their probabilities plotted against age at follow-up in Figs. S2 and S3. Transition intensities were then examined using parametric survival analysis applied to each transition type, focusing on the association with poor CVH, and adjusting for potential confounders. Table 3 shows results from Weibull and Royston-Parmar models for each of the 6 uncovered transitions. Both models gave comparable findings whereby poor CVH was associated with a 15 % increased risk of transition from "Healthy" to "Dementia"; a 33 % increased risk of transition from

Table 1
Study sample characteristics by sex: UK Biobank 2006–2021.

	Overall (N = 269,816)	Men (N = 127,095)	Women (N = 142,721)	P_{sex}
Demographic				
Baseline age, y, mean ± SE	60.42 ± 0.01	60.73 ± 0.02	60.16 ± 0.01	<0.001
Sex, % female	52.9	–	–	n/a
Race/ethnicity				
White	96.1	96.0	96.1	(Ref)
Black	0.9	0.8	1.0	<0.001
South Asian	1.4	1.7	1.2	<0.001
Other	1.6	1.5	1.7	<0.001
Non-White, %	3.9	4.0	3.9	
Household size	2.236 ± 0.002	2.311 ± 0.003	2.169 ± 0.003	<0.001
Socioeconomic				
Townsend Deprivation Index	−1.554 ± 0.006	−1.542 ± 0.008	−1.565 ± 0.008	0.042
Education				
Low	21.7	24.0	19.8	<0.001
Intermediate	39.8	35.0	44.0	(Ref)
High	38.5	41.0	36.2	<0.001
Income				
Less than £18,000	25.6	23.1	28.0	<0.001
£18,000–£29,999	27.8	26.6	28.8	(Ref)
£30,000–£51,999	24.7	25.6	23.9	<0.001
£52,000–£100,000	17.4	19.4	15.5	<0.001
greater than £100,000	4.5	5.2	3.8	<0.001
SES	−0.0296 ± 0.0014	−0.0067 ± 0.0020	−0.0501 ± 0.0018	<0.001
Life's essential 8, Mean±SE				
Total score	496.70 ± 0.18	484.96 ± 0.26	507.16 ± 0.25	<0.001
LE8z_rev	3.41E-11 ± 0.0019	+0.125 ± 0.003	−0.112 ± 0.003	<0.001
Lifestyle score	240.81 ± 0.12	249.80 ± 0.18	261.33 ± 0.16	<0.001
Diet component	33.91 ± 0.06	28.52 ± 0.085	38.71 ± 0.08	<0.001
Physical activity component	48.16 ± 0.07	49.54 ± 0.10	46.93 ± 0.09	<0.001
Smoking component	84.70 ± 0.06	82.27 ± 0.09	86.86 ± 0.07	<0.001
Sleep component	89.13 ± 0.04	89.48 ± 0.05	88.82 ± 0.05	<0.001
Biological score	240.81 ± 0.12	235.16 ± 0.16	245.83 ± 0.17	<0.001
BMI component	68.43 ± 0.05	66.08 ± 0.08	70.53 ± 0.08	<0.001
Lipids component	45.53 ± 0.05	47.72 ± 0.08	43.58 ± 0.07	<0.001
Glucose component	89.56 ± 0.04	88.21 ± 0.06	90.76 ± 0.05	<0.001
Blood pressure component	37.28 ± 0.06	33.15 ± 0.08	40.97 ± 0.09	<0.001
Cumulative incidence, %				
All-cause dementia	1.7	2.0	1.5	<0.001
Parkinson's Disease	0.7	1.0	0.5	<0.001
All-cause mortality, %	8.5	11.0	6.2	<0.001

Abbreviations: AD = Alzheimer's Disease; LE8 = Life's essential 8; $LE8_{z\_rev}$ = LE8 total score, z-scored, multiplied by −1; Ref = referent category; SE=Standard Error; UK=United Kingdom.

Notes: No multiple imputation was carried out in this analysis. P-value is associated with the parameter for sex in bivariate linear and multinomial logistic regression analyses, with the main outcome being a continuous or categorical characteristic, respectively. (Ref) is the referent category in the multinomial logistic regression model. Values are means ± SE or percentages. Note that sample sizes vary across LE8 sub-scores and components as well as SES components due to proration.

"Healthy" to "Death" and an 18 % increased risk for the transition from "PD" to "Death". Supplementary Table 1 indicates that the Weibull model is among the better-fitting parametric models in comparison with other distributional formulations for the hazards.

The Weibull model presented in Table 3 was used to forecast survival probability for each of the six transitions. These predictions are illustrated in Fig. S4 and specifically focus on the major exposure for poor CVH, comparing individuals with an LE8z_rev of +2 to those with a score of −2. After setting the exposure to −2 and +2, the survival probabilities were also predicted. The disparities in survival probabilities between these two levels of exposure were also assessed after the fact while keeping the other covariates same as found in the study population. This disparity was observed among individuals with baseline ages 50y through 79y when they were followed till age 80y. According to estimations using local polynomials, there was a substantial difference in survival rates between transitions 2, 3, and 5 between exposed and unexposed groups at the age of 80 years. Specifically, having an LE8z_rev of +2 considerably reduced survival rates for these three transitions (from being healthy to developing dementia and from being healthy to death, and from PD to death). Additionally, Supplementary Table 2 offers descriptive data regarding these changes in survival.

Finally, sub-scores and components of LE8 were individually modeled against each of the 6 transition intensities using a series of Weibull parametric survival models. Supplementary Table 3 indicates that not all LE8 components had consistent associations with the 6 transition intensities, particularly in line with what was uncovered for the total score. In fact, for transition 1, while the total score was not associated with the transition from Healthy → PD, the physical activity component was shown to be potentially protective against PD occurrence, as was the glucose component. The opposite trend was found for smoking, lipids, and blood pressure components. For transition 2, the total and sub-scores (reverse coded) were positively associated with dementia incidence starting from the healthy state. This was reflected mainly by the physical activity, smoking, and glucose components, but the reverse pattern was found for the lipids component. The latter finding of a potential deleterious effect of elevated HDL-C on health was found for transition 3 (Healthy → Death, i.e. transition 3), although all other components were in consistent pattern with the total and sub-score findings of a direct relationship between poor CVH with mortality risk. The transition from PD to dementia was inversely related to the glucose component but positively related to the lipids components following the previous findings for transitions 1 and 3. In contrast, the transition from PD to mortality was directly related to poor CVH, based LE8z_rev total score and sub-scores. More specifically, those associations were driven by physical activity, smoking components, and glucose components. The lifestyle and biological sub-scores of poor CVH both were associated with transition 6 (Dementia to death), mainly driven by the physical activity and smoking components (See supplementary code and Output at: https://github.com/baydounm/UKB-paper15-supplementarydata).

4. Discussion

The study examined the link between poor CVH and transitions between healthy, dementia, PD, and death in 269,816 UK Biobank participants aged 50 years or older. It found that poor CVH was linked to a 14 % increased risk of all-cause dementia and a 31 % increased risk of all-cause mortality. However, there was no association between poor CVH and Healthy→PD, although poor CVH was directly associated with three transitions, namely PD → mortality, healthy → dementia and healthy → mortality. The study also found that not all LE8 components had consistent associations with the six transition intensities. Physical activity and glucose levels were found to be protective against PD occurrence while smoking, lipids, and blood pressure components had opposite trends. The transition from PD to dementia was inversely

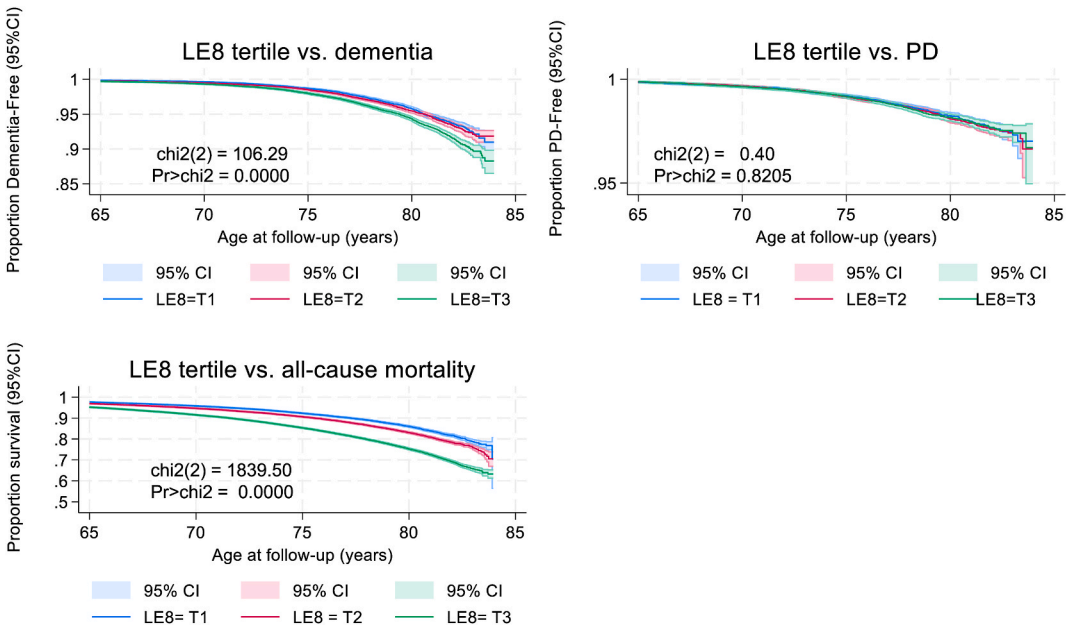

Fig. 1. Tertiles of LE8 by each of 3 outcomes: All-cause dementia, PD and mortality: UK Biobank 2006–2021 *Abbreviations*: chi2 = Chi-square test, Log-rank test; CI=Confidence Interval; LE8 = Life's Essential 8; PD=Parkinson's Disease; T1 = First tertile; T2 = Second Tertile; T3 = Third Tertile; UK=United Kingdom. *Notes:* Kaplan-Meier estimates of probabilities in all-cause dementia-free, PD-free and survival states.

Table 2
Association between poor CVH (LE_{8z_rev}) and each of 3 types of events, overall and by sex: Cox PH models, UK Biobank 2006-2021.[a].

	$LE8_{zrev}$ HR with 95 % CI	P $_{LE8zrev}$
All-cause dementia		
Overall, N = 269,816	**1.14 (1.11;1.18)**	**<0.001**
Men, N = 127,095	**1.15 (1.10;1.20)**	**<0.001**
Women, N = 142,721	**1.13 (1.08;1.18)**	**<0.001**
Parkinson's Disease		
Overall, N = 269,816	0.98 (0.94; 1.03)	0.44
Men, N = 127,095	0.97 (0.91; 1.02)	0.26
Women, N = 142,721	1.01 (0.93; 1.09)	0.81
All-cause mortality		
Overall, N = 269,816	**1.31 (1.29; 1.33)**	**<0.001**
Men, N = 127,095	**1.31 (1.29; 1.34)**	**<0.001**
Women, N = 142,721	**1.31 (1.29; 1.34)**	**<0.001**

Abbreviations: CI=Confidence Interval; CVH=Cardiovascular health; HR=Hazard Ratio; LE8 = Life's Essential 8; $LE8_{z\_rev}$ = LE8 total score, z-scored, multiplied by −1; PD=Parkinson's Disease; PH=Proportional Hazards; SD=Standard Deviation; SES=Socio-economic status z-score UK=United Kingdom.

[a] All Cox proportional hazards models were adjusted for baseline age, sex, race/ethnicity (Non-White vs. White), household size and SES z-score. Interaction between $LE8_{zrev}$ and sex was tested, by including a 2-way interaction term in the main adjusted model. Values are hazard ratios with 95 % CI. 1 SD of $LE8_{z\_rev}$ is equivalent to 93-point decrement in LE8 total score.

[b] $P < 0.05$ for null hypothesis that $\gamma = 0$, whereby γ is the parameter for 2-way interaction between sex and $LE8_{zr\_ev}$ in the unstratified fully adjusted model.

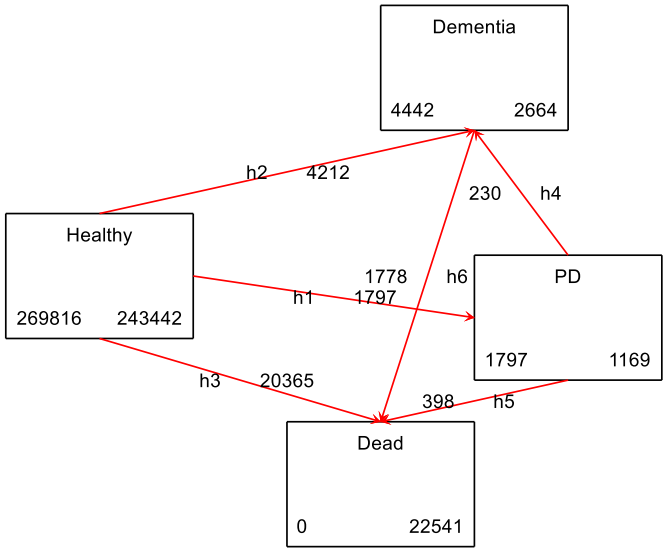

Fig. 2. Multistate transition boxes: UK Biobank 2006–2021 *Abbreviations*: h1 through h6: 6 types of transitions; PD=Parkinson's Disease; UK=United Kingdom.
Notes: Multistate boxes obtained from the *msboxes* command after *msset* in Stata, produces number of participants in each state, those that leave that particular state to transition into a different state and the remaining participants in that state. The sample sizes shown are within the final selected sample (See Fig. S1).

related to glucose but positively related to lipids. Poor CVH was associated with dementia to death, mainly driven by physical activity and smoking.

Studies investigating the relationship between CVD and PD have remained controversial. Inflammation, insulin resistance, lipid metabolism, and oxidative stress are shared between CVD and PD (Potashkin et al., 2020). However, these shared biological processes between PD and CVD make it uncertain if these are also shared risk factors (Potashkin et al., 2020). A national study from Korea reported that PD was associated with a higher risk for developing CVD, with an associated increased risk for myocardial infarction, ischemic stroke, and congestive heart failure ranging between 42 % and 65 % on average, and close to 2.7-folds increased risk for all-cause mortality with a HR of 2.7 [95 % CI, 2.60–2.81]) (Park et al., 2020). Additionally, a population-based study from Sweden (n = 101790 subjects) found that lower serum triglycerides and systolic blood pressure increased the risk of PD after a follow-up period of 2–8 years (Vikdahl et al., 2015). In contrast, in a U.S.-based study, carotid stenosis and ECG abnormalities were found before motor signs of PD (Jain et al., 2012). Furthermore, a study of U.S. veterans found that physical fitness, smoking, and younger age were associated with a lower incidence of PD. (Müller and Myers, 2018).

Table 3
Parametric survival models (Weibull and flexible, Royston-Parmar) for the association between poor CVH (LE8zrev) and six transitions between four states (healthy, PD, dementia, and death): UK Biobank 2006–2021.

	HR	95 % CI	P
Transition 1:Healthy→PD			
Weibull	0.98	(0.94; 1.03)	0.50
Royston-Parmar	0.99	(0.94; 1.03)	0.56
Transition 2: Healthy→Dementia			
Weibull	**1.15**	**(1.12;1.19)**	**<0.001**
Royston-Parmar	**1.15**	**(1.12;1.19)**	**<0.001**
Transition 3: Healthy→Mortality			
Weibull	**1.33**	**(1.31;1.35)**	**<0.001**
Royston-Parmar	**1.33**	**(1.32;1.35)**	**<0.001**
Transition 4: PD→Dementia			
Weibull	1.07	(0.93; 1.23)	0.37
Royston-Parmar	1.07	(0.93; 1.23)	0.35
Transition 5: PD → Mortality			
Weibull	**1.18**	**(1.06;1.31)**	**0.002**
Royston-Parmar	**1.18**	**(1.06;1.31)**	**0.002**
Transition 6: Dementia→ Mortality			
Weibull	***1.05***	***(1.00;1.10)***	***0.056***
Royston-Parmar	***1.05***	***(1.00;1.10)***	***0.057***

Abbreviations: CI=Confidence Interval; HR=Hazard Ratio; LE8 = Life's Essential 8; PD=Parkinson's Disease; SES=Socio-economic status z-score; UK=United Kingdom.
[a] Models were adjusted for baseline age, sex, race/ethnicity (Non-White vs. White), household size and SES.

Based on our study findings, LE8 metrics and the total score in particular may not accurately reflect the incidence of Parkinson's Disease (PD) due to several reasons. Firstly, LE8 focuses on cardiovascular health, which is a different area of focus from PD, a neurodegenerative disorder. Secondly, the risk factors that drive cardiovascular disease might not play a central role in PD's neurodegenerative pathways. Thirdly, the key drivers of PD may include factors not captured by LE8, such as environmental toxins or genetic mutations. Fourthly, the timing and disease latency of PD may not coincide with the critical period of PD pathogenesis. Finally, the statistical power and effect size of LE8 may not be sufficient to detect these modest effects.

Previous research has established a strong link between dementia and CVH, demonstrating a U- or J-shaped association between specific CVH variables and the risk of dementia in old age (Michaud et al., 2018; van Dalen et al., 2022). Obesity, diabetes, dyslipidemia, and high blood pressure in middle age have all been linked to CVD, as well as a higher risk of dementia and cognitive decline (Samieri et al., 2018). Dementia risk is nonetheless reduced by optimal CVH measures (i.e., LS7) (Cho et al., 2022; Samieri et al., 2018; Wu et al., 2023). Even increasing heart health in middle age reduces the incidence of dementia and raises CVH (Sedaghat et al., 2023), showing a dose-dependent linear association (Wu et al., 2023).

Poor CVH as defined via Life's Simple 7 increases the risk of all-cause mortality through the increase of both CVD mortality and non-CVD mortality Kwaśniak-Butowska et al., 2021; van Dalen et al., 2022; Michaud et al., 2018; Samieri et al., 2018; Wu et al., 2023; Cho et al., 2022; Sedaghat et al., 2023; Iadecola, 2013). The relationship between poor CVH and CVD mortality is fairly well-established and directly explained by the impact of CVH risk factors on the function of the heart and vasculature. As a result, the vast majority of deaths due to CVD are from heart attacks and strokes. However, the pathways for non-CVD mortality due to poorer CVH are complex, often interrelated, and may be explained by disruptions of endothelial function, activation of inflammatory markers, immunological changes, development of secondary CVDs, and detrimental effects on the function of organs such as the liver and kidney. Among the Western nations (e.g. UK and USA), cancers, lung diseases, liver disorders, and kidney dysfunction/failure rank among the leading causes of death; all of these are directly or indirectly associated with poorer CVH (e.g. smoking and lung cancer, blood pressure, and kidney failure, BMI/exercise, and fatty liver diseases). Interestingly, these risk factors and associated outcomes have within the past decade also been linked with PD and dementia (e.g. waste circumference/exercise and PD, smoking and dementia, NAFLD/liver dysfunction and AD).

Several patho-physiologial mechansims may explain the heightened risk for dementia and all-cause mortality with poorer CVH among healthy individuals (de la Torre, 2012; Di Marco et al., 2015; Iadecola, 2013; Lloyd-Jones et al., 2010). Specifically, suboptimal CVH initiates a series of pathological events, including compromised blood flow, microvascular injury, systemic inflammation, metabolic irregularities, oxidative stress, and endothelial dysfunction (de la Torre, 2012; Di Marco et al., 2015; Iadecola, 2013; Lloyd-Jones et al., 2010). These pathways jointly compromise the integrity of brain and systemic vascular networks, promoting neurodegeneration (resulting in dementia) and life-threatening cardiovascular incidents, which combined elevate death rates (de la Torre, 2012; Di Marco et al., 2015; Iadecola, 2013; Lloyd-Jones et al., 2010).

CVH is closely connected to dementia through increased risk and poor cardiac prognosis. Researchers found that dementia will supersede cardiovascular disease as the most common cause of mortality and that cognitive decline, dementia, and motor worsening result from a deteriorating cardiovascular risk profile (Bloem et al., 2021; van de Vorst, 2016; van de Vorst et al., 2015, 2016). Individuals with dementia and cardiovascular diseases had an increased risk of overall mortality than individuals with dementia alone (Finsterer et al., 2021; Jeong et al., 2021; Scorza et al., 2018; Tolosa et al., 2021). Poor CVH, along with gut involvement, is followed by brain dysfunction such as PD, as has been purported in the Braak Hypothesis (Bloem et al., 2021; Finsterer et al., 2021; Jeong et al., 2021; Scorza et al., 2018; van de Vorst et al., 2016). Findings regarding therapy to decrease cardiovascular disease and its impact on brain health are inconsistent, with some researchers uncovering detrimental effects of statin usage on brain function (Beydoun et al., 2011; Schultz et al., 2018; Zhou et al., 2021). In fact, the relationship between statins and cognition is complex, with mixed findings across observational studies, with large-scale trials showing no significant effect (Beydoun et al., 2011; Schultz et al., 2018; Zhou et al., 2021). However, a connection between PD and poor prognosis of cardiovascular disease due to autonomic dysfunction was also uncovered, leading to a need to monitor cardiovascular disease risk factors such as thiamine deficiency (Chelliah et al., 2022; Finsterer et al., 2021; Goncalves et al., 2022; Ramsey and Arnold, 2022; Scorza et al., 2018). Furthermore, the occurrence of myocardial infarction is related to an increased risk of cognitive decline (Thong et al., 2023). Nonetheless, the precise frequency of development of coronary heart disease from PD is still unknown (Geethadevi et al., 2023; Scorza et al., 2018; Thong et al., 2023). Imaging studies with prospective designs and extensive data collection on physical and biological markers of heart and brain function can lead to an improved understanding of the connection between PD and CVH (Tolosa et al., 2021).

The intersections between CVH, PD, and dementia are complex but could potentially explain the current study's observations. A common comorbidity of PD is cerebrovascular lesions (Bloem et al., 2021), which are associated with CVH risks (i.e., stroke) and cognitive decline (Windham et al., 2015). PD was significantly associated with approximately a 1.7-fold increased risk for stroke, although that was not the case for myocardial infarction or cardiovascular mortality risks (Alves et al., 2020b). It is speculated that the association may be attributed to autonomic dysfunction (Alves et al., 2020b), though the exact mechanism is still unknown. Indeed, autonomic dysfunction was shown to precede the diagnosis of stroke and dementia, particularly in some subgroups (e.g., adults 60 years of age or older and/or men (Weinstein et al., 2021). While the clinical prognosis for PD varies across individuals (Bloem et al., 2021), individuals with PD have shown an increased risk of developing dementia(Astrom et al., 2022). Specifically, approximately 25 %–50 % of individuals with PD have been shown to

develop mild cognitive impairment (MCI) or dementia within 5 years of their PD diagnosis (Broeders et al., 2013; Pedersen et al., 2013). Consequently, the current study's findings provide support that CVH may be a pertinent determinant for PD cases that are at risk for dementia diagnosis.

Thus, the study confirms the link between poor CVH and higher mortality and dementia risk and risk of death in PD. However, it does not reliably predict PD incidence, suggesting additional risk factors may contribute to PD's etiology. The study emphasizes the importance of optimal cardiovascular health in reducing cognitive decline and premature death, and calls for further research into unique risk factors contributing to PD. Consequently, future research is warranted to examine these interconnections. Potential strategies to mitigate the effects of poor CVH on various outcomes and transitions that were of interest in our study include early screening and risk assessment, lifestyle modification programs, integrated chronic disease management, community-based health initiatives, policy-level interventions, and healthcare system integration (Laddu et al., 2021; Schwalm et al., 2016). Screening for poor CVH involves standardized assessments of LE8 components, targeting high-risk populations (Laddu et al., 2021; Schwalm et al., 2016). Lifestyle modifications include promoting heart-healthy diets, physical activity, and smoking cessation programs. Integrated chronic disease management includes medication adherence, regular monitoring, and interdisciplinary care models (Laddu et al., 2021; Schwalm et al., 2016). Policy-level interventions include urban planning, food and nutrition policies, and collaboration with community organizations and insurers (Laddu et al., 2021; Schwalm et al., 2016).

4.1. Strengths and limitations

This study analyzed a large UK Biobank sample over a long-term period, considering demographic, economic, lifestyle, and health-related factors. It used advanced statistical techniques to analyze the relationships between CVH, dementia, and mortality risk. Cox PH models were used to examine the relationship between CVH, dementia, PD, and death. Multistate models were used to understand the complex progression between these variables. The study offered a comprehensive evaluation of pathways involving CVH in dementia and PD, rather than evaluating these variables as individual endpoints.

Nevertheless, this study consists mainly of volunteers recruited through a non-probability sampling strategy, which limits its representativeness of the broader UK adult population. The cohort is generally healthier, more well-educated, and predominantly White (>95 %), potentially restricting the generalizability of our findings to more diverse populations with different socioeconomic, genetic, and environmental backgrounds. Additionally, our study is observational in nature, which precludes causal inference. Residual confounding remains a concern, as we could not fully account for unmeasured or inadequately measured factors such as other medication use (e.g., antihypertensives, lipid-lowering agents, psychotropic drugs), genetic predisposition (e.g., APOE-ε4 status for dementia risk), or lifestyle factors that may influence both CVH metrics and cognitive outcomes. Another critical consideration is the potential for reverse causality. Prodromal dementia or PD may influence CVH metrics, particularly physical activity, diet, and sleep patterns, leading to changes in metabolic and vascular health before clinical diagnosis. Such bidirectional relationships complicate interpretation, as individuals with early neurodegeneration may already experience declines in CVH before disease onset. Furthermore, the reliance on self-reported data for some LE8 components introduces the risk of recall bias and misclassification, which may differentially affect participants with early cognitive decline. Objective measures of health behaviors and biomarker-based assessments could help mitigate this limitation in future studies. Finally, while our multistate models provide valuable insights into transitions between cognitive states, they rely on assumptions such as the Markov assumption, which posits that future transitions depend only on the current state rather than the duration or specific path leading to that state. This simplification may not fully capture the complexity of disease progression, particularly in conditions where cumulative exposures or disease trajectories play a critical role.

5. Conclusions

Poor CVH increases the risk of dementia and mortality rates, especially in people with PD. Maintaining good CVH can prevent or delay these events. CVH deterioration worsens cognitive decline by reducing blood flow to the brain, causing inflammation, and accumulating risk factors. It also increases the likelihood of death, especially in those transitioning from good health to PD. Preserving cardiovascular well-being is crucial for primary prevention of dementia and early death from all causes. Implementing public health measures promoting heart-healthy lifestyles could significantly reduce dementia's impact and extend lifespan.

CRediT authorship contribution statement

Michael F. Georgescu: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Data curation, Conceptualization. **May A. Beydoun:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jordan Weiss:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Data curation, Conceptualization. **Jagdish Kubchandani:** Writing – review & editing, Writing – original draft, Conceptualization. **Sri Banerjee:** Writing – review & editing, Writing – original draft, Conceptualization. **Alyssa A. Gamaldo:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Michele K. Evans:** Writing – review & editing, Writing – original draft, Supervision, Software, Resources, Project administration, Investigation, Funding acquisition, Conceptualization. **Alan B. Zonderman:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Consent statement

The studies with human participants were reviewed and approved by the UK Biobank, which has approval from various Institutional Review Boards, including the North West Multi-center Research Ethics Committee for the United Kingdom, the National Information Governance Board for Health and Social Care for England and Wales, and the Community Health Index Advisory Group for Scotland. All participants provided informed permission for the study using a touch-screen interface that necessitated acceptance to each statement on the consent form and the participant's signature on an electronic pad. Written informed permission was not necessary for this investigation since it complied with national laws and institutional regulations.

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Declaration of competing interest

All authors declare no conflict of interest.

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Abbreviations

CVH = Cardiovascular Health
PD = Parkinson's Disease
CVD = Cardiovascular Disease
CHD = Coronary Heart Disease
HF = Heart Failure
AF = Atrial Fibrillation
AHA = American Heart Association
LS7 = Life's Simple 7
BMI = Body Mass Index
LE8 = Life's Essential 8
SES = Socioeconomic Status
TDI = Townsend Deprivation Index
PH = Cox Proportional Hazards
AD PRS = Alzheimer's Disease Polygenic Risk Score

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2025.100986.

Data availability

The authors do not have permission to share data.

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