European Journal of Neurology

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE OPEN ACCESS

Accelerated Biological Aging and Longitudinal Progression of Cardiometabolic Disease, Subsequent Dementia, and Death: A Multistate Analysis

Ning Zhang[1] | Haojiang Zuo[1] | Jiajie Cai[1] | Yi Xiang[1] | Yuan Zhang[1] | Hongmei Zhang[1] | Yifan Hu[1] | Hao Xu[2] | Xiong Xiao[1] | Xing Zhao[1]

[1]West China School of Public Health and West China Fourth Hospital, Sichuan University, Chengdu, CN, China | [2]State Key Laboratory of Oral Diseases, National Clinical Research Center for Oral Diseases, Research Unit of Oral Carcinogenesis and Management, Chinese Academy of Medical Sciences, West China Hospital of Stomatology, Sichuan University, Chengdu, CN, China

Correspondence: Xiong Xiao (xiaoxiong.scu@scu.edu.cn)

Received: 4 December 2024 | **Revised:** 6 May 2025 | **Accepted:** 15 May 2025

Funding: The study was supported by the National Natural Science Foundation of China (82273740) and the Natural Science Foundation of Sichuan Province (2024NSFSC0552, 2024NSFSC0563).

Keywords: biological aging | cardiometabolic diseases | dementia | disease progression

ABSTRACT

Background: The role of biological age (BA) acceleration in longitudinal disease progression from health to cardiometabolic disease (CMD), then to post-CMD dementia (including vascular dementia (VaD) and Alzheimer's disease (AD)), and finally to death remains unclear.

Methods: Using data from 284,723 UK Biobank participants, two established BA measures (Klemera-Doubal Method Biological Age [KDM-BA] and PhenoAge) were generated on the basis of baseline clinical biomarkers. Post-CMD dementia was defined as dementia that occurred after the first occurrence of CMD. Multistate analysis was constructed to examine the association between BA accelerations and longitudinal progression of post-CMD dementia. We further explored the role of two BA accelerations in CMD-specific transitions and dementia-specific transitions, respectively.

Results: Over a median follow-up of 13.7 years, 47,150 participants developed CMD, and 999 developed post-CMD dementia. Biologically older participants demonstrated robustly higher risks from healthy to CMD, then to post-CMD dementia, and finally to death. For the transition from baseline to CMD, adjusted HRs (95% CI) were 1.34 (1.32, 1.35) for each SD increase in KDM-BA acceleration and 1.19 (1.18, 1.20) for PhenoAge acceleration. For the transition from CMD to post-CMD dementia, HRs were 1.12 (1.04, 1.20) for KDM-BA acceleration and 1.10 (1.04, 1.17) for PhenoAge acceleration. Both BA accelerations were more strongly associated with the transition from CMD to post-CMD VaD than with the transition to post-CMD AD.

Conclusions: BA accelerations hold promise for identifying the disease progression of post-CMD dementia in routine clinical practice and slowing down disease progression through the interventions that slow down biological aging.

Ning Zhang and Haojiang Zuo joint first authorship.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2025 The Author(s). *European Journal of Neurology* published by John Wiley & Sons Ltd on behalf of European Academy of Neurology.

1 | Introduction

The aging of the population is occurring at an accelerated pace [1]. Dementia is one of the fastest-growing age-related diseases, expected to affect over 150 million by 2050 [2, 3]. Cardiometabolic diseases (CMDs, including heart disease, stroke, and type 2 diabetes [T2D]) are firmly established independent risk factors for dementia [4–9]. The dementia risk associated with CMDs was three times greater than that associated with high genetic risk [6]. The mechanisms of transition from CMD to post-CMD dementia include chronic cerebral hypoperfusion, disruption of the blood–brain barrier integrity, oxidative stress, and cerebral insulin resistance [4–9]. Advances in CMD management have led to improved survival, increasing the likelihood that individuals with CMD will develop post-CMD dementia over time. Longitudinal disease progression describes the sequence of events over time, providing more nuanced information crucial to the primary and secondary prevention of and to the management of patients at different disease stages [10]. Thus, given the limited availability of pre-symptom diagnosis and treatment of post-CMD dementia in daily practice [3], it is essential to understand the accumulation of post-CMD dementia over time and the relationship between potentially important factors and this progression.

Aging is the predominant risk factor for CMDs and dementia [11]. Unlike the inexorable increase in chronological age (CA), the biological aging process is amenable to intervention through pharmacological and lifestyle behavior [12, 13]. Accelerated biological aging induces increased oxidative stress, chronic inflammation, and deregulated nutrient sensing [14], which are strongly linked to the development of CMD and dementia. Given the existing evidence, it is plausible to hypothesize that biological age (BA) measures hold promise for tracking the longitudinal progression of post-CMD dementia. BA measures based on composite biomarkers that reflect the landscape of aging in multiple organs and systems are already available [15, 16]. Compared with other measures (e.g., telomere length and epigenetic clocks), composite biomarker BA is cost-effective while ensuring measurement accuracy, making it feasible for large population research and daily practice [17, 18]. Several studies have investigated the association of BA with CMDs, BA with dementia in the general population and subgroups [19–24]. However, such analyses based on the traditional survival model make it challenging to understand the impact of BA on the longitudinal disease progression. The associations of BAs with the longitudinal progression of post-CMD dementia and disease-specific dementia (i.e., Alzheimer's disease and vascular dementia) after CMD remain unclear.

The multistate model (MSM) extends the traditional survival model [25, 26]. The MSM provides a useful framework for modeling complex longitudinal disease accumulation data by incorporating multiple subsequent or competing events as transition states [25, 26]. Therefore, we conducted a multistate analysis to examine the associations between BA measures (i.e., Klemera-Doubal Method Biological Age [KDM-BA] [15] and PhenoAge [16]) and the risk of post-CMD dementia development, including transition from healthy to CMD, then to post-CMD dementia, and further to death (Figure 1). Furthermore, we investigated the associations of specific CMD (i.e., heart disease, stroke, and T2D) or specific dementia (i.e., Alzheimer's disease [AD] and vascular dementia [VaD]) along this transition pathway.

2 | Methods

2.1 | Study Participants

Participants in this study were drawn from the UK Biobank (UKB), a prospective cohort study with over half a million participants. As detailed previously [27], participants aged 37–73 years underwent assessments between 2006 and 2010. All participants provided written informed consent. The UKB was approved by the North West Multicenter Research Ethical Committee. This research was conducted using the UK Biobank Resource under the application number: 117,185.

We excluded participants with missing data on either KDM-BA or PhenoAge ($n = 173{,}315$), those diagnosed with CMDs or dementia before baseline ($n = 37{,}938$), and those with missing data on select covariates ($n = 5712$). To investigate the longitudinal progression of post-CMD dementia, we also excluded participants with dementia diagnosed before or on the same date as the first occurrence of CMD ($n = 669$). A total of 284,723 participants were included in the analysis to examine the role of BA in longitudinal disease progression. See Appendix Figure S1 for the selection flow chart of the participants. See Appendix Table S1 for sample sizes of clinical biomarkers for constructing BAs.

2.2 | Follow-Up for CMD, Post-CMD Dementia and Death

The disease progression included the following states: CMD, post-CMD dementia, and death. CMD was defined as the first incidence of heart disease, stroke, and T2D during follow-up. Post-CMD dementia was defined as dementia occurring after the first

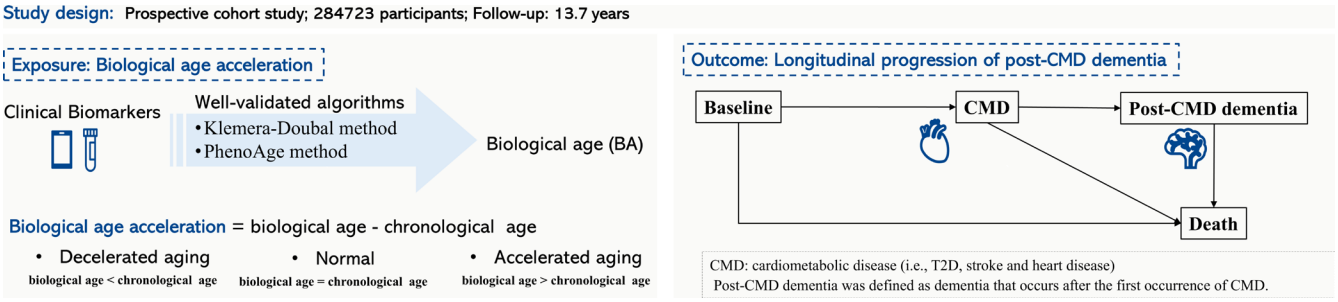

FIGURE 1 | Design of the study.

occurrence of CMD. Incidence of CMDs, dementia, and death was obtained by the following sources, including self-reported information, primary care data, and hospital admission data. Health data were available up to October 31, 2022, August 31, 2022, and May 31, 2022 for England, Scotland, and Wales, respectively. Follow-up was censored at death, loss to follow-up, or the last date with available information, whichever came first. According to previous studies [5, 28, 29], the CMD diagnoses were ascertained according to the corresponding International Classification of Diseases 10th revision (ICD-10) codes (I20 to I25, I48, I49, and I50 for heart diseases; I60 to I64 for stroke; E11 and E14 for T2D). Dementia was identified according to the corresponding ICD-10 codes: F00, F01, F02, F03, G30, as described in a previous study [30].

2.3 | Construction of Biological Age and Biological Age Acceleration

CA refers to an individual's actual age, calculated on the basis of the date of birth. However, individuals with the same CA may have different rates of biological aging [12, 13]. BA represents the predicted age on the basis of the extent of aging reflected by various biological markers [12, 13, 31–33]. Unlike CA, BA captures the rate of an individual's physiological aging which may be faster or slower than their CA. To quantify differences between participants in biological aging, BA acceleration is calculated as the difference between an individual's predicted BA and their CA [17, 18, 34]. A positive value indicates accelerated aging, whereas a negative value reflects decelerated aging. BA acceleration was the primary target exposure analyzed.

For the calculation of BA, we employed two well-validated methods on the basis of clinical biomarkers: the KDM-BA and PhenoAge [15, 16, 18, 34, 35]. The KDM algorithm is derived from regression analyses between multiple biological markers and CA in a reference population. An individual's KDM-BA estimate reflects the CA at which their physiological state is expected to be normal. Our previous studies described in detail the KDM-BA calculated from 18 biomarkers [17, 18]. Currently, there are well-established algorithms for calculating PhenoAge [19, 35, 36]. The PhenoAge algorithm is constructed on the basis of mortality risk prediction. Specifically, it first estimates mortality hazards using two models: one based on nine selected biomarkers and another based solely on CA in a reference population. PhenoAge is then derived by identifying the CA that corresponds to the same mortality hazard predicted by the model based on biomarkers. A detailed description of both methods is provided in the Appendix Text S1 and S2.

2.4 | Assessment of Covariates

As previously reported [5, 6, 19], the following covariates were obtained from the baseline questionnaires and physical examinations: age, sex, race, education, socioeconomic status (SES, i.e., Townsend Deprivation Index), smoking status, frequency of alcohol consumption, total physical activity, body mass index (BMI), and family history of CMDs or dementia. Detailed measures of these covariates are shown in Appendix Table S2.

2.5 | Statistical Analysis

We described the baseline characteristics of total participants, as well as those with CMD and post-CMD dementia. To assess the representativeness of the study population, we compared the characteristics of all UKB participants, those included in the study, and those excluded from the study.

Before the main analysis, we used the Cox model to estimate the associations of KDM-BA acceleration and PhenoAge acceleration with CMD, post-CMD dementia, and death, respectively. The proportional hazard assumption was checked using the Schoenfeld residuals method, and no violations were detected. Model 1 adjusted for age and sex. Model 2 was further adjusted for race, education, SES, smoking status, frequency of alcohol consumption, total physical activity, BMI, and family history of CMDs or dementia. Estimates of KDM-BA acceleration and PhenoAge acceleration were demonstrated per standard deviation (SD) increase for comparison.

In the main analyses, we used the MSMs to assess the role of the BA accelerations in the disease progression from healthy to incident CMD, then to post-CMD dementia, and ultimately to death. MSMs extend the traditional survival model to encompass more than two disease states, providing a useful framework for modeling complex longitudinal disease accumulation data [25] and have been widely applied in multimorbidity studies [19, 26, 28, 37–39]. There were five transitions between the three states: (1) baseline to CMD, (2) baseline to death from a disease other than CMDs, (3) CMD to post-CMD dementia, (4) CMD to death from any causes, and (5) post-CMD dementia to death from any causes. For participants whose death occurred on the same day as the CMD or post-CMD dementia diagnosis, we subtracted 0.5 days from the death date as the diagnosis date. To assess potential nonlinear associations between BA accelerations and disease progression, we used restricted cubic spline (RCS) models with three knots (at the 10th, 50th, and 90th percentiles). All MSMs and RCS models were adjusted for the same covariates as in the Cox models.

We further explored the disease-specific transitions. We separately assessed the associations between the two BA accelerations and each specific CMD (i.e., heart disease, stroke, and T2D) or specific dementia (i.e., AD and VaD) in the progression, respectively. For example, the transitions from healthy to stroke, then to post-stroke dementia, further to death; or the transitions from healthy to CMD, then to post-CMD AD, further to death.

We conducted several sensitivity analyses. First, for participants experiencing death and CMD or post-CMD dementia events on the same day, we calculated the entering date of the prior status using different time intervals (1, 30, and 365 days) to assess the impact on the results. Second, we excluded outcome events occurring within the first 6 months of follow-up in the MSMs to examine potential reverse causality. Third, we further adjusted for depression in MSMs, considering that

depression might be a potential confounder of BA and disease progression. Fourth, we included hypertension and hyperlipidemia as additional confounders in the MSMs. Fifth, we further considered four states (first CMD, cardiometabolic multimorbidity, subsequent dementia, and death) in the MSM. Sixth, we further explored the association between BA acceleration and all possible transitions of CMD and dementia comorbidity based on MSM. Finally, we tested the robustness of our results using homeostatic dysregulation age (HDAge), although HDAge is not a defined age measurement and is not directly comparable to KDM-BA and PhenoAge [22, 40]. This measure was derived by calculating the deviation of personal physiological and health reference sample (Appendix Text S3). We did all analyses with R version 4.1.1.

3 | Results

3.1 | Characteristics of the Participants

Among 284,723 participants, the mean age was 56.21 (SD 8.10) years, with 125,765 (44.17%) male participants. Characteristics of the study participants are shown in Table 1. Participants with CMD and post-CMD dementia were more likely to be older, male, have a lower education level, and show accelerated biological aging. Participants included in this study had similar baseline characteristics to those without available data (Appendix Table S3).

Numbers (percentages) of participants in longitudinal disease progression are shown in Figure 2. During a median follow-up

TABLE 1 | Baseline characteristics of study participants by incident disease states.[a]

Characteristics	Total (*N* = 284,723)	Participants with CMD (*N* = 47,150)	Participants with post-CMD dementia (*N* = 999)
Age at baseline, year	56.21 (8.10)	59.95 (7.21)	65.37 (4.01)
Male (%)	125,765 (44.17)	26,982 (57.26)	588 (58.86)
White ethnicity (%)	272,497 (95.71)	45,075 (95.60)	969 (97.00)
Education (%)			
No qualification	42,779 (15.02)	10,803 (22.91)	363 (36.34)
Any other qualification	144,627 (50.80)	23,490 (49.82)	445 (44.54)
Higher education	97,317 (34.18)	12,857 (27.27)	191 (19.11)
SES[b]	−1.47 (2.99)	−1.26 (3.12)	−1.11 (3.24)
Smoking status (%)			
Never	161,595 (56.76)	22,989 (48.76)	455 (45.55)
Previous	94,587 (33.22)	18,043 (38.27)	416 (41.64)
Current	28,541 (10.02)	6118 (12.98)	128 (12.81)
Frequency of alcohol consumption (%)			
Never	19,426 (6.82)	4039 (8.57)	127 (12.71)
< 3 times/week	137,608 (48.33)	22,493 (47.71)	441 (44.14)
≥ 3 times/week	127,689 (44.85)	20,618 (43.73)	431 (43.14)
Total physical activity (%)[c]			
Low	74,993 (26.39)	12,379 (26.25)	237 (23.72)
Medium	75,034 (26.35)	11,339 (24.05)	212 (21.22)
High	74,661 (26.22)	12,247 (25.97)	242 (24.22)
Unknown	60,035 (21.09)	11,185 (23.72)	308 (30.83)
BMI, kg/m^2	27.02 (4.52)	28.56 (5.00)	27.82 (4.69)
Family history (%)	189,196 (66.45)	34,033 (72.18)	743 (74.37)
KDM-BA acceleration	−0.43 (5.92)	1.61 (6.32)	1.35 (6.44)
PhenoAge acceleration	−5.22 (4.94)	−3.86 (5.58)	−3.38 (6.05)

Abbreviations: BA, biological aging; BMI, body mass index; CMD, cardiometabolic disease; SES, socioeconomic status.
[a]Data are expressed as mean (standard deviation) or numbers (percentage).
[b]SES was measured by the Townsend Deprivation Index.
[c]We included a separate category for missing data in physical activity, given the large proportion of missing data in this term.

of 13.7 years (interquartile range 13.0–14.3 years), 47,150 (16.56%) of baseline participants experienced CMD during follow-up. 999 (2.12%) participants with CMD developed post-CMD dementia, and 464 (46.45%) with post-CMD dementia died from any cause.

3.2 | BA Accelerations and Longitudinal Disease Progression of Post-CMD Dementia

The results from the Cox regression models indicated that both KDM-BA acceleration and PhenoAge acceleration were significantly associated with the risks of CMD, post-CMD dementia, and death, respectively (Appendix Table S4).

The MSM analysis results showed that both KDM-BA acceleration and PhenoAge acceleration were associated with an increased risk of all transitions, from baseline to CMD, then to post-CMD dementia, and ultimately to death, albeit to different extents (Table 2). In Model 2, the adjusted hazard ratios (HRs) for the transition from baseline to CMD were 1.34 (95% CI: 1.32, 1.35) for KDM-BA acceleration and 1.19 (95% CI: 1.18, 1.20) for PhenoAge acceleration. The associations were slightly attenuated for the transition from CMD to post-CMD dementia compared with the transition from baseline to CMD. Specifically, the HRs in Model 2 for the transition from CMD to post-CMD dementia were 1.12 (95% CI: 1.04, 1.20) for KDM-BA acceleration and 1.10 (95% CI: 1.04, 1.17) for PhenoAge acceleration. Higher estimates were observed in the transition from baseline to death than from CMD to death and from post-CMD dementia to death for both measures. J-shaped nonlinear relationships were observed for the associations of KDM-BA acceleration and PhenoAge acceleration with the progression of CMD, post-CMD dementia, and death (Figure 3).

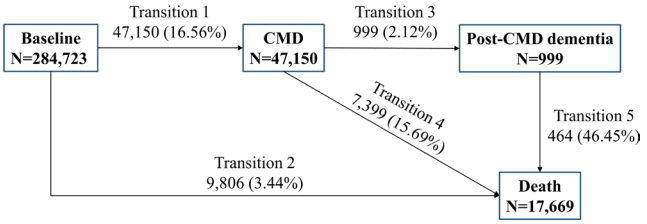

FIGURE 2 | Numbers (percentages) of participants from baseline to CMD, post-CMD dementia, and death.

3.3 | BA Accelerations and Disease-Specific Transitions

The results of the role of the two BA accelerations in each specific CMD in the disease progression are shown in Appendix Tables S5–S7. Compared with heart disease and stroke, two BA accelerations were more strongly associated with the transition from baseline to T2D. For the transition from baseline to T2D, the adjusted HRs were 1.88 (95% CI: 1.84, 1.92) for KDM-BA acceleration and 1.34 (95% CI: 1.32, 1.35) for PhenoAge acceleration. In terms of specific dementia in the progression (Tables 3 and 4), both BA accelerations were more strongly associated with the transition from CMD to post-CMD VaD compared with AD. For the transition from CMD to post-CMD VaD, the full adjusted HRs were 1.22 (95% CI: 1.07, 1.40) for the KDM-BA acceleration and 1.09 (95% CI: 0.99, 1.21) for the PhenoAge acceleration.

TABLE 2 | Associations of the accelerated biological aging with the risks of cardiometabolic disease, subsequent dementia, and death using multistate model ($N = 284,723$).

	Model 1		Model 2	
Longitudinal disease progression	**HRs (95% CIs)**	***p***	**HRs (95% CIs)**	***p***
KDM-BA acceleration				
Baseline → CMD	1.53 (1.52, 1.55)	< 0.001	1.34 (1.32, 1.35)	< 0.001
Baseline → death	1.31 (1.29, 1.34)	< 0.001	1.30 (1.27, 1.34)	< 0.001
CMD → post-CMD dementia	1.09 (1.03, 1.16)	0.004	1.12 (1.04, 1.20)	0.003
CMD → death	1.18 (1.16, 1.21)	< 0.001	1.19 (1.16, 1.22)	< 0.001
Post-CMD dementia → death	1.05 (0.97, 1.14)	0.244	1.10 (0.99, 1.22)	0.072
PhenoAge acceleration				
Baseline → CMD	1.28 (1.27, 1.29)	< 0.001	1.19 (1.18, 1.20)	< 0.001
Baseline → Death	1.34 (1.32, 1.36)	< 0.001	1.30 (1.28, 1.32)	< 0.001
CMD → post-CMD dementia	1.11 (1.06, 1.17)	< 0.001	1.10 (1.04, 1.17)	< 0.001
CMD → death	1.19 (1.17, 1.21)	< 0.001	1.17 (1.15, 1.19)	< 0.001
Post-CMD dementia → death	1.15 (1.07, 1.23)	< 0.001	1.17 (1.09, 1.27)	< 0.001

Note: HRs (95% CI) are results for per SD increase from multistate models. Model 1 adjusted for age, sex. Model 2 further adjusted for race, education, socioeconomic status, smoking status, frequency of alcohol consumption, total physical activity, BMI, and family history of CMDs or dementia.
Abbreviations: BA, biological aging; CMD, cardiometabolic disease.

3.4 | Result of Sensitivity Analyses

Our results remained robust across all sensitivity analyses (Appendix Tables S8–S21 and Appendix Figure S2).

4 | Discussion

Leveraging a prospective study of approximately 280,000 adults in the UKB, we assessed the association of two BA measures with the risk of transitions from healthy to CMD, then to post-CMD dementia, and further to death. Our MSM analysis showed that both KDM-BA acceleration and PhenoAge acceleration were associated with the longitudinal progression of post-CMD dementia, highlighting the promise of these measures for tracking the progression of post-CMD dementia. Both BA accelerations were more strongly associated with the transition from CMD to post-CMD VaD than with the transition to post-CMD AD. Our study suggests that BA acceleration could offer insights into the subclinical prevention of post-CMD dementia and subsequent death in the general middle-aged and elderly population.

Most studies have focused on the association between BA and the onset of a single disease in the general population or subgroups [20–24]. However, focusing solely on single-disease occurrence limits the ability to manage patients comprehensively across diverse disease trajectories. Understanding the transition from CMD to post-CMD dementia is crucial, as CMD contributes to dementia through chronic cerebral hypoperfusion, blood–brain barrier dysfunction, oxidative stress, and cerebral insulin resistance [4–9]. Vascular damage caused by CMD may promote β-amyloid accumulation, increasing dementia risk [4, 8, 9]. Moreover, previous study suggests a dose–response relationship between the number of CMD conditions and the subsequent dementia risk [4]. Although survival analysis strategies based on traditional Cox models are conventional in most previous studies, the competing risk from other disease states and death may violate the assumption of independent censoring, resulting in inaccurate risk estimates in multimorbidity settings [19, 26, 28]. Using MSMs, our results showed that the KDM-BA acceleration and PhenoAge acceleration were associated with all transitions from baseline to CMD, then to post-CMD dementia, and ultimately to death.

Our findings suggest that BA accelerations may have a sustained impact on the overall progression of post-CMD dementia. Baseline accelerated aging was associated with an increased risk of CMD during follow-up, which may inform primary prevention in participants free of CMD. Additionally, we found that baseline accelerated aging was associated with an increased risk of dementia after CMD, as well as the risk of subsequent death after CMD and post-CMD dementia. Given the widespread prevalence of CMD, the potential risk of post-CMD dementia, and the imperfect or inaccessible pre-symptomatic diagnosis and treatment measures for dementia [3, 5, 28], our findings highlight the value of secondary prevention in patients with CMD. Similar to a previous study [19], the results of RCS demonstrated J-shaped associations suggesting that the influence of BA acceleration on the risk of disease progression becomes more pronounced as the degree of BA acceleration increases.

Our findings suggest that the accelerated aging at the physiological level may capture the potential mechanism of post-CMD dementia progression. Although the two measures contain fewer indicators directly related to dementia, statistically significant associations were observed between BA accelerations and the transition from CMD to post-CMD dementia. This association may be due to BA measures indicating CMD-related factors, such as insulin resistance and oxidative stress, which play crucial roles in the pathway from CMD to post-CMD dementia, particularly for post-CMD VaD [41–44]. Regarding the development of CMD, we found that the associations of BA accelerations with progression to T2D were more pronounced than with progression to stroke and heart disease. This may be due to the fact that different organ systems age at different rates [45]. Metabolic dysfunction, especially insulin resistance, may be among the earliest indicators of aging, influencing the cardiovascular system [45]. We did not observe stronger associations between BA acceleration and the transition from healthy to stroke or stroke to dementia when compared to other CMD types. This could be due to the fact that KDM-BA and PhenoAge predominantly reflect chronic aging features, which, while related to the development of CMD and subsequent dementia risk, may not fully capture the acute events associated with stroke, such as the acute inflammatory responses and neurotoxic effects [32, 46]. As distinct algorithms, KDM-BA and PhenoAge extract information pertaining to different aspects of aging. KDM-BA focuses on system integrity and homeostasis, while PhenoAge offers a more direct connection to mortality risk [15, 16]. This may explain the stronger association of PhenoAge acceleration with the transition from post-CMD dementia to death compared with KDM-BA acceleration in the later stages of disease progression.

There is currently no gold standard for the biological aging process. Commonly used BA measures include epigenetic clock, telomere length, and composite biomarker BA, each reflecting different facets of the aging process [31, 33]. Among these, the epigenetic clock is a robust predictor strongly correlated with CA and mortality, but its reliance on DNA methylation limits its practical use in large populations [33]. In contrast, clinical-based BA measures, like KDM-BA and PhenoAge, offer good accuracy and cost-effectiveness, making them suitable for large population research and clinical practice [17]. Additionally, the composite biomarker BAs has the advantage of detecting physiological alterations earlier than specific phenotype manifestations [32]. As the biological aging process can be influenced by various factors, these BAs provide a unique opportunity for intervening in age-related diseases [12, 13]. Therefore, the composite biomarker BAs hold promise for identifying and slowing the progression of post-CMD dementia in routine clinical practice.

5 | Strengths and Limitations

This study has several strengths. First, the present study estimated the relationship between BA accelerations and disease progression from CMD to post-dementia to death, providing insights for both primary and secondary prevention of CMD and dementia. Second, by incorporating multiple subsequent or competing events as transition states, the MSM used in this study distinguished the impact of BA accelerations on each transition in the longitudinal disease progression.

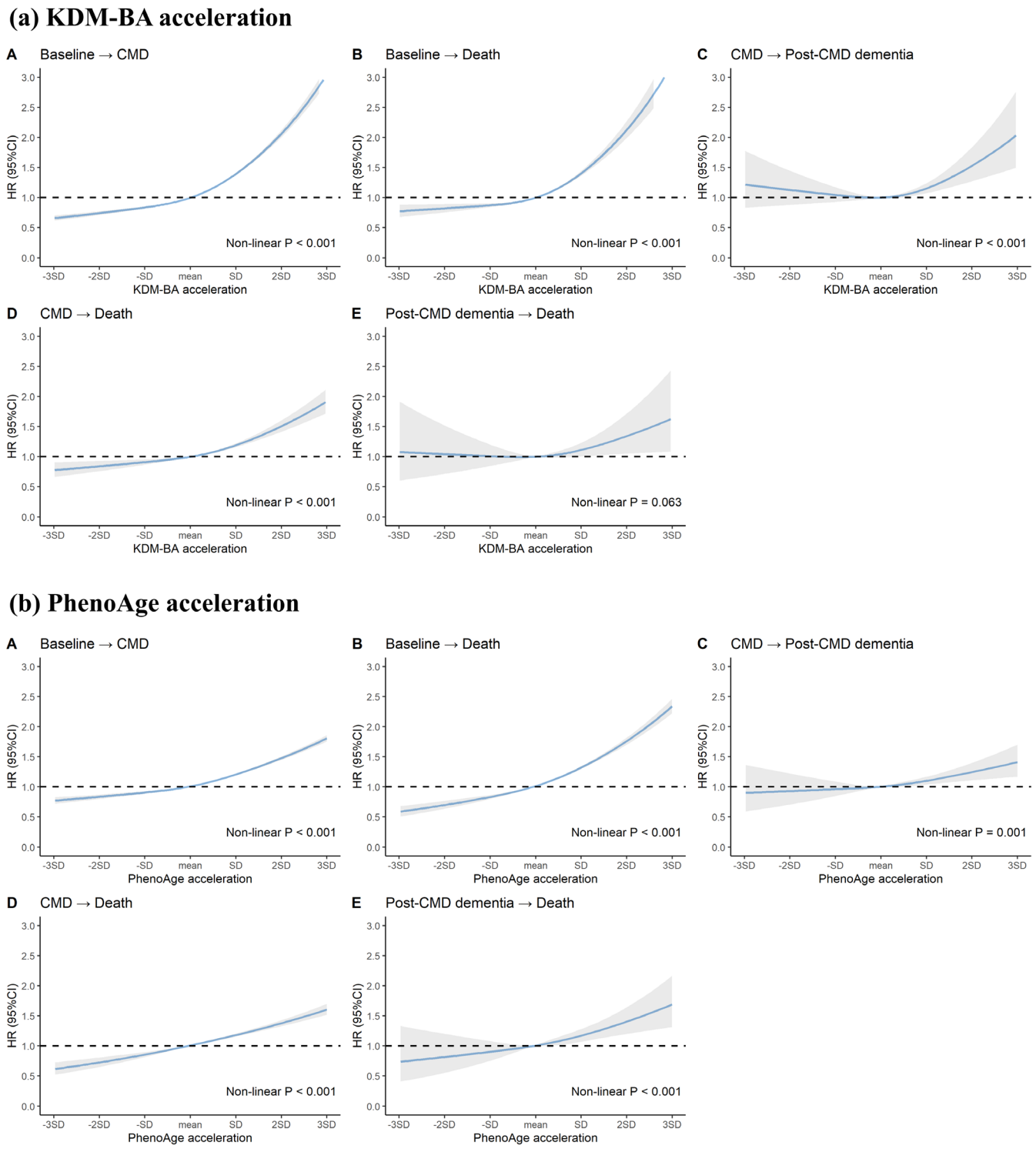

FIGURE 3 | Dose–response curves of the accelerated biological aging with the dynamic progression of CMD, post-CMD dementia, and death ($N = 284{,}723$). Solid lines: point estimates; shadows: 95% confidence interval.

Nonetheless, limitations are worth noting. First, for participants whose death date was the same as the diagnosis date of CMDs or post-CMD dementia, we used an interval of 0.5 days to calculate the onset date of the disease, which may introduce inaccuracies. However, sensitivity analyses using different time intervals did not significantly alter our results. Second, we lacked detailed information on participant CMD and dementia-related drug use, which may reduce the risk of subsequent disease progression. Third, although we used self-reported information, primary care data, and hospital admission data to track the onset of CMD and dementia during follow-up, there is still a possibility of underestimating cases of CMD or dementia. Fourth, most biochemical indicators used to construct BA were measured only at baseline, and we were

TABLE 3 | Associations of the accelerated biological aging with the risks of cardiometabolic disease, subsequent Alzheimer's disease, and death using multistate model ($N = 284,723$).

Longitudinal disease progression	Model 1	Model 2
	HRs (95% CIs)	HRs (95% CIs)
KDM-BA acceleration		
Baseline → CMD	1.53 (1.52, 1.55)	1.34 (1.32, 1.35)
Baseline → death	1.31 (1.29, 1.34)	1.30 (1.27, 1.34)
CMD → post-CMD AD	1.15 (1.04, 1.27)	1.15 (1.02, 1.29)
CMD → death	1.18 (1.15, 1.20)	1.19 (1.16, 1.22)
Post-CMD AD → death	1.08 (0.94, 1.25)	1.23 (1.01, 1.49)
PhenoAge acceleration		
Baseline → CMD	1.28 (1.27, 1.29)	1.19 (1.18, 1.20)
Baseline → death	1.34 (1.32, 1.36)	1.30 (1.28, 1.32)
CMD → post-CMD AD	1.05 (0.96, 1.15)	1.02 (0.93, 1.12)
CMD → death	1.19 (1.18, 1.21)	1.17 (1.15, 1.19)
Post-CMD AD → death	1.15 (1.02, 1.30)	1.20 (1.05, 1.38)

Note: HRs (95% CI) are results for per SD increase from multistate models. Model 1 adjusted for age, sex. Model 2 further adjusted for race, education, socioeconomic status, smoking status, frequency of alcohol consumption, total physical activity, BMI, and family history.
Abbreviations: AD, Alzheimer's disease; BA, biological aging; CMD, cardiometabolic disease.

TABLE 4 | Associations of the accelerated biological aging with the risks of cardiometabolic disease, subsequent vascular dementia, and death using multistate model ($N = 284,723$).

Disease progression	Model 1	Model 2
	HR (95% CI)	HR (95% CI)
KDM-BA acceleration		
Baseline → CMD	1.53 (1.52, 1.55)	1.34 (1.32, 1.35)
Baseline → Death	1.31 (1.29, 1.34)	1.30 (1.27, 1.34)
CMD → Post-CMD VaD	1.15 (1.03, 1.29)	1.22 (1.07, 1.40)
CMD → death	1.18 (1.15, 1.20)	1.18 (1.15, 1.21)
Post-CMD VaD → death	1.14 (0.99, 1.32)	1.17 (0.97, 1.42)
PhenoAge acceleration		
Baseline → CMD	1.28 (1.27, 1.29)	1.19 (1.18, 1.20)
Baseline → death	1.34 (1.32, 1.36)	1.30 (1.28, 1.32)
CMD → post-CMD VaD	1.10 (1.00, 1.22)	1.09 (0.99, 1.21)
CMD → death	1.19 (1.18, 1.21)	1.17 (1.15, 1.19)
Post-CMD VaD → death	1.13 (0.99, 1.30)	1.15 (0.99, 1.35)

Note: HRs (95% CI) are results for per SD increase from multistate models. Model 1 adjusted for age, sex. Model 2 further adjusted for race, education, socioeconomic status, smoking status, frequency of alcohol consumption, total physical activity, BMI, and family history.
Abbreviations: BA, biological aging; CMD, cardiometabolic disease; VaD, vascular dementia.

unable to capture changes over time. Although a follow-up assessment was conducted for a subset of participants (approximately 20,000), the limited sample size poses a risk of selection bias, reduces statistical power, and may result in fewer positive outcomes, especially for post-CMD dementia. Fifth, the UKB population consists primarily of Caucasians and is composed of volunteers, who may be healthier than the general population. Additionally, due to the availability of BA data, our study included only approximately 60% of the total UKB cohort. These factors may limit the generalizability of our findings, and caution is needed when extrapolating the results to other populations. Finally, despite reasonable control for confounders, the presence of residual confounding cannot be entirely ruled out.

6 | Conclusion

The present study identified KDM-BA acceleration and PhenoAge acceleration as being associated with the risk of transitions from healthy to CMD, then to post-CMD dementia, and further to death. Both BA accelerations were more strongly associated with the transition from CMD to post-CMD VaD than with the transition to post-CMD AD. Our study suggests that the cost-effectiveness composite biomarker BAs hold promise for identifying disease progression of post-CMD dementia in routine clinical practice and slowing down disease progression through the intervention measures that slow down biological aging.

Author Contributions

Ning Zhang: writing – review and editing, writing – original draft, conceptualization, software, formal analysis, supervision, methodology, investigation. **Haojiang Zuo:** writing – original draft, formal analysis. **Jiajie Cai:** software, methodology. **Yi Xiang:** software, methodology. **Yuan Zhang:** software. **Hongmei Zhang:** methodology. **Yifan Hu:** supervision. **Hao Xu:** resources. **Xiong Xiao:** resources, writing – review and editing, writing – original draft, funding acquisition, validation. **Xing Zhao:** project administration, visualization.

Acknowledgements

This research has been conducted under the UK Biobank Application Number: 117185. We thank all participants involved in the UK Biobank.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

UK Biobank data are available online at https://www.ukbiobank.ac.uk.

References

1. World Health Organization, "Ageing and Health," accessed December 11t, 2023, https://www.who.int/news-room/fact-sheets/detail/ageing-and-health.

2. M. Kivipelto, F. Mangialasche, and T. Ngandu, "Lifestyle Interventions to Prevent Cognitive Impairment, Dementia and Alzheimer Disease," *Nature Reviews Neurology* 14, no. 11 (2018): 653–666, https://doi.org/10.1038/s41582-018-0070-3.

3. G. Livingston, J. Huntley, A. Sommerlad, et al., "Dementia Prevention, Intervention, and Care: 2020 Report of the Lancet Commission," *Lancet* 396, no. 10248 (2020): 413–446, https://doi.org/10.1016/s0140-6736(20)30367-6.

4. A. Dove, A. Marseglia, Y. Shang, et al., "Cardiometabolic Multimorbidity Accelerates Cognitive Decline and Dementia Progression," *Alzheimer's & Dementia* 19, no. 3 (2023): 821–830, https://doi.org/10.1002/alz.12708.

5. A. Dove, J. Guo, A. Marseglia, et al., "Cardiometabolic Multimorbidity and Incident Dementia: The Swedish Twin Registry," *European Heart Journal* 44, no. 7 (2023): 573–582, https://doi.org/10.1093/eurheartj/ehac744.

6. X. Y. Tai, M. Veldsman, D. M. Lyall, et al., "Cardiometabolic Multimorbidity, Genetic Risk, and Dementia: A Prospective Cohort Study," *Lancet Healthy Longev* 3, no. 6 (2022): e428–e436, https://doi.org/10.1016/s2666-7568(22)00117-9.

7. Y. Jin, J. Liang, C. Hong, R. Liang, and Y. Luo, "Cardiometabolic Multimorbidity, Lifestyle Behaviours, and Cognitive Function: A Multicohort Study," *Lancet Healthy Longev* 4, no. 6 (2023): e265–e273, https://doi.org/10.1016/s2666-7568(23)00054-5.

8. C. Liu, R. Liu, N. Tian, et al., "Cardiometabolic Multimorbidity, Peripheral Biomarkers, and Dementia in Rural Older Adults: The MIND-China Study," *Alzheimer's & Dementia* 20, no. 9 (2024): 6133–6145, https://doi.org/10.1002/alz.14091.

9. J. Luo, I. J. Rasmussen, B. G. Nordestgaard, A. Tybjærg-Hansen, J. Q. Thomassen, and R. Frikke-Schmidt, "Cardiovascular Diseases and Risk of Dementia in the General Population," *European Journal of Preventive Cardiology* (2025), https://doi.org/10.1093/eurjpc/zwaf129.

10. S. Wilkes, "Data Analysis With Competing Risks and Intermediate States," *Journal of Biopharmaceutical Statistics* 26, no. 1 (2016): 187–188, https://doi.org/10.1080/10543406.2016.1107709.

11. D. A. Stakos, K. Stamatelopoulos, D. Bampatsias, et al., "The Alzheimer's Disease Amyloid-Beta Hypothesis in Cardiovascular Aging and Disease: JACC Focus Seminar," *Journal of the American College of Cardiology* 75, no. 8 (2020): 952–967, https://doi.org/10.1016/j.jacc.2019.12.033.

12. N. Barzilai, A. M. Cuervo, and S. Austad, "Aging as a Biological Target for Prevention and Therapy," *Journal of the American Medical Association* 320, no. 13 (2018): 1321–1322, https://doi.org/10.1001/jama.2018.9562.

13. J. Campisi, P. Kapahi, G. J. Lithgow, S. Melov, J. C. Newman, and E. Verdin, "From Discoveries in Ageing Research to Therapeutics for Healthy Ageing," *Nature* 571, no. 7764 (2019): 183–192, https://doi.org/10.1038/s41586-019-1365-2.

14. S. T. Skou, F. S. Mair, M. Fortin, et al., "Multimorbidity," *Nature Reviews. Disease Primers* 8, no. 1 (2022): 48, https://doi.org/10.1038/s41572-022-00376-4.

15. P. Klemera and S. Doubal, "A New Approach to the Concept and Computation of Biological Age," *Mechanisms of Ageing and Development* 127, no. 3 (2006): 240–248, https://doi.org/10.1016/j.mad.2005.10.004.

16. M. E. Levine, A. T. Lu, A. Quach, et al., "An Epigenetic Biomarker of Aging for Lifespan and Healthspan," *Aging (Albany NY)* 10, no. 4 (2018): 573–591, https://doi.org/10.18632/aging.101414.

17. Y. Xiang, H. Xu, H. Chen, et al., "Tea Consumption and Attenuation of Biological Aging: A Longitudinal Analysis From Two Cohort Studies," *Lancet Regional Health—Western Pacific* 42 (2024): 100955, https://doi.org/10.1016/j.lanwpc.2023.100955.

18. H. Chen, J. Yin, Y. Xiang, et al., "Alcohol Consumption and Accelerated Biological Ageing in Middle-Aged and Older People: A Longitudinal Study From Two Cohorts," *Addiction* 119, no. 8 (2024): 1387–1399, https://doi.org/10.1111/add.16501.

19. M. J. Jiang, S. F. Tian, S. Z. Liu, et al., "Accelerated Biological Aging Elevates the Risk of Cardiometabolic Multimorbidity and Mortality," *Nature Cardiovascular Research* 3, no. 3 (2024): 332–342, https://doi.org/10.1038/s44161-024-00438-8.

20. R. Mao, F. Wang, Y. Zhong, X. Meng, T. Zhang, and J. Li, "Association of Biological Age Acceleration With Cardiac Morphology, Function, and Incident Heart Failure: Insights From UK Biobank Participants," *European Heart Journal Cardiovascular Imaging* 25 (2024): 1315–1323, https://doi.org/10.1093/ehjci/jeae126.

21. R. Waziry, Y. Gu, A. K. Boehme, and O. A. Williams, "Measures of Aging Biology in Saliva and Blood as Novel Biomarkers for Stroke and Heart Disease in Older Adults," *Neurology* 101, no. 23 (2023): e2355–e2363, https://doi.org/10.1212/wnl.0000000000207909.

22. J. K. L. Mak, C. E. McMurran, and S. Hägg, "Clinical Biomarker-Based Biological Ageing and Future Risk of Neurological Disorders in the UK Biobank," *Journal of Neurology, Neurosurgery, and Psychiatry* 95 (2023): 481–484, https://doi.org/10.1136/jnnp-2023-331917.

23. A. Thomas, C. P. Ryan, A. Caspi, et al., "Diet, Pace of Biological Aging, and Risk of Dementia in the Framingham Heart Study," *Annals of Neurology* 95, no. 6 (2024): 1069–1079, https://doi.org/10.1002/ana.26900.

24. Y. He, Y. Jia, Y. Li, et al., "Accelerated Biological Aging: Unveiling the Path to Cardiometabolic Multimorbidity, Dementia, and Mortality," *Frontiers in Public Health* 12 (2024): 1423016, https://doi.org/10.3389/fpubh.2024.1423016.

25. H. Putter, M. Fiocco, and R. B. Geskus, "Tutorial in Biostatistics: Competing Risks and Multi-State Models," *Statistics in Medicine* 26, no. 11 (2007): 2389–2430, https://doi.org/10.1002/sim.2712.

26. N. Zhang, X. Liu, L. Wang, et al., "Lifestyle Factors and Their Relative Contributions to Longitudinal Progression of Cardio-Renal-Metabolic Multimorbidity: A Prospective Cohort Study," *Cardiovascular Diabetology* 23, no. 1 (2024): 265, https://doi.org/10.1186/s12933-024-02347-3.

27. C. Sudlow, J. Gallacher, N. Allen, et al., "UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age," *PLoS Medicine* 12, no. 3 (2015): e1001779, https://doi.org/10.1371/journal.pmed.1001779.

28. Y. Han, Y. Hu, C. Yu, et al., "Lifestyle, Cardiometabolic Disease, and Multimorbidity in a Prospective Chinese Study," *European Heart Journal* 42, no. 34 (2021): 3374–3384, https://doi.org/10.1093/eurheartj/ehab413.

29. F. K. Ho, S. R. Gray, P. Welsh, et al., "Associations of Fat and Carbohydrate Intake With Cardiovascular Disease and Mortality: Prospective Cohort Study of UK Biobank Participants," *BMJ* 368 (2020): m688, https://doi.org/10.1136/bmj.m688.

30. Y. Zhang, S. D. Chen, Y. T. Deng, et al., "Identifying Modifiable Factors and Their Joint Effect on Dementia Risk in the UK Biobank," *Nature Human Behaviour* 7, no. 7 (2023): 1185–1195, https://doi.org/10.1038/s41562-023-01585-x.

31. D. W. Belsky, T. E. Moffitt, A. A. Cohen, et al., "Eleven Telomere, Epigenetic Clock, and Biomarker-Composite Quantifications of Biological Aging: Do They Measure the Same Thing?," *American Journal of Epidemiology* 187, no. 6 (2018): 1220–1230, https://doi.org/10.1093/aje/kwx346.

32. L. Chen, Y. Zhang, C. Yu, et al., "Modeling Biological Age Using Blood Biomarkers and Physical Measurements in Chinese Adults," *eBioMedicine* 89 (2023): 104458, https://doi.org/10.1016/j.ebiom.2023.104458.

33. J. Jylhävä, N. L. Pedersen, and S. Hägg, "Biological Age Predictors," *eBioMedicine* 21 (2017): 29–36, https://doi.org/10.1016/j.ebiom.2017.03.046.

34. X. Gao, Y. Wang, Z. Song, M. Jiang, T. Huang, and A. A. Baccarelli, "Early-Life Risk Factors, Accelerated Biological Aging, and the Late-Life Risk of Mortality and Morbidity," *QJM* 117 (2023): 257–268, https://doi.org/10.1093/qjmed/hcad247.

35. X. Gao, T. Geng, M. Jiang, et al., "Accelerated Biological Aging and Risk of Depression and Anxiety: Evidence From 424,299 UK Biobank Participants," *Nature Communications* 14, no. 1 (2023): 2277, https://doi.org/10.1038/s41467-023-38013-7.

36. D. C. Parker, B. N. Bartlett, H. J. Cohen, et al., "Association of Blood Chemistry Quantifications of Biological Aging With Disability and Mortality in Older Adults," *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences* 75, no. 9 (2020): 1671–1679, https://doi.org/10.1093/gerona/glz219.

37. S. Zhang, Z. M. Qian, L. Chen, et al., "Exposure to Air Pollution During Pre-Hypertension and Subsequent Hypertension, Cardiovascular Disease, and Death: A Trajectory Analysis of the UK Biobank Cohort," *Environmental Health Perspectives* 131, no. 1 (2023): 17008, https://doi.org/10.1289/ehp10967.

38. H. Freisling, V. Viallon, H. Lennon, et al., "Lifestyle Factors and Risk of Multimorbidity of Cancer and Cardiometabolic Diseases: A Multinational Cohort Study," *BMC Medicine* 18, no. 1 (2020): 5, https://doi.org/10.1186/s12916-019-1474-7.

39. Y. Pang, Y. Han, C. Yu, et al., "The Role of Lifestyle Factors on Comorbidity of Chronic Liver Disease and Cardiometabolic Disease in Chinese Population: A Prospective Cohort Study," *Lancet Regional Health–Western Pacific* 28 (2022): 100564, https://doi.org/10.1016/j.lanwpc.2022.100564.

40. H. Wu, L. Huang, S. Zhang, Y. Zhang, and Y. Lan, "Daytime Napping, Biological Aging and Cognitive Function Among Middle-Aged and Older Chinese: Insights From the China Health and Retirement Longitudinal Study," *Frontiers in Public Health* 11 (2023): 1294948, https://doi.org/10.3389/fpubh.2023.1294948.

41. L. L. Beason-Held, C. I. Kerley, S. Chaganti, et al., "Health Conditions Associated With Alzheimer's Disease and Vascular Dementia," *Annals of Neurology* 93, no. 4 (2023): 805–818, https://doi.org/10.1002/ana.26584.

42. G. J. Biessels and F. Despa, "Cognitive Decline and Dementia in Diabetes Mellitus: Mechanisms and Clinical Implications," *Nature Reviews. Endocrinology* 14, no. 10 (2018): 591–604, https://doi.org/10.1038/s41574-018-0048-7.

43. M. P. Pase, N. A. Grima, C. K. Stough, A. Scholey, and A. Pipingas, "Cardiovascular Disease Risk and Cerebral Blood Flow Velocity," *Stroke* 43, no. 10 (2012): 2803–2805, https://doi.org/10.1161/strokeaha.112.666727.

44. M. Y. Donath, D. T. Meier, and M. Böni-Schnetzler, "Inflammation in the Pathophysiology and Therapy of Cardiometabolic Disease," *Endocrine Reviews* 40, no. 4 (2019): 1080–1091, https://doi.org/10.1210/er.2019-00002.

45. Y. E. Tian, V. Cropley, A. B. Maier, N. T. Lautenschlager, M. Breakspear, and A. Zalesky, "Heterogeneous Aging Across Multiple Organ Systems and Prediction of Chronic Disease and Mortality," *Nature Medicine* 29, no. 5 (2023): 1221–1231, https://doi.org/10.1038/s41591-023-02296-6.

46. N. S. Rost, A. Brodtmann, M. P. Pase, et al., "Post-Stroke Cognitive Impairment and Dementia," *Circulation Research* 130, no. 8 (2022): 1252–1271, https://doi.org/10.1161/circresaha.122.319951.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.