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Associations of combined accelerated biological aging and genetic susceptibility with incident dementia: a prospective study in the UK Biobank

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Abstract

Background Accelerated biological aging has been verified to be a critical risk factor for a number of age-related diseases, but its role in dementia remained unclear. Whether it modified the effects of genetic factors was also unknown. This study evaluated the associations between accelerated biological aging and dementia and the moderating role of accelerated biological aging in the genetic susceptibility to the disease.

Methods We included 200,731 participants in the UK biobank. Nine clinical blood biomarkers and chronological age were used to calculate Phenotypic age acceleration (PhenoAgeAccel), which is a novel indicator for accelerated biological aging. The associations of PhenoAgeAccel with dementia, both young-onset and late-onset dementia, were assessed by Cox proportional hazard models. Apolipoprotein E (*APOE*) alleles and polygenic risk scores (PRS) were used to evaluate the genetic risk of dementia. The interactions between genetic susceptibility and biological aging were tested on both multiplicative and additive scales.

Results These findings showed individuals who were in the highest quartile of PhenoAgeAccel had a higher risk with incidence of dementia compared to individuals in the lowest quartile of PhenoAgeAccel (*HR*: 1.145 (95% *CI*: 1.050, 1.249)). Individuals with biologically older had a higher risk of dementia than individuals with biologically younger (*HR*: 1.069 (95% *CI*: 1.004, 1.138)). Furthermore, compared to individuals with biologically younger and low *APOE* ε4-related genetic risk, individuals with biologically younger and high *APOE* ε4-related genetic risk (*HR*:3.048 (95% *CI*: 2.811, 3.305)) had a higher risk of dementia than individuals with biologically older and high *APOE* ε4-related genetic risk (*HR*: 2.765 (95% *CI*: 2.523, 3.029)). Meanwhile, referring to low dementia PRS and biologically younger, the risk of dementia increased by 72.7% (*HR*: 1.727 (95% *CI*: 1.538, 1.939) in the biologically younger and high PRS group and 58.7% (*HR*: 1.587 (95% *CI*: 1.404, 1.793) in the biologically older and high PRS group, respectively. The negative interactions between PhenoAgeAccel with *APOE* ε4 and PRS were also tested on the additive scale.

Conclusions Accelerated biological aging could bring the extra risk of dementia but attenuate the effects of genetic risk on dementia. These findings provide insights for precise prevention and intervention of dementia.

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Keywords UK Biobank, Accelerated biological aging, Dementia, Apolipoprotein E, Polygenetic risk score, Relative excess risk, Attributable proportion

Background

Dementia is a growing public health challenge as life expectancy increases, and the aging of the population leads to a substantial increase in the prevalence of dementia and cognitive decline. Globally, about 57.4 million people with dementia in 2019, and this number will increase to 152.8 million in 2050 [1]. Global societal costs of dementia have reached about US $ 1313.4 billion, including US $213.2 billion (16%) in direct medical costs in 2019 [2]. To reduce the disease burden of dementia, it is essential to identify the risk factors and monitor the health status of adults with dementia. This disease is further grouped into two types, young-onset and late-onset, according to whether the onset of dementia occurs before or after the age of 65 years old. Risk factors for these two types are somewhat different [3]. Only a limited number of lifestyle factors (alcohol use and social isolation) are significantly related to increased risk of young-onset dementia (YOD), while more lifestyle-related factors have been demonstrated in late-onset dementia (LOD), and there are some unique blood marker factors that may raise the risk of young-onset dementia, such as vitamin D, and high C-reactive protein levels [4, 5].

Accelerated biological aging indicates a premature decline in homeostasis, which has been widely recognized as a major risk factor for death and age-related disease [6]. Dementia is associated with premature aging, accompanied by functional declines in cognition and the brain [7]. Phenotypes which relate to biological aging, including cell senescence, immunosenescence, and shortened telomere length, are involved in dementia pathogenesis [8, 9]. Recently, biological aging was defined and measured by a series of biomarkers, including organ function biomarkers such as blood pressure and inflammatory and metabolic biomarkers of molecular changes such as cellular senescence and telomere shortening [10]. Phenotypic age (Phenoage), the first plasma proteomic aging clock, was calculated based on the Gompertz mortality model and has strong predictive power for all-cause mortality [11]. Phenoage was calculated by nine clinical chemistry biomarkers and chronological age, which may be an expression of multiple hallmarks of cellular and intracellular aging. Multiple studies have demonstrated that Phenoage has a strong ability to capture morbidity and mortality across a variety of populations [12]. Moreover, the clinical and biochemical indicators used to calculate Phenoage are more readily available than other molecular measures of aging, making it more suitable for evaluating the effects of biological aging on health status. Further research on the effect of accelerated aging, whether biological age exceeds chronological age, is more relevant to timely intervention to prevent diseases. Although many studies have explored the relationship between accelerated aging and dementia, summarizing all this evidence, we failed to find robust evidence that adults with dementia had a faster-accelerated aging [10, 13]. Since biological aging also may impact the age of onset, exploring the differences in its effects on young-onset and late-onset dementia is valuable, but to our knowledge, no studies have focused on this topic.

In addition, the apolipoprotein E (*APOE*) ε4 allele was first reported by Corder et al. as a key risk marker of dementia [14] and has since been validated in a number of cohort studies worldwide [15]. Besides, accumulating evidence has shown that other single nucleotide polymorphisms (SNPs) also play a major role in the development of dementia [16]. Polygenic risk score (PRS), calculated by dementia-related SNPs, was increasingly being considered as a risk factor for dementia. The associations between genetic susceptibility and the risk of dementia may differ according to chronological age, since chronological age alone cannot capture sufficient variation among individuals in the rate of aging and risk of age-related diseases [13]. Exploration of the moderating role of accelerated biological aging on genetic risk could provide innovative insights into risk identification.

Hence, in this study, we aimed to evaluate the association between accelerated biological aging and the risk of dementia and whether this association varied between young-onset and late-onset dementia. Furthermore, we assessed the joint effects and interactions between accelerated biological aging and genetic susceptibility in the development of dementia as well as on young-onset and late-onset dementia.

Methods

Study population

The UK Biobank was a detailed, long-term prospective health study that recruited more than half a million participants aged 40–69 years at 22 assessment centers between 2006 and 2010. After participants had completed the informed consent process, personal health information, physical measurement data, biological sample data, medical records, and genotype data were collected. The design and methods of the UK Biobank have been detailed in previously published studies [17]. Our study included all participants with

clinical biomarkers necessary for calculating Phenoage and dementia status. Following exclusion criteria, we excluded 30,341 non-white individuals, 346 individuals with dementia at baseline, 17,973 with missing genetic data, 195,896 with missing control variables, and 56,891 participants under 50. Ultimately, 200,731 participants were included in this study. Figure 1 shows the detailed process of data cleaning. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Phenoage and phenotypic age acceleration calculation

Phenoage was developed using data from the Third National Health and Nutrition Examination Survey (NHANES III) and fully validated in the NHANES IV for its effectiveness in predicting the incidence rates of various age-related diseases and mortality risk [18]. In brief, a lambda value of 0.0192 was selected as the threshold through ten-fold cross-validation, and a Cox penalized regression model was applied to 42 clinical biomarkers and chronological age in NHANES III. Nine clinical biomarkers and chronological age were selected for inclusion in a parametric proportional hazards model following Gompertz distribution, and 120-month mortality risk was converted into units in years, finally obtaining the estimate of Phenoage. The nine clinical biomarkers were albumin(g/L), creatinine (μmol/L), glucose (mmol/L), C-reactive protein (mg/dL), lymphocyte percent (%), mean cell volume (fL), red cell distribution width (%), alkaline phosphatase(U/L), and white blood cell count (1000 cells/μL). The formula for calculating the Phenoage was as follows:

$$\text{PhenoAge} = 141.50225 + \frac{ln\left[-0.00553 \times ln\left(1 - \text{MortalityRisk}\right)\right]}{0.090165}$$

$$\text{MortalityRisk} = 1 - exp\left[\frac{-1.51714 \times \exp(x_b)}{0.0076927}\right]$$

$$\begin{aligned} x_b = &-19.907 - 0.0336 \times \text{Albumin} + 0.0095 \times \text{Creatinine} + 0.1953 \times \text{Glucose} + 0.0954 \times ln\,(\text{C} - \text{reactive protein}) \\ &- 0.0120 \times \text{Lymphocyte percent} + 0.0268 \times \text{Mean cell volume} + 0.3306 \times \text{Red cell distribution width} \\ &+ 0.00188 \times \text{Alkaline phosphatase} + 0.0554 \times \text{White blood cell count} + 0.0804 \times \text{Chronological age} \end{aligned}$$

We further calculated phenotypic age acceleration (PhenoAgeAccel) characterized by the residuals from linear regression of the Phenoage on chronological age [19]. PhenoAgeAccel represented the relationship between the estimated Phenoage and the predicted Phenoage under the premise of considering chronological age. PhenoAgeAccel > 0 was categorized as biologically older, and PhenoAgeAccel ≤ 0 was categorized as biologically younger.

APOE ε4 allele and the polygenetic risk score for dementia

The UK Biobank Genotype data were identified using the UK BiLEVE Axiom array and the UK Biobank Axiom array. All participants' genomic data, such as genome-wide genotyping, whole-genome sequence data, and telomere length, were available. Previous studies have confirmed that the polymorphism of the *APOE* genotype was a combination of two single nucleotide polymorphisms (SNP), rs429358 and rs7412, resulting in six common genotypes (ε2/ε2, ε2/ε3, ε3/ε3, ε3/ε4, ε2/ε4, ε4/ε4) [20]. We divided individuals into high *APOE* ε4-related genetic risk (ε3/ε4, ε2/ε4, ε4/ε4) and low *APOE* ε4-related genetic risk (ε2/ε2, ε2/ε3, ε3/ε3) based on the number of *APOE* ε4 alleles [21]. Referring to previously published related studies [22] and excluding one SNP with minor allele frequency < 0.005 [22], 38 SNPs significant for dementia were ultimately identified to calculate polygenetic risk score (PRS) (details are in Additional file 1: Table S1). The 38 SNPs were recoded as 0, 1, and 2 based on the number of risk alleles, and corresponding weighted risk estimates were obtained from the International Alzheimer's Disease Genomics Project [23]. The PRS for dementia was calculated using the following formula: $\text{Dementia PRS} = \beta_1 \times SNP_1 + \beta_2 \times SNP_2 + \cdots + \beta_{38} \times SNP_{38}$. Higher scores indicate higher genetic susceptibility to dementia [24]. Participants' genetic susceptibility was categorized into low (≤ quartile 1), intermediate (quartile 1 to quartile 3), and high (≥ quartile 3) based on the quartile distribution of the PRS in the entire sample.

Outcome assessment

The main outcome of this study was all-cause dementia. The UK Biobank Outcomes Adjudication Group developed algorithms based on the data from hospital admissions, primary care, and death registers during follow-up to identify all-cause dementia, which was relatively accurate with positive predictive values ranging from 80 to 92%, sensitivities of about 78%, and specificity ranging from 92.0 to 96.6% [25]. The code list for dementia was detailed in Additional file 1: Table S2. In addition, considering that different subtypes of dementia may be affected

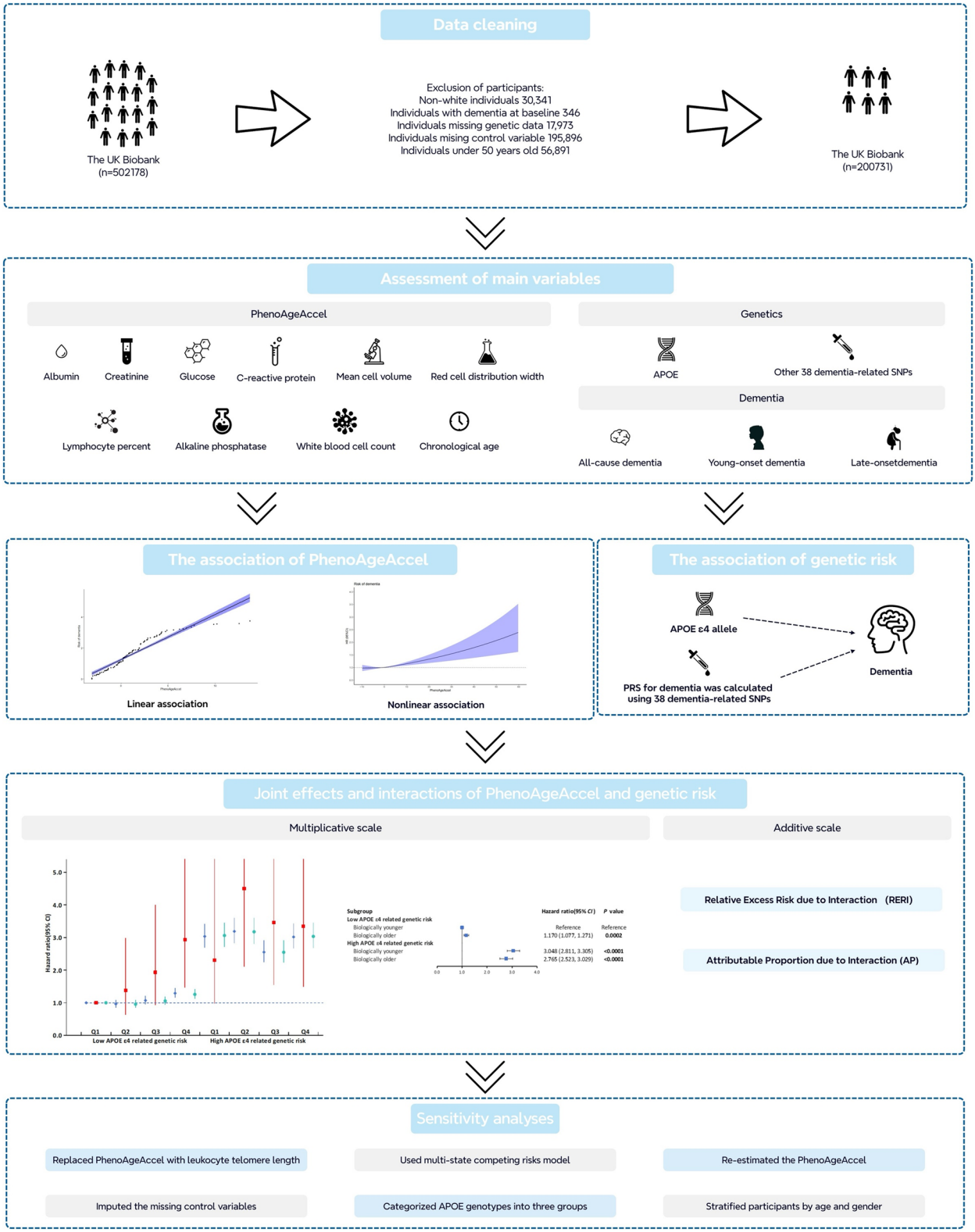

Fig. 1 Study design and analysis process. Abbreviations: PhenoAgeAccel, phenotypic age acceleration; PRS, polygenic risk score

by varied genetic and environmental factors [26] and demonstrate distinct clinical characteristics [27], individuals were further grouped into YOD (younger than 65 years) and LOD (65 years and older) based on the onset age of dementia.

Covariates

Based on previously published research and some authoritative dementia prevention guidelines [24, 28, 29], we identified several potential confounding factors including age, gender, education, Townsend deprivation index, BMI, smoking status, alcohol intake, physical activity, social isolation, healthy diet score, hearing problem, depression, diabetes, cardiovascular diseases, cancer, cataract, and any other serious medical and family history of dementia. Details were provided in Additional file 1: Table S3 [21, 30–35]. When the genetic factors were involved in the models, the first 10 genetic principal components, genotyping array, and relatedness (genetic kinship) were also adjusted.

Statistical analysis

Cox proportional hazards regression, with the follow-up time (in months) as the time metric, was used to estimate the association of PhenoAgeAccel, *APOE* genotype, and PRS with the risk of dementia, reporting the corresponding hazard ratios (*HR*s) and 95% confidence interval (*CI*s). The follow-up time was from the baseline assessment to the minimum of the following: time of incident all-cause dementia, time of exiting the study, time of death, or end time of the study. Schoenfeld residuals method was used to test the proportional hazards assumption. No significant results indicated the variables violated the proportional hazards assumption. The potential nonlinear association between PhenoAgeAccel and the risk of dementia was assessed by a restricted cubic spline. All these analyses were adjusted for the covariates.

To investigate the interaction between *APOE* genotype and PRS with PhenoAgeAccel on risk of dementia, we entered *APOE* genotype × PhenoAgeAccel and PRS × PhenoAgeAccel interaction terms into multivariable-adjusted models. The interaction terms were transformed into a multi-categorical variable considering the potential multicollinearity. On the additive scale, relative excess risk due to interaction (*RERI*), attributable proportion due to interaction (*AP*), and the corresponding 95% *CI*s were used to quantify interaction. The interaction was regarded as insignificant if the 95% *CI*s calculated using the "delta" method included zero. On the multiplicative scale, the significance of the interaction terms coefficient was used to test for interaction. The multiplicative interaction examined whether the relative risk of biologically older vs biologically younger varied across high and low genetic risk groups. By contrast, the additive interaction assessed whether the difference in absolute risk of dementia between biologically older and biologically younger differed between the two genetic risk groups. Therefore, from a public health viewpoint, we focused more on the biological association evidence provided by additive interaction [36].

We did several sensitivity analyses to assess the robustness of our findings. [1] Relevant reviews reported that leukocyte telomere length was the most extensively studied biological age indicator [37]; therefore, we used leukocyte telomere length as a proxy for PhenoAgeAccel and evaluated its association with all-cause dementia. [2] The traditional Cox proportional hazards model ignored the competing effect of other outcome events (such as death) on the risk of dementia [38]. Therefore, we used a multi-state competing risks model to analyze the impact of PhenoAgeAccel on the risk from baseline to dementia onset and death. [3] We reconstructed the coefficients for the ten variables needed to calculate the Phenoage using the R package "BigAge" based on the NHANES III data and calculated the new PhenoAgeAccel for participants in the UK Biobank then repeated the main analyses to assess the robustness [39]. [4] We imputed the missing control variables by multiple imputation. [5] We categorized *APOE* genotypes into 0 (ε2/ε2, ε2/ε3, ε3/ε3), 1 (ε3/ε4, ε2/ε4), and 2 (ε4/ε4) according to the number of *APOE* ε4 alleles and repeated the analysis of the interaction between *APOE* genotypes and PhenoAgeAccel on the risk of all-cause dementia. [6] To ensure the interactions in different gender and age groups were robust, we stratified participants according to gender and whether they were younger than 65 years and repeated the analysis of the interactions between *APOE* genotype and PRS with PhenoAgeAccel on the risk of all-cause dementia.

All statistical analyses were conducted using the R software (version 4.3.1), and a two-tailed *P*-value less than 0.05 was considered statistically significant.

Results

Baseline characteristics of participants

Of the 200,731 participants who met the inclusion and exclusion criteria, the mean chronological age was 60.13 ± 5.39 years, the mean duration of follow-up was 12.65 ± 0.78 years, 97,256 (48.45%) participants were male, and 4508 (2.25%) participants developed dementia during follow-up (Additional file 1: Table S4). During follow-up, individuals who suffered from dementia had higher PhenoAgeAccel, PRS, and *APOE* genetic risk than those without dementia ($P < 0.001$).

Table 1. Associations of the PhenoAgeAccel with the risk of dementia[a]

Variables	All-cause dementia		Young-onset dementia (YOD)		Late-onset dementia (LOD)	
	Hazard ratio (95% *CI*)	*P* value	Hazard ratio (95% *CI*)	*P* value	Hazard ratio (95% *CI*)	*P* value
PhenoAgeAccel (Per 5-year increase)	1.051 (1.025, 1.077)	<0.0001[b]	1.254 (1.139, 1.380)	<0.0001[b]	1.041 (1.015, 1.069)	0.0018[b]
PhenoAgeAccel (Quartile)						
Quartile 1	1 (Reference)	NA[c]	1 (Reference)	NA[c]	1 (Reference)	NA[c]
Quartile 2	1.003 (0.920, 1.093)	0.9511	1.612 (0.929, 2.796)	0.0892	0.993 (0.910, 1.084)	0.8720
Quartile 3	0.955 (0.874, 1.043)	0.3046	1.721 (0.996, 2.974)	0.0516	0.942 (0.862, 1.031)	0.1978
Quartile 4	1.145 (1.050, 1.249)	0.0023[b]	2.289 (1.340, 3.911)	0.0024[b]	1.124 (1.030, 1.229)	0.0091[b]
PhenoAgeAccel (Binary)						
Biologically younger	1 (Reference)	NA[c]	1 (Reference)	NA[c]	1 (Reference)	NA[c]
Biologically older	1.069 (1.004, 1.138)	0.0384[b]	1.046 (1.036, 2.059)	0.0306[b]	1.024 (0.961, 1.092)	0.4591

[a] Reporting the corresponding hazard ratios (*HR*s) and 95% confidence interval (*CI*) in the Cox proportional-hazards regression adjusted for age, gender, education, Townsend deprivation index, BMI, smoking status, alcohol intake, physical activity, social isolation, healthy diet score, hearing problem, depression, diabetes, cardiovascular diseases, cancer, cataract, any other serious medical and family history of dementia

[b] *P*-values were statistically significant (< 0.05)

[c] NA indicated not applicable

Associations of the PhenoAgeAccel with the risk of dementia

In the fully adjusted model, each 5-year increase in PhenoAgeAccel increased the extra risk of all-cause dementia, YOD, and LOD by 5.1% (95% *CI*: 2.5%, 7.7%), 25.4% (95% *CI*: 13.9%, 38.0%), and 4.1% (95% *CI*: 1.5%, 6.9%), respectively (Table 1). In dose–response analysis, Additional file 1: Fig. S1 shows the non-linear positive association between PhenoAgeAccel and the risk of dementia, which illustrates a rapidly increasing risk of dementia with extremely accelerated biological aging. In addition, participants who were in the highest quartile of PhenoAgeAccel had a higher risk of dementia onset compared to participants in the lowest quartile of PhenoAgeAccel (all-cause dementia *HR*: 1.145 (95% *CI*: 1.050, 1.249); YOD *HR*: 2.289 (95% *CI*: 1.340, 3.911); LOD *HR*: 1.124 (95% *CI*: 1.030, 1.229)) (Table 1). Compared to participants who were biologically younger, those who were biologically older had a higher risk of all-cause dementia and YOD (all-cause dementia *HR*: 1.069 (95% *CI*: 1.004, 1.138); YOD *HR*: 1.046 (95% *CI*: 1.036, 2.059)) (Table 1). In males and those younger than 65 years, the effects of biologically older on all-cause dementia remained significant, with *HR*s of 1.125 (95% *CI*: 1.035, 1.223) and 1.318 (95% *CI*: 1.090, 1.593), respectively. Furthermore, similar effects were recorded in sensitivity analyses by replacing biological age indicators (Additional file 1: Table S5), considering competing mortality risk (Additional file 1: Table S6) and recalculating new PhenoAgeAccel (Additional file 1: Table S7).

Associations of APOE-ε4-related genetic risk and the polygenetic risk score with the risk of dementia

During follow-up, participants with dementia had a significantly higher *APOE*-ε4-related genetic risk and the PRS than those without dementia (Additional file 1: Table S4). In the Cox proportional hazards model, positive associations were observed between *APOE*-ε4-related genetic risk with the risk of dementia (*HR*: 2.714 (95% *CI*: 2.559, 2.879)). Moreover, compared to participants with low dementia PRS, participants with intermediate dementia PRS and high dementia PRS had a higher risk of dementia onset (intermediate dementia PRS *HR*: 1.186 (95% *CI*: 1.098, 1.281); high dementia PRS *HR*: 1.582 (95% *CI*: 1.456, 1.720)).

Joint effects and interactions of the PhenoAgeAccel and APOE ε4-related genetic risk

The risk of dementia onset was associated with PhenoAgeAccel and *APOE* ε4-related genetic risk in dose–response manner. Among individuals with low *APOE* ε4-related genetic risk, the risk of dementia elevated with the increases in PhenoAgeAccel. Inconsistently, the association of PhenoAgeAccel with dementia did not increase linearly in individuals at the high *APOE* ε4-related genetic risk. To be specific, individuals who were in quartile 2 in terms of PhenoAgeAccel had the highest risk of incident dementia compared with individuals who were in quartile 1 (all-cause dementia *HR*: 3.190, 95% *CI* (2.822, 3.608); YOD *HR*: 4.500, 95% *CI* (2.100, 9.642); LOD *HR*: 3.177, 95% *CI* (2.805, 3.599)) (Fig. 2A).

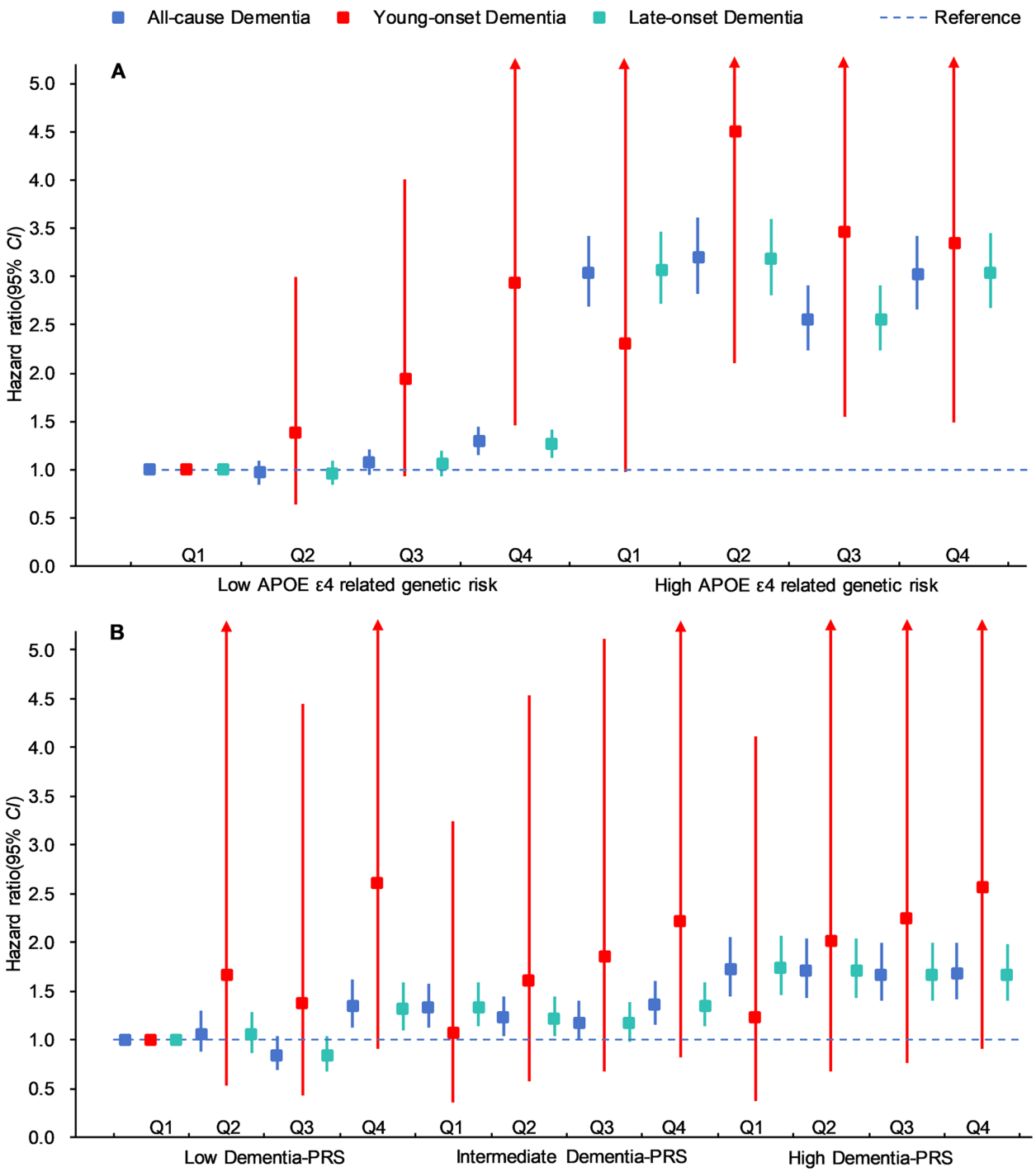

Fig. 2 Joint effects of the PhenoAgeAccel (by population quartiles) with the genetic risk on dementia risk. **A** The joint effects of the PhenoAgeAccel and *APOE* ε4-related genetic risk on the risk of dementia. **B** The joint effects of the PhenoAgeAccel and the PRS on the risk of dementia. The *APOE* ε4-related genetic risk was divided into high *APOE* ε4-related genetic risk (ε3/ε4, ε2/ε4, ε4/ε4) and low *APOE* ε4-related genetic risk (ε2/ε2, ε2/ε3, ε3/ε3) based on the number of *APOE* ε4 alleles. The PRS were categorized into low (≤ quartile 1), intermediate (quartile 1 to quartile 3), and high (≥ quartile 3) based on the quartile distribution of the PRS in the entire sample. Reporting the corresponding hazard ratios (*HR*s) and 95% confidence interval (*CI*s) in the Cox proportional hazards regression adjusted for age, gender, education, Townsend deprivation index, BMI, smoking status, alcohol intake, physical activity, social isolation, healthy diet score, hearing problem, depression, diabetes, cardiovascular diseases, cancer, cataract, and any other serious medical and family history of dementia

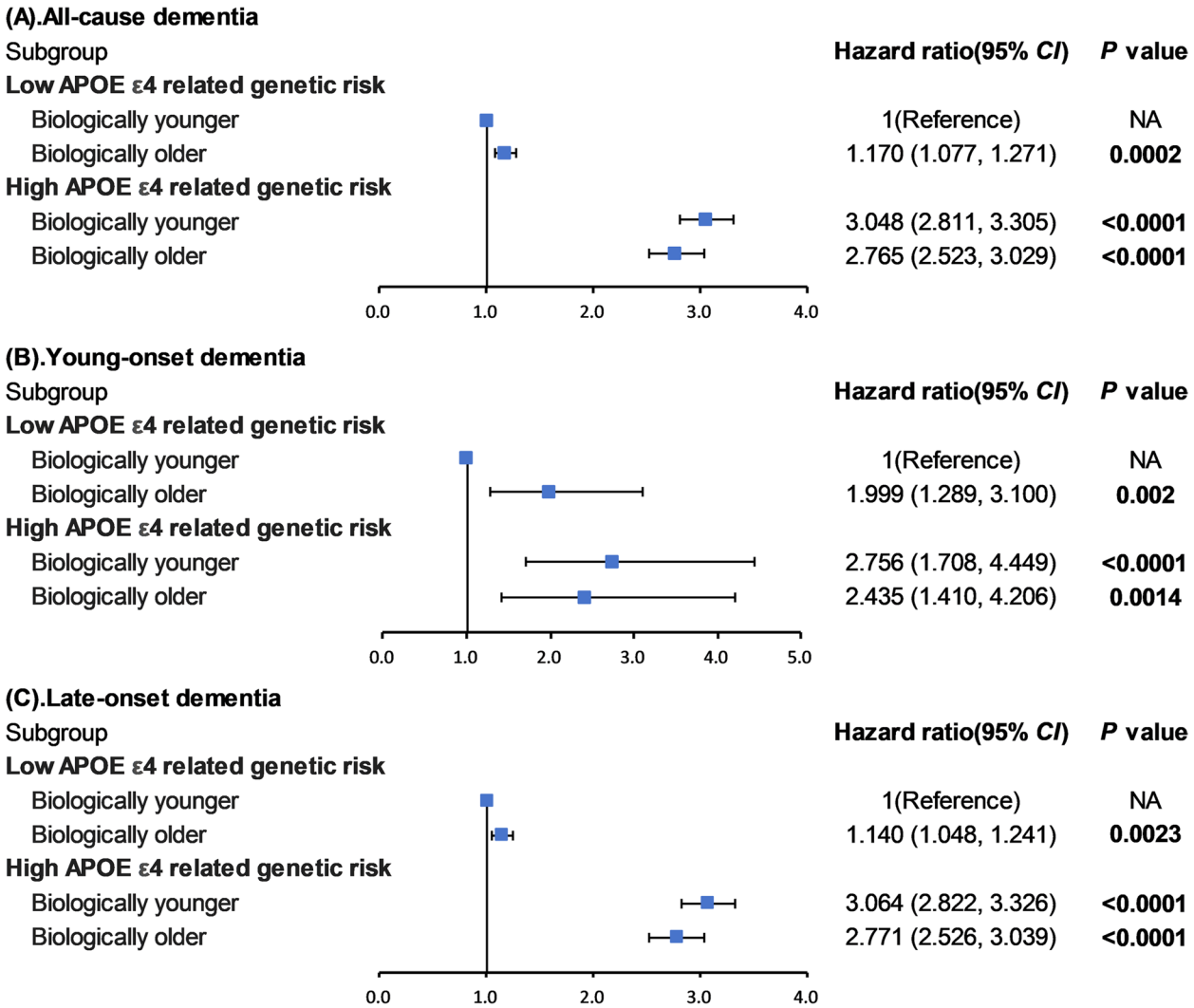

Fig. 3 Joint effects of the binary PhenoAgeAccel and *APOE* ε4-related genetic risk on dementia risk. **A** The risk of all-cause dementia onset. **B** The risk of young-onset dementia. **C** The risk of late-onset dementia. The *APOE* ε4-related genetic risk was divided into high *APOE* ε4-related genetic risk (ε3/ε4, ε2/ε4, ε4/ε4) and low *APOE* ε4-related genetic risk (ε2/ε2, ε2/ε3, ε3/ε3) based on the number of *APOE* ε4 alleles. Reporting the corresponding hazard ratios (*HRs*) and 95% confidence interval (*CIs*) in the Cox proportional hazards regression adjusted for age, gender, education, Townsend deprivation index, BMI, smoking status, alcohol intake, physical activity, social isolation, healthy diet score, hearing problem, depression, diabetes, cardiovascular diseases, cancer, cataract, and any other serious medical and family history of dementia

Meanwhile, Fig. 3 showed the joint effect of the binary PhenoAgeAccel and *APOE* ε4-related genetic risk on the risk of dementia. Participants with biologically older and high *APOE* ε4-related genetic risk had the extra risk of dementia onset, compared to participants with biologically younger and low *APOE* ε4-related genetic risk (all-cause dementia *HR*: 2.765 (95% *CI*: 2.523, 3.029); YOD *HR*: 2.435 (95% *CI*: 1.410, 4.206); LOD *HR*: 2.771 (95% *CI*:2.526, 3.039)); however, these extra risks were relative less than participant with biologically younger and high *APOE* ε4-related genetic risk. Similar associations remain consistent when PhenoAgeAccel was replaced by a new indicator (Additional file 1: Fig. S2, Additional file 1: Fig. S3), when the *APOE* ε4-related genetic risk was categorized into three levels (Additional file 1: Fig. S3, Additional file 1: Fig. S4), and when the population was stratified by age (Additional file 1: Fig. S3, Additional file 1: Fig. S5) and gender (Additional file 1: Fig. S3, Additional file 1: Fig. S6).

The estimated additive interaction effect suggested that biologically older may attenuate the positive effect of *APOE* ε4-related genetic risk on the risk of all-cause dementia and LOD. Specifically, when high *APOE* ε4-related genetic risk and biologically older

Table 2. Relative Excess Risk and Attributable Proportion between PhenoAgeAccel with *APOE* ε4 related genetic risk[a]

Variables	High *APOE* ε4 related genetic risk	
	***RERI* (95%*CI*)[b]**	***AP* (95%*CI*)[c]**
All-cause dementia		
Biologically older	-0.454 (-0.728, -0.179)[d]	-0.164(-0.269,-0.059)[d]
Young-onset dementia		
Biologically older	-1.320 (-2.969, 0.329)	-0.542 (-1.324, 0.240)
Late-onset dementia		
Biologically older	-0.434 (-0.713, -0.155)[d]	-0.157 (-0.263, -0.050)[d]

[a] Reporting the Relative Excess Risk due to Interaction (*RERI*), Attributable Proportion due to interaction (*AP*), and the corresponding 95%*CI*s in the Cox proportional-hazards regression adjusted for age, gender, education, Townsend deprivation index, BMI, smoking status, alcohol intake, physical activity, social isolation, healthy diet score, hearing problem, depression, diabetes, cardiovascular diseases, cancer, cataract, any other serious medical and family history of dementia

[b] *RERI* indicated the Relative Excess Risk due to Interaction

[c] *AP* indicated Attributable Proportion due to Interaction

[d] *P*-values were statistically significant (< 0.05)

coexisted, the risk of all-cause dementia decreased by 0.454 (*RERI*: − 0.454, 95% *CI*: − 0.728, -0.179), and the risk of LOD decreased by 0.434 (*RERI*: − 0.434, 95% *CI*: − 0.713, − 0.155) compared to when each factor was present alone (Table 2). The interaction accounts for 16.4% (*AP*: − 0.164, 95% *CI*: − 0.269, − 0.059) and 15.7% (*AP*: − 0.157, 95% *CI*: − 0.263, − 0.050) of the total risk, respectively (Table 2). The significant additive interaction effect on all-cause dementia was also found in males. Other sensitivity analyses demonstrated the robustness of these results (Additional file 1: Table S8). In addition, the significant multiplicative interactions were observed in models with all three types dementia as outcomes (all-cause dementia: $P < 0.001$; young-onset dementia: $P = 0.018$; late-onset dementia: $P < 0.001$).

sJoint effects and interactions of the PhenoAgeAccel and the polygenetic risk score on the risk of dementia

In the joint effects analysis, although the changes of PRS and PhenoAgeAccel on the risk of YOD were insignificant (Figs. 2B and 4B), the joint effects of PRS and PhenoAgeAccel on the risk of all-cause dementia and LOD showed statistically significant dose–response relationship. Figure 2B shows that the risk of dementia did not completely increase with PhenoAgeAccel in the individuals with intermediate-PRS and high-PRS. Meanwhile, referring to low dementia PRS and biologically younger, the risk of all-cause dementia and LOD increased by 58.7% (*HR*: 1.587, 95% *CI*: 1.404, 1.793) and 57.9% (*HR*: 1.579, 95% *CI*: 1.394, 1.788), respectively, in the high dementia PRS and biologically older group (Fig. 4A, C), which both relative lower than in the biologically younger. After recalculating the PhenoAgeAccel and stratifying by age and gender, similar patterns of associations were observed (Additional file 1: Fig. S7, Additional file 1: Fig. S8, Additional file 1: Fig. S9, Additional file 1: Fig. S10).

We also analyzed the interaction effect of PRS and PhenoAgeAccel on the risk of dementia onset. The results indicated that the multiplicative and additive interactions between intermediate PRS and PhenoAgeAccel on the risk of all-cause dementia, YOD, and LOD were insignificant, whereas the interactions between high PRS and PhenoAgeAccel on the risk of all-cause dementia (*RERI*: − 0.255, 95% *CI*: − 0.486, − 0.024; *AP*: − 0.161, 95% *CI*: − 0.308, − 0.015; *P* value for multiplicative interaction = 0.022) and LOD (*RERI*: − 0.272, 95% *CI*: − 0.508, − 0.036; *AP*: − 0.172, 95% *CI*: − 0.323, − 0.022; *P* value for multiplicative interaction = 0.023) were statistically significant (Table 3). This study failed to find the robust additive interactions between high PRS and PhenoAgeAccel in sensitivity analysis (Additional file 1: Table S9).

Discussion

In this study, the effect of PhenoAgeAccel, a novel measurement of biological aging, on the risk of dementia was assessed, and for the first time, we delved into the effects on young-onset and late-onset dementia, respectively. The results suggested that PhenoAgeAccel was significantly related to an increased risk of dementia, as well as young-onset and late-onset dementia, which were robust to the varied indicators for accelerated aging. Furthermore, we also found that PhenoAgeAccel modified the effects of genetic risk (*APOE* ε4 and PRS) on dementia, and the interacted effects between PhenoAgeAccel and genetic risk were demonstrated both on the multiplicative scale and additive scale, which provided insights that were more valuable to the development of public health interventions for dementia.

Molecular hallmarks can reflect biological aging. Therefore, a series of biomarkers have been used to estimate biological age and measure biological aging, for example, "aging clocks" derived from transcriptomic, metabolomic, proteomic, and epigenetic data and telomere length. Consistent with our study, in the Framingham Heart Study Offspring Cohort, Karen et al. found that accelerated DunedinPACE, calculated from Epigenome, increased the risk of developing dementia with an *HR* of 1.27 [40]. On the contrary, another study, in 486 monozygotic twins, found no evidence for the association of blood DNAmAge with declined cognitive abilities [41]. Recently, great enthusiasm has also been paid for Phenoage, a novelty measurement of biological aging, as a potential risk for dementia due to its easy availability.

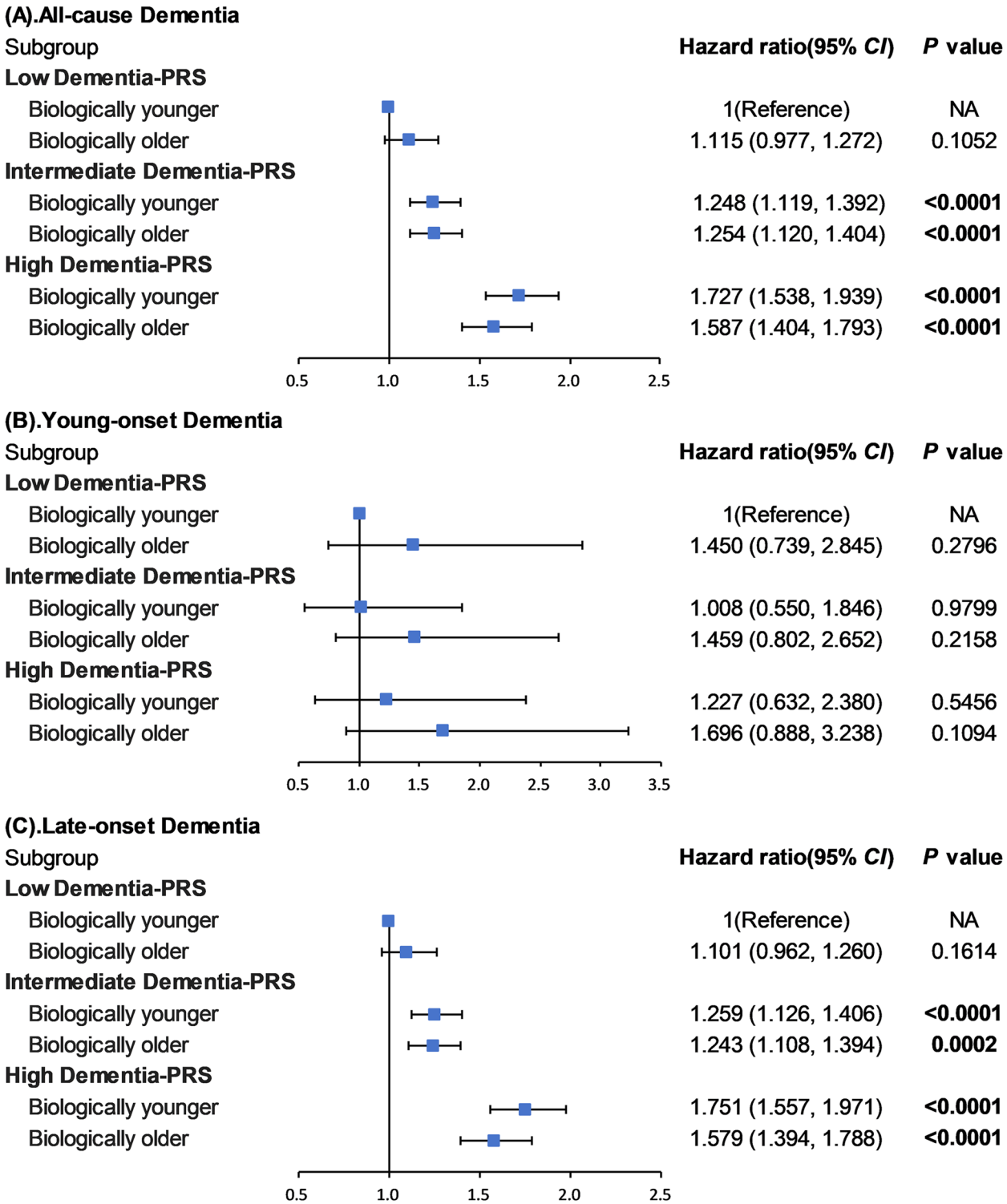

Fig. 4 Joint effects of the binary PhenoAgeAccel and the polygenetic risk score (PRS) on dementia risk. **A** The risk of all-cause dementia onset. **B** The risk of young-onset dementia. **C** The risk of late-onset dementia. The PRS were categorized into low (≤ quartile 1), intermediate (quartile 1 to quartile 3), and high (≥ quartile 3) based on the quartile distribution of the PRS in the entire sample. Reporting the corresponding hazard ratios (*HR*s) and 95% confidence interval (*CI*s) in the Cox proportional hazards regression adjusted for age, gender, education, Townsend deprivation index, BMI, smoking status, alcohol intake, physical activity, social isolation, healthy diet score, hearing problem, depression, diabetes, cardiovascular diseases, cancer, cataract, and any other serious medical and family history of dementia

Table 3. Relative Excess Risk and Attributable Proportion between PhenoAgeAccel with polygenetic risk score (PRS)[a]

Variables	Intermediate PRS		High PRS	
	RERI (95%*CI*)[b]	*AP* (95%*CI*)[c]	*RERI* (95%*CI*)[b]	*AP* (95%*CI*)[c]
All-cause dementia				
Biologically older	-0.111 (-0.288, 0.067)	-0.090 (-0.232, 0.052)	-0.255 (-0.486, -0.024)[d]	-0.161 (-0.308, -0.015)[d]
Young-onset dementia				
Biologically older	0.005 (-0.960, 0.970)	0.004 (-0.682, 0.689)	0.026 (-1.149, 1.201)	0.015 (-0.673, 0.704)
Late-onset dementia				
Biologically older	-0.118 (-0.298, 0.063)	-0.096 (-0.242, 0.049)	-0.272 (-0.508, -0.036)[d]	-0.172 (-0.323, -0.022)[d]

[a] Reporting the Relative Excess Risk due to Interaction (*RERI*), Attributable Proportion due to interaction (*AP*), and the corresponding 95%*CI*s in the Cox proportional-hazards regression adjusted for age, gender, education, Townsend deprivation index, BMI, smoking status, alcohol intake, physical activity, social isolation, healthy diet score, hearing problem, depression, diabetes, cardiovascular diseases, cancer, cataract, any other serious medical and family history of dementia

[b] *RERI* indicated the Relative Excess Risk due to Interaction

[c] *AP* indicated Attributable Proportion due to Interaction

[d] *P*-values were statistically significant (< 0.05)

However, research on the relationship between PhenoAgeAccel and dementia has still not yielded consistent results [42, 43]. Two recent reviews focused on biological aging in dementia claimed that there was insufficient evidence supporting accelerated biological aging was related to an increase in the risk of dementia [10, 13]. The limited sample sizes of previous research, about hundreds to thousands, have prevented more robust results. To our knowledge, this is the first study, based on a large cohort survey, to assess the key role of PhenoAgeAccel in the development of dementia. To obtain robust estimates, we performed several sensitivity analyses. Stratifying by age, the significant association only observed in those younger than 65 years old. Previous studies suggested that biological age increased slower than chronological age throughout the human life cycle, especially in older adults [44], which could explain the above result that the effect of PhenoAgeAccel tended to insignificant in the older age group. In addition, the biological age, calculated by molecular biomarkers, of males was greater than that of females support our finding that the significant effect of PhenoAgeAccel was observed in males [37]. This study further classified dementia into two subtypes, young-onset and late-onset dementia, which did not change the significant associations. Meanwhile, PhenoAgeAccel was initially used to predict longevity and mortality [45]. Failure to identify the dying population from individuals with undiagnosed dementia may introduce bias in Cox models, so we constructed a competing risk model to re-estimate the risk of dementia, with death as a competing risk event. The effects of PhenoAgeAccel remained significant. Moreover, considering the bias that may introduce due to the calculation of PhenoAgeAccel, we re-estimated the model to calculate a new PhenoAgeAccel and replaced it with leukocyte telomere length, which is a complex trait associated with biological aging [46]. Consistent relationships were observed for the new PhenoAgeAccel and leukocyte telomere length. These reliable results demonstrated that a series of personalized, targeted interventions could be used to prevent the occurrence of dementia by identifying adults with accelerated biological aging. Various mechanisms supported that accelerated biological aging was implicated in the incidence of dementia. As the organism ages biologically, concentrations of tumor necrosis factor, C-reactive protein, interleukin 6, and other inflammatory molecules create a pro-inflammatory environment. The pro-inflammatory led to an increase in the risk of dementia [47]. In addition, the disorder of adipokine expression appeared with aging could lead to obesity, which in turn was associated with dementia [48]. Furthermore, biological aging indicated the process of cellular senescence, which was usually accompanied by DNA damage, telomere shortening, and telomerase insufficiency. All of these might contribute to the development of dementia through lymphopenia-induced T cell proliferation and re-modeling of the T cell repertoire [49].

This study indicated that genetic factors (*APOE* ε4 and PRS) played key roles in the development of dementia, which has been suggested by compelling evidence [14, 50]. To identify high-risk individuals, previous studies also examined whether biological aging modified the effects of genetic risk on rheumatoid arthritis and chronic respiratory diseases [51, 52]. To our knowledge, our study is the first time to assess the moderating role of biological aging in the effects of genetic susceptibility on dementia as well as young-onset and late-onset dementia. Interestingly, our findings suggested that for individuals with high genetic risk, the risk of dementia was not increased by PhenoAgeAccel completely. Specifically, the

individuals at highest risk of dementia were those with high genetic risk and were biologically younger, not biologically older. Furthermore, this study found the effect of the negative interaction between PhenoAgeAccel and genetic susceptibility, both *APOE* ε4 and dementia-related PRS, on the risk of dementia. One previous study evaluated the association between *APOE* ε4 and AD, and this association differed according to chronological age, with the strongest effect at 65–70 years [53]. The highest risk of dementia was not observed in the individuals with the highest genetic risk and oldest age, which was similar to our findings. Furthermore, considering the chronological age may bias the moderating effects of biological aging, we not only adjusted for the chronological age in all models but also classified dementia into young-onset and late-onset dementia according to the onset of dementia. Similar estimates were found in a study with late-onset dementia as an outcome. However, a significant additive joint effect was not observed in the studies with young-onset dementia, which may be due to a limited number of young-onset dementia events. In the age-stratified analysis, the negative interaction between biological aging and *APOE* ε4 on the risk of dementia remained significant. Previous studies suggested that a decline in the expression of genes occurred as the DNA methyltransferase state was enhanced [54]. Thus, as an indicator of DNA methyltransferase, PhenoAgeAccel increases may lead to decreases in the expression levels of genes, including *APOE* and other dementia-related genes, and then a negative interaction was observed. Furthermore, Kuo et al. suggested the genetic factors only could explain 0.50% of the variance in Phenoage [55], which indicated accelerated biological aging was more influenced by environmental components rather than heredity. The bias that may be introduced due to the potential relationship between genetic factors and PhenoAgeAccel was limited. This robust finding suggests that targeting individuals with high genetic susceptibility to dementia through anti-aging, such as senolytic medicine, is not enough and that other interventions should be implemented.

The present study also has several limitations. First, these findings were obtained using the UK Biobank; all the participants were white; more studies should be further assessed to determine whether the results of this study can be generalized to more varied populations. Second, although the PhenoAgeAccel was easier calculated by blood marker, and we varied the calculation of it and replaced it with leukocyte telomere length, all the measurements of accelerated biological aging in this study may not be accurate enough to characterize dementia. Third, since our study was observational, we failed to establish a direct causal relationship between accelerated biological aging and dementia. Fourth, PhenoAgeAccel was calculated only at baseline. Thus, we failed to evaluate the effect of biological age changes on the risk of dementia. Finally, despite controlling for several confounding factors and performing varied sensitivity analyses, unobserved confounders, selection bias, and measurement errors could have biased our estimates.

Conclusions

In conclusion, this study verified that the accelerated biological aging measured by PhenoAgeAccel was consistently related to an increased risk of dementia and the two subtypes, young-onset dementia and late-onset dementia. Furthermore, PhenoAgeAccel may moderate the effects of genetic factors on dementia. Considering the easy and effective availability of PhenoAgeAccel, it could be utilized as an innovative clinical composite biomarker to guide precise prevention for dementia. Interventions to slow biological aging may be more essential for individuals with low genetic susceptibility to dementia. Conversely, for individuals with high genetic susceptibility, more interventions need to be implemented besides just anti-aging.

Abbreviations

PhenoAgeAccel	Phenotypic age acceleration
APOE	Apolipoprotein E
PRS	Polygenic risk scores
HR	The Hazard ratio
95% *CI*	95% Confidence intervals
RERI	Relative excess risk due to interaction
AP	Attributable proportion due to interaction
Phenoage	Phenotypic age
SNPs	Single nucleotide polymorphisms
STROBE	The Strengthening the Reporting of Observational Studies in Epidemiology
NHANES III	The Third National Health and Nutrition Examination Survey
YOD	Young-onset dementia
LOD	Late-onset dementia

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-024-03640-4.

Additional file 1: Table S1 38 genetic variants included in the polygenic risk score (PRS) of dementia. Table S2 Dementia code list generated by UK Biobank Outcome Adjudication Group. Table S3 Type and Description of Study Covariates. Table S4 The distribution of participants' baseline characteristics. Table S5 The associations of the leukocyte telomere length with the risk of dementia (fully adjusted model)a. Table S6 The associations of the PhenoAgeAccel with the risk of dementia in multi-state competing risks model (fully adjusted model)a. Table S7 The associations of the new PhenoAgeAccel with the risk of dementia (fully adjusted model) a. Table S8 Relative Excess Risk (RERI) and Attributable Proportion (AP) for additive interaction between PhenoAgeAccel and APOE ε4-related genetic risk on the risk of all-cause dementia onset*. Table S9 Relative Excess Risk (RERI) and Attributable Proportion (AP) for additive interaction between PhenoAgeAccel and the polygenetic risk score (PRS) on the risk of all-cause dementia onset*. Fig. S1 The nonlinear associations between PhenoAgeAccel and the risk of dementia by restricted cubic spline. Fig.

S2 The joint effects of the new PhenoAgeAccel (by quartiles) and APOE ε4-related genetic risk on the risk of all-cause dementia. Fig. S3 The joint effects of the binary PhenoAgeAccel and APOE ε4-related genetic risk on the risk of all-cause dementia onset. Fig. S4 The joint effects of the PhenoAgeAccel (by quartiles) and multi-class APOE ε4-related genetic risk on the risk of all-cause dementia onset. Fig. S5 The joint effects of the PhenoAgeAccel (by quartiles) and APOE ε4-related genetic risk on the risk of all-cause dementia onset stratified by age. Fig. S6 The joint effects of the PhenoAgeAccel (by quartiles) and APOE ε4-related genetic risk on the risk of all-cause dementia onset stratified by gender. Fig. S7 The joint effects of the new PhenoAgeAccel (by quartiles) and the polygenetic risk score (PRS) on the risk of all-cause dementia onset. Fig. S8 The joint effects of the PhenoAgeAccel (by quartiles) and the polygenetic risk score (PRS) on the risk of all-cause dementia onset stratified by age. Fig. S9 The joint effects of the PhenoAgeAccel (by quartiles) and the polygenetic risk score (PRS) on the risk of all-cause dementia onset stratified by gender. Fig. S10 The joint effects of the binary PhenoAgeAccel and the polygenetic risk score (PRS) on the risk of all-cause dementia onset.

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Authors' contributions
Concept and design: Zirong Ye, Haoxiang Lang, Xiaochun Chen, Jiawei Xin; Accessed and verified the data: Zirong Ye, Haoxiang Lang, Bihao Peng; Software and Validation: Zirong Ye, Zishan Xie, Siyu Duan, Bihao Peng; Drafting of the manuscript: Zirong Ye, Haoxiang Lang, Zishan Xie; Critical review of the manuscript for important intellectual content: All authors; Statistical analysis: Zirong Ye, Haoxiang Lang, Zishan Xie, Siyu Duan; Obtained funding: Ya Fang, Jiawei Xin; Supervision: Xiaochun Chen, Ya Fang, Jiawei Xin. All authors read and approved the final manuscript.

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Availability of data and materials
The dataset supporting the conclusions of this article is available in the UK Biobank repository (Application ID: 177,200), [unique persistent identifier and hyperlink to dataset in https://www.ukbiobank.ac.uk/].

Declarations

Ethics approval and consent to participate
All participants have provided informed written consent, and the UK Biobank had ethical approval from the North West Multicentre Research Ethics Committee (The Research Ethics Committee (REC) reference number: 16/NW/0274, https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/uk-biobank-a-large-scale-prospective-epidemiological-resource/). Additional ethical clearance was not required for researchers when using the UKB data.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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