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# Association of accelerated phenotypic aging, genetic risk, and lifestyle with progression of type 2 diabetes: a prospective study using multi-state model

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## Abstract

**Background** Aging is a major risk factor for type 2 diabetes (T2D), but individuals of the same chronological age may vary in their biological aging rate. The associations of Phenotypic Age Acceleration (PhenoAgeAccel), a new accelerated biological aging indicator based on clinical chemistry biomarkers, with the risk of dynamic progression remain unclear. We aimed to assess these associations and examine whether these associations varied by genetic risk and lifestyle.

**Methods** We conducted a prospective cohort study that included 376,083 adults free of T2D and diabetes-related events at baseline in UK Biobank. PhenoAgeAccel > 0 and ≤ 0 were defined as biologically older and younger than chronological age. The outcomes of interest were incident T2D, diabetic complications, and mortality. Hazard ratios (HRs) with 95% confidence intervals (CIs) and population attributable fractions (PAFs) for these associations were calculated using multi-state model.

**Results** During a median follow-up of 13.7 years, 17,615 participants developed T2D, of whom, 4,524 subsequently developed complications, and 28,373 died. Being biologically older was associated with increased risks of transitions from baseline to T2D (HR 1.77, 95% CI 1.71–1.82; PAF 24.8 [95% CI 23.5–26.2]), from T2D to diabetic complications (1.10, 1.04–1.17; 4.4 [1.4–7.4]), from baseline to all-cause death (1.53, 1.49–1.57; 17.6 [16.6–18.6]), from T2D to all-cause death (1.14, 1.03–1.26; 7.4 [1.8–13.0]), and from diabetic complications to all-cause death (1.32, 1.15–1.51; 15.4 [7.5–23.2]) than being biologically younger. Additionally, participants with older biological age and high genetic risk had a higher risk of incident T2D (4.76, 4.43–5.12; 18.2 [17.5–19.0]) than those with younger biological age and low genetic risk. Compared with participants with younger biological age and healthy lifestyle, those with older biological age and unhealthy lifestyle had higher risks of transitions in the T2D trajectory, with HRs and PAFs ranging from 1.34 (1.16–1.55; 3.7 [1.8–5.6]) to 5.39 (5.01–5.79; 13.0 [12.4–13.6]).

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**Conclusions** PhenoAgeAccel was consistently associated with an increased risk of all transitions in T2D progression. It has the potential to be combined with genetic risk to identify early T2D incidence risk and may guide interventions throughout T2D progression while tracking their effectiveness.

**Keywords** Phenotypic aging, Type 2 diabetes, Diabetic complication, Multi-state model, Genetic risk, Healthy lifestyle

## Background

Type 2 diabetes (T2D) affects approximately 500 million adults worldwide and is projected to reach 700 million by 2045 [1, 2]. More than half of T2D patients develop diabetic complications later in life, which are the leading causes of disability and mortality [3–6]. Assessing the risk of T2D progression in the life course is crucial for timely and effective prevention and intervention. Aging is widely recognized as a primary risk factor for T2D [7]. However, individuals of the same chronological age may vary in their aging rate, resulting in different susceptibility to disease and death [8]. Therefore, it is essential to explore the role of biological aging in the incidence and development of T2D. Differentiating aging in individuals of the same chronological age, particularly in early life, may help identify high-risk subpopulations and aid in prevention to reduce the global burden of T2D [9].

Phenotypic age acceleration (PhenoAgeAccel) is a valuable measurement of biological age acceleration using clinical biomarkers, representing various aging characteristics at the cellular and intracellular levels. Compared to previous indicators based on omics data for measuring biological age, PhenoAgeAccel is easier to obtain and calculate. Multiple studies have demonstrated that PhenoAgeAccel has a strong predictive capability over chronological age and clinical applicability in capturing morbidity and mortality across diverse populations [10, 11]. Previous studies have primarily found that PhenoAgeAccel was associated with a single transition in T2D trajectory [12–14]. However, it remained unknown whether PhenoAgeAccel has an impact on the entire dynamic progression of T2D, including transitions from T2D-free (baseline) to T2D, then to diabetic complications, and finally to death [15]. Understanding the varying impacts of PhenoAgeAccel on the risks of these transitions can enhance dynamic predictions of T2D progression, thereby preventing or delaying disease progression, which is significant for alleviating the global burden of diabetes [16]. To address this gap and promote the clinical application of PhenoAgeAccel, we explore the role of PhenoAgeAccel in all transitions within the T2D trajectory using multi-state models, an extension of the traditional Cox proportional hazards model, allowing for the simultaneous analysis of multiple subsequent or competing disease pathways and assessing the differential impacts of risk factors at various stages

of transition, thereby improving the overall prediction of event risk [17].

Notably, PhenoAgeAccel is also influenced by various genetic and environmental factors [8]. Studies have shown that single nucleotide polymorphisms (SNPs) associated with PhenoAgeAccel are enriched in biological processes involving immunity and inflammation, which are closely related to T2D [18, 19]. Multi-omics research indicates that genetic risk may play a key role in the pathogenesis of T2D [20–22]. However, the joint effect between PhenoAgeAccel and genetic risk on the onset of T2D remains unclear. Additionally, studies have found that healthy behaviors can explain approximately 10% of the variance in PhenoAgeAccel, suggesting that PhenoAgeAccel may be influenced by modifiable lifestyle [23]. It is necessary to investigate the joint effects of PhenoAgeAccel and lifestyle to provide new insights into the potential mechanisms through which a healthy lifestyle may contribute to reducing adverse health outcomes.

Using data from the UK biobank, we aimed to comprehensively assess the associations of PhenoAgeAccel with transitions from baseline to incident T2D, then to diabetic complications, and finally to death in the UK Biobank as well as whether those associations differed by lifestyle and genetic risk.

## Methods

### Study design

The UK Biobank is a large prospective cohort study, recruiting over 0.5 million UK residents aged 37–73 years between 2006 and 2010 [24]. At recruitment, each participant completed a touch-screen questionnaire about demographics, socioeconomic status, and lifestyle factors. Physical measurements and biological biomarkers were also collected. After excluding participants who had withdrawn consent ( $n=191$ ), those with type 2 diabetes and diabetes-related events at baseline and those with occurrences of diabetes-related events before T2D diagnosis ( $n=61,579$ ), and those with missing information on PhenoAge ( $n=64,588$ ), 376,083 participants were included (Additional file 1: Fig. S1).

### Assessment of phenotypic age acceleration

PhenoAgeAccel indicates whether a person appears biologically older or younger than expected. PhenoAgeAccel

was calculated based on chronological age and nine biomarkers (including albumin, creatinine, glucose, [log] C-reactive protein [CRP], lymphocyte percent, mean cell volume, red blood cell distribution width, alkaline phosphatase, and white blood cell count) [18]. A negative value indicated phenotypic age less than chronological age. Details of the calculation are available in the Additional file 1. PhenoAgeAccel was classified into biological old ( $<0$ ) and biological youth ( $\geq 0$ ). Additionally, we categorized PhenoAgeAccel into three groups based on quartiles: low (bottom quartiles), medium (quartiles 2–3), and high (top quartiles).

### Follow-up and ascertainment of outcomes

The outcomes of interest were incident T2D, diabetic complication, and all-cause and cause-specific mortality, ascertained from self-reported information, hospital admission data, and death records. Diabetes complications were defined as the co-presence of T2D and at least one of the following diseases: diabetic eye diseases, diabetic kidney diseases, diabetic neuropathy diseases, cardiovascular diseases, and peripheral vascular diseases [25]. The detailed definition of outcomes is presented in Additional file 1: Table S1–S2. All the participants were followed from their enrollment date until the date of the outcome of interest, death, loss to follow-up, or the study censoring date (31 October 2022 for England, 31 August 2022 for Scotland, and 31 May 2022 for Wales for hospital inpatient data, and 30 November 2022 for death data), whichever occurred first.

### Assessment of covariates

The covariates adjustment set was determined by a directed acyclic graph (Additional file 1: Fig. S2) [26], including sociodemographic factors, lifestyle behaviors, and health status. The assessment and categories of covariates are displayed in Additional file 1: Table S3. Missing data on covariates were replaced using multiple imputation by chained equations [27]. Participants with imputed data exhibited similar baseline characteristics to those without imputation (Additional file 1: Table S4).

Six lifestyle behaviors including smoking status, alcohol status, dietary habits, physical activity, sleep status, and body shape were used to calculate healthy lifestyle scores [28]. Each lifestyle was scored as healthy (1 point) if recommended targets were achieved. Detailed definitions of healthy lifestyle are presented in the Additional file 1 [29, 30]. The overall healthy lifestyle score was the sum of individual scores for the six lifestyle behaviors, ranging from 0 to 6, with a higher score indicating a healthier lifestyle. Participants were categorized into three groups:

favorable lifestyle (5–6), intermediate lifestyle (2–4), and unfavorable lifestyle (0–1).

Genetic risk for T2D was assessed using the Polygenic Risk Score (PRS) provided by UK Biobank. The standard PRS was calculated for all individuals in the UK Biobank, trained on external data only, while the enhanced PRS was calculated for a testing subgroup of 104,231 individuals in the UK Biobank. In our analytic sample, we had data for 370,030 participants to calculate standard PRS for T2D, and data for 78,288 participants to calculate enhanced PRS for T2D. PRS was classified as low (lowest quintile), medium (quintiles 2–4), or high (highest quintile) risk [31].

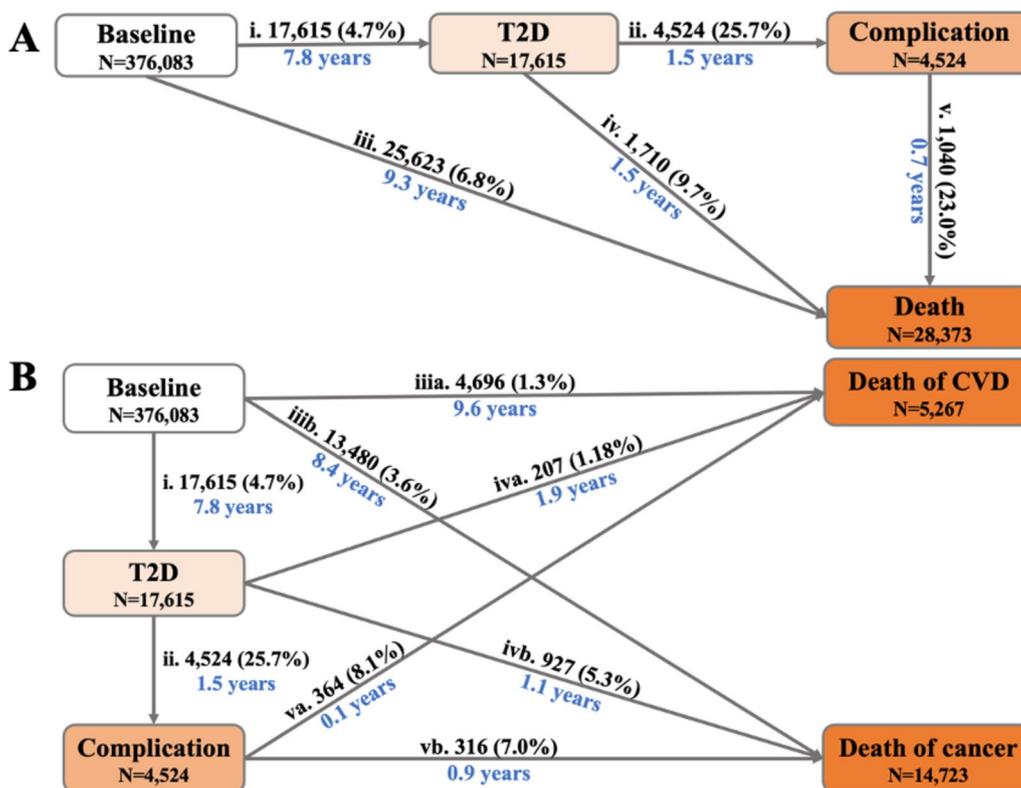
### Statistical analysis

Multi-state models were applied to estimate the hazard ratio (HR) and corresponding 95% confidence interval (CI) of the associations between PhenoAgeAccel and the trajectory from baseline to T2D, subsequently to diabetic complications, and finally to death. We constructed five transitions based on the natural trajectory of T2D and previous studies: (i) free of T2D to incident T2D; (ii) T2D to diabetic complication; (iii) free of T2D to death; (iv) T2D to death; and (v) diabetic complications to death (transition pattern A, Fig. 1A) [25]. We further considered two leading causes of death (cardiovascular disease (CVD) and cancer), resulting in eight transitions (transition pattern B, Fig. 1B), and repeated the multi-state model analysis.

To assess the impact of genetic risk on the associations, we explored the joint associations between PhenoAgeAccel and PRS on the risk of incident T2D. Moreover, we also investigated the combined impact of PhenoAgeAccel and lifestyle on the transitions in the T2D trajectory to evaluate the potential modification effect of lifestyle. The additive interaction was assessed by calculating the relative excess risk due to interaction and the attributable proportion due to interaction with 95% CIs.

Furthermore, we calculated the population-attributable fractions (PAFs) to quantify the proportion of events in all transitions of the T2D trajectory that would not occur in this population if a risk factor were eliminated, assuming that these associations are causal [32]. Detailed calculation of PAFs is available in the Additional file 1 [33, 34]. In addition, we calculated Harrell's C-statistics and Area Under the Curve under various covariates combinations to measure the additional predictive performance for the occurrence and prognosis of T2D improved by PhenoAgeAccel [35].

We performed several sensitivity analyses to test the robustness of the main results: (1) excluding participants who entered different states on the same date, those with T2D diagnosed within the first two and five years of



**Fig. 1** Transition pattern from baseline to T2D, complication, and all-cause mortality and transition pattern B from baseline to T2D, complication, and specific-cause mortality. The data along the arrows represent the numbers (percentages) of transitions, and data below the arrow represents the corresponding median time interval of transfer between different states. Diabetes complications included diabetic eye diseases, diabetic kidney diseases, diabetic neuropathy diseases, cardiovascular diseases, peripheral vascular diseases, and metabolic events. Complication is defined as the presence of at least one of the diabetes complications after the diagnosis of incident T2D. For participants entering different stages on the same date, we calculated the entering date of the theoretically prior state as the date of the latter state minus 0.5 days. Abbreviation: T2D, type 2 diabetes; CVD, cardiovascular disease

follow-up, those with cancer at baseline, or those without complete data of covariates; (2) recalculating the entering date of the prior state using different time intervals instead of 0.5 days; (3) exploring the dose–response relationships between PhenoAgeAccel and the risk of T2D progression in all transitions using restricted cubic spline regression [36]; (4) assessing whether the associations between PhenoAgeAccel and the T2D trajectory are consistent when stratified by baseline characteristics; (5) adjusting for the use of cholesterol and blood pressure medication or the intake of exogenous hormones; (6) adjusting for metabolic-related biomarkers (systolic blood pressure, HbA1C, glucose, and total cholesterol); (7) retraining the coefficients in the PhenoAge construction formula using UK Biobank data through five-fold cross-validation and calculating a new PhenoAgeAccel to repeat the main analysis; (8) repeating joint effect analysis between PhenoAgeAccel and lifestyle that excluding BMI and reclassifying lifestyle categories; and (9) using death caused by diabetes or diabetes complications.

Statistical analyses were conducted using R software (version 4.3.2). The multi-state models were constructed using the “mstate” package. PAR was calculated using the “AF” package. Two-tailed  $P < 0.05$  was considered statistically significant.

## Results

### Descriptive results

Of the 376,083 participants (44.6% males, 91.2% white), the median age was 57 years (interquartile range: 50–63 years) and 40.7% were biologically older. Compared to biologically younger participants, biologically older participants were more likely to be female, have lower income and education level, be obese, lead unhealthy lifestyle, and develop hypertension and high cholesterol (Additional file 1: Table S5–S6).

During a median follow-up period of 13.7 years (interquartile range: 13.0–14.3 years), 17,615 (4.68%) participants developed T2D. Of all incident T2D patients, 1,710 (9.71%) died without experiencing diabetic

complications, and 4,524 (25.68%) developed diabetic complications, and afterward, 1,040 (22.99%) died from all causes (Fig. 1A). Participants with higher PhenoAgeAccel tended to have increased risks of developing T2D, complications, or death (Additional file 1: Fig S3, Table S7-S8).

#### Association between PhenoAgeAccel and transitions in the T2D trajectory

The relative risks of all transitions in the T2D trajectory by PhenoAgeAccel category, and the corresponding PAFs, which quantify the proportion of events attributed to accelerated phenotypic aging, are shown in Table 1 (transition pattern A). Compared with biologically younger participants, biologically older participants had significantly higher risks of all transitions. For example, an HR of 1.77 (95% CI 1.71 to 1.82; PAF 24.8 [95% CI 23.5 to 26.2]) for transition from baseline to T2D indicates that, among all individuals at baseline, those biologically older had a 1.77 times higher risk of developing T2D compared to those biologically younger. And the HRs were 1.10 (95% CI 1.04 to 1.17; PAF 4.4 [95% CI 1.4 to 7.4]) for transition from T2D to diabetic complication, 1.53 (95% CI 1.49 to 1.57; PAF 17.6 [95% CI 16.6 to 18.6]) for transition from baseline to all-cause death, 1.14 (95% CI 1.03 to 1.26; PAF 7.4 [95% CI 1.8 to 13.0]) for transition from T2D to all-cause death, and 1.32 (95% CI 1.15 to 1.51; PAF 15.4 [95% CI 7.5 to 23.2]) for transition from diabetic complications to all-cause death, respectively. Similar associations were observed when using continuous PhenoAgeAccel and quartiles of PhenoAgeAccel.

The estimated cumulative transition probabilities from one state to another for 55-year-old participants increased with time during follow-up (Additional file 1: Fig. S4). Biologically older participants had higher cumulative transition probabilities for all transitions in the T2D trajectory compared with biologically younger participants (all  $P < 0.05$ ). Moreover, the model with PhenoAgeAccel achieved higher discriminatory power and better predictive performance than the model without PhenoAgeAccel (average C index: 0.662 vs 0.679,  $P < 0.001$ ; average AUC: 0.637 vs 0.655,  $P < 0.001$ , Additional file 1: Table S9).

When we decomposed all-cause mortality into CVD mortality and cancer mortality, we observed differential associations of PhenoAgeAccel with transitions from baseline, T2D, or diabetic complications to specific mortality (transition pattern B, Table 2). Specifically, biologically older participants had a higher risk of transition from baseline to CVD mortality (HR 1.66, 95% CI 1.57 to 1.76; PAF 23.0 [95% CI 20.4 to 25.5]) than to cancer mortality (HR 1.40, 95% CI 1.35 to 1.45; PAF 14.2 [95% CI 12.8 to 15.7]), and a higher risk of transition from

diabetic complications to CVD mortality (HR 1.45, 95% CI 1.15 to 1.83; PAF 20.8 [95% CI 8.0 to 33.7]) than to cancer mortality (HR 1.09, 95% CI 0.86 to 1.38; PAF 5.1 [95% CI -9.9 to 20.1]). For the transition from T2D to mortality, an increase in PhenoAgeAccel per 5 years was associated with a higher risk of CVD mortality (HR 1.18, 95% CI 1.06 to 1.32). No significant association was found between PhenoAgeAccel and the transition from T2D to cancer mortality.

#### Joint effect of genetic risk and lifestyle with PhenoAgeAccel

Additional file 1: Table S10 presents the significant association of PRS with the risk of incident T2D. Figure 2 shows the risk of incident T2D for combined PhenoAgeAccel and genetic risk. Participants with older biological age and high standard PRS had a higher risk of incident T2D (HR 4.76, 95% CI 4.43 to 5.13; PAF 18.2 [95% CI 17.5 to 19.0]) than those with younger biological age and low standard PRS. Similar results were found in analyses with enhanced PRS. Significant additive interactions of PhenoAgeAccel with both standard and enhanced PRS on the risk of incident T2D were observed (Additional file 1: Table S11).

The risks of transitions in the T2D trajectory according to lifestyle are provided in Additional file 1: Table S12. These risks were higher among those who have unhealthier lifestyle than those who have the healthiest lifestyle. Figure 3 shows the risks of transitions in the T2D trajectory for combined PhenoAgeAccel and lifestyle. Compared to participants with younger biological age and favorable lifestyle, those with older biological age and unfavorable lifestyle had increased risks of transitions from baseline to T2D (HR 5.39, 95% CI 5.01 to 5.79; PAF 3.0 [95% CI 12.4 to 13.6]), from T2D to diabetic complications (HR 1.34, 95% CI 1.16 to 1.55; PAF 3.7 [95% CI 1.8 to 5.6]), from baseline to all-cause death (HR 2.64, 95% CI 2.51 to 2.78; PAF 7.5 [95% CI 7.1 to 7.9]), from T2D to all-cause death (HR 1.62, 95% CI 1.27 to 2.06; PAF 7.2 [95% CI 3.8 to 10.6]), and from diabetic complications to all-cause death (HR 1.65, 95% CI 1.20 to 2.27; PAF 8.2 [95% CI 3.2 to 13.2]). Significant additive interaction effects between lifestyle and PhenoAgeAccel were observed for all transitions except for the transition from T2D to diabetic complications (Additional file 1: Table S13).

#### Sensitivity analyses

The results were not substantially altered in sensitivity analyses (Additional file 1: Tables S14–S28, Fig S5). Although the point estimates for the association between phenotypic aging and progression from T2D or diabetes complications to death caused by diabetes or its complications were greater than 1, the confidence intervals

**Table 1** Associations between PhenoAgeAccel and transitions from baseline to T2D, complication, and death using the multi-state model

| Transition            | PhenoAgeAccel <sup>a</sup>  | No. of cases<br>(Incidence per 1,000 PYs) | HR <sup>b</sup><br>(95% CI) | PAF% <sup>c</sup><br>(95% CI) |
|-----------------------|-----------------------------|---|-----------------------------|-------------------------------|
| Baseline to T2D       | <b>Per 5 years increase</b> | 17,615(3.58)                              | 1.34(1.32,1.35)             |                               |
|                       | <b>Category</b>             |   |                             |                               |
|                       | Biologically younger        | 7,033(2.37)                               | Reference                   | Reference                     |
|                       | Biologically older          | 10,582(5.42)                              | 1.77(1.71,1.82)             | 24.8 (23.5, 26.2)             |
|                       | <b>Quantiles</b>            |   |                             |                               |
|                       | Low                         | 2,432(1.84)                               | Reference                   | Reference                     |
|                       | Intermediate                | 8,126(3.19)                               | 1.44(1.37,1.50)             | 13.3 (11.7, 14.8)             |
| High                  | 7,057(6.67)                 | 2.46(2.35,2.58)                           | 23.0 (21.9, 24.1)           |                               |
|                       | <b>P for trend</b>          |   | < 0.001                     |                               |
| Baseline to Death     | <b>Per 5 years increase</b> | 25,623(5.20)                              | 1.32(1.30,1.33)             |                               |
|                       | <b>Category</b>             |   |                             |                               |
|                       | Biologically younger        | 12,074(4.06)                              | Reference                   | Reference                     |
|                       | Biologically older          | 13,549(6.94)                              | 1.53(1.49,1.57)             | 17.6 (16.6, 18.6)             |
|                       | <b>Quantiles</b>            |   |                             |                               |
|                       | Low                         | 4,861(3.68)                               | Reference                   | Reference                     |
|                       | Intermediate                | 12,007(4.72)                              | 1.18(1.15,1.23)             | 6.9 (5.5, 8.2)                |
| High                  | 8,755(8.28)                 | 1.92(1.85,1.99)                           | 16.0 (15.2, 16.9)           |                               |
|                       | <b>P for trend</b>          |   | < 0.001                     |                               |
| T2D to Complication   | <b>Per 5 years increase</b> | 4,524(54.24)                              | 1.09(1.06,1.11)             |                               |
|                       | <b>Category</b>             |   |                             |                               |
|                       | Biologically younger        | 1,702(52.14)                              | Reference                   | Reference                     |
|                       | Biologically older          | 2,822(55.60)                              | 1.10(1.04,1.17)             | 4.4 (1.4, 7.4)                |
|                       | <b>Quantiles</b>            |   |                             |                               |
|                       | Low                         | 569(50.36)                                | Reference                   |                               |
|                       | Intermediate                | 1,983(51.79)                              | 1.06(0.97,1.17)             | 2.1 (-1.3, 5.5)               |
| High                  | 1,972(58.33)                | 1.24(1.12,1.36)                           | 6.4 (3.3, 9.5)              |                               |
|                       | <b>P for trend</b>          |   | < 0.001                     |                               |
| T2D to Death          | <b>Per 5 years increase</b> | 1,710(20.50)                              | 1.14(1.09,1.18)             |                               |
|                       | <b>Category</b>             |   |                             |                               |
|                       | Biologically younger        | 635(19.45)                                | Reference                   | Reference                     |
|                       | Biologically older          | 1,075(21.18)                              | 1.14(1.03,1.26)             | 7.4 (1.8, 13.0)               |
|                       | <b>Quantiles</b>            |   |                             |                               |
|                       | Low                         | 215(19.03)                                | Reference                   |                               |
|                       | Intermediate                | 719(18.78)                                | 1.04(0.89,1.21)             | 1.4 (-4.6, 7.5)               |
| High                  | 776(22.95)                  | 1.34(1.15,1.56)                           | 11.0 (5.5, 16.5)            |                               |
|                       | <b>P for trend</b>          |   | < 0.001                     |                               |
| Complication to Death | <b>Per 5 years increase</b> | 1,040(68.58)                              | 1.13(1.08,1.18)             |                               |
|                       | <b>Category</b>             |   |                             |                               |
|                       | Biologically younger        | 320(56.81)                                | Reference                   | Reference                     |
|                       | Biologically older          | 720(75.53)                                | 1.32(1.15,1.51)             | 15.4 (7.5, 23.2)              |
|                       | <b>Quantiles</b>            |   |                             |                               |
|                       | Low                         | 107(52.37)                                | Reference                   | Reference                     |
|                       | Intermediate                | 396(61.24)                                | 1.14(0.92,1.42)             | 4.6 (-3.1, 12.2)              |
| High                  | 537(80.67)                  | 1.52(1.23,1.88)                           | 16.2 (8.3, 24.2)            |                               |
|                       | <b>P for trend</b>          |   | < 0.001                     |                               |

**Abbreviation:** HR hazard ratio, CI confidence interval, PAF population attributable fraction, PYs person-years, T2D type 2 diabetes

<sup>a</sup> PhenoAgeAccel was classified into two groups: biologically younger (PhenoAgeAccel ≤ 0) and biologically older (PhenoAgeAccel > 0). It was also divided into three quartile-based groups: low (bottom quantiles), medium (quantiles 2–3), and high (top quantiles)

<sup>b</sup> Multi-state model adjusted for age, sex, race, income, education, family history, obesity, smoking status, drinking status, physical activity, healthy diet, sleep status, hypertension, high cholesterol, and cancer

<sup>c</sup> PAFs at the median follow-up time of the study population were reported

included 1 (Table S28). This may be due to the small number of deaths, which resulted in limited statistical power. When stratified by sociodemographic characteristics, the positive associations of PhenoAgeAccel with all transitions in the T2D trajectory were relatively consistent across all subgroups (Additional file 1: Fig. S6). The monotonic increasing dose–response relationships further showed positive associations between PhenoAgeAccel and all transitions across the range of PhenoAgeAccel (Additional file 1: Fig. S7).

## Discussion

In this large prospective cohort study based on the UK Biobank, we found that accelerated phenotypic aging was associated with increased risks of transitions from baseline to T2D, then to diabetic complication, and finally to all-cause death. For specific-cause death, associations were more pronounced in transitions from baseline, T2D, or complications to CVD mortality compared to cancer mortality. We also found that participants with older biological age and high genetic risk had higher risks of incident T2D than those with younger biological age and low genetic risk. Participants with older biological age and unhealthy lifestyle had higher risks of T2D trajectory compared to those with younger biological age and healthy lifestyle.

Several studies have found positive associations between accelerated biological aging and the risk of a single transition in the T2D trajectory [14, 37–40]. A meta-analysis of 156 studies revealed a significant correlation between accelerated biological aging and incident T2D [37]. Additionally, a prospective cohort study including 5,278 T2D patients from NHANES found that accelerated biological aging increased the risk of progression from T2D to all-cause mortality [14]. However, these studies did not fully evaluate the effect of accelerated biological aging on transitions across the entire trajectory of T2D, failing to compare these inter-transition effects. Our study further provided novel insights into the continuous influence of accelerated biological aging on the trajectory of T2D by modeling the full course of the disease using multistate models. We found that accelerated phenotypic aging increased the risk of all transitions in T2D trajectory. When comparing the effects of accelerated phenotypic aging on different transitions, we additionally found that the association of PhenoAgeAccel with transition from diabetic complication to all-cause death was slightly stronger than the association of PhenoAgeAccel with transition from T2D to all-cause death, suggesting a potential impact of accelerated phenotypic aging on premature death in patients with diabetic complication [15]. Our finding highlights the importance of providing timely intervention for patients with T2D or

diabetic complications to reduce the additional risk of mortality [41].

The potential biological mechanisms linking accelerated phenotypic aging and risk of transitions in the T2D trajectory have been proposed. Several large population-based studies and their meta-analyses have shown that a higher PhenoAgeAccel value is a proxy of abnormal biomarkers, which play an important role in the development of inflammation and insulin resistance, potentially increasing the risk of T2D development [42–44]. This may elucidate our finding that accelerated phenotypic aging was associated with an increased risk of incident T2D. Additionally, T2D itself may represent a pro-aging state, as metabolic changes caused by T2D, such as hyperglycemia and altered lipid metabolism, stimulate the formation of senescent cells [45]. These senescent cells further play a major role in the development of various diabetic complications [46, 47]. This may explain why we found a higher risk associated with accelerated phenotypic aging in the transition from T2D to diabetic complications.

When regarding cause-specific mortality, we also found that accelerated phenotypic aging was associated with higher risks of transitions from baseline, T2D, or diabetic complications to CVD mortality than cancer mortality. A NHANES study from the US involving 5,278 T2D participants found that each 1-year increase in PhenoAgeAccel was associated with a 4% increase in both CVD and cancer mortality using traditional Cox regression models [14]. Using multi-state models, we also found that accelerated phenotypic aging significantly increases the risk of transitions from T2D to all-cause and CVD mortality. However, regarding cancer mortality, we did not find significant associations between PhenoAgeAccel and transitions from T2D and diabetic complications to cancer mortality. The differences in cancer mortality between the NHANES study and our study may be attributed to the incomparability of estimates due to the distinct analytic strategies and statistical models. Compared with the traditional Cox regression models used in previous studies, the multi-stage models can decompose this transition into three mutually exclusive transitions: from T2D alone to diabetic complications, from T2D alone to cause-specific death, and from diabetic complications to cause-specific death, allowing for the assessment of independent effects of PhenoAgeAccel on each transition.

Previous research demonstrated that PRS may serve as an indicator of genetic risk and is associated with the risk of incident T2D [48]. The same result was found in our study. We further observed that high genetic risk strengthened the association of PhenoAgeAccel and the risk of incident T2D. Genes associated with accelerated phenotypic aging, such as the APOE e4 determinant,

**Table 2** Associations between PhenoAgeAccel and transitions from baseline, T2D, complication, to specific death using the multi-state model

| Transition                              | PhenoAgeAccel <sup>a</sup>  | No. of cases<br>(Incidence per 1,000<br>PYs) | HR <sup>b</sup> (95% CI) | PAF% <sup>c</sup> (95% CI) |
|---|-----------------------------|--|--------------------------|----------------------------|
| <b>Baseline to cancer mortality</b>     | <b>Per 5 years increase</b> | 13,480(2.74)                                 | 1.26(1.25,1.28)          |                            |
|   | <b>Category</b>             |  |                          |                            |
|   | Biologically younger        | 6,728(2.26)                                  | Reference                | Reference                  |
|   | Biologically older          | 6,752(3.46)                                  | 1.40(1.35,1.45)          | 14.2 (12.8,15.7)           |
|   | <b>Quantiles</b>            |  |                          |                            |
|   | Low                         | 2,738(2.07)                                  | Reference                | Reference                  |
|   | Intermediate                | 6,534(2.57)                                  | 1.16(1.11,1.22)          | 6.5 (4.7,8.4)              |
| High                                    | 4,208(3.98)                 | 1.69(1.61,1.78)                              | 13.1 (11.9,14.3)         |                            |
|   | <b>P for trend</b>          |  | < 0.001                  |                            |
| <b>Baseline to CVD mortality</b>        | <b>Per 5 years increase</b> | 4,696(0.95)                                  | 1.34(1.31,1.37)          |                            |
|   | <b>Category</b>             |  |                          |                            |
|   | Biologically younger        | 2,055(0.69)                                  | Reference                | Reference                  |
|   | Biologically older          | 2,641(1.35)                                  | 1.66(1.57,1.76)          | 23.0 (20.4,25.5)           |
|   | <b>Quantiles</b>            |  |                          |                            |
|   | Low                         | 758(0.57)                                    | Reference                | Reference                  |
|   | Intermediate                | 2,200(0.86)                                  | 1.33(1.23,1.45)          | 11.2 (8.2,14.2)            |
| High                                    | 1,738(1.64)                 | 2.26(2.07,2.47)                              | 21.8 (19.7,24.0)         |                            |
|   | <b>P for trend</b>          |  | < 0.001                  |                            |
| <b>T2D to cancer mortality</b>          | <b>Per 5 years increase</b> | 927(11.11)                                   | 1.04(0.99,1.11)          |                            |
|   | <b>Category</b>             |  |                          |                            |
|   | Biologically younger        | 367(11.24)                                   | Reference                | Reference                  |
|   | Biologically older          | 560(11.03)                                   | 1.04(0.91,1.20)          | 2.5 (-5.2,10.2)            |
|   | <b>Quantiles</b>            |  |                          |                            |
|   | Low                         | 129(11.42)                                   | Reference                | Reference                  |
|   | Intermediate                | 412(10.76)                                   | 1.01(0.83,1.23)          | 0.4 (-8.3,9.1)             |
| High                                    | 386(11.42)                  | 1.14(0.93,1.39)                              | 4.8 (-2.8,12.4)          |                            |
|   | <b>P for trend</b>          |  | 0.115                    |                            |
| <b>T2D to CVD mortality</b>             | <b>Per 5 years increase</b> | 207(2.48)                                    | 1.18(1.06,1.32)          |                            |
|   | <b>Category</b>             |  |                          |                            |
|   | Biologically younger        | 77(2.36)                                     | Reference                | Reference                  |
|   | Biologically older          | 130(2.56)                                    | 1.09(0.81,1.45)          | 5.0 (-12.1,22.1)           |
|   | <b>Quantiles</b>            |  |                          |                            |
|   | Low                         | 23(2.04)                                     | Reference                | Reference                  |
|   | Intermediate                | 88(2.30)                                     | 1.14(0.72,1.82)          | 5.2 (-12.1,22.5)           |
| High                                    | 96(2.84)                    | 1.44(0.91,2.29)                              | 14.6 (-2.0,31.2)         |                            |
|   | <b>P for trend</b>          |  | 0.065                    |                            |
| <b>Complication to cancer mortality</b> | <b>Per 5 years increase</b> | 316(20.84)                                   | 1.03(0.94,1.12)          |                            |
|   | <b>Category</b>             |  |                          |                            |
|   | Biologically younger        | 106(18.82)                                   | Reference                | Reference                  |
|   | Biologically older          | 210(22.03)                                   | 1.09(0.86,1.38)          | 5.1 (-9.9,20.1)            |
|   | <b>Quantiles</b>            |  |                          |                            |
|   | Low                         | 39(19.09)                                    | Reference                | Reference                  |
|   | Intermediate                | 125(19.33)                                   | 0.97(0.68,1.40)          | -1.0 (-16.0,13.9)          |
| High                                    | 152(22.83)                  | 1.10(0.76,1.57)                              | 4.0 (-11.9,19.8)         |                            |
|   | <b>P for trend</b>          |  | 0.431                    |                            |

**Table 2** (continued)

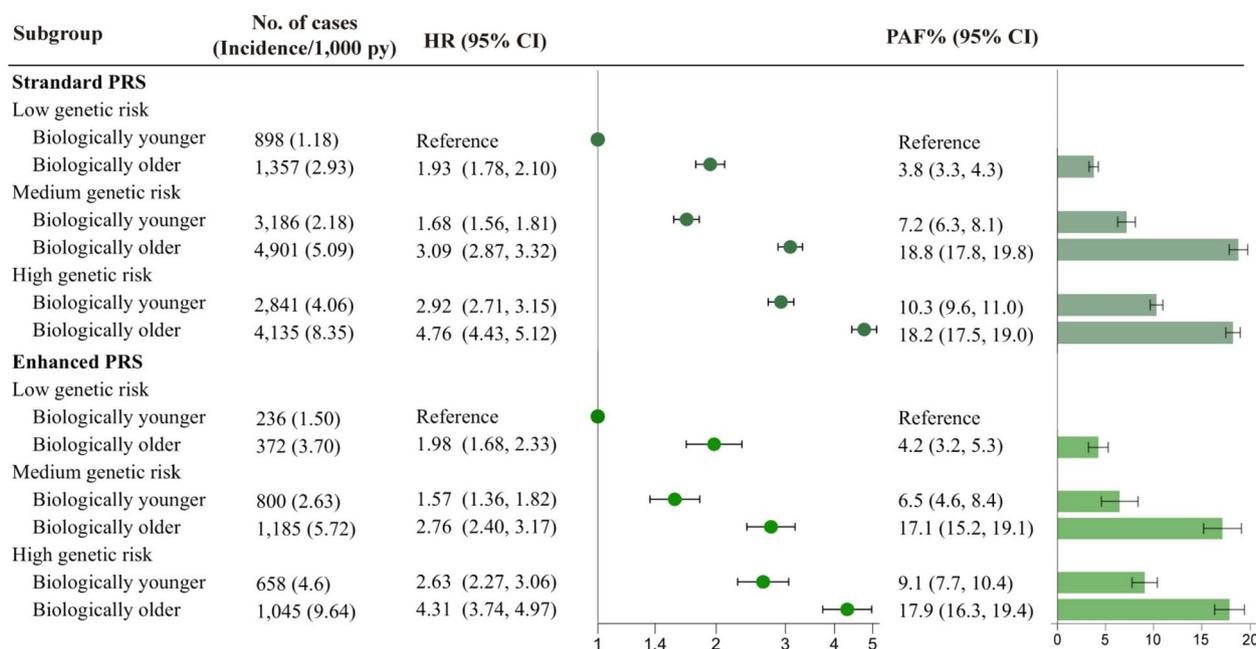
| Transition                    | PhenoAgeAccel <sup>a</sup> | No. of cases (Incidence per 1,000 PYs) | HR <sup>b</sup> (95% CI) | PAF% <sup>c</sup> (95% CI) |
|-------------------------------|----------------------------|--|--------------------------|----------------------------|
| Complication to CVD mortality | Per 5 years increase       | 364(24.00)                             | 1.12(1.04,1.21)          |                            |
|                               | <b>Category</b>            |  |                          |                            |
|                               | Biologically younger       | 107(18.99)                             | Reference                | Reference                  |
|                               | Biologically older         | 257(26.96)                             | 1.45(1.15,1.83)          | 20.8 (8.0,33.7)            |
|                               | <b>Quantiles</b>           |  |                          |                            |
|                               | Low                        | 35(17.13)                              | Reference                | Reference                  |
|                               | Intermediate               | 135(20.88)                             | 1.21(0.83,1.76)          | 6.3 (−6.2,18.8)            |
|                               | High                       | 194(29.14)                             | 1.72(1.19,2.49)          | 21.3 (8.5,34.2)            |
|                               | <b>P for trend</b>         |  | < 0.001                  |                            |

Abbreviation: HR hazard ratio; CI confidence interval, PAF population attributable fraction, PYs person-years, T2D type 2 diabetes, CVD cardiovascular disease

<sup>a</sup> PhenoAgeAccel was classified into two groups: biologically younger (PhenoAgeAccel ≤ 0) and biologically older (PhenoAgeAccel > 0). It was also divided into three quartile-based groups: low (bottom quantiles), medium (quantiles 2–3), and high (top quantiles)

<sup>b</sup> Multi-state model adjusted for age, sex, race, income, education, family history, obesity, smoking status, drinking status, physical activity, healthy diet, sleep status, hypertension, high cholesterol, and cancer

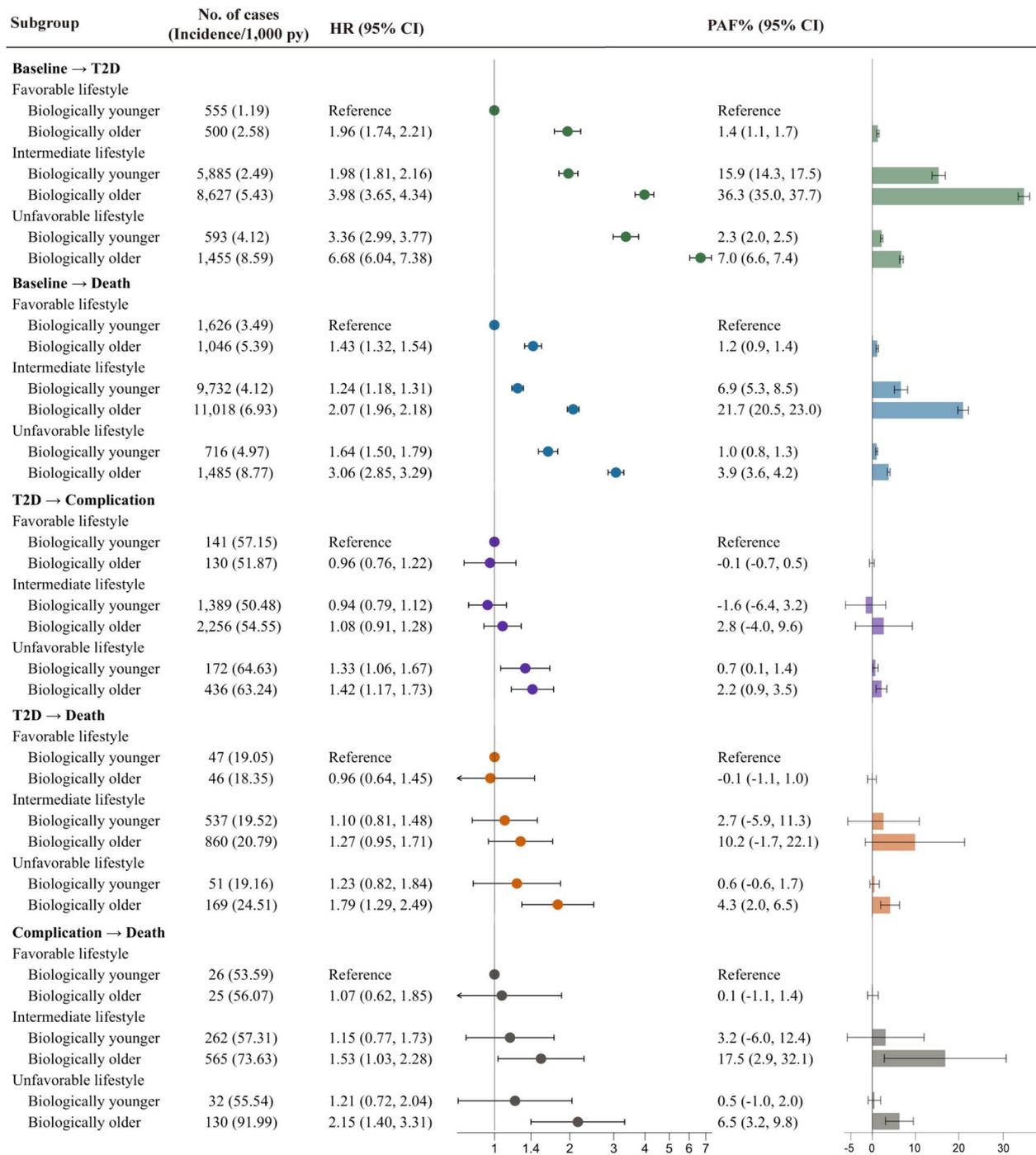
<sup>c</sup> PAFs at the median follow-up time of the study population were reported



**Fig. 2** Joint effects of PhenoAgeAccel and genetic risk on risk of incident T2D. Cox proportional hazard regression model adjusted for age, sex, race, income, education, family history, obesity, smoking status, drinking status, physical activity, healthy diet, sleep status, hypertension, high cholesterol, cancer, genotyping batch, and genetic principal components. PAFs at the median follow-up time of the study population were reported. Abbreviation: HR, hazard ratio; CI, confidence interval; PYs, person-years; PAF, population attributable fraction; T2D, type 2 diabetes; PRS, polygenic risk score

are enriched in immune system pathways, which are also associated with an increased risk of developing type 2 diabetes [19, 49]. Therefore, individuals with a high genetic risk may be more likely to experience accelerated

aging, aggregating the risk of developing T2D. This result suggests that PhenoAgeAccel could be combined with genetic risk for T2D risk identification. Given the validity and accessibility of PhenoAgeAccel, it holds promise



**Fig. 3** Joint effects of PhenoAgeAccel and lifestyle on risk of transitions in T2D trajectory. Multi-state model adjusted for age, sex, race, income, education, family history, hypertension, high cholesterol, and cancer. PAFs at the median follow-up time of the study population were reported. Abbreviation: HR, hazard ratio; CI, confidence interval; PYs, person-years; PAF, population attributable fraction; T2D, type 2 diabetes

as a novel clinical composite biomarker for guiding the precise prevention of T2D in high-risk populations. Additionally, our study provides novel evidence about the joint effects of lifestyle with PhenoAgeAccel on T2D

trajectory from healthy to T2D, then to diabetic complications, and finally to death. Previous studies have found that unhealthy lifestyle increases the risk of developing T2D [50, 51]. However, the impact of lifestyle on the T2D

trajectory and its joint effect with PhenoAgeAccel remain unclear. We observed that unhealthy lifestyle increases the risk of T2D trajectory and unhealthy lifestyle further enhanced the association of PhenoAgeAccel and the risk of T2D trajectory. Unhealthy lifestyle, such as lack of exercise and insufficient sleep, can elevate oxidative and inflammatory responses in the body, which are the primary pathways through which accelerated aging impacts health [7, 52]. These findings suggest that PhenoAgeAccel may serve as a potential intermediate phenotype to assess the impact of lifestyle interventions and other treatments on slowing aging, thereby slowing T2D progression and reducing the burden of complications [53, 54].

Several strengths of this study are as follows. Firstly, the use of a multi-state model enables us to compare the impacts of PhenoAgeAccel on the different transitions of the T2D trajectory and rule out the competing risk from death compared with traditional Cox regression models. Secondly, the large sample size of the UK Biobank provided sufficient statistical power to these analyses, and the prospective nature allowed for a clear temporal sequence between exposure and outcome, reducing potential reverse causation. Additionally, a series of sensitivity analyses confirmed the robustness of our results. Finally, the wide range of individual-level information on sociodemographic factors, lifestyle factors, and medical conditions collected in the UK Biobank enables us to minimize confounding bias as much as possible and explore potential effect modifications.

This study also has some limitations. Firstly, we calculated PhenoAgeAccel at baseline but failed to include time-varying measurements for PhenoAgeAccel or other covariates in our analysis. Although our use of a multi-state model allows covariate effects to vary across different stages of disease progression, the absence of time-varying covariates may limit our ability to fully capture changes in these covariates over time. Future studies could utilize longitudinal data to explore association between changes in biological age and disease progression after controlling for significant time-varying confounding, and investigate whether the reversal of biological aging may reduce the risk of disease progression. Secondly, most participants in the UK Biobank were white, limiting the generalizability of the study findings to populations with different genetic backgrounds. Further research is needed to validate our results in more diverse populations. Thirdly, the participants in the UK Biobank were healthier than the general UK population and less susceptible to accelerated aging, which may have led to conservative results due to healthy volunteer bias [55, 56]. Finally, the definition and classification criteria for lifestyle in our study may not fully capture the variation in lifestyle habits. However, using different definitions

and categorizations of lifestyle yielded similar results on the combined effect of lifestyle and PhenoAgeAccel.

## Conclusions

Our study indicates that participants with accelerated phenotypic aging have higher risks of T2D occurrence and progression compared to those with unaccelerated phenotypic aging. PhenoAgeAccel may serve as an effective tool, in combination with genetic risk, for identifying the incidence risk of T2D at an early stage, and as an intermediate phenotype to guide interventions at all stages of T2D progression and to track the effectiveness of those interventions.

## Abbreviations

|               |                                   |
|---------------|-----------------------------------|
| T2D           | Type 2 diabetes;                  |
| PhenoAgeAccel | Phenotypic age acceleration       |
| PRS           | Polygenic Risk Score              |
| HR            | Hazard ratio                      |
| CI            | Confidence interval               |
| PAFs          | Population-attributable fractions |

## Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12916-024-03832-y>.

Additional file 1: Assessment of PhenoAgeAccel. Assessment of Lifestyle. Calculation of PAF. Figures S1-S7. Fig. S1-The selection flow chart. Fig. S2-Directed acyclic graph. Fig. S3-The distribution of PhenoAgeAccel. Fig. S4-Cumulative transition probability of five transitions. Fig. S5-Correlations of UKB- and NHANES-Derived PhenoAge. Fig. S6-Associations of PhenoAgeAccel with T2D trajectory, stratified by baseline characteristics. Fig. S7-Nonlinear Associations of PhenoAgeAccel with T2D trajectory. Table S1-S28. Table S1-ICD codes used to identify T2D and Diabetes complications. Table S2-ICD codes used to identify cause-specific mortality. Table S3-The definition and measurements of covariates. Table S4-Comparison of characteristics between data with imputation and without imputation. Table S5-Baseline characteristics of the participants. Table S6-PhenoAgeAccel of participants stratified by lifestyle factors. Table S7-Associations of PhenoAgeAccel with T2D and mortality. Table S8-Associations between PhenoAgeAccel and Diabetes complications in the T2D population. Table S9-The Harrell's C-statistics and AUC of PhenoAgeAccel and risk factors with T2D progression. Table S10-Associations between Genetic risk and T2D. Table S11-Additive interaction effect for PhenoAgeAccel and PRS. Table S12-Associations between Lifestyle and T2D progression. Table S13-Additive interaction effect for PhenoAgeAccel and lifestyle. Table S14-Sensitivity analysis excluding participants entering different states on the same date. Table S15-Sensitivity analysis using 0.5-year intervals. Table S16-Sensitivity analysis using 1-year intervals. Table S17-Sensitivity analysis using 3-year intervals. Table S18-Sensitivity analysis excluding events in the first two years of follow-up. Table S19-Sensitivity analysis excluding events in the first five years of follow-up. Table S20-Sensitivity analysis excluding baseline cancer cases. Table S21-Sensitivity analysis in participants with complete covariate data. Table S22-Sensitivity analysis adjusting for the usage of cholesterol and blood pressure medication or the taking of exogenous hormones. Table S23-Sensitivity analysis adjusting for systolic blood pressure, HbA1C, glucose, and total cholesterol. Table S24-Coefficients of biomarkers for UKB-derived PhenoAge retrained. Table S25-Sensitivity analysis using UKB-derived PhenoAgeAccel. Table S26-Sensitivity analysis using lifestyle scores excluding BMI. Table S27-Sensitivity analysis using reclassified lifestyle categories. Table S28-Sensitivity analysis using death caused by diabetes or diabetes complications.

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### Authors' contributions

YFY and GYQ are corresponding authors and senior authors who contributed equally to this study. LLP and YHL are joint first authors with equal contribution. CH and YFH had full access to all the data in this study and take full responsibility for the integrity of the data and the accuracy of the data analysis. YFY and GYQ conceived and designed the study. LLP, YHL, CH, YFH, RLL, KCW, and YY undertook the statistical analysis. LLP and YHL drafted the manuscript. YFY and GYQ are the guarantors. All authors provided critical input to the analyses, interpreted the data, and revised the manuscript critically. The corresponding authors attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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### Data availability

No datasets were generated or analysed during the current study.

### Declarations

#### Ethics approval and consent to participate

This study was approved by the North West Multicenter Research Ethics Committee (11/NW/0382), and informed consent was provided by all participants (application number 96511).

#### Consent for publication

Not applicable.

#### Competing Interests

The authors declare no competing interests.

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