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Abdominal adiposity and accelerated biological aging in relation to general and cardiovascular aging in Chinese adults

Running title: Abdominal adiposity and biological aging

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Abstract

Background: Abdominal adiposity may contribute to both general and cardiovascular aging, yet the extent to which accelerated biological age (BA) at distinct molecular levels mediates these effects has not been fully elucidated.

Methods: Three BA measures were constructed using metabolomics (MetaboAge, n=4,391), clinical biomarkers (KDM-BA, n=12,369), and DNA methylation (DNAm PhenoAge, n=980) within the prospective China Kadoorie Biobank and their predictive accuracy for all-cause mortality were evaluated. We explored the potential causal effects of abdominal adiposity, measured by waist-to-hip ratio (WHR) and WHR adjusted for body mass index (WHRadjBMI), on BA acceleration using observational study and Mendelian randomization. We further investigated the extent to which BA accelerations mediated the effects of abdominal adiposity on cardiovascular aging (assessed by atherosclerotic cardiovascular disease [ASCVD] incidence and mortality) and general aging (assessed by all-cause mortality and frailty index).

Results: Both MetaboAge and KDM-BA improved prediction for all-cause mortality beyond chronological age (AUROC difference: MetaboAge=0.040, KDM-BA=0.012, P<0.001). In observational analyses, abdominal adiposity was associated with accelerated aging across all three BA clocks, with effect estimates ranging from 0.055 (95% CI: 0.038, 0.073) for the association between WHR and KDM-BA acceleration to 0.107 (0.044, 0.170) for the association between WHRadjBMI and DNAm PhenoAge acceleration. These associations remained significant in Mendelian randomization analyses. Mediation analyses revealed that acceleration of MetaboAge and KDM-BA partially explained the effects of abdominal adiposity on cardiovascular aging (%mediated: 6.0%–25.3%), while all three BA clocks accelerations mediated associations with general aging assessed by all-cause mortality (%mediated: 17.6%–60.6%), with MetaboAge contributing the largest proportion of mediation. Additionally, KDM-BA acceleration mediated the association between abdominal adiposity and frailty index.

Conclusions: Abdominal adiposity is associated with aging acceleration across multiple biological domains, especially via metabolic alterations captured by MetaboAge. Our findings demonstrated that targeting abdominal adiposity-related metabolic dysfunction may mitigate age-related conditions.

Keywords: abdominal adiposity; aging; biological age clock; metabolomics; DNA methylation

What is already known on this topic

While the effects of general adiposity on biological aging have been widely explored, abdominal adiposity remained relatively understudied. In particular, it remains unclear how multiple omics-based measures capture distinct biological pathways through which abdominal adiposity affects age-related conditions.

What this study adds

Abdominal adiposity was positively associated with accelerated biological aging, as measured by metabolomics-, clinical biomarker-, and DNA methylation-based clocks, in both observational and Mendelian randomization analyses. Notably, MetaboAge mediated a greater proportion of the effect of abdominal adiposity on cardiovascular and general aging.

How this study might affect research, practice or policy

Anti-aging interventions targeting metabolic dysregulation can effectively attenuate the impact of abdominal adiposity on age-related conditions.

Introduction

Obesity, characterized by excess body fat, is one of the key modifiable risk factors for adverse outcome[1]. The harmful effects of obesity vary according to the distribution of body fat[2]. Existing evidence suggests that abdominal adiposity exhibits a stronger and more consistent association with cardiovascular disease (CVD) outcomes and all-cause mortality than general adiposity, even after accounting for overall body mass[3 4]. In contrast to general adiposity, abdominal adiposity is characterized by an excess of visceral adipose tissue, which is more likely to drive systemic metabolic dysregulation, chronic low-grade inflammation, and subsequent multi-organ dysfunction[5]. These processes are core mechanisms underlying the progressive loss of physiological integrity observed during aging[6], with particularly pronounced effects on cardiovascular aging[7].

Aging is a heterogeneous process, and individuals with the same chronological age (CA) may have different biological age (BA)[6]. In the past decade, the emergence of biological clocks constructed with molecular and imaging biomarkers has allowed BA to be assessed at diverse levels[6]. Building on these advances, several studies have applied BA clocks derived from DNA methylation (DNAm)[8-10] and imaging data[11] to examine the impact of abdominal adiposity on biological aging, yet the results remain inconsistent. These studies focused on a single dimension of BA, limiting the ability to comprehensively evaluate how abdominal adiposity affects aging across multiple biological domains. Furthermore, existing studies have been largely restricted to associations of exposure with BA clocks, without formally assessing the potential mediating role of accelerated BA[11] . Thus, the role of aging as an essential mechanistic pathway connecting abdominal adiposity to adverse outcomes remains to be determined.

Therefore, we aimed to systematically evaluate the role of abdominal adiposity in biological aging at multiple biological levels. Specifically, we generated three BA clocks derived from metabolomics, clinical biomarkers, and DNAm in the China Kadoorie Biobank (CKB) leveraging previously established algorithms, and assessed their predictive performance for cardiovascular and general aging. We then investigated the effects of abdominal adiposity on these BA measures using both observational and Mendelian randomization approaches. Finally, we evaluated the mediating role of these BA clocks in the associations between abdominal adiposity and cardiovascular and general aging.

Methods

Study design and population

The CKB is a prospective cohort of 512,724 adults aged 30–79 years recruited from 10 regions in China between 2004 and 2008, with study design and follow-up described previously[12].

This study was based on three nested case–control sub-studies within the CKB with available genotyping data, including clinical biochemistry, metabolomics, and DNAm. Clinical biochemistry data for 16 biomarkers were available for 18,172 participants. Among these, 4,662 participants underwent targeted nuclear magnetic resonance metabolomics profiling of 225 metabolic measures, and 988 subsequently had DNAm measured using the Illumina EPIC array. Analyses were restricted to participants free of CVD at baseline, yielding sample sizes of 12,369, 4,391, and 980 for blood biomarker–, metabolomics–, and DNAm-based BA, respectively (**Figure 1**). Study design and inclusion criteria are detailed in the **Supplementary Methods** and **Supplementary Figure 1**.

Assessment of adiposity, cardiovascular and general aging

Abdominal adiposity was measured using waist-to-hip ratio (WHR) and WHR adjusted for body mass index (WHRadjBMI), and the latter was calculated through inverse normal transformation of WHR after adjustment for age, sex, region, and BMI. General adiposity was measured by BMI for comparison.

Cardiovascular aging was assessed using atherosclerotic cardiovascular disease (ASCVD) incidence and mortality, and general aging using all-cause mortality and the frailty index. In CKB, vital status and disease incidence were ascertained through electronic linkage to death and disease registries and national health insurance databases using unique personal identifiers, supplemented by annual active follow-up[12]. ASCVD was defined according to the 10th International Classification of Diseases code codes I20–I25 and I63. Follow-up was censored on Dec 31, 2022. The frailty index was generated using established methods[13] (**Supplemental Methods**), based on 28 CA-related variables covering physical measurements, medical conditions, symptoms, and signs, and calculated as the mean of these variables, with higher values indicating greater frailty.

Construction of biological Age clocks

We computed three BA measures based on metabolomics, clinical biochemistry biomarkers, and DNAm data, applying previously validated algorithms. MetaboAge was generated separately in men and women following the previous procedures in UK Biobank[14], using mortality-associated metabolic biomarkers selected by LASSO-Cox model and modeled with the Gompertz proportional hazards framework. The Klemera-Doubal method BA (KDM-BA) was trained on CA in men and women separately using 16 biochemical parameters and 9 physical measurements, as previously published in CKB[15]. DNAm PhenoAge was computed using Levine's methods[16] with DNAm data.

Both MetaboAge and DNAm PhenoAge were developed within a mortality-trained Gompertz framework, thereby enabling direct comparison. Age acceleration was calculated as the residual of regressing BA on CA to quantify deviations of BA clocks from CA. Participants were categorized as decelerated (<Q1), normal (Q1–Q3), or accelerated (>Q3) based on quartiles of BA acceleration. Detailed information on construction of BA was provided in **Supplementary Methods**.

Genetic risk score for abdominal adiposity and BA accelerations

For abdominal adiposity, genetic risk scores (GRS) were computed using single nucleotide polymorphisms obtained from genome-wide association study (GWAS) of the UK Biobank and effect sizes of conditional and joint analyses as weights[17]. For the three BA accelerations, GRSs were calculated using variants obtained from *de novo* GWASs, which were conducted using BOLT-LMM v2.3.4 software, with rank-based inverse-normal transformed BA acceleration as input (**Supplemental Methods**). After a standardized quality control and clumping procedure, variants associated with BA accelerations were selected at significance levels of 1×10^{-4}. Weighted GRS was then constructed based on these independent variants, with weights derived from effect sizes estimated of GWAS. The instrumental strength of GRS was assessed with F-statistics and R^2 (**Supplemental Methods**).

Statistical analysis

First, we evaluated the validity of three BAs as measures of aging. The predictive accuracy of each BA measure for all-cause mortality was assessed using the area under the receiver operating characteristic curve (AUROC), and pairwise differences between AUROCs were tested using DeLong's method.

We then evaluated the associations between abdominal adiposity and BA as well as age-related

conditions. In observational analyses, linear regression models were used to assess the associations between abdominal obesity and acceleration of each BA clock. The associations between abdominal obesity and age-related conditions were evaluated using Cox proportional hazards models for ASCVD and all-cause mortality, and linear regression models for the frailty index. To account for potential confounding, we fitted multivariable models with 5-year age groups and study regions as stratification variables. Model 1 adjusted for sex only. Model 2 was further adjusted for educational attainment. Model 3 further adjusted for lifestyle factors, including smoking, alcohol consumption, physical activity, and intake of fresh vegetables, fruits, and red meat. Analyses involving DNAm PhenoAge acceleration were additionally adjusted for cell-type proportions and batch effects, and this adjustment was applied consistently across all relevant analyses. Given that the study population was derived from nested case-control studies, inverse probability weighting was applied in regression analyses involving adiposity-related traits and BA accelerations to account for potential selection bias. Proportional hazards assumption was evaluated using scaled Schoenfeld residuals (**Supplementary Table 4**).

To investigate potential causal relationships, Mendelian randomization analyses were conducted to assess the genetic associations between abdominal adiposity and BA acceleration for each BA clock using a two-stage least squares approach. In the first stage, linear regression models were fitted with each GRS as the independent variable and adiposity-related traits as the dependent variables to obtain genetically predicted abdominal adiposity measures. In the second stage, the associations between genetically predicted adiposity-related traits and acceleration of each BA clock or age-related conditions were estimated using linear or Cox regression models among participants with available genotyping data. Both stages were adjusted for age, sex, study region,

genotyping array, and 11 principal components.

Finally, mediation analyses were conducted within an observational framework to quantify the extent to which BA acceleration mediated the associations between abdominal adiposity and age-related conditions at the population level. The indirect effect of the mediation analysis was obtained using the product of coefficients method, whereby the effect of abdominal adiposity on BA acceleration and the effect of BA acceleration on age-related conditions (conditional on abdominal adiposity) were sequentially estimated and multiplied. The proportion mediated was calculated as the ratio of the indirect effect to the total effect, with 95% confidence intervals derived from bootstrapping. Covariate adjustment and stratification variables in mediation analyses were consistent with those applied in the observational analyses described above.

The statistical analysis was performed using R statistical software version 4.1.3. The threshold of significance was considered to be $P<0.05$.

Results

Baseline characteristics of study participants

For the participants in the construction of BA clocks, the mean CA was 47.2-57.0 years, and females accounted for 43.7%-52.3%. The mean BMI was 23.3±3.4 kg/m² and the mean WHR was 0.90±0.10. Compared with participants with decelerated BA, those with accelerated BA were more likely to be rural residents, have lower education and physical activity, consume fresh fruit less frequently, take glucose-lowering medications, and have diabetes or hypertension at baseline (**Table 1**).

Predictive accuracy of BA clocks for all-cause mortality

The correlation coefficients between CA and MetaboAge, KDM-BA, and DNAm PhenoAge were

0.719, 0.992, and 0.792, respectively (P<0.001). Both MetaboAge (AUROC: 0.759 [0.744–0.774]) and KDM-BA (0.752 [0.743–0.760]) significantly outperformed CA (0.719 [0.703–0.736] and 0.740 [0.731–0.749], respectively; P<0.01) in predicting all-cause mortality (**Figure 2**). However, DNAm PhenoAge did not significantly improve the prediction of all-cause mortality compared to CA (P=0.80).

Associations of abdominal adiposity with BA accelerations

Abdominal adiposity was positively associated with acceleration of all three BA clocks in the observational analyses and associations were robust across stepwise adjusted models (**Table 2**). In the fully adjusted model (Model 3), MetaboAge, KDM-BA, and DNAm PhenoAge acceleration were all significantly associated with WHR, with the strongest association observed for DNAm PhenoAge (β: 0.084 [0.056, 0.113], 0.055 [0.038, 0.073], 0.097 [0.028, 0.165], respectively). For WHRadjBMI, DNAm PhenoAge acceleration again showed the strongest association (β: 0.107 [0.044, 0.170]), whereas MetaboAge and KDM-BA accelerations demonstrated weaker and comparable effect estimates (β: 0.067 [0.041, 0.093] and 0.068 [0.052, 0.084], respectively). For general adiposity, BMI showed a significant association only with MetaboAge acceleration, but not with acceleration of KDM-BA or DNAm PhenoAge (**Table 2**).

In Mendelian randomization analyses, genetically predicted abdominal adiposity showed consistent positive associations with acceleration across all three BA measures (all P<0.05, **Table 2**). Notably, DNAm PhenoAge remained showing the strongest associations with both WHR and WHRadjBMI.

Associations of BA accelerations with cardiovascular and general aging

Except for DNAm PhenoAge with incident ASCVD, BA accelerations were positively associated

with other age-related conditions in observational analyses, with slightly attenuated associations after adjusting for education and lifestyle factors (**Table 3**). In Model 3, MetaboAge acceleration showed the strongest associations with ASCVD and all-cause mortality (HR: 1.20 [1.14, 1.26] for ASCVD incidence, 1.59 [1.46, 1.73] for ASCVD mortality, and 1.58 [1.49, 1.66] for all-cause mortality). In contrast, KDM-BA acceleration exhibited the strongest association with the frailty index (β: 0.189 [0.173, 0.205]).

In Mendelian randomization analyses, positive genetic associations persisted for MetaboAge acceleration with ASCVD and all-cause mortality, KDM-BA acceleration with ASCVD, all-cause mortality, and frailty index, and DNAm PhenoAge acceleration with all-cause mortality (**Table 3**).

Mediation effect of BA accelerations in the associations of abdominal adiposity with cardiovascular and general aging

We focused on BA accelerations showing significant associations with abdominal adiposity and age-related conditions in both observational and Mendelian randomization analyses, as illustrated in **Figure 3**.

The effects of abdominal adiposity on cardiovascular aging were partially mediated through acceleration of MetaboAge and KDM-BA (**Supplementary Table 6-7, Figure 3**). For the associations of WHR with ASCVD incidence and mortality, MetaboAge acceleration accounted for 10.5% and 25.3% of the effects, respectively, while the corresponding mediation proportions for WHRadjBMI were 17.6% and 22.7%. Mediation through KDM-BA acceleration was consistently smaller than that through MetaboAge acceleration, with proportions of 6.0%, 9.7%, 15.3%, and 13.4%, respectively.

The impact of abdominal adiposity on general aging was reflected across multiple BA measures.

For all-cause mortality, a substantial proportion of the association with WHR was mediated by MetaboAge acceleration (60.6%), with smaller contributions from KDM-BA (28.9%) and DNAm PhenoAge acceleration (25.3%) (**Supplementary Table 8**). Mediation proportions for WHRadjBMI were consistently lower, at 32.9%, 24.0%, and 17.6%, respectively. For frailty index, mediation was observed only for KDM-BA acceleration, accounting for 3.0% and 6.5% of the associations with WHR and WHRadjBMI, respectively (**Supplementary Table 9, Figure 3**).

Discussion

In the current study, we generated MetaboAge, KDM-BA, and DNAm PhenoAge with omics data and validated algorithms. Using both observational and genetic analyses, we demonstrated that abdominal adiposity contributes to accelerated biological aging across metabolic, clinical, and epigenetic BA measures. Mediation analyses revealed that MetaboAge and KDM-BA partially mediated the effects of abdominal adiposity on cardiovascular aging, while all three BA clocks explained a substantial proportion of its impact on general aging.

Previous studies examining the relationship between adiposity and biological aging have predominantly focused on general adiposity[18-21], and only four studies assessed the associations between abdominal adiposity and BA, yielding inconsistent results. A cross-sectional study in Taiwan (N=2,474) reported a positive association between WHR and DNAm PhenoAge acceleration in men but not in women[9], whereas a US study including 2,758 non-Hispanic White women showed a positive association between WHR and DNAm PhenoAge acceleration adjusting for BMI[8]. However, a longitudinal study (N=1,041) reported null associations between WHR decrease and change in DNAm PhenoAge[10]. A recent imaging-based study in the UK Biobank (N=21,241) revealed that total abdominal and visceral adipose tissue, as well as abdominal

subcutaneous adipose tissue in males, were associated with increased cardiovascular age estimated from image-derived traits[11]. Although subsequent two-sample Mendelian randomization did not identify significant associations between visceral or abdominal subcutaneous adipose tissue and cardiovascular age, the presence of sample overlap may have introduced weak instrument bias and attenuated the causal estimates[11]. By contrast, our Mendelian randomization analyses with stronger instrumental variables provide genetic evidence supporting a potential causal relationship of abdominal adiposity on accelerating biological aging across multiple biological domains.

Abdominal adiposity is biologically distinct from general adiposity, as centrally distributed fat is more metabolically active and exerts disproportionate effects on systemic metabolic homeostasis and aging-related pathways[22]. Abdominal fat accumulation promotes insulin resistance, dyslipidemia, and ectopic lipid deposition, thereby accelerating vascular dysfunction and cardiac remodeling—key features of cardiovascular aging[2]. This may explain the comparatively greater mediating contribution of MetaboAge to the effects of abdominal adiposity on general aging and, especially cardiovascular aging. In contrast, DNAm PhenoAge was developed by incorporating preliminarily mortality-associated immune biomarkers, including lymphocyte percent, red cell distribution width, and white blood cell count, and may therefore preferentially capture aging pathways related to immune dysregulation and epigenetic reprogramming[16]. These processes may be more closely related to systemic aging and mortality risk than to cardiovascular-specific structural and functional changes, which may account for the observed mediation of the association between abdominal adiposity and general aging, but not cardiovascular aging, by DNAm PhenoAge. In contrast, KDM-BA constructed with physical measurements and blood

biomarkers integrated information from multiple organs and systems[15], allowing a more comprehensive assessment of the aging status. In our study, KDM-BA captured the impact of abdominal adiposity on all four age-related conditions, which represent distinct but complementary dimensions of aging. Notably, its robust association with frailty index, a measure reflecting functional aspects of aging, highlights its ability to capture physiological decline.

The effects of weight management on abdominal adiposity have been evaluated recently. Meta-analysis of randomized clinical trials demonstrated that dietary interventions such as meal replacement and vegetarian diet can effectively reduce waist circumference in patients with diabetes or metabolic syndrome[25 26]. Behavioral interventions delivered in primary care and the emerging anti-obesity drugs GLP-1 receptor agonists have also shown to reduce waist circumference in obesity or overweight individuals[27 28]. Despite these trials, strategies specifically targeting abdominal adiposity rather than overall body weight remain limited. Our study provides an alternative perspective for mitigating the adverse health outcomes of abdominal adiposity by intervening in metabolic dysregulation. In addition, given the long follow-up required to observe clinical endpoints in randomized trials, the predictive value of our BA measures highlights their potential as surrogate endpoints.

The present study has several strengths. First, we integrated multi-omics data and constructed three BA clocks to comprehensively assess the impact of abdominal adiposity on aging at multiple molecular levels. Second, our study utilized strong instrumental variables to infer causality between abdominal adiposity and BA measures and examine the predictive accuracy of BA clocks for age-related conditions. Third, the prospective cohort design enabled us to track the aging process and observe the long-term effects of BA accelerations and age-related conditions, thereby establishing

a reasonable temporal sequence. Several limitations should be acknowledged. First, the causal inference among abdominal adiposity, age accelerations and age-related conditions were limited to the CKB cohort and external validation was warranted. Second, although Mendelian randomization was used to strengthen causal inference, residual confounding and reverse causality cannot be fully excluded. Third, the sample sizes differed substantially across analyses of three BA measures, which may affect statistical power and comparability. However, inverse probability weighting was applied to partially mitigate this issue. Finally, our participants were derived from nested case–control studies, which may lead to an overrepresentation of cases and limit generalizability of absolute risk estimates. Nevertheless, as cases and controls were sampled from the same well-defined population, the internal validity of the association estimates is less likely to be materially affected.

In conclusion, abdominal adiposity is associated with accelerated biological aging across multiple biological domains, thereby contributing to subsequent age-related conditions. MetaboAge demonstrated a comparatively stronger mediating effect between abdominal adiposity and both general and cardiovascular aging, highlighting the pivotal role of metabolic perturbations in linking abdominal fat accumulation to adverse outcomes. These findings underscore the importance of considering fat distribution in aging research, and highlight the potential for metabolically targeted interventions to slow biological aging in individuals with abdominal obesity. Moreover, interventions aimed at modulating aging process itself may help mitigate adverse health consequences associated with abdominal adiposity, offering a complementary strategy to traditional lifestyle or weight management approaches.

List of abbreviations

CVD: cardiovascular disease

CA: chronological age

BA: biological age

DNAm: DNA methylation

CKB: China Kadoorie Biobank

WHR: waist-to-hip ratio

BMI: body mass index

WHRadjBMI: waist-to-hip ratio adjusted for body mass index

ASCVD: atherosclerotic cardiovascular disease

KDM-BA: Klemera-Doubal method biological age

GRS: genetic risk score

GWAS: genome-wide association study

AUROC: area under the receiver operating characteristic curve

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Competing interests

The authors declare that they do not have any conflicts of interest to disclose.

Contributorship

YP accepts full responsibility for the work and serves as the guarantor. YP conceptualised and designed this study. ZW analysed the data, did the statistical analyses, designed the figures and wrote the manuscript. JL performed data verification and validation. JS, LY, YC, HD, DS, and JC critically revised the manuscript for intellectual content. JL, CY, DS, PP, and MY organised the resources and logistics at each study centre and contributed to community engagement, ethical approval, participant enrolment, investigation, and project administration. JL, ZC, LL, and YP were responsible for funding acquisition. ZC, LL, and YP accessed and verified the underlying data. All authors had full access to all the data in the study, read and approved the final manuscript before publication, and had final responsibility for the decision to submit for publication.

Patient and Public Involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or

dissemination plans of this research.

Ethics statements

The study protocol was approved by the Ethical Review Committee of Peking University Health Science Center. All participants provided written informed consent.

Data sharing statement

Further information on the China Kadoorie Biobank, including data access procedures, is available at https://www.ckbiobank.org/data-access.

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Figure legends

Figure 1. Study overview

Abbreviations: WHR, waist-to-hip ratio; WHRadjBMI, waist-to-hip ratio adjusted for body mass index; ASCVD, atherosclerotic cardiovascular disease; MetaboAge, metabolic age; KDM, Klemera and Doubal's method; BA, biological age; DNAm, DNA methylation; SD, standard deviation; NS, not significant.

Figure 2. Predictive accuracy of biological age clocks for all-cause mortality

Abbreviations: MetaboAge, metabolic age; KDM, Klemera and Doubal's method; BA, biological age; DNAm, DNA methylation; CA, chronological age; AUROC, area under the receiver operating characteristic curve; CI, confidence interval.

Figure 3. Mediating effects of BA acceleration on the associations between adiposity-related traits and age-related conditions

Linear models were used to assess the association of WHRadjBMI and BA acceleration, and the effects of WHRadjBMI and KDM-BA acceleration on frailty index. Cox proportional hazard model was used to evaluate the effects of WHRadjBMI and BA acceleration on ASCVD incidence, ASCVD mortality, and all-cause mortality. All models were adjusted for sex, educational attainment, and lifestyle factors (including smoking status, alcohol consumption, physical activity, and intake of fresh vegetables, fruits, and red meat) with age grouped in 5-year intervals and study region included as stratification variables. Models for DNAm PhenoAge further adjusted for cell-type proportions and batch effects. WHRadjBMI, BA acceleration, and frailty index were Z-transformed in these models. Dashed arrows denote non-significance in genetic analysis. *P<0.05; **P<0.01;

***P<0.001

Abbreviations: MetaboAge, metabolic age; KDM, Klemera and Doubal's method; BA, biological age; DNAm, DNA methylation; NS, not significant; HR, hazard ratio; WHRadjBMI, waist-to-hip ratio adjusted for body mass index; ASCVD, atherosclerotic cardiovascular disease.

Table 1. Baseline characteristics of participants in the construction of KDM-BA

Baseline characteristics	Overall (N=12,369)	Deceleration (N=3,092)	Normal (N=6,184)	Acceleration (N=3,093)	*P*
Sociodemographic characteristic					
Age, year	57.0 ± 10.5	57.6 ± 10.3	56.3 ± 10.6	57.8 ± 10.5	<0.001
Female, %	6215 (50.2)	626 (20.2)	4758 (76.9)	831 (26.9)	<0.001
Urban, %	3690 (29.8)	1154 (37.3)	1827 (29.5)	709 (22.9)	<0.001
Middle school and above, %	4732 (38.3)	1517 (49.1)	2172 (35.1)	1043 (33.7)	<0.001
Fasting time, h	4.7 ± 4.8	5.0 ± 5.0	4.8 ± 4.8	4.2 ± 4.3	<0.001
Lifestyle factors					
Current smoking[a], %	4534 (36.7)	1604 (51.9)	1199 (19.4)	1731 (56.0)	<0.001
Weekly drinking, %	1893 (15.3)	765 (24.7)	536 (8.7)	592 (19.1)	<0.001
Total physical activity, MET-h/day	18.8 ± 13.6	20.0 ± 15.0	18.8 ± 12.8	17.4 ± 13.3	<0.001
Dietary habits					
Days consumed fresh vegetables /week	6.8 ± 0.9	6.8 ± 0.8	6.8 ± 1.0	6.8 ± 1.0	<0.001
Days consumed fresh fruits /week	1.8 ± 2.4	2.1 ± 2.6	1.9 ± 2.5	1.4 ± 2.1	<0.001
Days consumed red meat /week	3.0 ± 2.6	3.2 ± 2.7	2.8 ± 2.6	3.0 ± 2.6	<0.001
Adiposity					<0.001
BMI, kg/m^2	23.3 ± 3.4	23.3 ± 3.1	23.6 ± 3.5	22.9 ± 3.6	<0.001
Waist circumference, cm	80.1 ± 9.8	80.6 ± 9.2	79.7 ± 9.8	80.2 ± 10.2	<0.001
WHR	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	<0.001
Fat percentage, %	26.3 ± 9.0	23.3 ± 7.7	29.3 ± 8.6	23.4 ± 8.8	<0.001
Family history of, %					
Heart attack	430 (3.5)	131 (4.2)	221 (3.6)	78 (2.5)	<0.001
Stroke	2679 (21.7)	753 (24.4)	1375 (22.3)	551 (17.9)	<0.001
Cancer	2019 (16.4)	598 (19.4)	1034 (16.8)	387 (12.5)	<0.001
Medication of, %					
Antihypertensives	2157 (17.4)	385 (12.5)	1102 (17.8)	670 (21.7)	<0.001
Antidiabetics	295 (2.4)	50 (1.6)	165 (2.7)	80 (2.6)	<0.001
Prevalent hypertension, %	6799 (55.0)	1405 (45.4)	3358 (54.3)	2036 (65.8)	<0.001
Prevalent diabetes, %	823 (6.7)	158 (5.1)	418 (6.8)	247 (8.0)	<0.001

Participants were grouped according to quartiles of KDM-BA acceleration: those below Q1 were classified as the Decelerated group, those between Q1 and Q3 as the Normal group, and those above Q3 as the Accelerated group. Differences across BA acceleration groups were assessed using ANOVA or χ^2 tests.

Abbreviations: MET, metabolic equivalent of task; BMI, body mass index; WHR, waist-to-hip ratio.

[a]Former smoker who had stopped smoking due to illness was classified as current smoker.

Table 2. Associations between adiposity-related traits and biological age acceleration

Model	WHR		WHRadjBMI		BMI	
	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
MetaboAge acceleration						
Model 1	0.083 (0.055, 0.111)	**<0.001**	0.069 (0.043, 0.094)	**<0.001**	0.033 (0.006, 0.059)	**0.015**
Model 2	0.083 (0.054, 0.111)	**<0.001**	0.068 (0.043, 0.094)	**<0.001**	0.033 (0.007, 0.059)	**0.014**
Model 3	0.084 (0.056, 0.113)	**<0.001**	0.067 (0.041, 0.093)	**<0.001**	0.036 (0.009, 0.062)	**0.009**
Mendelian randomization	0.354 (0.074, 0.634)	**0.013**	0.227 (0.025, 0.429)	**0.027**	0.187 (0.016, 0.358)	**0.032**
KDM-BA acceleration						
Model 1	0.051 (0.033, 0.068)	**<0.001**	0.068 (0.052, 0.085)	**<0.001**	-0.016 (-0.034, 0.002)	0.075
Model 2	0.050 (0.033, 0.068)	**<0.001**	0.068 (0.052, 0.084)	**<0.001**	-0.015 (-0.032, 0.003)	0.098
Model 3	0.055 (0.038, 0.073)	**<0.001**	0.068 (0.052, 0.084)	**<0.001**	-0.006 (-0.024, 0.012)	0.502
Mendelian randomization	0.422 (0.233, 0.610)	**<0.001**	0.168 (0.031, 0.305)	**0.016**	0.120 (0.010, 0.229)	**0.033**
DNAm PhenoAge acceleration						
Model 1	0.082 (0.015, 0.150)	**0.017**	0.104 (0.041, 0.167)	**0.001**	-0.021 (-0.084, 0.041)	0.502
Model 2	0.083 (0.016, 0.151)	**0.016**	0.104 (0.041, 0.166)	**0.001**	-0.020 (-0.083, 0.042)	0.528
Model 3	0.097 (0.028, 0.165)	**0.006**	0.107 (0.044, 0.170)	**0.001**	-0.008 (-0.071, 0.055)	0.804
Mendelian randomization	0.780 (0.019, 1.541)	**0.045**	0.979 (0.445, 1.514)	**<0.001**	0.044 (-0.382, 0.469)	0.841

Linear models were used in the observational analysis and Mendelian randomization. In the observational analyses, 5-year age groups and study regions were included as stratification variables in all models. Model 1 adjusted for sex only, Model 2 was further adjusted for educational attainment, and Model 3 additionally adjusted for lifestyle factors, including smoking status, alcohol consumption, physical activity, and intake of fresh vegetables, fruits, and red meat. Analysis for DNAm PhenoAge further adjusted for cell-type proportions and batch effects. In Mendelian randomization, the model adjusted for age, age squared, sex, study regions, genotyping array, and 11 principal components in both stages. Adiposity-related traits and BA accelerations were Z-transformed in all models.

Abbreviations: MetaboAge, metabolic age; KDM, Klemera and Doubal's method; BA, biological age; DNAm, DNA methylation.

Table 3. Associations of biological age acceleration with cardiovascular and general aging

Model	ASCVD incidence		ASCVD mortality		All-cause mortality		Frailty index	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	β (95% CI)	*P*
MetaboAge acceleration								
No. of cases (%)	2473 (56.3)		578 (13.2)		1357 (30.9)		-	
Model 1	1.21 (1.16, 1.27)	**<0.001**	1.62 (1.48, 1.76)	**<0.001**	1.61 (1.52, 1.70)	**<0.001**	0.164 (0.136, 0.191)	**<0.001**
Model 2	1.21 (1.15, 1.27)	**<0.001**	1.61 (1.48, 1.75)	**<0.001**	1.60 (1.51, 1.69)	**<0.001**	0.162 (0.134, 0.189)	**<0.001**
Model 3	1.20 (1.14, 1.26)	**<0.001**	1.59 (1.46, 1.73)	**<0.001**	1.58 (1.49, 1.66)	**<0.001**	0.147 (0.120, 0.175)	**<0.001**
Mendelian randomization	1.03 (1.01, 1.06)	**0.023**	1.09 (1.03, 1.16)	**0.005**	1.06 (1.03, 1.09)	**<0.001**	0.012 (-0.001, 0.026)	0.069
KDM-BA acceleration								
No. of cases (%)	6968 (56.3)		1320 (10.7)		5293 (42.8)		-	
Model 1	1.18 (1.15, 1.21)	**<0.001**	1.35 (1.28, 1.43)	**<0.001**	1.42 (1.38, 1.45)	**<0.001**	0.213 (0.196, 0.229)	**<0.001**
Model 2	1.18 (1.15, 1.21)	**<0.001**	1.35 (1.28, 1.42)	**<0.001**	1.41 (1.37, 1.45)	**<0.001**	0.211 (0.195, 0.227)	**<0.001**
Model 3	1.17 (1.14, 1.20)	**<0.001**	1.31 (1.24, 1.38)	**<0.001**	1.38 (1.35, 1.42)	**<0.001**	0.189 (0.173, 0.205)	**<0.001**
Mendelian randomization	1.04 (1.01, 1.07)	**0.008**	1.11 (1.03, 1.19)	**0.005**	1.13 (1.09, 1.17)	**<0.001**	0.038 (0.023, 0.054)	**<0.001**
DNAm PhenoAge acceleration								
No. of cases (%)	587 (59.9)		325 (33.2)		383 (39.1)		-	
Model 1	1.08 (0.99, 1.18)	0.070	1.17 (1.05, 1.31)	**0.006**	1.19 (1.08, 1.32)	**0.001**	0.062 (0.004, 0.120)	**0.036**
Model 2	1.08 (0.99, 1.18)	0.071	1.17 (1.04, 1.31)	**0.006**	1.19 (1.08, 1.32)	**0.001**	0.062 (0.004, 0.120)	**0.036**
Model 3	1.09 (0.99, 1.19)	0.065	1.17 (1.04, 1.31)	**0.008**	1.19 (1.07, 1.32)	**0.001**	0.059 (0.001, 0.116)	**0.046**
Mendelian randomization	0.99 (0.97, 1.02)	0.454	1.04 (0.98, 1.11)	0.194	1.03 (1.01, 1.07)	**0.039**	-0.006 (-0.020, 0.007)	0.340

Linear models were used in the observational analysis for frailty index and the first stage in Mendelian randomization analyses. Cox proportional hazard model was used in the observational analysis and the second stage in Mendelian randomization analyses for ASCVD and all-cause mortality. In the observational analyses, 5-year age groups and study regions were included as stratification variables in all models. Model 1 adjusted for sex only, Model 2 was further adjusted for educational attainment, and Model 3 additionally adjusted for lifestyle factors, including smoking status, alcohol consumption, physical activity, and intake of fresh vegetables, fruits, and red meat. Analysis for DNAm PhenoAge further adjusted for cell-type proportions and batch

effects. In Mendelian randomization, the model adjusted for age, age squared, sex, study regions, genotyping array, and 11 principal components in both stages. Biological age accelerations and frailty index were Z-transformed in all models.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; HR, hazard ratio; CI, confidence interval; MetaboAge, metabolic age; KDM, Klemera and Doubal's method; BA, biological age; DNAm, DNA methylation.