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Original Article

Accelerated Epigenetic Aging in Diabetes: Socio-Biological Pathways of Health Inequity

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ABSTRACT: Type 2 diabetes mellitus (T2DM) is an aging-related disease with greater incidence in older African Americans (AAs) than whites, but studies on racial disparity in epigenetic aging pathways are scarce; specifically, socio-biological aging processes are not well characterized. We investigated biological aging acceleration (aging accel) with development of T2DM and additionally, insulin resistance (IR) of nondiabetic women at baseline in cross-section. We estimated the extent to which social adversity explained AAs' greater aging accel and, together with accelerated aging, mediated their greater burden of glucometabolic outcomes. Clinical and social determinants of health (SDOH) variables and genome-wide DNA methylation data were extracted from the Women's Health Initiative with > 1,500 postmenopausal non-diabetic women. Diabetic outcome was followed for a mean of 19 years, and baseline IR was measured using fasting serum samples. Aging accel metrics were calculated with Levine's clock, and mediation effects of SDOH and aging accel was estimated via Multiple Mediation analyses. Greater aging accel was observed in T2DM, albeit with only univariate significance and IR and in AAs rather than whites. SDOH was associated with greater aging accel, but its impact on greater accelerated aging in AAs varied and in combination, was minimal. Although aging accel has greater influence than SDOH on the racial difference in glucometabolic outcomes, these parameters jointly mediated to only a limited extent T2DM/IR pathways by race. Our mediation findings are exploratory and hypothesis-generating and thus, our results warrant validation studies to better understand socio-glucometabolic pathways shared by epigenetic aging processes and to inform early risk stratification among at-risk older women for disease prevention and reduced racial health inequity.

Keywords: aging acceleration, African American, DNA methylation, older postmenopausal women, epigenetic aging, health inequity, social determinants of health, Type 2 diabetes

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a global epidemic whose burden is expected to worsen over time, affecting an estimated 693 million people worldwide in 2045 [1, 2]. T2DM, as the most prevalent diabetic form, accounts for about 90% of new cases among people older than age 40 [3, 4], thus representing a state of accelerated aging [5]. In particular, older African Americans (AAs) have twice the incidence of T2DM that whites have in the U.S [6, 7].

Aging involves a gradual decline in multiple biological functions over time, leading to increased risk for age-associated diseases such as T2DM [8, 9]. However, individuals of the same age markedly vary in their susceptibility for T2DM, which can be attributed to the different rates of biological aging acceleration (aging

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accel) between individuals. Therefore, studies have focused on deciphering the hallmarks of biological aging to understand aging-related loss of tissue function and to more precisely predict age-associated diseases [10-12]. The cellular bases of aging processes have been identified as cellular senescence, altered intercellular communication, stem cell exhaustion, telomere shortening, genomic instability, and more recently, epigenetic deregulation [5, 13].

Given that T2DM is a complex, multifactorial disease whose development depends on interactions between genes and environmental exposures, one common pathway connecting T2DM to the gene–environment interplay is the epigenome. Indeed, the establishment and maintenance of epigenetic modification are susceptible to environmental lifestyle factors such as diet and exercise, the two major behavioral risk factors for T2DM [14-16]. Thus, the epigenetic mechanism has been considered the most plausible pathway underlying gene–environment interactions in the development of age-related T2DM and relevant phenotypes such as insulin resistance (IR). In particular, DNA methylation (DNAm), the best-known major epigenetic alteration, is a robust genome-wide reversible biomarker of biological age, which is validated as outperforming other aging markers in relation to aging and aging-related phenotypes [17]. Using DNAm, "epigenetic clocks" were developed as novel biological aging predictors. A greater DNAm-based epigenetic age than chronological age of an individual is termed "epigenetic aging accel," reflecting a proxy measure of faster aging [18] and constitutes a strong prediction scale for premature mortality [19], early onset of age-attributable diseases, including cardiometabolic morbidities [20, 21], changes in physical and cognitive fitness [22], and some health lifestyles such as obesity, fat-rich diet, and smoking [23, 24]. Of note, previous methylation studies detected differentially methylated regions and individual DNAm sites among T2DM individuals, in contrast with nondiabetic individuals, highlighting many of these DNAm signatures that overlap between islet cells and whole blood [25]. Also, DNAm-based epigenetic aging accel in T2DM individuals was observed in both islets and blood [10, 26]. These findings suggest that blood-based DNAm is an accessible, useful surrogate marker for aging that reflects multiple metabolic diabetic pathways. However, most DNAm-based T2DM studies have been cross-sectional, making inference of a temporal relationship difficult.

In addition, different races demonstrate varying aging processes, e.g., AA women have the shortest life expectancy (78 years) than other racial and ethnic groups (e.g., whites women, 81 years), implying earlier declines in health status and faster aging [27, 28]. But studies on the racial differences in biological aging processes and relevant biomarkers are limited. Better characterizing an aging-related biomarker can provide insight into this underlying racial difference in aging and have the potential for use as a unique risk predictor for the disease, thereby contributing to reducing the diabetic health disparity.

In our present study, we addressed these gaps by prospectively examining older women for their T2DM incidence in association with baseline epigenetic aging accel metrics measured in peripheral blood lymphocytes (PBLs). Additionally, we investigated an association between IR status of women who were not diabetic and aging accel in cross section. We examined whether aging accel scales vary by race (AAs vs. whites) and to what extent the aging discrepancy explains the racial disparity in T2DM development/IR status (Fig. 1A).

Non-medical environmental factors, specifically adverse social exposures, represent low support of the social determinants of health (SDOH), contributing to epigenetic aging accel [29]. Cumulative effect of low source of SDOH also affects individuals' health outcomes. Indeed, SDOH can be more important than lifestyle choices in increasing the risk for T2DM [30, 31], but studies for the influence of SDOH on DNAm-based aging in relation to T2DM are lacking. Further, SDOH are stand-alone mediators of the difference in T2DM incidence between AAs and whites [32]. Considering this evidence, we hypothesized that 1) lower support of SDOH is associated with greater aging accel and has a substantial contribution to greater aging accel in AAs than in whites (Fig. 1B) and that 2) SDOH and aging accel jointly explain the greater incidence of T2DM and higher prevalence of IR in AAs (Fig. 1C).

Globally, more than 50% of diabetic individuals are unaware of their condition, hence at risk for subsequent diabetic complications [33]. Thus, a better biomarker for T2DM risk can promote earlier, more accurate risk stratification for high-risk individuals who would benefit from targeted interventions. Whereas chronological aging is uniform and unchangeable, the rate of biological aging accel, as an individualized, more-precise risk predictor, is modifiable depending on individual genetics and environmental exposures. Our study was aimed to better understand biological aging pathways in T2DM development from the perspective of racial disparity and, further, to investigate the role of SDOH in mediating accelerated aging and greater disease risk among AA minorities. Illuminating the mechanistic links between potentially modifiable factors such as social risk and accelerated aging may support the development of interventions and policy shifts targeted at reducing health inequities in T2DM.

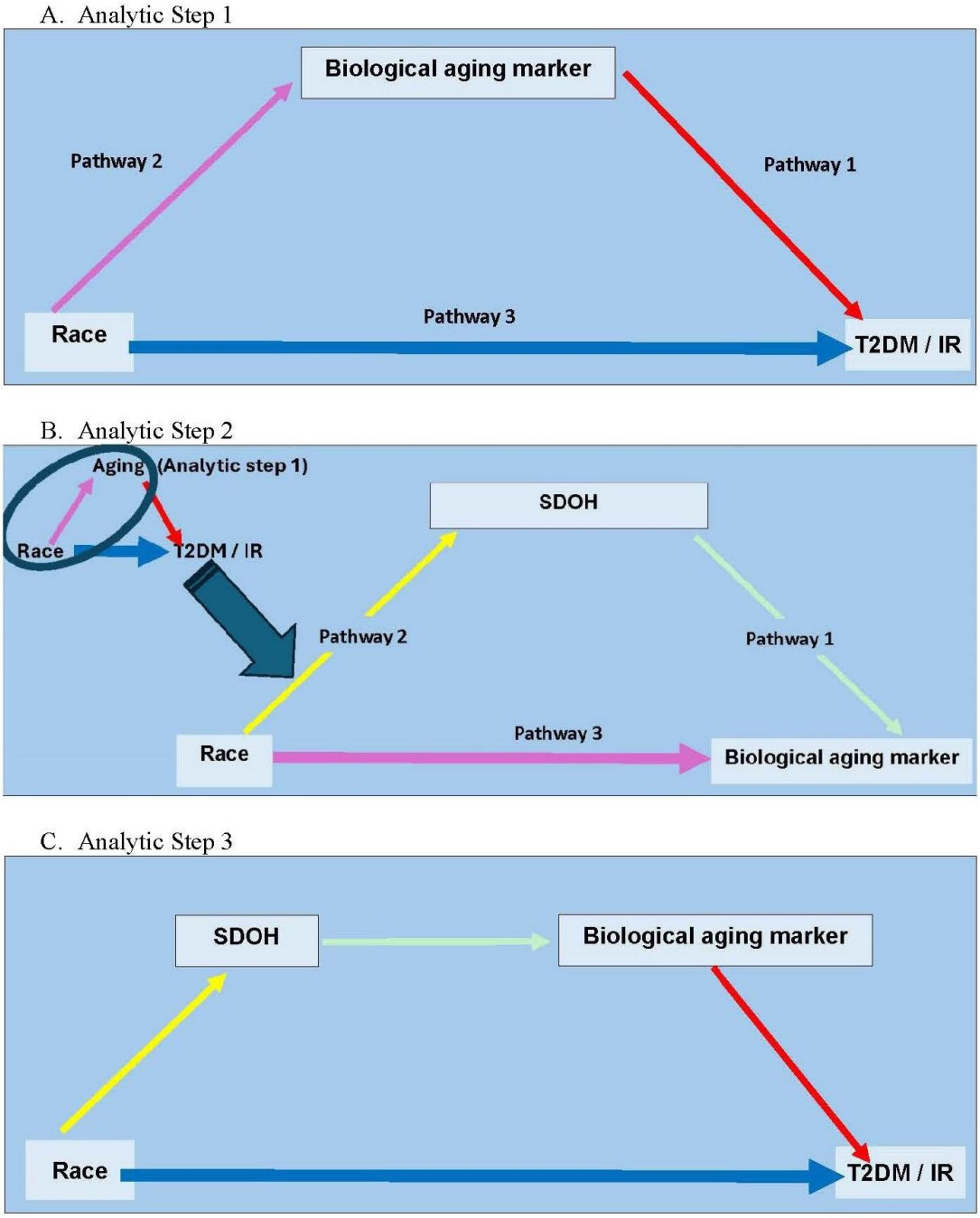

Figure 1. Diagrams of tested analytic steps and relevant pathways. (T2DM, type 2 diabetes mellitus; IR, insulin resistance; SDOH, social determinants of health.) (**A)** Analytic Step 1: Racial difference in T2DM/IR (pathway 3) via aging acceleration (pathways 1 and 2). (**B)** Analytic Step 2: Racial difference in aging acceleration (pathway 3) via SDOH (pathways 1 and 2). (**C)** Analytic Step 3: Racial difference in T2DM/IR via joint pathways of SDOH and aging acceleration (from SDOH to aging acceleration)

MATERIALS AND METHODS

Study population

We utilized data from the Women's Health Initiative Database for Genotypes and Phenotypes (WHI-dbGaP) genomic repository, comprising postmenopausal women, 50–79 years old, who were recruited from 1993 through 1998 at more than 40 U.S. designated clinical centers. The study has followed active participants annually for their physiological clinical data as well as disease updates [34, 35]. Of the WHI-dbGaP resources, the BAA23 is the

largest ancillary study with available PBL-based genome-wide DNAm data [36]. From the total of 2,107 women in this study, 676 AAs and 998 whites were initially selected for the current study (Fig. S1). We excluded 173 women whose DM data were missing during follow-up and/or had been diagnosed with DM at baseline, remaining 1,501 (565 AAs and 936 whites) in this study. Over the long-term follow-up period (mean, 19 years; range, 12–28 years), 171 (30%) of the AAs and 223 (24%) of the whites developed T2DM. We performed a separate cross-sectional analysis of non-DM women's IR status in association with aging accel, both measured at enrollment, including 1,468 (554 AAs and 914 whites) whose data on IR were available. Among them, 186 (34%) AAs and 234 (26%) whites were categorized as the IR group. The Institutional Review Boards of the University of California, Los Angeles and each WHI clinical center approved this study.

Data collection and glucometabolic outcomes (T2DM and IR)

Clinical and self-reported data collection had been performed on the basis of WHI's standardized written protocols and data quality assurance procedures, yielding demographic and socioeconomic information (age; race; ethnicity; education; family income; any medical insurance; social support), medical and reproductive histories (hypertension ever; high cholesterol requiring pills; oophorectomy history; hormone replacement therapy; ages at menopause and menarche), and lifestyle/behavior variables (physical activity; years of regular smoking). Participants had also completed a food frequency questionnaire, which was validated by 24-hour dietary recall. For this study, we included the Healthy Eating Index-2015 [HEI-2015] total score; scores for fatty acids, whole fruits, and total vegetables components; dietary alcohol intake; and frequency of alcohol consumption. Trained staff had measured anthropometric characteristics, including height, weight, and waist and hip circumferences at baseline. We categorized selected SDOH variables as follows: education, < college vs. ≥ college; family income, < \$20,000, \$20,000–\$49,999, \$50,000–\$99,999, and ≥ \$100,000; any medical insurance, no vs. yes. Social support was measured as a composite score from 9 questions, adapted from the Medical Outcomes Study [37], ranging from 9 to 45, where a greater score indicates more social support. The social support scores were further binarily stratified by the media.

T2DM development was assessed by self-report of taking pills or insulin shots for DM (no vs. yes) during the mean follow-up period of 19 years. Fasting serum samples drawn from the WHI participants at enrollment were assayed for glucose via the hexokinase method on a Hitachi 747 analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN) and insulin via radioimmunoassay (Linco Research, Inc., St. Louis, MO) or automated ES300 method (Boehringer Mannheim Diagnostics, Indianapolis, IN), both of which were comparable for insulin measures [38]. Homeostatic model assessment–IR (HOMA-IR) was estimated as glucose (unit: mg/dl) × insulin (unit: μIU/ml) / 405 [39] and binarily classified with a 2.9 cutoff value, above which level reflects significant IR [40, 41].

Epigenetic clock and accelerated aging scales

Illumina 450BeadChip was used to generate a PBL-based global DNAm array, which was normalized via beta-mixture quantile [42] and batch-adjusted with random intercept for plate and chip and a fixed effect for row [43], resulting in a total of 482,421 CpG dinucleotides (CpGs). To address the DNAm stability from stored samples [44], we adopted Horvath's application [18], controlling for heterogeneities in leukocyte composition in measuring DNAm age: $CD4^+$ T cells, natural killer cells, monocytes, and granulocytes assessed from Houseman's method [45] and plasma blasts, $CD8^+CD28^-CD45RA^-$ T cells, and naïve CD8 T cells from Horvath's method [18]. We further reported differences in these cell components by race, T2DM, IR, and SDOH variables (Table S1).

While the first-generation clocks [17, 46] demonstrate weaker relationships with health outcomes and clinical cardiometabolic indicators [11], the second-generation clocks were developed based on the correlation between methylation and health risk scores. Among the latter, Levine's clock integrates 10 clinical factors, including albumin, glucose, and C-reactive protein, and calculates a clinical phenotypic aging score with 513 relevant CpGs [47]. Levine's clock outperforms others in predicting mortality and age-related cardiometabolic morbidities [47, 48] across multiple tissues and organs. We thus generated Levine's clock for each individual as a composite scale from a linear combination of the weighted CpGs by using an available online tool [18, 49] and the *methylclock* annotation Bioconductor package.

Statistical analysis

Epigenetic aging accel was estimated with two metrics: 1) AgeAccelDiff, subtraction of chronological age from DNAm age and 2) intrinsic epigenetic age acceleration (IEAA), the residual from regressing DNAm age on chronological age, which was further adjusted for leukocyte cell proportions. The IEAA thus reflects cellular aging accel independent of varying DNAm levels due to individuals' heterogeneity in cell components [50].

In Pathways (Path, hereafter) 1 and 2 of Analytic Step 1, differences in aging accel by T2DM/IR and by race were examined, respectively, using unpaired two-sample *t* or Kruskal-Wallis testing if continuous variables were skewed or had outliers. In Path 1, T2DM/IR was regressed on each aging accel scale, indicating 1-unit increase in aging accel associated with a glucometabolic outcome risk. The aging scale was further analyzed with a 10-year interval or binary predictor (negative vs. positive aging accel). In Path 2's regression analysis, aging accel was examined with continuous or binary outcomes, representing the magnitude of difference in aging accel by race. In Path 3, results of regression analysis indicated the degree of racial difference (white as reference) in T2DM/IR outcomes. In each path's analytic model, we accounted for the following covariates: Model 1, univariate analysis; Model 2, Model 1 plus body mass index (BMI) and waist-to-hip ratio (WHR); and Model 3, Model 2 plus all other covariates (age, race, hypertension ever, high cholesterol requiring pills, fatty acids, whole fruits and vegetables, and a total score from HEI-2015, dietary alcohol, alcohol intake frequency, physical activity, years of regular smoking, oophorectomy history, hormone replacement therapy, ages of menopause and menarche, education, family income, any insurance, and social support) except tested variables.

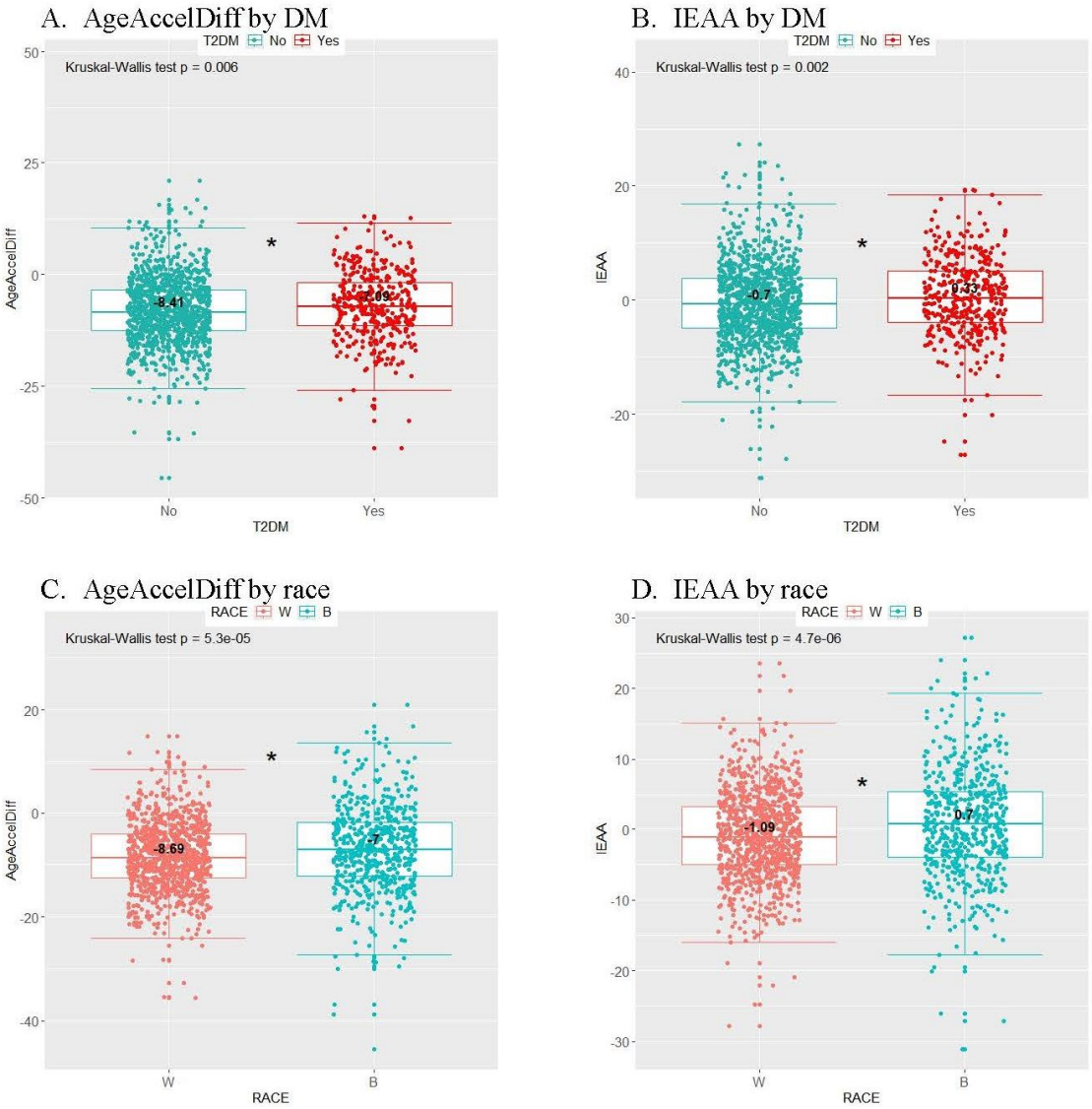

Figure 2. Analytic Step 1: Distribution of AgeAccelDiff and IEAA by T2DM and race. (**A and B)** Path 1; (**C and D)** Path 2. (non-T2DM [n = 1,107] vs. T2DM [n = 394]; W [n = 936] vs. B [n = 565]. * indicates a statistical difference between groups. AgeAccelDiff, epigenetic age acceleration as departure of DNAmAge from chronological age; B, blacks [African Americans]; T2DM, type 2 diabetes mellitus development; IEAA, intrinsic epigenetic age acceleration as residuals adjusted for cell composition; W, whites.) **(A)** AgeAccelDiff by T2DM. **(B)** IEAA by T2DM. **(C)** AgeAccelDiff by race. **(D)** IEAA by race.

In Paths 1 and 2 of Analytic Step 2, the difference in individual SDOH by aging accel and race, respectively, were evaluated using unpaired two-sample *t* or Kruskal-Wallis testing as appropriate and, for Path 2, each SDOH was further regressed on race, indicating the extent of racial difference in the social construct. Of note, with ordinal income outcomes, we performed the ordinal logistic regression by meeting the proportional odds assumption.

To evaluate the mediation effect of SDOH on greater aging accel in AAs than in whites, a proportional effect (an indirect effect/total effect) of an individual SDOH was estimated with the Sobel inferential test. The joint effect of the combined SDOH was examined using a General Multiple Mediation analytic test with bootstrapping, which was specifically designed to deal with scenarios involving multiple mediators [51, 52]. Finally, using the General Multiple Mediation analytic approach, we estimated the total and direct associations between race and T2DM/IR, and on this association, an indirect, mediation effect of SDOH in combination and aging accel, both separately and jointly was investigated. R packages bda and mma were used.

Table 1. Analytic Step 1, composed of 3 pathways: Association of biological aging parameters (AgeAccelDiff and IEAA) with T2DM (Path 1) and racial difference in biological aging parameter (Path 2) and T2DM (Path 3).

		Model 1*			Model 2**			Model 3***	
<Path 1>	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
AgeAccelDiff¥	**1.019**	**(1.003, 1.035)**	**0.018**	1.008	(0.992, 1.025)	0.318	1.010	(0.990, 1.031)	0.337
IEAA¥	**1.025**	**(1.008, 1.042)**	**0.004**	1.013	(0.995, 1.031)	0.166	1.012	(0.990, 1.035)	0.277
<Path 2>	**Beta**	**95% CI**	***P***	**Beta**	**95% CI**	***P***	**Beta**	**95% CI**	***P***
AgeAccelDiff€	**1.468**	**(0.694, 2.241)**	**0.0002**	**1.126**	**(0.337, 1.915)**	**0.005**	**1.498**	**(0.384, 2.613)**	**0.008**
	OR	**95% CI**	***P***	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
	1.908	**(1.419, 2.569)**	**0.00002**	**1.752**	**(1.290, 2.380)**	**0.0003**	**1.877**	**(1.209, 2.915)**	**0.005**
IEAA€	**Beta**	**95% CI**	***P***	**Beta**	**95% CI**	***P***	**Beta**	**95% CI**	***P***
	1.739	**(1.026, 2.451)**	**1.84E-06**	**1.433**	**(0.709, 2.158)**	**0.0001**	**1.866**	**(0.843, 2.889)**	**0.0004**
	OR	**95% CI**	***P***	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
	1.508	**(1.223, 1.861)**	**0.0001**	**1.404**	**(1.130, 1.746)**	**0.002**	**1.776**	**(1.297, 2.439)**	**0.0003**
<Path 3>	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Race	**1.388**	**(1.097, 1.753)**	**0.006**	1.165	(0.909, 1.492)	0.226	0.790	(0.546, 1.137)	0.207

AgeAccelDiff, epigenetic age acceleration as departure of DNAmAge from chronological age; CI, confidence interval; T2DM, type 2 diabetes mellitus development; IEAA, intrinsic epigenetic age acceleration as residuals adjusted for cell composition; OR, odds ratio. Numbers in bold face are statistically significant.

* Model 1: Path 1 = T2DM regressed on biological aging parameter; Path 2 = biological aging parameters regressed on race (whites as reference); Path 3 = T2DM regressed on race (whites as reference).

** Model 2: Model 1 further included body mass index and waist-to-hip ratio as covariates.

*** Model 3: Model 2 further included all other covariates (age, race, hypertension ever, high cholesterol requiring pills, fatty acids, whole fruits, vegetables, total score from Healthy Eating Index-2015, dietary alcohol, alcohol intake frequency, physical activity, years of regular smoking, oophorectomy history, hormone replacement therapy, ages of menopause and menarche, education, family income, any insurance, and social support [except tested variable(s)]).

¥ Results were similar when the biological aging parameter was analyzed as a 10-year interval or the binary (negative vs. positive age acceleration).

€ The biological aging parameter was analyzed as either continuous or binary outcomes (negative vs. positive age acceleration).

RESULTS

Analytic Step 1 (Fig. 1A)

In both the AgeAccelDiff and IEAA aging accel metrics, women who developed T2DM showed greater aging accel than women who did not develop T2DM (Path 1, Fig. 2A and 2B and Table 1), with statistical significance in univariate analyses only. Similar results were observed when comparing the IR and non-IR groups: greater aging accel scores observed in women with IR than in those without IR, which were statistically significant in the fully adjusted models (Fig. S2A and S2B and Table S2). In the Path 2 analyses of both T2DM and IR groups, AA women substantially had a greater aging accel than whites (Fig. s 2C and 2D; Fig. S2C and S2D), demonstrating approximately 50% and 90% higher likelihoods of increased aging accel on AgeAccelDiff and IEAA outcomes, respectively (Table 1 and Table S2). In the Path 3 analysis for the racial difference in T2DM/IR, a greater incidence of T2DM (about 40%) and higher prevalence of IR (about 50%) were observed in AAs than in whites, but statistical significance did not remain in the full models.

Analytic Step 2 (Fig. 1B)

In both T2DM and IR groups, the two aging accel metrics showed similar patterns in Path 1 in association with SDOH: lower aging accel associated with higher educational level, greater family income in a dose-response fashion, any medical insurance, and greater social support (Fig. 3 and Fig. S3). Of note, except for

social support, all other SDOH variables' adverse effects were statistically significant on the basis of univariate analyses in relation to accelerated aging. In the Path 2 analyses of racial difference in SDOH variables, the status of no medical insurance was more prevalent in AA women than in whites in Models 1 and 2 (Tables S3 and S4) whereas a higher educational level was found in more AAs than in whites.

Table 2. Analytic Step 2, Path 3: Racial difference in the biological aging parameter (AgeAccelDiff as a continuous outcome) and the mediation effect of SDOH (both individually and in combination).

	T2DM				IR			
	Beta¶	**(95% CI)**	***P***	**%§, *P***	**Beta¶**	**(95% CI)**	***P***	**%§, *P***
Race	**1.336**	**(0.278, 2.395)**	**0.013**		**1.275**	**(0.201, 2.349)**	**0.020**	
Race plus education	**1.446**	**(0.382, 2.510)**	**0.008**	8%, 0.705	**1.426**	**(0.348, 2.504)**	**0.010**	12%, 0.536
Race plus income	**1.292**	**(0.202, 2.381)**	**0.020**	3%, 0.882	**1.229**	**(0.123, 2.334)**	**0.029**	4%, 0.626
Race plus insurance	**1.275**	**(0.212, 2.339)**	**0.019**	4%, 0.162	1.207	(0.129, 2.286)	0.165	5%, 0.152
Race plus social support	**1.147**	**(0.072, 2.222)**	**0.037**	14%, 0.825	1.075	(-0.015, 2.166)	0.053	16%, 0.778
Joint mediation¥	**%**	**(95% CI)**			**%**	**(95% CI)**		
	1%	(-0.182, 0.146)			2%	(-0.160, 0.151)		

AgeAccelDiff, epigenetic age acceleration as departure of DNAmAge from chronological age; CI, confidence interval; T2DM, type 2 diabetes mellitus development; IR, insulin resistance; SDOH, social determinants of health. Numbers in bold face are statistically significant.

¶ Results are presented from multivariate analysis including covariates (age, hypertension ever, high cholesterol requiring pills, fatty acids, whole fruits, vegetables, total score from Healthy Eating Index-2015, dietary alcohol, alcohol intake frequency, physical activity, years of regular smoking, oophorectomy history, hormone replacement therapy, ages of menopause and menarche, body mass index, and waist-to-hip ratio [except tested variable(s)]).

§ The proportional effect of an individual SDOH was evaluated by the Sobel test.

¥ The effect of joint mediation combining all modeled SDOH was estimated, and its inferential test was performed via a General Multiple Mediation analytic approach developed by Yu and Li [51, 52].

In the Path 3 of racial disparity in accelerated aging, we conducted mediation tests for the effect of SDOH, both individually and jointly, on the greater aging accel in AAs than in whites. In both T2DM and IR groups with AgeAccelDiff outcomes (Table 2), the magnitudes of mediation effects varied by SDOH type, but the IR group relatively showed higher cross-sectional mediation impacts than the T2DM group. For instance, greater aging accel in AAs than in whites was explained by education (8% in the T2DM group vs. 12% in the IR group) and also, it was accounted for social support (14% vs. 16%, respectively). These estimations were not, however, statistically significant. The joint mediation effect of the combined SDOH was minimal (1% or 2%) in both T2DM and IR groups, again without support from statistical power. For IEAA outcomes (Table 3), the effect sizes of the mediation effects were relatively smaller than those for AgeAccelDiff, with ≤ 10% and ≤ 2% of the greater accelerated aging in AAs explained through the individual and combined SDOH, respectively. Likewise, neither the individual nor the joint mediation effects of SDOH were statistically significant. Our sensitivity analyses with both aging accel scales as binary outcomes yielded consistent results (Tables S5 and S6).

Table 3. Analytic Step 2, Path 3: Racial difference in the biological aging parameter (IEAA as a continuous outcome) and mediation effect of SDOH

	T2DM				IR			
	Beta¶	**(95% CI)**	***P***	**%§, *P***	**Beta¶**	**(95% CI)**	***P***	**%§, *P***
Race	**1.780**	**(0.808, 2.752)**	**0.0003**		**1.719**	**(0.734, 2.704)**	**0.001**	
Race plus education	**1.849**	**(0.872, 2.827)**	**0.0002**	4%, 0.705	**1.829**	**(0.838, 2.819)**	**0.0003**	6%, 0.538
Race plus income	**1.757**	**(0.757, 2.757)**	**0.001**	1%, 0.882	**1.696**	**(0.683, 2.709)**	**0.001**	1%, 0.624
Race plus insurance	**1.690**	**(0.714, 2.667)**	**0.001**	5%, 0.165	**1.623**	**(0.633, 2.612)**	**0.001**	5%, 0.161
Race plus social support	**1.618**	**(0.633, 2.603)**	**0.001**	9%, 0.824	**1.547**	**(0.548, 2.546)**	**0.002**	10%, 0.777
Joint mediation¥	**%**	**(95% CI)**			**%**	**(95% CI)**		
	2%	(-0.128, 0.180)			1.5%	(-0.149, 0.190)		

T2DM, type 2 diabetes mellitus development; CI, confidence interval; IEAA, intrinsic epigenetic age acceleration as residuals adjusted for cell composition; IR, insulin resistance; SDOH, social determinants of health. Numbers in bold face are statistically significant.

¶ Results are presented from multivariate analysis including covariates (age, hypertension ever, high cholesterol requiring pills, fatty acids, whole fruits, vegetables, total score from Healthy Eating Index-2015, dietary alcohol, alcohol intake frequency, physical activity, years of regular smoking, oophorectomy history, hormone replacement therapy, ages of menopause and menarche, body mass index, and waist-to-hip ratio [except tested variable(s)]).

§ The proportional effect of an individual SDOH was evaluated by the Sobel test.

¥ The effect of joint mediation combining all modeled SDOH was estimated, and its inferential test was performed via a General Multiple Mediation analytic approach developed by Yu and Li [51, 52].

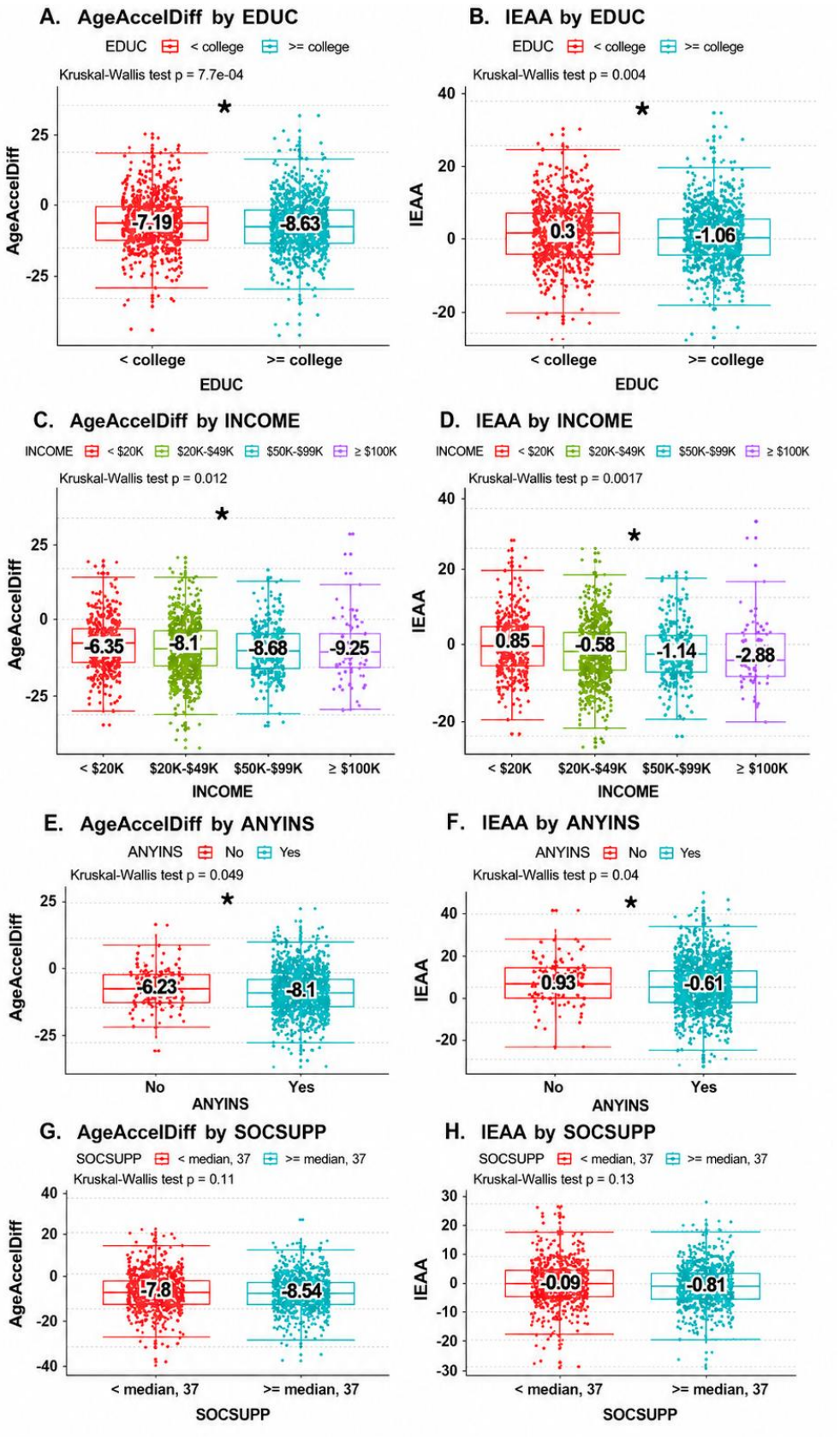
A. AgeAccelDiff by EDUC
EDUC < college >= college
Kruskal-Wallis test p = 7.7e-04
AgeAccelDiff
-7.19
-8.63
< college
>= college
EDUC
B. IEAA by EDUC
EDUC < college >= college
Kruskal-Wallis test p = 0.004
IEAA
0.3
-1.06
< college
>= college
EDUC
C. AgeAccelDiff by INCOME
INCOME < $20K $20K-$49K $50K-$99K ≥ $100K
Kruskal-Wallis test p = 0.012
AgeAccelDiff
-6.35
-8.1
-8.68
-9.25
< $20K
$20K-$49K
$50K-$99K
≥ $100K
INCOME
D. IEAA by INCOME
INCOME < $20K $20K-$49K $50K-$99K ≥ $100K
Kruskal-Wallis test p = 0.0017
IEAA
0.85
-0.58
-1.14
-2.88
< $20K
$20K-$49K
$50K-$99K
≥ $100K
INCOME
E. AgeAccelDiff by ANYINS
ANYINS No Yes
Kruskal-Wallis test p = 0.049
AgeAccelDiff
-6.23
-8.1
No
Yes
ANYINS
F. IEAA by ANYINS
ANYINS No Yes
Kruskal-Wallis test p = 0.04
IEAA
0.93
-0.61
No
Yes
ANYINS
G. AgeAccelDiff by SOCSUPP
SOCSUPP < median, 37 >= median, 37
Kruskal-Wallis test p = 0.11
AgeAccelDiff
-7.8
-8.54
< median, 37
>= median, 37
SOCSUPP
H. IEAA by SOCSUPP
SOCSUPP < median, 37 >= median, 37
Kruskal-Wallis test p = 0.13
IEAA
-0.09
-0.81
< median, 37
>= median, 37
SOCSUPP

Figure 3. T2DM data: Analytic Step 2, Path 1. Distributions of AgeAccelDiff and IEAA by social determinants of health. (EDUC, < college [n = 640] vs. ≥ college [n = 850]; INCOME, < $20,000 [n = 375], $20,000–$49,999 [n = 695], $50,000–$99,999 [n = 277], and ≥ $100,000 [n = 70]; ANYINS, no [n = 81] vs. yes [n = 1,403]; SOCSUPP, lower than a median [n = 679] vs. equal to or greater than a median [n = 777]. * indicates a statistical difference between groups. AgeAccelDiff, epigenetic age acceleration as departure of DNAmAge from chronological age; ANYINS, any insurance variable categorized; T2DM, type 2 diabetes development; EDUC, education variable categorized; IEAA, intrinsic epigenetic age acceleration as residuals adjusted for cell composition; INCOME, family income variable categorized; SOCSUPP, social support construct categorized.) **(A)** AgeAccelDiff by EDUC. **(B)** IEAA by EDUC. **(C)** AgeAccelDiff by INCOME. **(D)** IEAA by INCOME. **(E)** AgeAccelDiff by ANYINS. **(F)** IEAA by ANYINS. **(G)** AgeAccelDiff by SOCSUPP. **(H)** IEAA by SOCSUPP.

Analytic Step 3 (Fig. 1C and 4)

In the Step 3 mediation analyses of SDOH and aging accel in the racial disparity pathways of T2DM and IR, we found, in both aging accel metrics, at least a two-times-greater impact of aging accel than the combined SDOH in mediating the AAs' higher incidence of T2DM and greater prevalence of IR. Our estimates for the joint effects of SDOH and aging accel further indicated its greater influence on racial difference in IR status than that in T2DM incidence. However, given that the total and direct effects of race on each glucometabolic outcome did not differ much, the SDOH and aging accel parameters together played a limited role in distinguishing the pathway of T2DM/IR between the races.

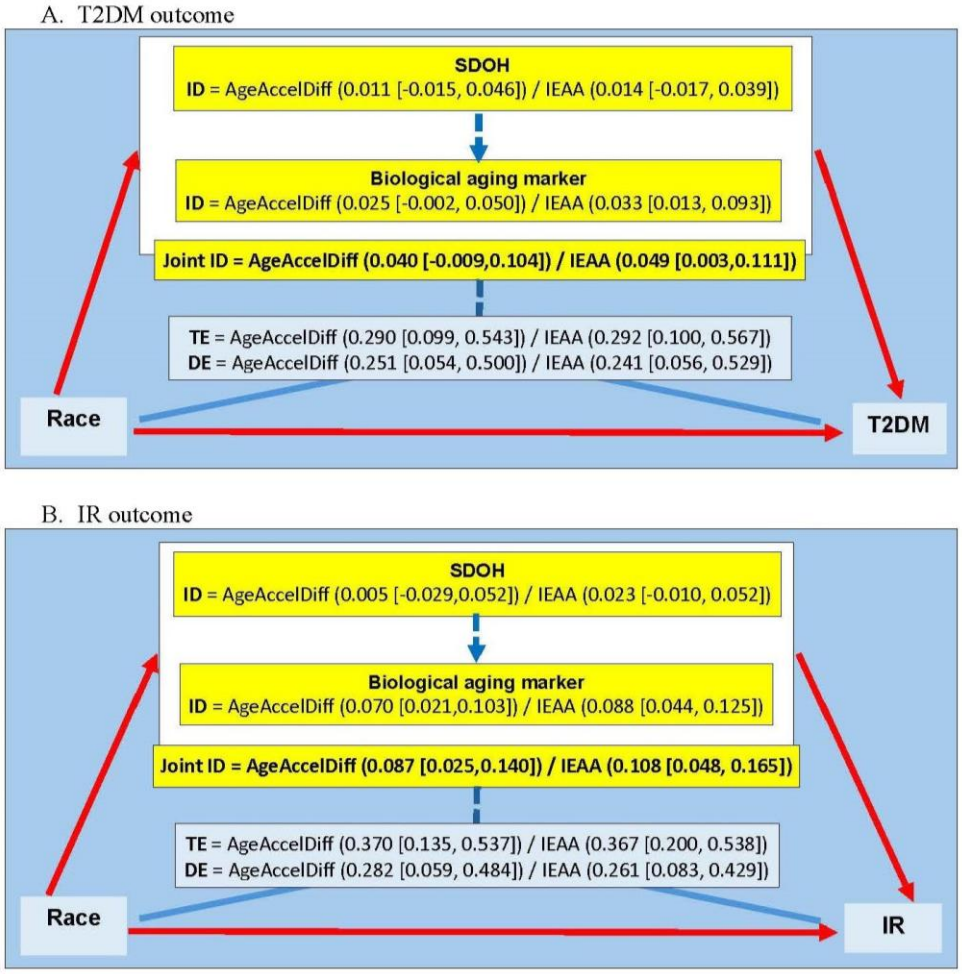

Figure 4. Analytic Step 3: Mediation effects of SDOH and biological aging marker in separate and joint analyses. (Note: Results are presented from univariate analyses with effect sizes [95% confidence intervals (CIs)] because in adjusted analyses, 95% CIs are unavailable in relation to missing data. AgeAccelDiff, epigenetic age acceleration as departure of DNAmAge from chronological age; DE, direct effect; T2DM, type 2 diabetes development; ID, indirect, mediation effect; IEAA, intrinsic epigenetic age acceleration as residuals adjusted for cell composition; IR, insulin resistance; SDOH, social determinants of health; TE, total effect.) **(A)** T2DM outcome. **(B)** IR outcome

DISCUSSION

It is noteworthy that very few epigenetic studies have been conducted in AAs, so the existing epigenome-based aging mechanism, based on studies analyzing mostly whites, may not be directly applicable to the AA subpopulation. Also, studies on epigenetic aging in relation to T2DM are scarce, e.g., only 25 population-based reports from 16 countries through 2024 [53]. Since aging is the leading risk factor of T2DM, limiting healthspan among old people [3, 4], and the racial disparity of T2DM increases with age [6, 7, 54], we addressed these deficits in the current study by focusing on older postmenopausal women for their T2DM incidence and its most critical precursor, IR status [55, 56]; we estimated one second-generation clock, Levine's aging accel metrics, and compared accelerated aging between the two races, examining to what extent the greater aging accel of AAs explained their more prevalent glucometabolic outcomes. The hallmarks of biological aging can be measured at both the molecular and cellular levels with various biomarkers, including telomere shortening, genomic and epigenomic instabilities, loss of proteostasis, disabled macro-autophagy, and chronic inflammation [5, 13]. In particular, telomere length has been studied as subclinical measures of organ function and morphology in the heart, peripheral vasculature, and kidney [57-59], but various measurement techniques and its relatively weak linkage to aging-related conditions hinder its use as a universal marker for biological aging [60]. Epigenetic alteration, including dynamic DNAm, has recently been at the center of attention for its outperformance relative to other aging markers in its strong association with aging, longevity, and aging-related diseases [17, 61]. Of note, Bacos et al's study [25] demonstrated more than 200 aging-associated DNAm markers in loci associated with T2DM and many of them are shared by human islets and blood. This indicates that a blood-based aging marker is an accessible, useful surrogate aging predictor for T2DM risk. Indeed, our findings indicated greater aging accel measured in PBLs in women with T2DM incidence, albeit with significance only in the univariate analysis, and IR prevalence, consistent with previous findings [10, 26, 62]. Given that AAs' epigenetic aging accel is positively associated with obesity, a major risk factor for T2DM/IR [63], our hypotheses were established by exhibiting AAs' greater aging accel than whites and its influence on their higher incidence of T2DM and prevalence of IR. However, our results from the mediation analyses showed a minimal effect of accelerated aging on those greater glucometabolic outcomes in AAs compared with whites. This may be the results from a lack of statistical power related to the small racial variability in T2DM/IR outcomes, calling for a larger, independent validation study.

Social-environmental factors representative of SDOH, such as socioeconomic status (SES) and educational level, contribute to health inequities, clinically affecting health outcomes [64]. For instance, low SES at the individual level, low household income level, and less social capitol and cohesion, is demonstrably related to a higher risk for developing T2DM [65]. Selected SDOH also accelerate epigenetic aging [29, 66]. However, the influence of SDOH on the biological aging processes in T2DM is less well characterized, as evidenced by the existence of only 15 published reports available as of 2025 [53]. Our results from the Path 1 of Analytic Step 2 highlighted that social adversities were associated with greater aging accel, corresponding with previous findings [48, 67-69].

Considering that SDOH are strong mediators of the racial disparity in T2DM [32] and the lack of relevant studies on this mediating role of SDOH in epigenetic aging pathways, we examined the complex glucometabolic pathways estimating the extent to which SDOH and aging accel, in separation and together, mediate the greater T2DM/IR outcomes in AAs than in whites. Our findings indicated insignificant influence of SDOH and aging accel, both individually and jointly, on AAs' higher incidence of T2DM and greater prevalence of IR. This may have resulted from less racial variability of SDOH, yielding low support from statistical power. Moreover, the currently available epigenetic clocks may not be credible enough to thoroughly detect the effect of social risk exposures on racial differences in biological aging processes. This requires the development of a new epigenetic clock, one that can fully address the comprehensive, long-term effects of SDOH on the aging process, thus accurately evaluating the impact of social adversity on differing aging and aging-related glucometabolic conditions between the races.

By focusing on older women, our data integrated comprehensive woman-specific reproductive histories as covariates in the analyses. With more than 1,500 participants, we prospectively followed for diabetic outcomes over a long period as well as non-diabetic IR status at baseline, thus providing two different glucometabolic scenarios over the course of aging. Our additional analysis with the first-generation clocks such as Horvath's, Hannum's, and Grim's revealed their insignificant association with T2DM and a bit higher aging accel in whites than in AAs. Thus, our findings are specific to the Levine's aging clock, which integrates inflammatory and metabolic phenotypes, well-established factors underlying cardio-metabolic pathways. However, our study has several shortcomings. Tested aging accel scores were not measured longitudinally in relation to

disease outcomes. T2DM incidence was measured by self-reports of diabetes pills or insulin shots. This approach may miss undiagnosed and/or diet-controlled cases of diabetes and those identified by blood tests but not treated with DM medication, implying potential selection bias; thus, we advise caution in interpreting the results. Multi-omics data, including transcriptomics, proteomics, and metabolomics, could facilitate systematic elucidation of aging metabolic mechanisms. Also, although our PBL-based aging measures represent a systemic approach to understanding aging-related disease processes, correlation studies with measures in multiple tissues such as islets, liver, muscle, and fat would be required to conclude a more comprehensive reflection across tissues. Lastly, our selected SDOH variables capture only part of social adversity, not fully representing structural racism, neighborhood context, food access, healthcare quality, chronic stress, or lifetime socioeconomic exposure. Indeed, SDOH involve complicated, hierarchical social pathways, so investigating a variety of SDOH variables in a multilevel structure may fully unravel socio-biological aging mechanisms in glucometabolic outcomes.

Overall, our study suggests greater aging accel in relation to T2DM (in univariate analysis only) and IR (in cross-section analysis) and in AAs than in whites and, further, SDOH-induced accelerated aging that mediates AAs' greater glucometabolic outcomes to a minimal extent. Our results warrant further validation studies with epigenetically longitudinal and independent, multi-omics datasets. Our study contributes to a better understanding of socio-glucometabolic pathways shared by epigenetic aging processes. This may improve early risk stratification among at-risk older women, which is useful to clinicians and epidemiologists. This may also inform public health researchers of interventions to address social adversity and policy shifts for T2DM and IR prevention and reduced racial health inequity.

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Availability of data and materials

Data is available in accordance with policies developed by the NHLBI and WHI in order to protect sensitive participant information and approved by the Fred Hutchinson Cancer Research Center, which currently serves as the IRB of record for the WHI. Data requests may be made by emailing helpdesk@WHI.org.

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Competing interests

All authors declare that they have no competing interests.

Ethics approval and consent to participate

All the participant data for the WHI used in this study were deidentified by the NHLBI and WHI and consent was obtained from the participants at the source. The study was approved by the institutional review boards of each participating clinical center of the WHI and the University of California, Los Angeles.

Consent for publication

The content of this manuscript has not been previously published and is not under consideration for publication elsewhere.

Authors' contributions

SYJ conceived and designed the study, conducted the analyses, interpreted results, and drafted the manuscript. SYJ approved the final version to be published. SYJ has also full access to all study data.

Supplementary Materials

The Supplementary data can be found online at: www.aginganddisease.org/EN/10.14336/AD.2026.0553.

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