Diabetes Care
American Diabetes Association

Diabetes, Prediabetes, and Brain Aging: The Role of Healthy Lifestyle

Abigail Dove, Jiao Wang, Huijie Huang, Michelle M. Dunk, Sakura Sakakibara, Marc Guitart-Masip, Goran Papenberg, and Weili Xu

Diabetes Care 2024;47(10):1794–1802 | https://doi.org/10.2337/dc24-0860

Aim

To investigate the relationship between (pre)diabetes and older brain age, and whether this can be attenuated by modifiable lifestyle factors

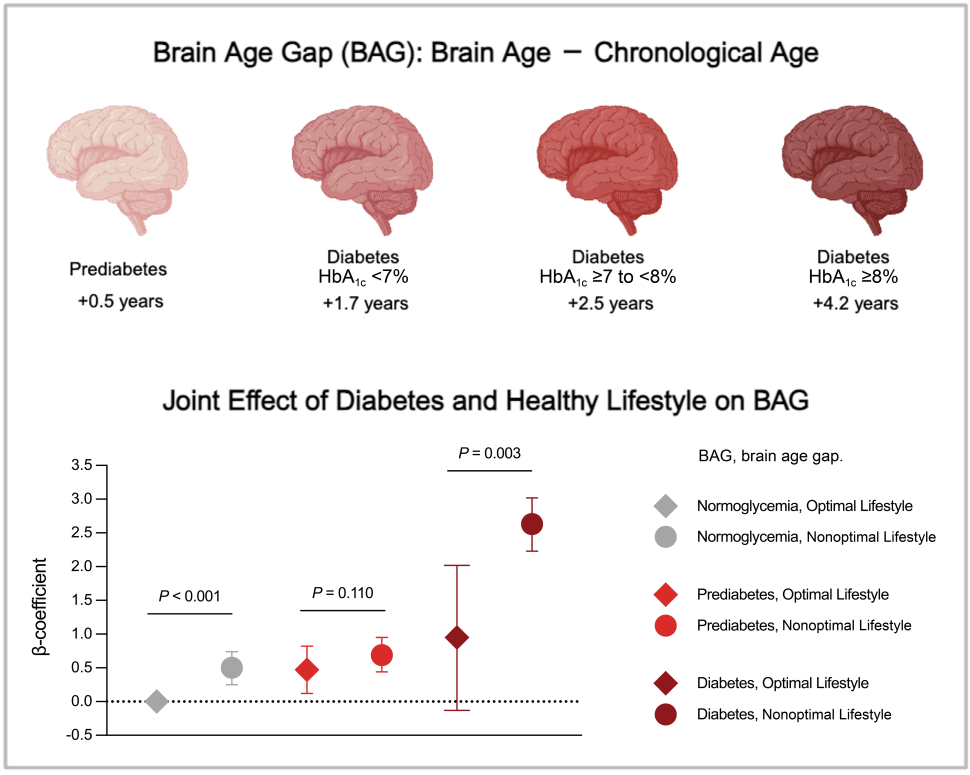
Methods

N = 31,229 UK Biobank participants (40-70y)

Exposures:
- (Pre)diabetes was defined based on medical history and measured HbA_{1c} values
- Healthy lifestyle was defined as no smoking, no heavy drinking, and high physical activity

Outcome:
- Brain age was estimated using a machine learning model based on 1,079 brain MRI phenotypes

Group differences were compared using multivariable linear regression models



Conclusion: Diabetes and even prediabetes are associated with accelerated brain aging, but this may be attenuated by a healthy lifestyle. The results highlight diabetes and prediabetes as ideal targets for lifestyle-based interventions to promote brain health.

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Diabetes is a well-established risk factor for dementia, but the role of (pre)diabetes in the early stages of brain aging is unclear.
- **What are the specific questions we wanted to answer?**
  Is (pre)diabetes related to accelerated brain aging? Can this be attenuated by healthy lifestyle?
- **What did we find?**
  Hyperglycemia, including diabetes and even prediabetes, is associated with accelerated brain aging, but this may be attenuated by physical activity and avoidance of smoking and heavy drinking.
- **What are the implications of our findings?**
  The results highlight the potential of modifiable lifestyle behaviors to compensate against the detrimental influence of (pre)diabetes on brain health.

Diabetes, Prediabetes, and Brain Aging: The Role of Healthy Lifestyle

Abigail Dove,[1] Jiao Wang,[2,3] Huijie Huang,[2] Michelle M. Dunk,[1] Sakura Sakakibara,[1] Marc Guitart-Masip,[1] Goran Papenberg,[1] and Weili Xu[1,2]

Diabetes Care 2024;47:1794–1802 | https://doi.org/10.2337/dc24-0860

ORIGINAL ARTICLE

OBJECTIVE

Diabetes is a well-known risk factor for dementia. We investigated the association between (pre)diabetes and older brain age and whether this can be attenuated by modifiable lifestyle behaviors.

RESEARCH DESIGN AND METHODS

The study included 31,229 dementia-free adults from the UK Biobank between the ages of 40 and 70 years. Glycemic status (normoglycemia, prediabetes, or diabetes) was ascertained based on medical history, medication use, and HbA_{1c} measured at baseline. Information on cardiometabolic risk factors (obesity, hypertension, low HDL, and high triglycerides) and lifestyle behaviors (smoking, drinking, and physical activity) was also collected at baseline. Participants underwent up to two brain MRI scans over 11 years of follow-up. Brain age was estimated using a machine learning model based on 1,079 brain MRI phenotypes and used to calculate brain age gap (BAG; i.e., brain age minus chronological age).

RESULTS

At baseline, 13,518 participants (43.3%) had prediabetes and 1,149 (3.7%) had diabetes. Prediabetes (β = 0.22 [95% CI 0.10, 0.34]) and diabetes (2.01 [1.70, 2.32]) were both associated with significantly higher BAG, and diabetes was further associated with significant increase in BAG over time (0.27 [0.01, 0.53]). The association between (pre)diabetes and higher BAG was more pronounced in men and in people with two or more cardiometabolic risk factors. In joint exposure analysis, having a healthy lifestyle (i.e., no smoking, no heavy drinking, and high physical activity) significantly attenuated the diabetes-BAG association.

CONCLUSIONS

Diabetes and even prediabetes are associated with accelerated brain aging, especially among men and people with poor cardiometabolic health. However, a healthy lifestyle may counteract this.

Type 2 diabetes (hereafter, diabetes) is a well-established risk factor for cognitive impairment and has been associated with approximately double the risk of dementia (1–3). In brain MRI studies, diabetes has been related to global brain atrophy, increased burden of small-vessel disease, and microstructural lesions before the onset of cognitive symptoms (4). While prediabetes has been related to more modest levels of many of the cerebrovascular and neurodegenerative abnormalities associated with overt diabetes in some MRI studies (5,6), the association of prediabetes with cognitive

[1]Aging Research Center, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden
[2]Department of Epidemiology and Biostatistics, School of Public Health, Tianjin Medical University, Tianjin, China
[3]Department of Epidemiology, College of Preventive Medicine, Third Military Medical University, Chongqing, China

Corresponding author: Abigail Dove, abigail.dove@ki.se

Received 25 April 2024 and accepted 8 July 2024

This article contains supplementary material online at https://doi.org/10.2337/figshare.26417971.

G.P. and W.X. are co-last authors.

decline and dementia remains controversial, with previous studies reporting conflicting results (7–10).

Recently, modeling methods have been introduced to estimate brain age based on MRI features such as volume loss, cortical thinning, white matter degradation, loss of gyrification, and ventricle enlargement (11). Brain age gap (BAG) reflects the difference between brain age and chronological age. Having an older-appearing brain for one's chronological age—that is, a high BAG—can indicate deviation from the normal aging process and has been linked to mortality and increased risk of cognitive decline and dementia (11). Early detection of accelerated brain aging could support timely identification and intervention for people who are most at risk for developing dementia.

A growing body of cross-sectional studies has linked diabetes to brain age that is between 0.85 and 4.6 years older than chronological age (12–18), but longitudinal evidence on the association between diabetes and changes in brain age is lacking, and the relationship between prediabetes and brain age has not been explored. Given the heterogeneity of the diabetes population, another important consideration is how clinically relevant factors, such as sex, comorbidities, and lifestyle behaviors, might influence the association between (pre)diabetes and brain age. A variety of lifestyle behaviors, including physical activity and smoking/alcohol avoidance, have been related to decelerated brain aging (12,16, 19,20), but whether a healthy lifestyle can counteract the detrimental influence of (pre)diabetes is unknown.

To address these questions, we comprehensively investigated the relationship between hyperglycemia and brain aging, leveraging detailed neuroimaging data from the UK Biobank covering six different MRI modalities in >30,000 middle-aged and older adults. Specifically, we aimed to *1*) examine the cross-sectional and longitudinal relationship between (pre)-diabetes and BAG; *2*) explore the role of sex and cardiometabolic risk factors in these associations; and *3*) investigate whether a healthy lifestyle, characterized by high physical activity and abstention from smoking and heavy drinking, can attenuate the influence of (pre)diabetes on BAG.

RESEARCH DESIGN AND METHODS

Study Design and Population

The UK Biobank is an ongoing longitudinal study including >500,000 adults between the ages of 40 and 70 from across the United Kingdom (21). Between 2006 and 2010, participants took part in a baseline examination at 1 of 22 assessment centers across the country consisting of physical and medical assessments and a series of questionnaires about sociodemographic information and lifestyle behaviors. Approximately 9 years later, between 2014 and 2020, >40,000 participants additionally underwent a brain MRI scan. Beginning in 2019, participants were invited to return for a follow-up brain MRI scan.

Selection of the study population is illustrated in Supplementary Fig. 1. The analysis was restricted to 34,296 participants who underwent brain MRI scans and had complete information on all available imaging-derived phenotypes (IDPs). We then excluded 630 participants with chronic neurological disorders (including dementia) at the time of the MRI scan (see Supplementary Table 1 for details), 15 with type 1 diabetes, and 2,422 with missing information on baseline HbA_{1c}, leaving a sample of 31,229, including 2,414 who underwent two MRI scans.

All data collection procedures have been approved by the UK National Research Ethics Service (Ref 11/NW/0382) and the use of the data for the present analyses were additionally approved by the Regional Ethical Review Board in Stockholm, Sweden (Ref 2024-00520-01). All participants provided informed consent at baseline.

Assessment of Prediabetes and Diabetes

Baseline diabetes and prediabetes were defined according to the American Diabetes Association standard diagnostic criteria (22). Participants were classified as having diabetes if they had any one of the following: medical record of diabetes, use of glucose-lowering medications, self-reported history of diabetes, or HbA_{1c} ≥6.5% (see Supplementary Table 2 for field codes). Among diabetes-free participants, prediabetes was defined as HbA_{1c} 5.7% to 6.4%, and normoglycemia was defined as HbA_{1c} <5.7%. Diabetes was further categorized according to level of glycemic control: <7.0% (well-controlled), ≥7.0 to <8.0% (moderately controlled), or ≥8.0% (poorly controlled) (23).

Acquisition of Brain IDPs

Brain MRI scans were conducted using a Siemens Skyra 3T scanner. Detailed descriptions of the UK Biobank brain MRI image acquisition and processing protocols have been previously published (24,25) and are summarized in Supplementary Table 3.

A total of 1,079 IDPs were extracted across six MRI modalities: 165 from T1-weighted MRI, 1 from T2-fluid attenuated inversion recovery (FLAIR), 14 from T2*, 675 from diffusion MRI, 210 from resting-state functional MRI (fMRI), and 14 from task fMRI. Briefly, T1-weighted imaging provides information on the volume and thickness of different brain regions, T2-FLAIR imaging detects white matter hyperintensities (reflecting vascular brain damage), T2* detects brain microbleeds, diffusion MRI assesses white matter microstructural integrity, resting-state fMRI measures brain activity at rest for assessment of intrinsic functional connectivity of neural networks, and task fMRI does so when the participant is performing a task or experiencing a sensory stimulus (in this case, a face/shapes matching task) (24). A full list of all 1,079 IDPs is provided in Supplementary Material.

Machine Learning-Based Estimation of Brain Age and BAG

The procedure for brain age estimation has been described in previous studies (26,27). A detailed description is available in the Supplementary Material, and the workflow is illustrated in Supplementary Fig. 2.

Briefly, from the entire sample of participants with complete brain MRI data (N = 34,296), we first identified 4,355 healthy individuals between the ages of 40 and 70 with no ICD-10 diagnoses and who were free from self-reported long-term illness, disability, or frailty (Field ID: 2188) and self-reported fair or poor health status (Field ID: 2178) (Supplementary Table 4). These participants were randomly allocated in a 4:1 ratio to a training set (n = 3,484) and a validation set (n = 871). Next, all 1,079 IDPs were Z standardized and nine machine learning models were trained for modeling brain age in the training set. These included

least absolute shrinkage and selection operator regression (LASSO), eXtreme gradient boosting, and support vector regression, which were combined with three possible feature selection strategies (no feature selection, FeatureWiz, or recursive feature elimination with cross validation). Bayesian optimization was performed to optimize the hyperparameters of all nine models through 100 epochs (Supplementary Tables 5 and 6). Once optimized, all nine models were applied to the validation set so that their performance could be compared. Ultimately, the LASSO model without feature selection achieved the lowest mean absolute error (Supplementary Table 7) and was therefore chosen to predict brain age for the entire sample. Of the 1,079 IDPs, 285 contributed significantly to the brain age estimate and are listed in Supplementary Table 8.

Next, because brain age tends to be overpredicted in younger individuals and underpredicted in older individuals, we corrected brain age estimates for age bias as follows (28,29): $brain\ age_{corrected} = [brain\ age_{original} - \beta/\alpha]$, where coefficients α and β are the slope and intercept of $brain\ age_{training\ set} = \alpha \times chronological\ age_{training\ set} + \beta$ (Supplementary Fig. 3).

Finally, BAG, which represents the difference between an individual's brain age and their chronological age, was calculated as $BAG = brain\ age - age_{time\ of\ MRI}$. Positive values for BAG indicate a brain that is older (i.e., less healthy) and negative values for BAG indicate a brain that is younger (i.e., more healthy) than expected based on the individual's chronological age.

Assessment of Covariates

Sociodemographic Factors

Education (college/university vs. not) was dichotomized based on the highest level of formal education attained. Socioeconomic status (SES) was assessed using the Townsend deprivation index, a measure of neighborhood-level socioeconomic deprivation based on the prevalence of unemployment, household overcrowding, car nonownership, and home nonownership in a given postcode of residence.

Cardiometabolic Risk Factors

Cardiometabolic risk factor burden was operationalized in terms of the components of the metabolic syndrome (MetS) (30). BMI was calculated using height and weight measurements from the baseline examination and classified as underweight (<20 kg/m^2), normal weight (≥ 20 to <25 kg/m^2), overweight (≥ 25 to <30 kg/m^2), or obese (≥ 30 kg/m^2). Hypertension was defined based on self-report, blood pressure measurement (systolic $\geq$140 mmHg, diastolic $\geq$90 mmHg), or antihypertensive medication use. HDL cholesterol and triglycerides were measured from blood samples collected at baseline. A score reflecting cardiometabolic risk factor burden (ranging from 0 to 4) was generated according to the total number of MetS components present, including obesity, hypertension, low HDL ($<$40 mg/dL [1.03 mmol/L] for men and $<$50 mg/dL [1.29 mmol/L] for women), and high triglycerides ($\geq$150 mg/dL [1.7 mmol/L]). (Notably, the fifth MetS component, hyperglycemia, was not included because it was already considered as the exposure in all analyses.)

Lifestyle Behaviors

Information was collected on three readily modifiable lifestyle behaviors: smoking, alcohol drinking, and physical activity. Smoking status was categorized as nonsmoker, former smoker, or current smoker according to self-report. Intake of various alcoholic beverages was self-reported and converted into U.K. alcohol units (1 unit = 8 g ethanol) (31). Alcohol consumption was categorized as nondrinker, light/moderate drinking ($\leq$14 units/week), or heavy drinking ($>$14 units/week) according to current U.K. guidelines on alcohol consumption for both men and women (32). Physical activity was measured using the International Physical Activity Questionnaire. Participants were classified as inactive ($<$600 MET-min/week), moderate (600 to $<$3,000 MET-min/week), or active ($\geq$3,000 MET-min/week); 600 MET-min/week is equivalent to the World Health Organization recommendation of 150 min of moderate-intensity or 75 min of vigorous physical activity per week (33). An optimal lifestyle was defined as never smoking, no or light/moderate alcohol consumption, and high physical activity.

Alzheimer Disease-Related Polygenic Risk Score

Alzheimer disease (AD)-related polygenic risk score (PRS_{AD}) was obtained from the UK Biobank's Standard PRS Set (34). Briefly, PRS_{AD} represents the Z-standardized sum of each participant's number of AD-related alleles (including the well-known *APOE* ε4 polymorphism) weighted by the strength of each allele's association with AD (34).

Statistical Analysis

Baseline characteristics of the study participants by glycemic status were assessed using χ^2 tests for categorical variables and one-way ANOVA for continuous variables.

Linear regression models were used to estimate β-coefficients and 95% CIs for the association between glycemic status at baseline and BAG at the time of brain MRI. Least-squares means of BAG in the normoglycemia, prediabetes, and diabetes groups were additionally estimated from the margins of the linear regression models. Similar analyses were conducted using HbA_{1c} as a continuous variable. Restricted cubic splines with three knots at fixed percentiles of the HbA_{1c} distribution (10th, 50th, and 90th) were used to model the possible nonlinear association between HbA_{1c} and BAG. Among participants who underwent two brain MRI scans, linear mixed-effects models were used to estimate β-coefficients and 95% CIs for the association between glycemic status and changes in BAG between the first and second scans. The fixed effect included baseline glycemic status, follow-up time (in years), and their interaction. The random effect included random intercept and slope, allowing individual differences in BAG to be reflected at baseline and across follow-up.

Next, stratified linear regression models were used to explore the role of sex (women vs. men) and cardiometabolic health (0–1 vs. $\geq$2 risk factors) in the association between glycemic status and BAG. Finally, we performed joint exposure analysis by incorporating a six-category indicator variable that combined glycemic status (normoglycemia, prediabetes, or diabetes) and lifestyle (optimal or nonoptimal) into the linear regression model. Interactions between glycemic status and sex, cardiometabolic risk factor level, and lifestyle were assessed by incorporating the cross-product term into the models.

All models were first basic adjusted for sociodemographic factors (i.e., age, sex, education, and SES), followed by further adjustment for number of cardiometabolic risk factors, lifestyle behaviors (i.e.,

smoking, alcohol consumption, and physical activity), and PRS_{AD}. Missing values for covariates were imputed using fully conditional specification, with estimates pooled from five iterations.

In sensitivity analysis, we repeated the main analyses *1*) using BAG calculated based on brain age estimates from other candidate machine learning models; *2*) using nonimputed data; *3*) after adding an additional covariate for brain MRI assessment center; *4*) after excluding participants with possible prodromal/undiagnosed dementia (i.e., incident dementia during follow-up; $n = 42$) or possible cognitive impairment (i.e., baseline cognitive test scores <25th percentile; $n = 7{,}806$) to minimize the possibility of reverse causality; and *5*) using diabetes status defined at the time of brain MRI scan to address the possibility of changes in glycemic status since baseline. All analyses were performed using Stata SE 16.0 software (StataCorp, College Station, TX). *P* values <0.05 were considered statistically significant.

Data and Resource Availability

Requests for access to the UK Biobank data can be made here: https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access.

RESULTS

Baseline Characteristics

Baseline characteristics of the 31,229 study participants (mean age 54.8 ± 7.5; 53.0% female) are summarized in Table 1. At baseline, 13,518 participants (43.3%) had prediabetes and 1,149 (3.7%) had diabetes. Compared with participants with normoglycemia, those with (pre)diabetes were more likely to be older, male, have a lower education level and SES, be physically inactive, and have cardiometabolic risk factors. The study sample was comparatively younger and had greater educational attainment, higher SES, and a more favorable cardiometabolic risk profile compared with the UK Biobank population as a whole (Supplementary Table 9).

Prediabetes, Diabetes, and BAG

Compared with normoglycemia, prediabetes (β = 0.22 [95% CI 0.10, 0.34]) and diabetes (β = 2.01 [1.70, 2.32]) were

Table 1—Baseline characteristics of the 31,229 study participants by glycemic status

Characteristics	Full sample (*N* = 31,229)	By glycemic status: Normoglycemia (*n* = 16,562)	Prediabetes (*n* = 13,518)	Diabetes (*n* = 1,149)	*P* value
Age, years					
At baseline	54.8 ± 7.5	53.1 ± 7.5	56.7 ± 7.1*	57.5 ± 7.0*	<0.001
At time of brain MRI	63.7 ± 7.6	62.0 ± 7.6	65.6 ± 7.2*	66.4 ± 7.2*	<0.001
Female sex	16,556 (53.0)	9,015 (54.4)	7,105 (52.6)	436 (38.0)	<0.001
College/university-educated	14,503 (46.6)	8,006 (48.5)	6,038 (44.8)	459 (40.2)	<0.001
Townsend deprivation index	−1.9 ± 2.7	−1.9 ± 2.7	−2.0 ± 2.7	−1.5 ± 2.9*	<0.001
BMI, kg/m^2	26.5 ± 4.2	25.9 ± 3.8	26.9 ± 4.3*	30.2 ± 5.5*	<0.001
Underweight (<20)	799 (2.6)	490 (3.0)	302 (2.2)	7 (0.6)	<0.001
Normal (20–25)	11,651 (37.3)	6,870 (41.5)	4,613 (34.2)	168 (14.6)	
Overweight (25–30)	13,382 (42.9)	7,020 (42.4)	5,910 (43.8)	452 (39.4)	
Obese (≥30)	5,367 (17.2)	2,163 (13.1)	2,683 (19.9)	521 (45.4)	
Hypertension	6,594 (21.1)	2,832 (17.1)	3,197 (23.7)	565 (49.2)	<0.001
HDL, mg/dL	57.2 ± 14.6	58.1 ± 14.5	57.0 ± 14.5*	48.6 ± 13.2*	<0.001
Triglycerides, mg/dL	144.5 ± 84.0	135.0 ± 79.3	152.5 ± 85.3*	186.4 ± 108.8*	<0.001
HbA_{1c}, %	5.7 ± 0.5	5.4 ± 0.2	5.9 ± 0.2*	7.1 ± 1.0*	<0.001
Smoking					<0.001
Nonsmoker	19,036 (61.1)	10,446 (63.2)	8,007 (59.4)	583 (50.8)	
Former smoker	10,258 (32.9)	5,241 (31.7)	4,537 (33.6)	480 (41.8)	
Current smoker	1,873 (6.0)	847 (5.1)	941 (7.0)	85 (7.4)	
Alcohol consumption					<0.001
Nondrinker	1,970 (7.2)	886 (6.0)	983 (8.4)	101 (10.4)	
Low/moderate drinking	11,785 (42.9)	6,237 (42.4)	5,134 (43.7)	414 (42.4)	
Heavy drinking	13,705 (49.9)	7,599 (51.6)	5,645 (48.0)	461 (47.2)	
Physical activity					<0.001
Low	4,880 (18.1)	2,575 (17.8)	2,049 (17.7)	256 (26.0)	
Moderate	11,320 (41.9)	6,022 (41.7)	4,896 (42.3)	402 (40.8)	
High	10,801 (40.0)	5,835 (40.4)	4,638 (40.0)	328 (33.3)	
APOE ε4 carrier	7,322 (27.5)	3,992 (28.1)	3,105 (27.1)	225 (23.8)	0.008
PRS_{AD}	0.04 ± 0.99	0.05 ± 0.99	0.04 ± 0.98	−0.04 ± 0.96*	0.026

Data are presented as means ± SD or *n* (%). Missing data: 92 for education level; 28 for Townsend deprivation index; 30 for BMI; 15 for hypertension; 4,030 for HDL; 1,406 for triglycerides; 62 for smoking status; 3,769 for alcohol consumption; 4,228 for physical activity level; 4,638 for *APOE* ε4 status; and 242 for PRS_{AD}. *Indicates significant (*P* value <0.05) pairwise comparison (reference group = normoglycemia).

associated with significantly higher BAG (Table 2). Specifically, brain age was on average 0.50 years older than chronological age among people with prediabetes and 2.29 years older than chronological age among people with diabetes (Fig. 1*A*). BAG rose as high as 4.18 years among people with poorly controlled diabetes (HbA_{1c} ≥8.0%). Consistent with this, HbA_{1c} as a continuous variable was associated with significantly higher BAG (β = 0.77 [0.65, 0.90]), and the restricted cubic spline analysis showed a strong increase in BAG with higher levels of HbA_{1c} (Fig. 1*B*).

In an exploratory longitudinal analysis among the 2,414 participants (7.7%) who underwent two brain MRI scans, diabetes was associated with a 0.27-year annual increase in BAG (Table 2 and Fig. 1*C*). No significant relationship was detected between prediabetes and changes in BAG, although HbA_{1c} as a continuous variable was associated with a significant increase in BAG (β = 0.13 [95% CI 0.03, 0.23]).

Sex- and Cardiometabolic Burden–Stratified Analyses

In stratified analyses (Fig. 2*A* and Supplementary Tables 10 and 11), the association between diabetes and higher BAG was more pronounced in men compared with women (β = 2.32 [95% CI 1.90, 2.74] vs. 1.51 [1.04, 1.99]) and people with a higher burden of cardiometabolic risk factors (0–1 risk factors: 1.91 [1.45, 2.36]; ≥2 risk factors: 2.20 [1.74, 2.66]). The same was true for prediabetes. Specifically, brain age was on average 0.75 years older than chronological age among men with prediabetes, compared with only 0.27 years older for women. Moreover, BAG rose to 2.63 years for men with diabetes compared with 1.76 years for women. Similarly, among individuals with two or more cardiometabolic risk factors, prediabetes and diabetes were associated with an average BAG of 1.32 and 3.08 years compared with 0.24 and 1.96 years, respectively, among their counterparts with a lower cardiometabolic risk factor burden.

Significant interactions were detected between glycemic status and both sex and cardiometabolic burden with respect to BAG ($P < 0.001$ for all).

Role of a Healthy Lifestyle

In joint exposure analysis, an optimal healthy lifestyle (i.e., nonsmoking, no or light/moderate drinking, and high physical activity) significantly attenuated the association between diabetes and BAG (Fig. 2*B* and Supplementary Table 12). Brain age was on average only 0.78 years older than chronological age among people with diabetes and an optimal lifestyle compared with 2.46 years older with a nonoptimal lifestyle. Therefore, healthy lifestyle was related to a 1.68-year reduction in BAG. More modest reductions in BAG were seen between individuals with normoglycemia and prediabetes and an optimal vs. nonoptimal lifestyle, respectively, although the difference for individuals with prediabetes was not statistically significant. A significant interaction was detected between glycemic status and lifestyle ($P = 0.04$).

Sensitivity Analyses

Sensitivity analyses are described in detail in the Supplementary Material. Overall, similar results were obtained when we repeated the analyses using BAG calculated based on brain age estimates from other candidate machine learning models (Supplementary Table 13), using nonimputed data (Supplementary Table 14), after additionally adjusting for brain MRI assessment center (Supplementary Table 15), after excluding 42 participants with possible prodromal/undiagnosed dementia (Supplementary Table 16), and after excluding 7,806 participants with possible cognitive impairment (Supplementary Table 16). Moreover, 558 people with normoglycemia or prediabetes transitioned to diabetes during the ∼9-year period between baseline and the first MRI scan (Supplementary Fig. 4), but results remained consistent using diabetes status defined at the time of this scan (Supplementary Table 17).

CONCLUSIONS

In this large-scale neuroimaging study, diabetes and even prediabetes were related to significantly older brain age in relation to chronological age, and diabetes was further associated with significant widening

Table 2—Cross-sectional and longitudinal associations between glycemic status and BAG: results from linear regression and linear mixed-effects models

		BAG			
		Basic adjusted		Multiadjusted	
Glycemic status	Participants (*n*)	β (95% CI)	*P* value	β (95% CI)	*P* value
Cross-sectional					
Normoglycemia	16,562	Reference		Reference	
Prediabetes	13,518	0.32 (0.20, 0.44)	<0.001	0.22 (0.10, 0.34)	<0.001
Diabetes	1,149	2.40 (2.10, 2.71)	<0.001	2.01 (1.70, 2.32)	<0.001
HbA_{1c} <7.0%	671	1.81 (1.42, 2.21)	<0.001	1.43 (1.04, 1.83)	<0.001
HbA_{1c} ≥7.0% to <8.0%	303	2.62 (2.04, 3.20)	<0.001	2.19 (1.61, 2.77)	<0.001
HbA_{1c} ≥8.0%	175	4.29 (3.53, 5.05)	<0.001	3.90 (3.15, 4.66)	<0.001
HbA_{1c} (continuous)		0.95 (0.82, 1.08)	<0.001	0.77 (0.65, 0.90)	<0.001
Longitudinal					
Normoglycemia × time	1,354	Reference		Reference	
Prediabetes × time	982	−0.03 (−0.12, 0.07)	0.597	−0.03 (−0.12, 0.07)	0.596
Diabetes × time	78	0.27 (0.01, 0.53)	0.045	0.27 (0.01, 0.53)	0.045
HbA_{1c} (continuous) × time		0.13 (0.03, 0.23)	0.012	0.13 (0.03, 0.23)	0.012

Basic-adjusted models included age, sex, education, and socioeconomic status. Multiadjusted models additionally included cardiometabolic risk factor burden, smoking status, alcohol drinking, physical activity, and PRS_{AD}.

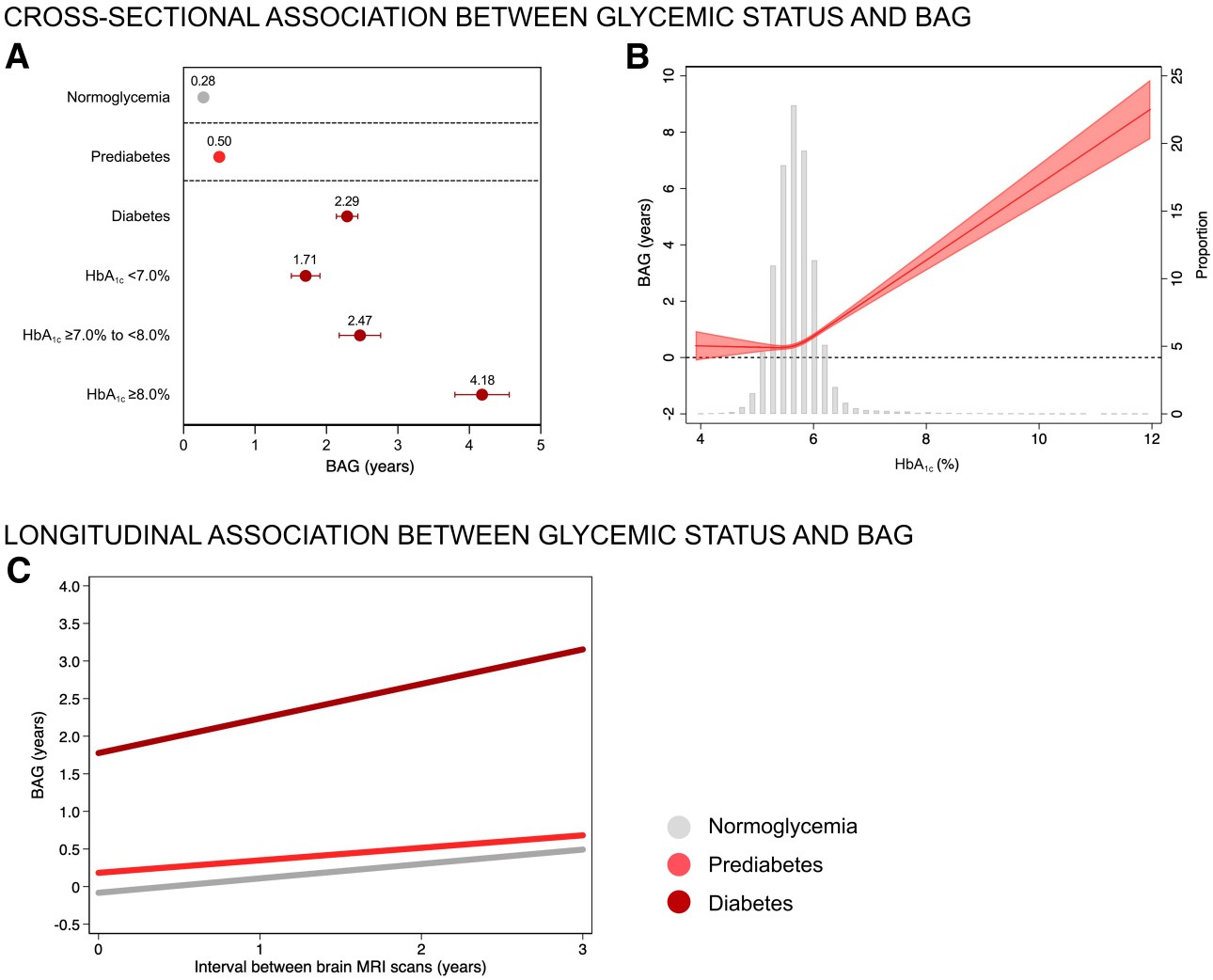


Figure 1—Relationship between glycemic status and BAG. *A*: Least-squares means and SDs of BAG in participants with normoglycemia, prediabetes, and diabetes. *B*: The relationship between HbA_{1c} (as a continuous variable) and BAG is modeled using restricted cubic splines. The red line and red shaded area represent the least-squares means and 95% CIs of BAG as a function of baseline HbA_{1c}. Gray bars represent the distribution of HbA_{1c} in the study population. *C*: The relationship between glycemic status and changes in BAG is modeled using linear mixed-effects models. All models were adjusted for age, sex, education, SES, cardiometabolic risk factor burden, smoking status, alcohol drinking, physical activity, and PRS_{AD}.

of the gap between brain and chronological age over time. These associations were more pronounced in men and people with poorer cardiometabolic health but may be counteracted with a healthy lifestyle characterized by physical activity and abstention from smoking and heavy drinking.

Diabetes was associated with a BAG of 2.29 years in the current study, consistent with previous reports in which diabetes has been related to a BAG between 0.85 and 4.6 years (12–16). Drawing on the >2,000 participants in our study who underwent two brain MRI scans, we further determined that diabetes was associated with a 0.27-year annual increase in BAG over time, a compelling signal that diabetes is related not only to older brain age but also to an accelerated pace of brain aging. In line with this, a small study (n = 25) exploring the longitudinal relationship between diabetes and brain aging reported that BAG widened by an estimated 0.2 years annually among people with diabetes (12).

Notably, whereas most previous studies estimated brain age used only T1-weighed imaging (12–15,17,18), ours leveraged information across six brain MRI modalities (T1-weighted imaging plus T2-FLAIR, T2*, diffusion MRI, resting-state fMRI, and task fMRI). A recent study also conducted using UK Biobank data concluded that whereas T1-weighted imaging is the MRI modality with the highest independent accuracy for brain age estimation, the best performance is achieved when multiple MRI modalities are combined (16).

Owing to our use of multimodal brain MRI data to estimate brain age, combined with the large sample size, we were able to detect a modest but highly statistically significant association between prediabetes ($P < 0.001$) and higher BAG. In light of conflicting findings on the relationship between prediabetes and cognitive impairment and dementia (7–10), our results provide compelling evidence that prediabetes may accelerate brain aging during the very earliest stages of dementia development. Given the substantial and growing prevalence of prediabetes—estimated at ~9% of the global population (35)—even a modest effect of prediabetes on brain health could make a

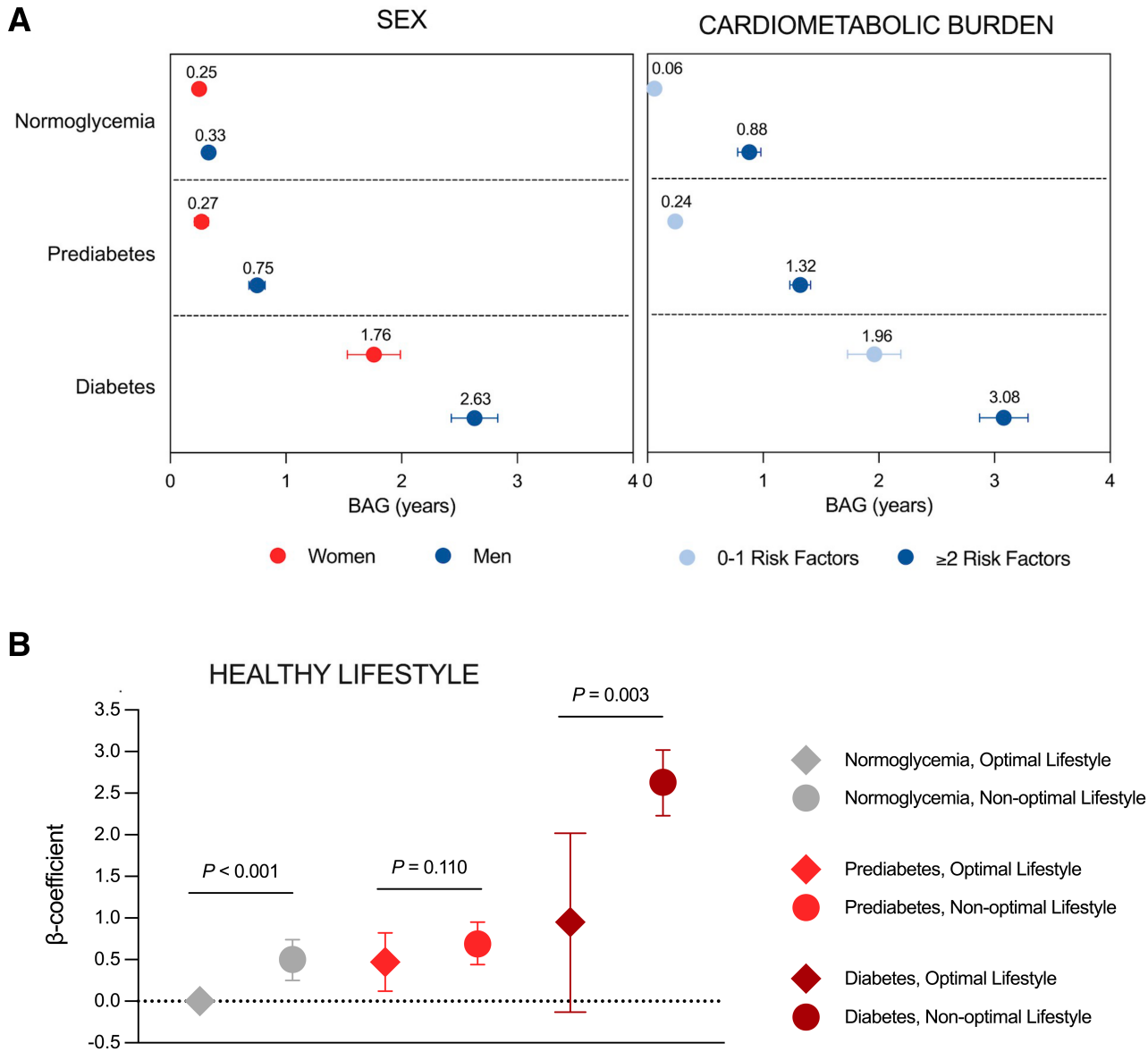


Figure 2—Role of sex, cardiometabolic risk factor burden, and healthy lifestyle in the association between glycemic status and BAG. *A*: Least-squares means and SDs of BAG among participants with normoglycemia, prediabetes, and diabetes, stratified by sex and cardiometabolic burden. Significant interactions were detected between glycemic status and sex ($P < 0.001$) and between glycemic status and cardiometabolic burden ($P < 0.001$). Models were adjusted for age, education, SES, cardiometabolic risk factor burden, smoking status, alcohol drinking, physical activity, and PRS_{AD} as well as sex or cardiometabolic risk factor burden, depending on the stratification factor. *B*: β-Coefficients for the joint effect on glycemic status and lifestyle on BAG. A significant interaction was detected between glycemic status and healthy lifestyle ($P = 0.04$). Models were adjusted for age, sex, education, SES, cardiometabolic risk factor burden, and PRS_{AD}. Note: The reference group was changed to (pre)diabetes and optimal lifestyle when assessing whether lifestyle significantly modified the (pre)diabetes-BAG association.

substantial difference at the population level. Encouragingly, prediabetes is a reversible state, and population-based studies have demonstrated that it is more common for people with prediabetes to regress to normoglycemia than progress to overt diabetes (36,37). Potential benefits for brain health could be yet another motivation to tighten glycemic control during this critical window.

Considering the heterogeneity of the diabetes population, we additionally investigated the role of a variety of other biological factors in the relationship between (pre)diabetes and brain age. In stratified analyses, the association between diabetes and higher BAG was more pronounced in men compared with women (2.63 vs. 1.76 years) and people with two or more as opposed to zero or one cardiometabolic risk factors (3.08 vs. 1.96 years). The prediabetes-BAG association was also stronger in men (0.75 vs. 0.27 years) and people with a higher cardiometabolic risk factor burden (1.32 vs. 0.24 years). Two previous studies have also reported a stronger relationship between brain age and diabetes among men (13,15), and the stronger diabetes-BAG association in in the context of a poorer cardiometabolic health is generally consistent with what has been observed for the diabetes-dementia association (2,3). These results highlight the complex interplay between hyperglycemia, sex, and cardiometabolic factors on brain health and underscore the

importance of identifying populations that may benefit most from preventative interventions.

Although lifestyle behaviors such as a healthy diet, smoking/alcohol avoidance, physical activity, and social engagement have been associated with younger brain age (12,16,19,20), a relevant and so-far unexplored question is whether a healthy lifestyle can counteract the damaging influence of existing risk factors, such as diabetes, on brain aging. In our study, a lifestyle characterized by high physical activity and avoidance of smoking and heavy drinking significantly attenuated the association between diabetes and higher BAG. These results provide the encouraging suggestion that adoption of these healthy lifestyle behaviors could improve brain health among people with diabetes, although interventional studies are warranted to verify this hypothesis. Our findings are consistent with previous studies highlighting the mitigating role of lifestyle behaviors in the association between diabetes and dementia (38,39) and emphasize the significance of a healthy lifestyle for not only cardiometabolic health but also the brain.

There are several potential biological pathways through which (pre)diabetes may impact brain health. Hyperglycemia, the defining pathophysiological feature of diabetes, can promote endothelial dysfunction, oxidative stress, systemic inflammation, and the accumulation of advanced glycation end products (1). Together these contribute to disruption of blood-brain barrier permeability (exposing the brain to potentially toxic substances, leading to abnormal neuronal activity), demyelination and loss of axons (leading to brain atrophy and disruptions in neurotransmitter signaling), and alterations in Ca^{2+} signaling (leading to excitotoxicity and disruptions in gene expression) (1). Additionally, the micro- and macrovascular complications of diabetes can contribute to brain atherosclerosis and cerebrovascular pathologies that may lower the threshold for neurodegeneration (1). Finally, the insulin resistance that characterizes diabetes has been linked to AD-related processes, including amyloid-β generation, τ-hyperphosphorylation, and impaired amyloid-β clearance (1). A healthy lifestyle may enhance cardiovascular and metabolic health, thereby minimizing the impact of hyperglycemia, insulin resistance, and vascular damage.

Strengths of this study include the large sample size and the use of multimodal brain MRI data to estimate brain age. However, some limitations should be acknowledged. First, healthy volunteer bias in the UK Biobank could limit the generalizability of our findings and may have contributed to an underestimation of the observed associations. Selection bias may be stronger in our sample because it was restricted to participants who underwent a brain MRI scan, a comparatively younger and more cardiometabolically healthy subgroup (Supplementary Table 9).

Second, diet could not be considered in the healthy lifestyle construct due to a high proportion of missing data (35%); additional analyses integrating diet into the optimal lifestyle measure are presented in Supplementary Table 18.

Third, there is the possibility of reverse causality insofar as having an older brain may contribute to the development of (pre)diabetes by making it more difficult to manage medical conditions and adhere to a healthy lifestyle. However, results remained consistent in sensitivity analyses excluding participants with possible cognitive impairment or prodromal dementia (Supplementary Table 16), suggesting that reverse causality is unlikely to have a major impact on our findings.

Additionally, misclassification of baseline glycemic status may have occurred because HbA_{1c} is less sensitive than alternative measures such as fasting plasma glucose or the oral glucose tolerance test (40). Moreover, because HbA_{1c} was measured only at baseline, we could not assess changes in glycemic control or progression/reversion of prediabetes in relation to BAG.

Finally, longitudinal data were available for only 2,414 participants (7.7%). Repeat collection of brain MRI scans is still ongoing, presenting an opportunity for future studies to explore the longitudinal relationship between (pre)diabetes and brain aging in greater detail.

In conclusion, the current study provides evidence that hyperglycemia—including diabetes and even prediabetes—may contribute to accelerated brain aging. These associations were more pronounced in men and people with poorer cardiometabolic health but were attenuated with a healthy lifestyle characterized by physical activity and abstention from smoking and heavy drinking. Our findings highlight diabetes and prediabetes as ideal targets for lifestyle-based interventions to promote brain health.

Acknowledgments. The authors would like to express their gratitude to the UK Biobank study participants and the staff involved in the UK Biobank data collection and management.

Funding. A.D. received funding from Alzheimerfonden (AF-993470) and Demensfonden. W.X. received grants from the Swedish Research Council (No. 2021-01647), the Swedish Council for Health, Working Life and Welfare (No. 2021-01826), Alzheimerfonden, and the Karolinska Institutet Board of Research. G.P. received funding from the Riksbankens Jubileumsfond (No. P20-0779) and Swedish Research Council (No. 2019-02804). M.G.M. received funding from the Marianne and Markus Wallenberg Foundation (No. 2020.0013) and Swedish Research Council (No. 2021-02046).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. A.D. conducted the statistical analyses, performed the literature search, and drafted the first version of the manuscript. A.D. and W.X. contributed to the conception and design of the study. J.W. and H.H. created the brain age variable. J.W., H.H., M.M.D., S.S., M.G.-M., G.P., and W.X. interpreted the data and provided critical revisions to the manuscript. All authors made a significant contribution to finalizing the manuscript and approved the final version for publication. A.D. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Handling Editors. The journal editors responsible for overseeing the review of the manuscript were Elizabeth Selvin and Alka M. Kanaya.

References

1. Biessels GJ, Despa F. Cognitive decline and dementia in diabetes mellitus: mechanisms and clinical implications. Nat Rev Endocrinol 2018;14:591–604

2. Biessels GJ, Strachan MWJ, Visseren FLJ, Kappelle LJ, Whitmer RA. Dementia and cognitive decline in type 2 diabetes and prediabetic stages: towards targeted interventions. Lancet Diabetes Endocrinol 2014;2:246–255

3. Srikanth V, Sinclair AJ, Hill-Briggs F, Moran C, Biessels GJ. Type 2 diabetes and cognitive dysfunction—towards effective management of both comorbidities. Lancet Diabetes Endocrinol 2020;8:535–545

4. Biessels GJ, Reijmer YD. Brain changes underlying cognitive dysfunction in diabetes: what can we learn from MRI? Diabetes 2014;63:2244–2252

5. van Agtmaal MJM, Houben AJHM, de Wit V, et al. Prediabetes is associated with structural brain abnormalities: the Maastricht Study. Diabetes Care 2018;41:2535–2543

6. Reitz C, Guzman VA, Narkhede A, DeCarli C, Brickman AM, Luchsinger JA. Relation of dysglycemia to structural brain changes in a multiethnic elderly cohort. J Am Geriatr Soc 2017;65:277–285

7. Tuligenga RH, Dugravot A, Tabák AG, et al. Midlife type 2 diabetes and poor glycaemic control as risk factors for cognitive decline in early old age: a post-hoc analysis of the Whitehall II cohort study. Lancet Diabetes Endocrinol 2014; 2:228–235
8. Rönnemaa E, Zethelius B, Sundelöf J, et al. Glucose metabolism and the risk of Alzheimer's disease and dementia: a population-based 12 year follow-up study in 71-year-old men. Dia-betologia 2009;52:1504–1510
9. Marseglia A, Fratiglioni L, Kalpouzos G, Wang R, Bäckman L, Xu W. Prediabetes and diabetes accelerate cognitive decline and predict micro-vascular lesions: a population-based cohort study. Alzheimers Dement 2019;15:25–33
10. Xu W, Qiu C, Winblad B, Fratiglioni L. The effect of borderline diabetes on the risk of dementia and Alzheimer's disease. Diabetes 2007;56:211–216
11. Cole JH, Marioni RE, Harris SE, Deary IJ. Brain age and other bodily 'ages': implications for neuropsychiatry. Mol Psychiatry 2019;24:266–281
12. Franke K, Gaser C, Manor B, et al. Advanced *BrainAGE* in older adults with type 2 diabetes mellitus. Front Aging Neurosci 2013;5:90
13. Jha MK, Fatt CRC, Minhajuddin A, Mayes TL, Berry JD, Trivedi MH. Accelerated brain aging in individuals with diabetes: association with poor glycemic control and increased all-cause mortality. Psychoneuroendocrinology 2022;145:105921
14. Casanova R, Walker KA, Justice JN, et al. Associations of plasma proteomics and age-related outcomes with brain age in a diverse cohort. Geroscience 2024;46:3861–3873
15. Kang SH, Liu M, Park G, et al. Different effects of cardiometabolic syndrome on brain age in relation to gender and ethnicity. Alzheimers Res Ther 2023;15:68
16. Cole JH. Multimodality neuroimaging brain-age in UK biobank: relationship to biomedical, lifestyle, and cognitive factors. Neurobiol Aging 2020;92:34–42
17. Kolbeinsson A, Filippi S, Panagakis Y, et al. Accelerated MRI-predicted brain ageing and its associations with cardiometabolic and brain disorders. Sci Rep 2020;10:19940
18. Sone D, Beheshti I, Shinagawa S, et al. Neuroimaging-derived brain age is associated with life satisfaction in cognitively unimpaired elderly: a community-based study. Transl Psychiatry 2022;12:25
19. Smith SM, Vidaurre D, Alfaro-Almagro F, Nichols TE, Miller KL. Estimation of brain age delta from brain imaging. Neuroimage 2019;200: 528–539
20. Franz CE, Hatton SN, Elman JA, et al. Lifestyle and the aging brain: interactive effects of modifiable lifestyle behaviors and cognitive ability in men from midlife to old age. Neurobiol Aging 2021;108:80–89
21. Sudlow C, Gallacher J, Allen N, et al. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med 2015;12:e1001779
22. ElSayed NA, Aleppo G, Aroda VR, et al.; American Diabetes Association. 2. Classification and diagnosis of diabetes: *Standards of Care in Diabetes—2023*. Diabetes Care 2023;46(Suppl. 1): S19–S40
23. ElSayed NA, Aleppo G, Aroda VR, et al.; American Diabetes Association. 6. Glycemic targets: *Standards of Care in Diabetes—2023*. Diabetes Care 2023;46(Suppl. 1):S97–S110
24. Miller KL, Alfaro-Almagro F, Bangerter NK, et al. Multimodal population brain imaging in the UK Biobank prospective epidemiological study. Nat Neurosci 2016;19:1523–1536
25. Alfaro-Almagro F, Jenkinson M, Bangerter NK, et al. Image processing and quality control for the first 10,000 brain imaging datasets from UK Biobank. Neuroimage 2018;166:400–424
26. Wang J, Huang H, Yang W, Dove A, Ma X, Xu W. Association between resting heart rate and machine learning-based brain age in middle- and older-age. J Prev Alzheimers Dis 2024;11: 1140–1147
27. Huang H, Wang J, Dunk MM, et al. Association of cardiovascular health with brain age estimated using machine learning methods in middle-aged and older adults. Neurology 2024; 103:e209530
28. Cole J, Ritchie S, Bastin M, et al. Brain age predicts mortality. Mol Psychiatry 2018;23:1385–1392
29. De Lange AMG, Cole JH. Commentary: Correction procedures in brain-age prediction. Neuroimage Clin 2020;26:102229
30. Grundy SM, Cleeman JI, Daniels SR, et al.; National Heart, Lung, and Blood Institute. Diagnosis and management of the metabolic syndrome: an American Heart Association/ National Heart, Lung, and Blood Institute scientific statement. Circulation 2005;112:2735–2752
31. Clarke T-K, Adams MJ, Davies G, et al. Genome-wide association study of alcohol consumption and genetic overlap with other health-related traits in UK Biobank (N=112 117). Mol Psychiatry 2017;22:1376–1384
32. UK Chief Medical Officers' Low Risk Drinking Guidelines. 2016. Accessed 10 April 2024. Available from https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/545937/UK_CMOs__report.pdf
33. Lloyd-Jones DM, Hong Y, Labarthe D, et al.; American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. Circulation 2010; 121:586–613
34. Thompson DJ, Wells D, Selzam S, et al. UK Biobank release and systematic evaluation of optimised polygenic risk scores for 53 diseases and quantitative traits. 1 August 2022 [preprint]. medRxiv 2022.06.16.22276246
35. Rooney MR, Fang M, Ogurtsova K, et al. Global prevalence of prediabetes. Diabetes Care 2023;46:1388–1394
36. Rooney MR, Rawlings AM, Pankow JS, et al. Risk of progression to diabetes among older adults with prediabetes. JAMA Intern Med 2021; 181:511–519
37. Shang Y, Marseglia A, Fratiglioni L, et al. Natural history of prediabetes in older adults from a population-based longitudinal study. J Intern Med 2019;286:326–340
38. Marseglia A, Wang H-X, Rizzuto D, Fratiglioni L, Xu W. Participating in mental, social, and physical leisure activities and having a rich social network reduce the incidence of diabetes-related dementia in a cohort of Swedish older adults. Diabetes Care 2019;42:232–239
39. Marseglia A, Darin-Mattsson A, Kalpouzos G, et al. Can active life mitigate the impact of diabetes on dementia and brain aging? Alzheimers Dement 2020;16:1534–1543
40. Guo F, Moellering DR, Garvey WT. Use of HbA1c for diagnoses of diabetes and prediabetes: comparison with diagnoses based on fasting and 2-hr glucose values and effects of gender, race, and age. Metab Syndr Relat Disord 2014;12: 258–268