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SHORT REPORT

Association of genetic risk score for Alzheimer's disease with late-life body mass index in all of us: Evaluating reverse causation

Minhyuk Choi[1] | **Scott C. Zimmerman**[1] | **Peter T. Buto**[1,2] | **Jingxuan Wang**[1] | **Willa D. Brenowitz**[1,3] | **Thomas J. Hoffmann**[1,4] | **Adina Zeki Al Hazzouri**[5] | **Katrina Kezios**[5] | **M. Maria Glymour**[2]

[1]Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, California, USA

[2]Department of Epidemiology, Boston University School of Public Health, Boston, Massachusetts, USA

[3]Kaiser Permanente Center for Health Research, Portland, Oregon, USA

[4]Institute for Human Genetics, University of California San Francisco, San Francisco, California, USA

[5]Department of Epidemiology, Columbia University, New York, New York, USA

Correspondence
Minhyuk Choi, Department of Epidemiology and Biostatistics, University of California San Francisco, Mission Hall, 550 16th Street, San Francisco, CA 94158 , USA.
Email: minhyuk.choi@ucsf.edu

M. Maria Glymour is the senior author

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Abstract

INTRODUCTION: Decreases in body mass index (BMI) may be early consequences of Alzheimer's disease (AD) pathophysiological changes. Previous research in the UK Biobank estimated that AD-related genes began affecting BMI around age 47. We assessed whether this result could be replicated using longitudinal data in an independent cohort.

METHODS: Using All of Us (AOU) (N = 197,619, aged 30+) data, we estimated linear mixed models for associations of Z-scored AD-Genetic Risk Score (AD-GRS) with BMI, stratified by decade of age. We calculated the earliest age at which AD-GRS was associated with differences in BMI using cross-validated models adjusted for demographics.

RESULTS: Higher AD-GRS was statistically associated with lower BMI in participants aged 60–70 (b = −0.060 [−0.113, −0.007]). Best fitting models suggested the inverse association of AD-GRS and BMI emerged beginning at ages 47–54.

DISCUSSION: AD genes accelerate age-related weight loss starting in middle age.

KEYWORDS
Alzheimer's disease, body mass index, cross-validation, genetic risk scores, Mendelian randomization

Highlights

- Understanding when physiological changes from amyloid pathology begin is key for AD prevention.
- Our findings indicate that AD-associated genes accelerate midlife weight loss, starting between 47 and 54 years.
- AD prevention research should consider that disease pathology likely begins by middle age.

1 | INTRODUCTION

The diagnosis of late-onset Alzheimer's disease (AD) is preceded by a prolonged process of accumulating cerebral pathology extending over many years.[1–3] While dominant hypotheses about the etiology of AD acknowledge a long prodromal period, the precise age at which the earliest signs of AD manifest remains unclear[4] because most early correlates may also be causes, rather than consequences, of AD. A recent report notes that the age-specific prevalence of amyloid positivity mirrors diagnosed disease 15–20 years later,[4,5] but it is unknown whether biological changes emerge even earlier. The average age of diagnosis of late-onset AD is around 75~80,[6–9] suggesting that the biological disease may typically begin in the late 50s or early 60s.

Understanding when physiological changes resulting from AD-related pathology begin is essential for identifying the earliest indicators of AD and developing effective prevention strategies.[10–13] Previous studies show that weight loss may be an early sign of AD.[14–18] Prior to the onset of dementia, alterations in nutritional status,[19] metabolism, and neurodegeneration[20–22] may influence body mass index (BMI). However, determining the earliest age at which weight loss potentially results from emergent AD pathophysiology poses challenges because higher midlife BMI is associated with a higher risk of AD.[21,23–26] Due to this bidirectional relationship between AD and weight loss, weight loss resulting from AD progression may not be easily identifiable. Observational studies evaluating BMI in mid to late life present conflicting estimates regarding the age at which lower BMI is associated with AD, ranging from 8 to 20 years before AD diagnosis.[25,27–28] Therefore, an analysis that accounts for reverse causation—where the long-term AD risk associated with high BMI in midlife may mask the declining BMI observed in the preclinical phase of AD—is essential to disentangle the temporal relationship between AD progression and changes in BMI. Pinpointing the age when AD-related BMI declines begin requires a model for the small decrements in weight that accumulate over years.

Our prior work, Brenowitz et al. (2021) addressed this "reverse causation" problem using reverse Mendelian randomization (MR).[29] Reverse MR utilizes genetic variants to examine the causal impact of the genetically determined phenotype (e.g., AD) on another condition (e.g., BMI).[30–33] The MR approach provides evidence of causality by leveraging genetic information, which is determined at conception and thereby establishes temporal order. Thus, any observed association between AD Genetic Risk Score (AD-GRS) and midlife BMI cannot be attributed to the influence of early or midlife BMI on AD or other unmeasured confounders, and changes in the association between AD-GRS and BMI at older ages could indicate when AD-related biological changes begin to impact BMI.

Based on this method we estimated that AD-related weight loss begins as early as age 47, indicating that weight loss in midlife could be an early physiological change associated with AD.[29] However, the use of the UK Biobank sample—in which the population was restricted to European genetic ancestry and the BMI was measured only once for each participant—was an important source of uncertainty.[29]

RESEARCH IN CONTEXT

1. **Systematic review**: We searched PubMed for literature on the association between late-life body mass index (BMI) and Alzheimer's disease (AD). Previous research suggests that weight loss in older individuals may reflect the very early consequences of AD-related changes. A single prior report on AD genes suggests AD-related weight loss may begin as early as midlife but this result has not been confirmed with longitudinal data.
2. **Interpretation**: Our findings suggest that AD-associated genes accelerate weight loss starting in midlife, between 47 and 54 years old.
3. **Future directions**: Future observational or interventional research on AD prevention should recognize that disease pathology likely begins by middle age.

Therefore, we sought to extend this work using National Institutes of Health (NIH) All of Us (AOU) Research Program, a novel dataset with a diverse, US-based population with longitudinal follow-up.[29] Using participants' repeated BMI measures, we assessed the relationship between genetic risk for late-onset AD and BMI among participants spanning mid- to late-life to estimate the earliest age at which BMI trajectories diverge for individuals based on genetic risk of AD.

2 | METHODS

2.1 | Study setting and participants

NIH AOU, a large-scale ongoing study detailed elsewhere,[34] has enrolled over 828,000 participants aged 18 years and older since it was launched in June 2017. Participants provided various types of health information, including genetic data, lifestyle surveys, physical measurements, and electronic health records which may trace back prior to enrollment.

From 287,650 AOU participants with at least one BMI record measured at age 30 or older, we excluded those missing data on genetics ($N = 78{,}928$), smoking ($N = 9524$), or gender ($N = 7074$). Our final eligible sample included 197,619 unique participants with 2,747,421 BMI records ($N = 830{,}935$ records measured after enrollment).

The AOU Research Program is reviewed by an internal human subjects review board and all participants provide informed consent. Secondary analyses of de-identified data from the AOU Research Program are not considered human subjects research.[34]

2.2 | Genotyping and genetic risk scores for AD

AOU provides genomic data from short-read whole genome sequencing (srWGS) genotyped from biosample DNA (blood and/or saliva)

provided by participants. The srWGS data, covering single nucleotide polymorphisms (SNPs) and insertions/deletions (indels), is stored in the Hail 0.2 Variant Dataset (VDS) and compressed sequence alignment (CRAM) formats. To ensure high data quality, AOU implements stringent quality control (QC) procedures, confirming sample quality and genetic variants within DNA sequences. Samples that do not meet QC thresholds are not released for further analysis.[35]

To construct the AD-GRS in AOU data, we used 25 loci associated with AD that reached genome-wide significance ($p < 5X10^{(-8)}$) at stage 1~3 from the Kunkle et al. meta-analyzed genome-wide association study (GWAS) of late-onset AD.[36] Among 25 loci, 23 present in the AOU were used for calculation. While our analyses were underway, a new GWAS meta-analysis was published, so for sensitivity analysis, we included 83 genome-wide significant variants from a meta-analysis of GWAS led by Bellenguez et al., which incorporated genetic data from the European Alzheimer & Dementia Biobank consortium.[37] All 83 loci were available for calculation in the AOU dataset. To each set of loci from the two studies, we added two SNPs used to characterize apolipoprotein E (*APOE*) ε4 allele status identified by Lambert et al.[38]

We calculated the AD-GRS by multiplying each individual's risk allele count for each locus by the coefficient (expressed as the log odds ratio) for that polymorphism and adding the products for all loci in each study (Table S1, Table S2). This step weights each SNP in proportion to the observed association with AD risk (either positive or negative). The scores can be interpreted as the log odds ratio for AD conferred by that individual's profile on the SNPs compared with a person who had the nonrisk allele at each locus. We converted the AD-GRS into a standardized *z*-score based on the sample mean and variance. This score has previously been shown to predict cognition and dementia-related death in the UK Biobank.[39–40] We also calculated a secondary score for each study excluding two SNPs related to *APOE* ε4 allele for sensitivity analysis.

2.3 | BMI

BMI was calculated based on measured height and weight (kg/m^2) recorded in electronic health records (EHRs). We used all available EHR records for each individual.

2.4 | Covariates

Date of birth, sex, race/ethnicity (Non-Hispanic Asian, Non-Hispanic Black, Hispanic, Non-Hispanic White, Other, Unknown), educational attainment (less than high school, high-school graduate, professional or vocational qualification, college graduate, unanswered), and smoking status (never, ever) were reported at enrollment. Age at BMI was calculated as the date BMI was measured minus date of birth. AOU provides principal components (PCs) related to genetic ancestry from a classifier trained on 16-dimensional principal component analysis (PCA) space;[41] we controlled for the first 10 PCs to adjust for population stratification.

2.5 | Statistical analysis

First, we estimated separate age-stratified linear mixed models with the AD-GRS as the primary predictor and BMI as the outcome, dividing participants into decades when BMI was measured, ranging from 30 to 39 years of age to 80+ years of age. Models were adjusted for age, sex, race, education, smoking, and the first 10 PCs.

Moreover, to more precisely pinpoint the specific age at which the AD-GRS was associated with lower BMI, narrower age-stratified linear mixed models were estimated, with participants grouped within a range of ± 1 year around the age of interest.

Finally, we used one randomly selected BMI record for each unique participant and fit linear regression models that allow outcome BMI to be associated with AD-GRS only after the threshold age. BMI was fit to a quadratic function of age (specified as *t* below), with interaction terms for linear and quadratic age with a threshold function to detect age of divergence ($t_{\text{threshold}}$), and covariates (sex, race, PC1~10, education, smoking; expressed as W_i, where *i* indexes across the covariates):

$$Y = b_0 + b_1 * t + b_2 * t^2 + b_3 * ADGRS_Z * I(t > t_{\text{threshold}}) * (t - t_{\text{threshold}}) + b_4 * \text{ADGRS}_Z * I(t > t_{\text{threshold}}) * (t - t_{\text{threshold}})^2 + \sum (b_i * W_i) \quad (1)$$

BMI Divergence Model Based on AD-GRS

$I(t > t_{\text{threshold}})$ is an indicator function that is zero when *t* is equal to or below the specified age threshold and one when age is above the threshold. This specification allows the predicted mean BMI to smoothly diverge based on the level of AD-GRS beginning at the specified threshold age. Below the threshold age, the association between AD-GRS and cognition (conditional on covariates) is constrained to zero so that the association between centered age and the outcome is estimated by $b_1 * t + b_2 * t^2$, matching the typical growth trajectory of BMI in adults. Above the age threshold, the indicator function turns on, and the predicted BMI is allowed to diverge smoothly from the curve expected when AD-GRS is zero. Based on this model specification, we evaluated threshold ages from 30 to 80 years and chose the model with the minimum mean squared error (MSE) in a 10-fold cross-validation,[42] which would suggest the minimum age at which AD-GRS would start to predict divergence in BMI. To visualize the predicted BMI trajectory by AD-GRS, we used the selected model to plot the predicted average BMI across age at the median values of covariates, grouped by higher versus lower (90th vs. 10th percentile) AD-GRS values.

We performed all analyses using four different sets of loci: the primary analysis involving 23 available loci from Kunkle et al. with two APOE ε4 alleles, and sensitivity analyses involving 23 available loci from Kunkle et al. without two APOE ε4 alleles,[36] and 83 loci from Bellenguez et al. with or without two APOE ε4 alleles.[37] Additionally, all analyses were conducted using body weight as outcome as another sensitivity analyses.

All analyses were performed using R version 4.3.2.[43] This study utilized data from the Controlled Tier Dataset [v7] of the AOU

Research Program, accessible to authorized users on the Researcher Workbench.

3 | RESULTS

The study cohort consisted of 2,747,421 BMI records from 197,619 unique individuals (an average of 140 BMI records per individual). The average age at enrollment was 55.9 years (SD = 14.2). At the time of BMI measurement, the age group with most BMI recordings was 60–69 years old (27.1%). Of the sample, 60.0% were female. The mean BMI across all measures was 30.7 (SD = 7.77) (Table 1).

In our primary analysis, AD-GRS was not significantly associated with BMI measurements taken when participants were ages 30–39 years (b = −0.019, 95% CI: −0.093, 0.056; p = 0.62), 40–49 years (b = 0.049, 95% CI: −0.022, 0.119; p = 0.176), or 50–59 years, (b = −0.012, 95% CI: −0.068, 0.044; p = 0.678). For BMI measures taken between ages 60–69 years, higher AD-GRS was associated with lower BMI (b = −0.06, 95% CI: −0.113, −0.007; p = 0.026), and the association was stronger for ages 70–79 years (b = −0.209, 95% CI: −0.272, −0.145; $p < 0.001$) and ages 80+ (b = −0.141, 95% CI: −0.259, −0.023; p = 0.019) (Table 2). Sensitivity analysis excluding two *APOE* ε4 alleles from the primary set of loci from Kunkle et al.[36] showed a generally similar pattern with the exception of the 80+ age group (b = 0.008, 95% CI: −0.096, 0.112; p = 0.885) where the coefficients were not statistically distinguishable from the null (Table S3). Sensitivity analyses using sets of loci from Bellenguez et al. with or without two *APOE* ε4 alleles as a secondary score[37] produced similar results to the primary analysis (Table 2, Table S3). Sensitivity analyses using body weight instead of BMI produced similar results to the primary analysis (Tables S4 and S5).

Estimates from the analysis with participants grouped within ± 1 year around the age of interest are plotted in Figure S1. In the primary analysis, the coefficient peaked at age 47 (46–48, b = 0.102, 95% CI: −0.013, 0.218; p = 0.093). The coefficient subsequently declined, first dropping below 0 at age 54. Sensitivity analyses generally followed a similar pattern, with the highest point ranging from age 42 to 51, and reaching negative values between ages 52 and 54. Sensitivity analyses using body weight followed the same pattern as the primary analysis (Figure S2).

The best-fitting model, based on the analysis comparing linear regression models with different age thresholds for the earliest influence of the AD-GRS on BMI, suggested that the model with an age threshold of 50 minimized the MSE, that is, had the best fit (Figure 1). Based on this best-fitting model, the demonstration of BMI of individuals with high versus low (90th vs. 10th percentile) AD-GRSs are shown in Figure 2. Sensitivity analysis excluding two *APOE* ε4 from the primary set of loci from Kunkle et al.[36] resulted in very imprecise estimates (Figure S3). Sensitivity analyses using AD-GRS based on Bellenguez et al. with or without two *APOE* ε4 alleles[37] suggested threshold ages of 50~51 (Figures S3 and S4). Sensitivity analyses using body weight suggested the same threshold ages (Figures S5 and S6).

TABLE 1 Characteristics of participants included in analysis of AD risk and BMI, in both aggregate counts (n = 2,747,421) and individual counts (n = 197,619)[a]

Variable (individual level)	Unique individuals (N = 197619)
Age at enrollment in years (mean [SD])	55.9 (14.2)
Gender	
Female (*N* [%])	118194 (59.8%)
Male (*N* [%])	79425 (40.2%)
Race/ethnicity	
Non-Hispanic Asian (*N* [%])	5130 (2.6%)
Non-Hispanic Black (*N* [%])	41072 (20.8%)
Hispanic (*N* [%])	34736 (17.6%)
Other (*N* [%])	5595 (2.8%)
Unknown (*N* [%])	3400 (1.7%)
Non-Hispanic White (*N* [%])	107686 (54.5%)
Smoking status	
Non-smoker (*N* [%])	112245 (56.8%)
Current smoker (*N* [%])	85374 (43.2%)
Education status	
College and above (*N* [%])	87166 (44.1%)
High school (*N* [%])	37207 (18.8%)
Less than high school (*N* [%])	20193 (10.2%)
Unanswered (*N* [%])	4272 (2.2%)
Some colleges (*N* [%])	48781 (24.7%)
AD-GRS (Mean [SD])	0.0487 (0.771)
Variable (Aggregate level)	**Aggregate counts (N = 2747421)**
Age at BMI measurement in years (mean [SD])	57.4 (13.3)
Age at BMI measurement by age categories	
30 ≤ Age < 40	355007 (12.9%)
40 ≤ Age < 50	448648 (16.3%)
50 ≤ Age < 60	698674 (25.4%)
60 ≤ Age < 70	745697 (27.1%)
70 ≤ Age < 80	406289 (14.8%)
80 ≤ Age	93106 (3.4%)
BMI value (mean [SD])[b]	30.7 (7.77)
BMI value by categories	
Underweight (BMI < 18.5)	28639 (1.0%)
Normal (18.5 ≤ BMI ≤ 24.9)	603650 (22.0%)
Overweight (25.0 ≤ BMI ≤ 29.9)	821613 (29.9%)
Obese (30.0 ≤ BMI ≤ 39.9)	953257 (34.7%)
Morbidly obese (39.9 < BMI)	340262 (12.4%)

Abbreviations: AD, Alzheimer's Disease; AD-GRS, AD-Genetic Risk Score; BMI, body mass index; SD, standard deviation.

[a]Demographic analysis was restricted to participants with SNPs data available from the Kunkle et al.[36]

[b]Weight (kg)/height (m)^2.[36]

TABLE 2 Association between AD-GRS and BMI stratified by age.

	Primary analysis: Kunkle et al. with 2 APOE ε4 alleles [36]				Sensitivity analysis: Bellenguez et al. with 2 APOE ε4 alleles [37]			
Age group	Estimate (β)	95% CI		*p*-value	Estimate (β)	95% CI		*p*-value
30 ≤ Age < 40	−0.019	−0.093	0.056	0.62	−0.012	−0.095	0.071	0.773
40 ≤ Age < 50	0.049	−0.022	0.119	0.176	0.042	−0.037	0.121	0.294
50 ≤ Age < 60	−0.012	−0.068	0.044	0.678	−0.007	−0.07	0.056	0.832
60 ≤ Age < 70	−0.06	−0.113	−0.007	0.026	−0.029	−0.088	0.03	0.329
70 ≤ Age < 80	−0.209	−0.272	−0.145	<0.001	−0.225	−0.296	−0.153	<0.001
80 ≤ Age	−0.141	−0.259	−0.023	0.019	−0.212	−0.345	−0.079	0.002

Note: Models were adjusted for age, sex, race, education, smoking, and 10 PCs to account for confounding by population stratification.
Abbreviations: AD-GRS, AD-Genetic Risk Score; APOE, apolipoprotein E; BMI, body mass index; CI, confidence interval; PCs, principal components.

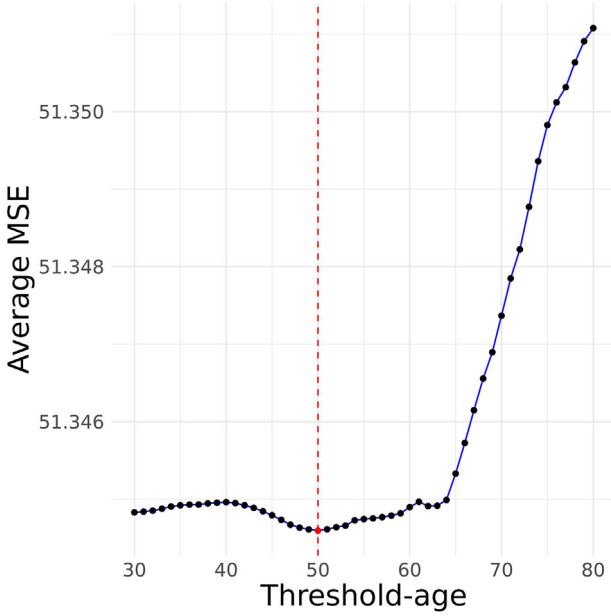

FIGURE 1 MSE of linear regression models with varying age thresholds, averaged across 10 folds, based on the primary analysis predicting BMI. The red dot indicates the age at which the average MSE across the 10 folds is the lowest. BMI, body mass index; MSE, mean squared prediction error.

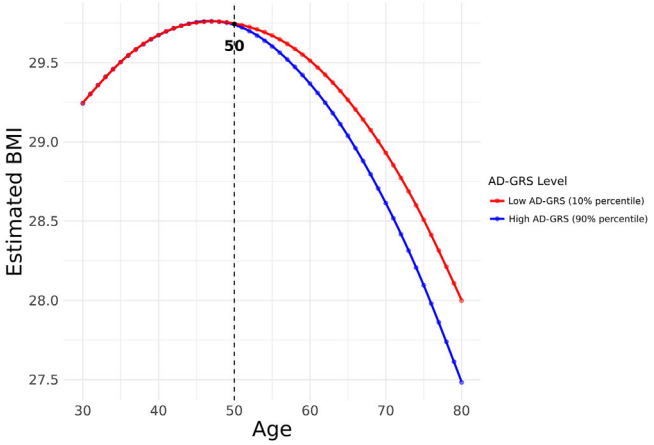

FIGURE 2 Age-related curves for BMI by AD-GRS level (10th percentile, Low: Red vs. 90th percentile, High: Blue) for the primary analysis. Based on the age-threshold model that produced the lowest MSE in the primary analysis (age = 50), the trajectory of estimated BMI for AD-GRS lower group (10th percentile: −0.998) versus the higher group (90th percentile: 1.450) was analyzed, with all other covariates set to their median values as follows: Gender: Female, Smoking status: Non-smoker, Education: College and above, Race/ethnicity: Non-Hispanic White, and median values for PCs 1-10 (PC1-10). The lowest age threshold for MSE is indicated by the black dotted line. AD-GRS, AD-Genetic Risk Score; BMI, body mass index; MSE, mean squared prediction error; PCs, principal components.

4 | DISCUSSION

In a large diverse US cohort, by ages 47–54 years, genetic determinants of AD were associated with weight loss. Accelerated weight loss accumulated so by ages 60–69, higher AD-GRS was significantly associated with lower BMI.

These findings suggest that weight loss as an early sign of AD may begin in middle age, nearly thirty years before the typical age of diagnosis. Based on our primary analysis, the association between AD-GRS and BMI flipped from slightly positive in people ages 40–49 to slightly negative in people ages 50–59. Additionally, a narrower age-stratified analysis indicates a threshold age between 47 and 54, where the coefficient begins to decline at age 47 and first crosses below zero at age 54. Our best estimate, based on age-threshold models, is age 50. While our prior work noted a significantly lower BMI associated with AD-GRS beginning in at ages 50–59 (b = −0.04 per 1 standard deviation [SD] in Z-score of AD-GRS, 95% CI: −0.07, −0.01), the confidence intervals for people ages 50–59 overlap with estimates in our analysis using AOU.[29] Our prior work suggested an initial divergence of BMI at approximately age 47.[29] The similarity in estimates between the two independent samples is remarkable and notably strengthens evidence that AD-related weight loss begins in middle age.

This study builds on prior research indicating that weight loss serves as a predictor for subsequent AD diagnosis[14–16,24,44] and neuropathologic burden.[45] Observational studies evaluating BMI in mid to late life present conflicting estimates regarding the age at which lower BMI is associated with AD, ranging from 8 to 20 years before AD

diagnosis.[25,27–28] Interpretation of these findings has been challenging because high BMI in midlife is an established predictor of increased AD risk. Our results indicate that the association between BMI in middle age and subsequent AD risk reflects the net consequence of the two opposing processes. Our reverse MR approach contributes to consolidating evidence concerning the timing of BMI changes in preclinical AD.[46] Through the examination of genetic risk, which is established at birth, we offer evidence that biological processes associated with the genetic risk of AD may lead to BMI reduction as early as age 47∼54 years. Weight loss in early AD could be influenced by poorer nutritional habits due to memory declines[19] or neurodegenerative changes[21,45] directly altering metabolism or appetite regulation.[20,47] Our findings, particularly the observed age-related differences in the association between AD and lower BMI, further support the hypothesis that pathophysiological processes leading to AD diagnosis also result in weight loss decades before diagnosis.[31]

Our analysis has several strengths. The large and diverse AOU dataset includes directly measured longitudinal BMI records. The use of linear mixed models with genetic variants for AD and age at repeatedly measured BMI ensures temporal order. With an average of nearly 14 BMI observations per individual, the random effects model is almost entirely identified from within-person changes in age.

A key limitation of this study is that we do not have biomarker or neuroimaging data to validate that these findings are driven by preclinical AD. However, UK Biobank analyses have shown similarly early changes in cognition and neuroimaging markers.[40] We cannot entirely dismiss the potential for selection bias[48,49] or pleiotropy in the AD-GRS which could influence our results.[30] Concerns about pleiotropy have especially focused on *APOE* ε4, which is by far the strongest genetic predictor of AD. We found very similar results, however, using the more recent 83-SNP score reported by Bellenguez et al. even without *APOE* ε4 alleles,[37] suggesting that the patterns are not entirely driven by *APOE* ε4 alleles.

Our study indicates that genetic factors that influence AD risk cause weight loss as early as age 47–54, decades before the typical age of AD diagnosis around 80 years. These results support the hypothesis that weight loss may manifest as an early physiological change associated with AD. By elucidating the timing of BMI changes in relation to genetic risk, our findings contribute to a better understanding of the early stages of AD development and may inform preventive interventions aimed at mitigating disease progression.

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CONFLICT OF INTEREST STATEMENT

M.C., P.T.B., T.J.H., and A.Z.A.H. have reported no conflicts of interest to disclose. Role of the Funder/Sponsor: The NIH had no role in the conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication. Author disclosures are available in the Supporting Information.

DISCLOSURES

S.C.Z. has reported receiving support for this work from NIH R01AG072681 and owning stock in Eli Lilly and Company, AbbVie, Inc., Abbott Laboratories, CRISPR Therapeutics, Gilead Sciences LLC, and Merck & Co., Inc., which were self-purchased. J.W. has reported receiving funding for this work from NIH/NIA, which was directed to his institution. W.D.B. has reported receiving grants from NIH/NIA (K01AG062722) and Kaiser Permanente Research Bank. K.K. has reported receiving a grant (K99AG084769) from NIA. M.M.G. has reported receiving grants from NIH/NIA and the Robert Wood Johnson Foundation. She has also reported royalties from Oxford University Press and participation on a Data Safety Monitoring Board for the SWAN (Study of Women Across the Nation).

CONSENT STATEMENT

The NIH AOU Research Program is reviewed by an internal human subject review board and all participants provide informed consent. Secondary analyses of de-identified data from the AOU Research Program are not considered human subjects research, verified by the Boston University internal human subjects review board.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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