

## Short Communication

# Patterns of Aging Changes in Bodyweight May Predict Alzheimer's Disease

Svetlana Ukraintseva<sup>a,\*</sup>, Hongzhe Duan<sup>a</sup>, Rachel Holmes<sup>a</sup>, Olivia Bagley<sup>a</sup>, Deqing Wu<sup>a</sup>, Arseniy Yashkin<sup>a</sup>, Alexander Kulminski<sup>a</sup>, Igor Akushevich<sup>a</sup>, Heather Whitson<sup>b,c</sup>, Eric Stallard<sup>a</sup>, Anatoliy Yashin<sup>a</sup> and Konstantin Arbeev<sup>a</sup>

<sup>a</sup>*Biodemography of Aging Research Unit (BARU), Social Science Research Institute, Duke University, Durham, NC, USA*

<sup>b</sup>*Center for Aging and Human Development, Duke University, Durham, NC, USA*

<sup>c</sup>*Geriatrics Research, Education, and Clinical Center (GRECC), Durham VA Medical Center, Durham, NC, USA*

Accepted 10 October 2023

Pre-press 11 December 2023

**Abstract.** Relationships between patterns of aging-changes in bodyweight and AD are not fully understood. We compared mean age-trajectories of weight between those who did and did not develop late-onset-AD, and evaluated impact of age at maximum weight (*AgeMax*), and slope of decline in weight, on AD risk. Women with late-onset-AD had lower weight three or more decades before AD onset, and ~10 years younger *AgeMax*, compared to AD-free women. *APOE4* carriers had younger *AgeMax* and steeper slope. Older *AgeMax* and flatter slope predicted lower AD risk. Premature decline in weight could be a sign of accelerated physical aging contributing to AD.

Keywords: Aging, Alzheimer's disease, *APOE4*, Framingham Heart Study, Health and Retirement Study, weight

## INTRODUCTION

Lower bodyweight has been associated with Alzheimer's disease (AD) and other dementias [1–5]. However, mechanisms behind such association remain poorly understood. The lower weight could be a consequence of already developing AD pathology in the body and a symptom of preclinical AD. Alternatively, it may be a risk factor for AD and a potential target for AD prevention. Despite a substantial amount of research connecting changes in weight at certain age intervals with risks of AD and other dementias [4–9], this direction remains under-

explored. The age-trajectories of weight evaluated over longer periods of life may provide better insights into the cause-and-effect relationship between patterns of aging-related changes in weight and AD. The  $\epsilon 4$  allele of *APOE* gene (a.k.a. *APOE4*), a major genetic risk factor for late-onset-AD, was also linked to lower weight/body mass index (BMI) in some studies [3, 10–13]; however, it is unclear how *APOE4* influences long-term changes in weight over the life course and whether this influence plays a significant role in AD.

In this study, we explored the relationships between late-onset-AD and patterns of aging-related changes in bodyweight, as well as the impact of *APOE4* on these patterns. We examined how long before AD onset individuals start to decline in weight compared to those who remain AD-free. We also

\*Correspondence to: Svetlana Ukraintseva, Biodemography of Aging Research Unit (BARU), Social Science Research Institute, Duke University, PO Box 90420, 2024 W. Main St., Durham, NC 27705, USA. Tel.: +1 919 668 2712; E-mail: svo@duke.edu.

Table 1  
Impact of carrying *APOE*  $\epsilon$ 4 allele on phenotypes characterizing age-trajectories of weight in HRS and FHS. White females (F) and males (M)

Phenotypes	Sex	OR (CI)	<i>p</i>	N(1)	N(0)
HRS					
Age at maximum weight ( $\geq 70$ versus $< 70$ years)	F	0.73 (0.64, 0.84)	7.60E-06	1542	2563
Slope of the weight (above versus below median)	F	0.67 (0.58, 0.78)	2.72E-07	1471	1456
Slope of the weight (above versus below median)	M	0.73 (0.61, 0.87)	4.29E-04	1121	1127
FHS					
Slope of the weight (above versus below median)	F	0.62 (0.42, 0.91)	0.015	335	221

LS, Life Span; N(1), number of people in group (1); N(0), number of people in group (0). Age at maximum weight (*AgeMax*), binary phenotype: (1) *AgeMax*  $\geq 70$  years versus (0) *AgeMax*  $< 70$  years; LS  $> 70$ . Slope of the weight (*Slope*), binary phenotype: (1) *Slope* above median versus (0) *Slope* below median; LS  $> 75$ . *Slope* was calculated as relative change in weight between ages 65–85: [Mean weight at ages 75–85 - Mean weight at ages 65–75]/Mean weight at ages 65–75 years. OR, Odds Ratio, refers to chances for *APOE*  $\epsilon$ 4 carriers to be in Group (1).

investigated key characteristics of the non-monotonic trajectories of weight changes during aging, such as the age at reaching maximum and the rate of subsequent decline, and evaluated their associations with AD risk.

## MATERIALS AND METHODS

### Data

The Framingham Heart Study (FHS) original cohort, and the Health and Retirement Study (HRS) data were used in this analysis. The FHS is a prospective, community-based, longitudinal cohort study, initiated in 1948 and continued since under direction of the National Heart, Lung and Blood Institute. The original cohort includes residents of Framingham, Massachusetts, predominantly White, who had extensive examinations, including detailed health history confirmed by a physician, a physical examination, laboratory testing, and genetic information, approximately every two years. The FHS v31 data distributed through the Database of Genotypes and Phenotypes (dbGaP; phs000007), containing information on 32 waves of examinations of 5180 individuals from the original cohort, were used in this study. The HRS is a longitudinal survey supported by the National Institute on Aging and the Social Security Administration that extensively surveys a representative sample of approximately 20,000 US residents for health, well-being, and retirement information. We used HRS RAND longitudinal file 2016 v1 including information on 13 waves (1992–2016), and seven entry cohorts distributed by the University of Michigan

(<https://hrs.isr.umich.edu/data-products>), and HRS v2 genetic information distributed by dbGaP (phs000428). Numbers of individuals included in particular analysis are shown in Table 1 and Figs. 1 and 2.

### Phenotypes

*Alzheimer's disease (AD)*. In FHS, a dementia review panel, which included a neurologist and a neuropsychologist, reviewed every case of cognitive decline and dementia. The diagnosis of AD was based on criteria for possible, probable, or definite AD from the Alzheimer's Disease and Related Disorders Association and the National Institute of Neurological and Communicative Disorders and Stroke (ADRDA–NINCDS) [14, 15]. In HRS, AD onset was assessed using the survey data, based on HRS questionnaires. In Waves 4–9, questions about memory-related diseases were asked, and since Wave 10, the respondents were asked if they have been told by the doctor that they have AD.

*Binary phenotypes characterizing patterns of aging changes in weight*. Behavior of non-monotonic mean age-trajectories of weight may be described by such characteristics as age at reaching maximum weight (*AgeMax*), and rate of change in weight (*Slope*). We created respective binary phenotypes (1 versus 0) categorizing such behavior. For *AgeMax*, group (0) included individuals with younger *AgeMax* ( $< 70$  years), and group (1) included individuals with older *AgeMax* ( $\geq 70$  years), with condition of survival to age older than 70 in both groups. *Slope* was calculated as relative change in weight between ages 65

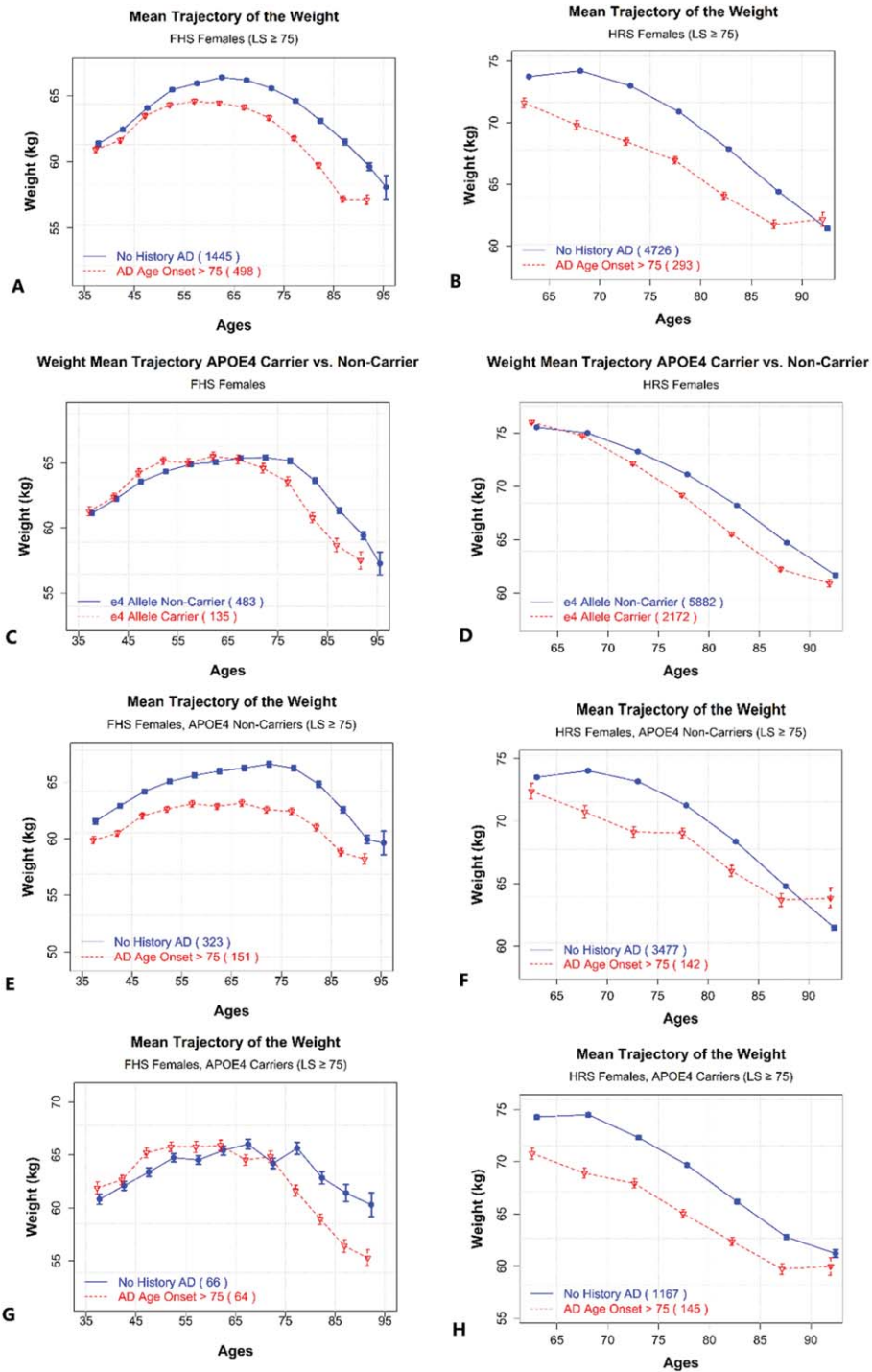


Fig. 1. (continued)

and 85. Group (0) included individuals with *Slope* below median (steeper decline in weight), and group (1) included individuals with *Slope* above median (flatter decline or non-declining pattern), with condition of survival to age older than 75 in both groups. For both *AgeMax* and *Slope* phenotypes, our working hypothesis was that being in group (1) could be more beneficial for older people than being in group (0), assuming that the ability to postpone/decelerate the decline in weight at older ages may reflect a slower physical aging with later onset of frailty [16].

### Analysis

*Age-trajectories of weight and probability of staying AD-free.* Using information about longitudinal changes in weight in FHS and HRS, we evaluated and compared mean trajectories of weight between ages 35 and 75, and up to age 95, in FHS participants who did and did not develop AD at ages 75+. Similarly, weight trajectories were evaluated and compared in HRS, though starting age was older (60 years) there due to low availability of younger ages in HRS data.

We also estimated impact of a younger versus older *AgeMax* on AD risk. Specifically, we compared trajectories of the probability of staying AD-free at ages 80+ for those who were alive at age 80 and reached maximum weight before age 75 vs. those who reached such maximum at or after age 75, in FHS and HRS, using the Cox proportional hazards model. Similarly, we estimated impact of *Slope* of the weight (steeper versus flatter) on trajectories of the probability of staying free of AD at ages 80+, in FHS and HRS.

We used the time-scale of chronological age with left truncation for age at entry. Follow-up was up to 25.75 years (median: 19.29, mean: 18.00, SD: 6.59). The proportionality of hazards assumption of the Cox model was tested using R-package *survival*.

All tests were insignificant ( $p$ -value > 0.05) and, therefore, supported this assumption.

*APOE  $\epsilon 4$  associations with phenotypes characterizing age-trajectories of weight.* We estimated associations between *APOE4* carrier status and main characteristics of mean age-trajectories of weight, such as *AgeMax* and *Slope*. In FHS, information about *APOE* genotypes was retrieved from dbGaP legacy data, without imputation. In HRS, genetic imputation data from dbGaP was used. The number of *APOE*  $\epsilon 4$  alleles carried by an individual was coded as 2 ( $\epsilon 4/\epsilon 4$ ), 1 ( $\epsilon 2/\epsilon 4$ ,  $\epsilon 3/\epsilon 4$ ), and 0 (other). This was then used to estimate associations between the number of  $\epsilon 4$  alleles and binary phenotypes characterizing age-trajectories of weight (Table 1, *Annotation*). Logistic regression models were used to test these associations in HRS and FHS. The covariates included birth year, education (0 – below high school, 1 – high school, 2 – above high school), and smoking (0 – non-smoker, 1 – smoker). SAS 9.4 software was used for statistical analysis. Both the case and control groups were restricted to have at least 50 participants. Males and females were analyzed separately. Analyses were stratified by race in HRS. The FHS includes mostly White participants, therefore, no stratification by race was done there.

## RESULTS

We compared the patterns of aging-related changes in weight between individuals who developed late-onset-AD and those who did not, taking into account the *APOE4* carrier status. We also evaluated the impact of age at reaching maximum weight, and the slope of weight decline, on the risk of AD. Results of our analyses are shown in Figs. 1 and 2, and Table 1. We found that women who developed AD at ages 75+ had, on average, lower body weight, starting as early as in their 40s, and a younger *AgeMax*, compared to

Fig. 1. Mean age-trajectories of weight for women with and without history of AD, and by *APOE4* carrier status. A) Age-patterns of weight for females with and without AD history. Dashed line – females with AD onset at ages 75+. Solid line – females without AD and with lifespan (LS) 75 years or older. FHS. B) Age-patterns of weight for females with and without AD history. Dashed line – females with AD onset at ages 75+. Solid line – females without AD and with lifespan (LS) 75 years or older. HRS. C) Age-patterns of weight for females with and without *APOE*  $\epsilon 4$  allele. Dashed line – females, who are  $\epsilon 4$  allele carriers. Solid line – females, who are  $\epsilon 4$  allele non-carriers. FHS. D) Age-patterns of weight for females with and without *APOE*  $\epsilon 4$  allele. Dashed line – females, who are  $\epsilon 4$  allele carriers. Solid line – females, who are  $\epsilon 4$  allele non-carriers. HRS. E) Age-patterns of weight for females without *APOE*  $\epsilon 4$  allele, by AD history. Dashed line – females with AD onset at ages 75+. Solid line – females without AD and with lifespan (LS) 75 years or older. FHS. F) Age-patterns of weight for females without *APOE*  $\epsilon 4$  allele, by AD history. Dashed line – females with AD onset at ages 75+. Solid line – females without AD and with lifespan (LS) 75 years or older. HRS. G) Age-patterns of weight for female *APOE*  $\epsilon 4$  allele carriers, by AD history. Dashed line – females with AD onset at ages 75+. Solid line – females without AD and with lifespan (LS) 75 years or older. FHS. H) Age-patterns of weight for female *APOE*  $\epsilon 4$  allele carriers, by AD history. Dashed line – females with AD onset at ages 75+. Solid line – females without AD and with lifespan (LS) 75 years or older. HRS.

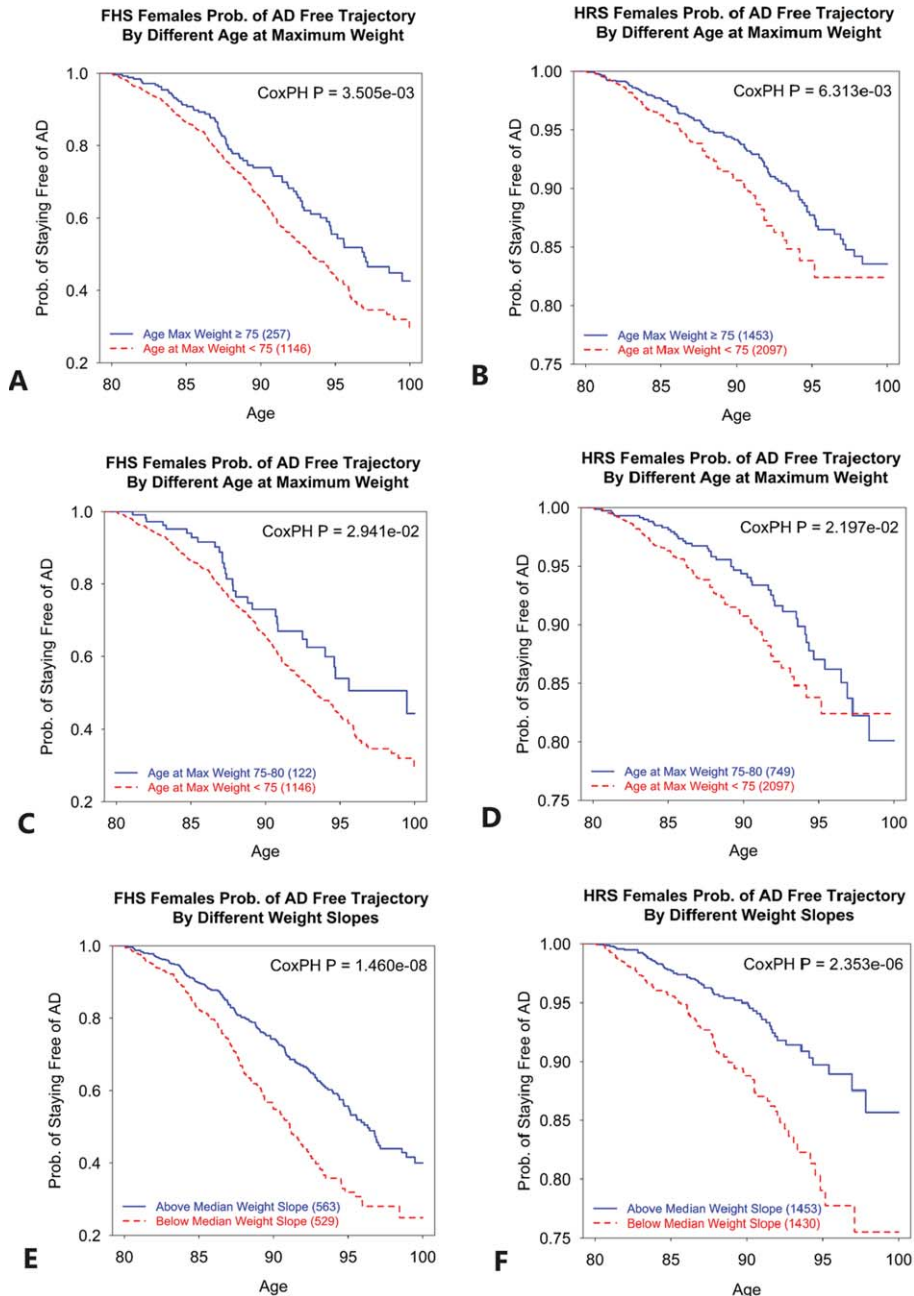


Fig. 2. Trajectories of probability of staying AD-free for women with different ages at maximum weight, and different slopes of weight. A) Probability of staying free of AD at ages 80+ for women who reached maximum weight at ages 75 or older (solid line), compared to those who reached maximum weight at ages younger than 75 (dashed line). FHS. B) Probability of staying free of AD at ages 80+ for women who reached maximum weight at ages 75 or older (solid line), compared to those who reached maximum weight at ages younger than 75 (dashed line). HRS. C) Probability of staying free of AD at ages 80+ for women who reached maximum weight at ages 75–80 (solid line), compared to those who reached maximum weight at ages younger than 75 (dashed line). FHS. D) Probability of staying free of AD at ages 80+ for women who reached maximum weight at ages 75–80 (solid line), compared to those who reached maximum weight at ages younger than 75 (dashed line). HRS. E) Probability of staying free of AD at ages 80+ for women with slope of weight change above median (solid line), meaning slower or no decline in weight, compared to women with slope of weight change below median (dashed line), meaning faster decline in weight. FHS. F) Probability of staying free of AD at ages 80+ for women with slope of weight change above median (solid line), meaning slower or no decline in weight, compared to women with slope of weight change below median (dashed line), meaning faster decline in weight. HRS. The CoxPH P is  $p$ -value for testing the null hypothesis that the regression coefficient for respective variable is zero.

women who did not have AD history (Fig. 1). No significant differences were found for males (trajectories not shown).

Similar relationships between AD and patterns of aging changes in weight were seen in carriers and non-carriers of *APOE4*, with older *AgeMax* seen in women without AD history (Fig. 1). Notably, in FHS with its longer follow up, a lower weight was observed in *APOE4* non-carriers with AD up to four decades before AD onset (Fig. 1). The same was not evident for *APOE4* carriers, though this might be because the latter group was relatively small in FHS.

Regardless of AD, *APOE4* carriers compared to non-carriers had lower weight starting around age 65 (Fig. 1). Analysis of associations between *APOE4* and binary phenotypes characterizing age-trajectories of weight, using logistic regression, found that carrying  $\epsilon 4$  alleles was associated with younger *AgeMax* in HRS, and with steeper slopes of the weight decline in both HRS and FHS, particularly in females (Table 1). For males, results were not significant in FHS. They were also not significant in Black HRS participants (not shown).

The analysis of the probability of staying free of AD, stratified by *AgeMax* (<75 versus  $\geq 75$ ), as well as by *Slope* (above versus below median), revealed that *AgeMax*  $\geq 75$  and flatter *Slope* were both significant predictors of a lower risk of AD after age 80 in women, in both FHS and HRS data (Fig. 2).

## DISCUSSION

Our study found that women who developed AD after age 75 had on average lower weight than AD-free women, seen as early as in their forties (Fig. 1). They also reached maximum values of weight about ten years earlier than AD-free women. This indicates that AD-relevant changes in the female body may start twenty, thirty or more years before clinical manifestation of AD. The weight loss could be an indicator of an underlying detrimental process (e.g., accelerated physical aging) which may contribute to AD risk. The early weight loss could also be a sign of already existing, hidden, AD. In the latter case, this would imply that the latent period between AD initiation and AD clinical manifestation could be very long, and that "late-onset" AD is actually disease that begins in early adulthood. The latter is not impossible and deserves further investigation. The lack of similar associations in men may point to female-specific hormonal changes during aging, such

as menopause-related metabolic transitions, including decline in estrogen levels, among others, which might contribute to the higher female vulnerability to neurological diseases, including AD [17]. This possibility also deserves further investigation.

This study revealed that older *AgeMax* and flatter *Slope* are both significant predictors of lower risk of AD in women (Fig. 2). Respectively, younger age at reaching maximum weight, and faster decline in weight towards older ages were associated with higher AD risk. This points to a major role of accelerated physical aging in AD, which was also suggested by others [18]. A more detailed analysis of the interaction between *AgeMax* and weight groups (that is, whether the association between *AgeMax* and AD risk varies in normal weight and overweight/obese groups) would also be helpful in future studies.

The number of *APOE*  $\epsilon 4$  alleles carried by an individual was associated with younger *AgeMax* and steeper *Slope* in our analysis (Table 1). This may point to a role of *APOE4* in accelerated aging too, though the mechanism needs clarification. It might involve, e.g., impaired physical resilience of *APOE4* carriers [19], among other factors. One should note, however, that female non-carriers of *APOE4*, who developed AD at ages 75+, had significantly lower weight and reached peak values of the weight at younger ages compared to non-carriers without AD history (Fig. 1). This means that the relationship between AD and lower weight, as well as aging changes in the weight, observed in this study, cannot be explained by the effects of *APOE4*. It remains to be determined whether or not *APOE4* influences AD risk through the biological effects of Apolipoprotein E on age-trajectories of weight. This could be addressed by further exploration of these relationships using causal inference approaches.

Our findings are also broadly in line with recent research that explored connections between temporal changes in BMI and dementia. A study of FHS offspring cohort with 76 cases of various dementias found BMI trends with first increasing and then declining mid-life pattern being associated with higher risk of dementia in later life [20]. Also, a British cohort study of the changes in BMI during 28 years before dementia diagnosis, found that BMI in dementia cases became lower starting 8 years before the diagnosis [9]. That study, however, used a mixture of dementia diagnoses, while our study is focused on AD.

In conclusion, women with AD onset after age 75 had lower bodyweight (as compared to AD-free

women) long before AD diagnosis, as early as in their forties. They also reached peak values of weight about ten years earlier than AD-free women. The observation that weight loss may precede clinical manifestation of AD by three or more decades is compatible with the idea that “late-onset” AD could be silently developing in the body since young adulthood and involve accelerated physical aging. In line, a higher age at maximum weight and a slower decline in weight were both significant predictors of lower risk of AD onset after age 80 in women. *APOE4* is unlikely to be the main factor responsible for the association between lower weight and AD risk, as *APOE4* non-carriers who developed AD had even lower weight than *APOE4* carriers with AD (prior to AD onset). Using causal inference approaches may further clarify the relationships between *APOE4*, weight loss, and AD.

## ACKNOWLEDGMENTS

The FHS is conducted and supported by the National Heart, Lung and Blood Institute (NHLBI) in collaboration with Boston University (N01 HC25195). The FHS data used for the analyses were obtained through the database of Genotypes and Phenotypes (dbGaP). The authors acknowledge investigators that contributed the phenotype and genotype data for this study. This manuscript was not prepared in collaboration with investigators of the FHS and does not necessarily reflect the opinions or views of the FHS, Boston University or the NHLBI. The HRS is sponsored by the National Institute on Aging (grant number U01AG009740) and is conducted by the University of Michigan. The HRS genetic data is sponsored by the National Institute on Aging (grant numbers U01AG009740, RC2AG036495, and RC4AG039029) and were obtained through dbGaP and the University of Michigan.

## FUNDING

This research was supported by the National Institutes of Health's National Institute on Aging (NIA/NIH), grants R01AG062623, RF1AG046860, R01AG070487, P30AG072958, and R01AG063971. This content is solely the responsibility of the authors and does not necessarily represent the official views of the NIA/NIH.

## CONFLICT OF INTEREST

Dr. Akushevich is an Editorial Board Member of this journal but was not involved in the peer-review process nor had access to any information regarding its peer-review.

All other authors have no conflict of interest to report.

## DATA AVAILABILITY

The authors cannot make FHS and HRS data freely available to other investigators due to dbGaP and the University of Michigan Data Use Certification Agreements restrictions; however, interested parties may contact these data providers to request access to the data through applicable data access request process.

## REFERENCES

- [1] Besser LM, Gill DP, Monsell SE, Brenowitz W, Meranus DH, Kukull W, Gustafson DR (2014) Body mass index, weight change, and clinical progression in mild cognitive impairment and Alzheimer disease. *Alzheimer Dis Assoc Disord* **28**, 36-43.
- [2] Alosco ML, Duskin J, Besser LM, Martin B, Chaisson CE, Gunstad J, Kowall NW, McKee AC, Strern RA, Tripodis Y (2017) Modeling the relationships among late-life body mass index, cerebrovascular disease, and Alzheimer's disease neuropathology in an autopsy sample of 1,421 subjects from the National Alzheimer's Coordinating Center Data Set. *J Alzheimers Dis* **57**, 953-968.
- [3] Bell SP, Liu D, Samuels LR, Shah AS, Gifford KA, Hohman TJ, Jefferson AL (2017) Late-life body mass index, rapid weight loss, Apolipoprotein E  $\epsilon$ 4 and the risk of cognitive decline and incident dementia. *J Nutr Health Aging* **21**, 1259-1267.
- [4] Wang C, Fu W, Cao S, Jiang H, Guo Y, Xv H, Liu J, Gan Y, Lu Z (2021) Weight loss and the risk of dementia: A meta-analysis of cohort studies. *Curr Alzheimer Res* **18**, 125-135.
- [5] Astell-Burt T, Navakatikyan MA, Feng X (2021) Behavioural change, weight loss and risk of dementia: A longitudinal study. *Prev Med* **145**, 106386.
- [6] Kang SY, Kim Y-J, Jang W, Son KY, Park HS, Kim YS (2021) Body mass index trajectories and the risk for Alzheimer's disease among older adults. *Sci Rep* **11**, 3087.
- [7] Kivimäki M, Luukkonen R, Batty GD, Ferrie JE, Pentti J, Nyberg ST, Shipley MJ, Alfredsson L, Fransson EI, Goldberg M, Knutsson A, Koskenvuo M, Kuosma E, Nordin M, Suominen SB, Theorell T, Vuoksimaa E, Westerholm P, Westerlund H, Zins M, Kivipelto M, Vahtera J, Kaprio J, Singh-Manoux A, Jokela M (2018) Body mass index and risk of dementia: Analysis of individual-level data from 1.3 million individuals. *Alzheimers Dement* **14**, 601-609.
- [8] Lee CM, Woodward M, Batty GD, Beiser AS, Bell S, Berr C, Bjertness E, Chalmers J, Clarke R, Dartigues J-F, Davis-Plourde K, Debette S, Angelantonio ED, Feart C, Frikke-Schmidt R, Gregson J, Haan MN, Hassing LB, Hayden KM, Hoeveraar-Blom MP, Kaprio J, Kivimäki M, Lappas G, Larson EB, LeBlanc ES, Lee A, Lui L-Y, van

- Charante EPM, Ninomiya T, Nordestgaard LT, Ohara T, Ohkuma T, Palviainen T, Peres K, Peters R, Qizilbash N, Richard E, Rosengren A, Seshadri S, Shipley MJ, Singh-Manoux A, Strand BH, van Gool WA, Vuoksima E, Yaffe K, Huxley RR (2020) Association of anthropometry and weight change with risk of dementia and its major subtypes: A meta-analysis consisting 2.8 million adults with 57 294 cases of dementia. *Obes Rev* **21**, 12989.
- [9] Singh-Manoux A, Dugravot A, Shipley MJ, Brunner EJ, Elbaz A, Sabia S, Kivimaki M (2018) Obesity trajectories and risk of dementia: 28 years of follow-up in the Whitehall II Study. *Alzheimers Dement* **14**, 178-186.
- [10] Kulminski AM, Loika Y, Culminskaya I, Huang J, Arbeevev KG, Bagley O, Feitosa MF, Zmuda JM, Christensen K, Yashin AI, Long Life Family Study Research Group (2019) Independent associations of TOMM40 and APOE variants with body mass index. *Ageing Cell* **18**, 12869.
- [11] Blautzik J, Kotz S, Brendel M, Sauerbeck J, Vettermann F, Winter Y, Bartenstein P, Ishii K, Rominger A, Alzheimer's Disease Neuroimaging Initiative (2018) Relationship between body mass index, ApoE4 status, and PET-based amyloid and neurodegeneration markers in amyloid-positive subjects with normal cognition or mild cognitive impairment. *J Alzheimers Dis* **65**, 781-791.
- [12] Bäckman K, Joas E, Waern M, Östling S, Guo X, Blennow K, Skoog I, Gustafson DR (2015) 37 years of body mass index and dementia: Effect modification by the APOE genotype: Observations from the Prospective Population Study of Women in Gothenburg, Sweden. *J Alzheimers Dis* **48**, 1119-1127.
- [13] Rajan KB, Skarupski KA, Rasmussen HE, Evans DA (2014) Gene-environment interaction of body mass index and apolipoprotein E  $\epsilon$ 4 allele on cognitive decline. *Alzheimer Dis Assoc Disord* **28**, 134-140.
- [14] Seshadri S, Beiser A, Au R, Wolf PA, Evans DA, Wilson RS, Petersen RC, Knopman DS, Rocca WA, Kawas CH, Corrada MM, Plassman BL, Langa KM, Chui HC (2011) Operationalizing diagnostic criteria for Alzheimer's disease and other age-related cognitive impairment-Part 2. *Alzheimers Dement* **7**, 35-52.
- [15] Bachman DL, Wolf PA, Linn R, Knoefel JE, Cobb J, Belanger A, D'Agostino RB, White LR (1992) Prevalence of dementia and probable senile dementia of the Alzheimer type in the Framingham Study. *Neurology* **42**, 115-119.
- [16] Crow RS, Petersen CL, Cook SB, Stevens CJ, Titus AJ, Mackenzie TA, Batsis JA (2020) Reported weight change in older adults and presence of frailty. *J Frailty Aging* **9**, 74-81.
- [17] Brinton RD, Yao J, Yin F, Mack WJ, Cadenas E (2015) Perimenopause as a neurological transition state. *Nat Rev Endocrinol* **11**, 393-405.
- [18] Leparulo A, Bisio M, Redolfi N, Pozzan T, Vassanelli S, Fasolato C (2022) Accelerated aging characterizes the early stage of Alzheimer's disease. *Cells* **11**, 238.
- [19] Ukraintseva S, Arbeevev K, Duan M, Akushevich I, Kulminski A, Stallard E, Yashin A (2021) Decline in biological resilience as key manifestation of aging: Potential mechanisms and role in health and longevity. *Mech Ageing Dev* **194**, 111418.
- [20] Li J, Liu C, Ang TFA, Au R (2023) BMI decline patterns and relation to dementia risk across four decades of follow-up in the Framingham Study. *Alzheimers Dement* **19**, 2520-2527.