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FEATURED ARTICLE

# Adiposity in the older population and the risk of dementia: The Rotterdam Study

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## Abstract

**Introduction:** We determined associations of total and regional adiposity with incident dementia among older adults.

**Methods:** Within the population-based Rotterdam Study, adiposity was measured as total, android, and gynoid fat mass using dual-energy X-ray absorptiometry in 3408 men and 4563 women, every 3 to 6 years between 2002 and 2016. Incident dementia was recorded until 2020.

**Results:** Higher adiposity measures were associated with a decreased risk of dementia in both sexes. After excluding the first 5 years of follow-up, only the association of gynoid fat among women remained significant (hazard ratio 0.85 [95% confidence interval 0.75–0.97] per standard deviation increase). No major differences in trajectories of adiposity measures were observed between dementia cases and dementia-free controls.

**Discussion:** Higher total and regional fat mass related to a decreased risk of dementia. These results may be explained by reverse causality, although a protective effect of adiposity cannot be excluded.

KEYWORDS
abdominal fat, adiposity, body composition, dementia, obesity

## Highlights

- Total and regional adiposity were assessed using dual-energy X-ray absorptiometry scans in 7971 older adults.
- All adiposity measures were associated with a decreased risk of dementia.
- The results suggest a beneficial effect of gynoid fat on the risk of dementia in women.
- Reverse causation and competing risk may explain these inverse associations.

Sanne S. Mooldijk and Tosca O. E. de Crom contributed equally to this study.

## 1 | INTRODUCTION

Obesity and dementia are both substantial public health problems worldwide.[1,2] Obesity during mid-life is a well-established risk factor for dementia later in life,[3–5] which may be explained by excessive adipose tissue.[6] Especially visceral fat, located around the abdominal organs, is thought to underlie this via metabolic dysfunction, for example, hypertension, insulin resistance, and dyslipidemia.[7,8]

Although visceral fat at older age likely affects the brain through similar metabolic dysfunctions, obesity at older age has consistently been linked to a decreased risk of dementia.[4,9–12] This may be explained by reverse causality, that is, weight loss caused by preclinical dementia symptoms,[13–15] but biological mechanisms for a protective effect of subcutaneous adipose tissue in the gynoid (i.e., hips) region have also been suggested.[16,17] These different health effects of adipose tissue deposits highlight the need to differentiate between total and regional adipose tissue, particularly in older adults, as adipose tissue increases and the distribution changes during the aging process.[18]

Yet, existing literature on the link between obesity and the risk of dementia mostly used body mass index (BMI) or waist circumference as marker of obesity, which do not necessarily reflect the amount and location of adipose tissue.[19–22] Alternatively, total and regional fat mass can be obtained using dual-energy X-ray absorptiometry (DXA), which allows the quantification of fat in the android (i.e., abdominal) and gynoid region.[21] Android fat accumulation is typically seen in men and includes visceral fat, while gynoid fat is typically seen in women and comprises of subcutaneous fat.

To improve the understanding of the effects of adiposity on the risk of dementia among older adults, we examined associations of measures of adiposity derived from DXA scans, namely total body mass, total fat mass, android fat mass, and gynoid fat mass, with the risk of dementia in men and women separately. In addition, to understand the potential role of reverse causality in this association, we determined trajectories of adiposity measures before dementia diagnosis and compared those to trajectories of dementia-free controls.

### RESEARCH IN CONTEXT

1. **Systematic Review**: We searched PubMed, Embase, and Cochrane library for studies reporting on the association between adiposity and the risk of dementia and found that a higher body mass during mid-life was linked to an increased risk of dementia, while body mass during late life was linked to a decreased dementia risk. Yet, studies that further investigated associations of total and regional adiposity with the risk of dementia are scarce.
2. **Interpretation**: Our findings of an association between more adipose tissue and a decreased risk of dementia in older adults may be explained by reverse causality and competing risks, although a protective effect of adipose tissue, particularly in the gynoid region, cannot be excluded.
3. **Future Directions**: We encourage further studies to investigate the effect of total and regional adiposity at older age on the risk of dementia, taking into account trajectories of adiposity measures starting early in life.

## 2 | METHODS

### 2.1 | Study setting and population

This study was embedded within the Rotterdam Study, a prospective population-based cohort study among individuals from the Ommoord district in Rotterdam, the Netherlands. Details regarding the design and rationale of the Rotterdam Study have been described elsewhere.[23] Briefly, the initial study (RS-I) started in 1990 with 7983 participants aged 55 years and older. The cohort was expanded in 2000 with 3011 participants aged 55 years and older (RS-II) and again in 2006 with 3932 participants aged 45 years and older (RS-III). All participants were invited to undergo an extensive follow-up examination every 4 to 6 years.

The Rotterdam Study has been approved by the Medical Ethics Committee of Erasmus Medical Center and by the board of the Netherlands Ministry of Health, Welfare, and Sports. Written informed consent was obtained from all participants.

Adiposity using DXA scans was measured from 2002 (RS-I-4), 2004 (RS-II-2), and 2006 (RS-III-1) onwards. Of the 9950 participants who were still alive and actively participating in the study by then, 8188 had data on adiposity measures available. We excluded participants without informed consent ($n = 50$), with prevalent dementia ($n = 88$), or who were insufficiently screened for dementia ($n = 79$; Figure S1 in supporting information). Of the 7971 participants remaining eligible for analyses, 3408 were men and 4563 were women.

### 2.2 | Measures of adiposity

Anthropometrics and adiposity were measured at the research center every 4 to 6 years between 2002 and 2016. Body weight in kilograms was measured using a digital scale and body height using a stadiometer, while participants were wearing indoor clothes without shoes. DXA (Prodigy and iDXA devices, GE Healthcare) scans were performed to obtain adiposity measures. As main outcomes, we used total body mass, total fat mass, android fat mass, and gynoid fat mass in kilograms. From these data, we additionally calculated commonly used indices of adiposity, namely BMI as body weight in kilograms divided by height in meters squared, fat mass index as total fat mass in kilograms divided by height in meters squared, and android and gynoid fat percentage by expressing fat mass in kilograms as a percentage of total android or gynoid mass in kilograms, respectively.

## 2.3 | Dementia

Participants were screened for dementia at Rotterdam Study baseline and every 4 to 6 years during follow-up examinations using the Mini-Mental State Examination (MMSE) and the Geriatric Mental Schedule (GMS) organic level. Those with an MMSE score of < 26 or a GMS organic level score of > 0 were further examined using the Cambridge Examination for Mental Disorders in the Elderly diagnostic interview. Additionally, participants were continuously under surveillance for dementia through electronic linkage between the study database and medical records from general practitioners and the Regional Institute of Outpatient Mental Health Care. The final diagnosis of dementia and its most common subtypes was made by a consensus panel led by a neurologist based on standard criteria for dementia (Diagnostic and Statistical Manual of Mental Disorders, 3rd edition revised), and for sub-diagnosis of Alzheimer's disease (AD; National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association). Follow-up for dementia was completed until January 1, 2020.

## 2.4 | Covariables

Covariables were determined at the round closest to the first available DXA scan. Education attainment, smoking status, and alcohol intake were ascertained during home interviews. Physical activity was assessed using the LASA Physical Activity Questionnaire and a modified version of the Zutphen Study Physical Activity Questionnaire and was expressed in metabolic equivalent of task (MET) hours per week. Depressive symptoms were evaluated with the validated Center for Epidemiologic Studies Depression Scale, which was converted to a sum score.[24] Diabetes mellitus was defined as having a fasting serum glucose of ≥7.0 mmol/L, use of blood glucose lowering medication, or being registered as having type 2 diabetes in records of general practitioners. Blood pressure was measured twice on the right arm with the participant in a sitting position using a random zero sphygmomanometer. The average of the two measurements was used. Total serum cholesterol and serum high-density lipoprotein (HDL) cholesterol were measured in fasting blood samples, collected at the research center. Dietary intake was determined using a validated 389-item food frequency questionnaire from which daily energy intake was determined using the Dutch Food Composition Tables (NEVO). A diet quality score reflecting adherence to the Dutch Dietary Guidelines was calculated by adding the adherence scores for 14 food components, as described in detail elsewhere.[25] Apolipoprotein E (*APOE*) genotype was obtained using polymerase chain reaction of coded DNA samples for RS-I and with bi-allelic TaqMan assay for RS-II and RS-III, and participants were classified as *APOE* ε4 carrier (1 or 2 alleles) or non-carrier.[26,27]

## 2.5 | Statistical analyses

The main analyses were conducted based on crude adiposity measures rather than their indices or percentages, because the use of indices may lead to spurious correlations.[28] To allow for comparison to existing literature that commonly used such indices, we repeated the analyses considering BMI, fat mass index, android fat percentage, and gynoid fat percentage.

We determined the associations between adiposity measures and the risk of dementia and AD using Cox proportional hazard models. The proportional hazards assumption was assessed using Schoenfeld residuals. Participants were censored when they were diagnosed with dementia, died, were lost to follow-up, or at the end of follow-up (January 1, 2020), whichever came first. All analyses were performed for men and women separately. We constructed three models. In model 1, we adjusted for height, age, and education attainment. In model 2, we further adjusted for smoking status, alcohol intake, physical activity, depressive symptoms, and *APOE* ε4 status. In model 3, we further adjusted for cardiovascular risk factors that are related to both adiposity and dementia, but are more likely to be mediators than confounders, namely systolic and diastolic blood pressure, diabetes, total cholesterol, and HDL cholesterol. Therefore, model 2 was considered the main model. Missing data on covariates (13% for physical activity, 7% for *APOE* ε4 status, 6% for smoking status, and < 5% for all other covariates) were imputed using five-fold multiple imputation. Daily energy intake and diet quality are also potential confounders of the associations. However, the number of missing values for these variables was relatively high (34%), limiting the ability to reliably include them in the main models. To explore whether diet explained the associations, we checked whether the results changed with further adjustment for daily energy intake and diet quality in addition to the covariates in model 2 as sensitivity analysis. The main analyses were repeated in subgroups for exploratory purposes: after stratifying for *APOE* ε4 status (carriers vs. non-carries), age (< 70 vs. ≥70 years), and BMI (< 25 vs. ≥25 kg/m$^2$). As suggested by previous literature, associations may differ by *APOE* ε4 status[29,30] and age.[4,9–12] Stratification by BMI was conducted to determine whether associations of adiposity with dementia are present, regardless of having a BMI considered healthy.

In addition, the main analyses were repeated after excluding the first 5 years of follow-up, to create insight into the potential impact of reverse causality. Moreover, the analyses were repeated with adiposity markers divided into tertiles to detect potential non-linear effects. To provide insight into the potential role of death as a competing risk for dementia, we repeated the main analyses with mortality as outcome. Furthermore, we visualized survival during follow-up by sex-, age-, and height-specific tertiles of adiposity measures in Kaplan–Meier survival curves.

For the trajectories of adiposity measures, participants who developed dementia (cases) during follow-up were matched with four participants who were free of dementia (controls) at the diagnosis date of the case. Matching was performed based on sex and birth year, resulting in a maximum age difference of a year. We constructed linear mixed models with random intercepts and slopes, adjusted for age and height, to determine trajectories of adiposity measures before the index date. Differences in the trajectories of cases and controls were allowed by adding an interaction term between time and case/control status. We also added splines with two knots to the time variable as

this significantly improved the fit of the model based on a likelihood ratio test with the models fitted under maximum likelihood procedure. To visualize whether differences in trajectories were statistically significant, we calculated 83.4% confidence intervals to archive a type 1 error probability of 0.05.[31]

All statistical analyses were conducted using R statistical software version 4.0.3. We considered results statistically significant when the *P*-value was below 0.05.

## 3 | RESULTS

Baseline characteristics are shown in Table 1. The mean age was 66.4 years (standard deviation 9.8) for men and 66.6 (10.2) for women. During a mean follow-up of 10.3 years, 293 men and 526 women developed dementia (incidence rates of 8.7 [95% confidence interval (CI) 7.7–9.7] and 10.9 [10.0–11.9] per 1000 person-years, respectively).

### 3.1 | Adiposity and the risk of dementia

Higher body mass, fat mass, android fat mass, and gynoid fat mass at baseline were associated with a decreased risk of dementia in both men and women, although not all statistically significant (Table 2). Risk estimates were similar when considering AD as outcome (Figure 1). In men, associations were especially seen for *APOE* ε4 carriers and for men aged ≥70 years at adiposity measurement, but not in *APOE* ε4 non-carriers and in men aged < 70 years. In women, the associations were consistent across the subgroups although the width of the confidence intervals differed. For both sexes, effect estimates for all adiposity markers attenuated after excluding the first 5 years of follow-up and only the association with gynoid fat in women remained significant (hazard ratio [HR; 95% CI] per standard deviation increase: 0.84 [0.75–0.93]). We found no indications of non-linear associations when analyzing the adiposity markers in tertiles (Table S1 in supporting information). Furthermore, additionally adjusting for daily energy intake and diet quality did not affect the association (data not shown), nor did repeating the analyses considering indices instead of crude adiposity measures as exposure (Table S2 in supporting information).

Survival curves showed subtle differences between tertiles of adiposity measures, namely a somewhat lower survival among men with higher total, android, and gynoid fat mass (Figure S2 in supporting information). Among women, survival was lower in participants with lower total or gynoid fat mass. Yet, when repeating the main analyses with mortality as the outcome, the risk of mortality did not differ with adiposity measures, except for a non-significantly lower risk of mortality with higher gynoid fat mass among women (Table S3 in supporting information).

### 3.2 | Trajectories of adiposity measures before dementia diagnosis

Of the 293 men and 526 women who developed dementia during follow-up, eight men and four women could not be matched with

**TABLE 1** Baseline characteristics of the total study population

| Characteristics | Men | Women |
|---|---|---|
| *N* | 3408 | 4563 |
| Age, years | 66.4 (9.8) | 66.6 (10.2) |
| Education attainment | | |
| Primary | 256 (8) | 545 (12) |
| Lower | 924 (27) | 2282 (51) |
| Intermediate | 1272 (38) | 1073 (24) |
| Higher | 930 (27) | 608 (13) |
| Smoking status | | |
| Never | 655 (21) | 1713 (40) |
| Former | 1996 (63) | 1876 (44) |
| Current | 510 (16) | 709 (16) |
| Energy intake, kcal/day | 2323 (734) | 2006 (642) |
| Dutch Dietary Guidelines, score | 6.6 (1.8) | 7.2 (1.9) |
| Alcohol intake, grams/day | 13.6 (14.0) | 6.9 (8.8) |
| Physical activity, MET hours/week | 65.1 (51.0) | 79.5 (53.1) |
| CES-D, score | 4.2 (5.7) | 6.7 (7.9) |
| Diabetes, yes | 476 (14) | 438 (10) |
| Systolic blood pressure, mmHg | 143.7 (20.7) | 142.9 (23.4) |
| Diastolic blood pressure, mmHg | 82.5 (11.2) | 81.1 (11.3) |
| Total cholesterol, mmol/L | 5.3 (1.0) | 5.8 (1.0) |
| High density lipoprotein cholesterol, mmol/L | 1.3 (0.3) | 1.6 (0.4) |
| *APOE* ε4 alleles | | |
| No allele | 2318 (72) | 3030 (72) |
| 1 allele | 805 (25) | 1108 (26) |
| 2 allele | 79 (2) | 71 (2) |
| General body composition measures | | |
| Height, cm | 176.1 (7.0) | 162.6 (6.5) |
| Body mass, kg | 85.4 (12.9) | 73.0 (13.1) |
| Body mass index, kg/m$^2$ | 27.5 (3.6) | 27.6 (4.7) |
| Fat mass, kg | 25.0 (8.4) | 29.1 (9.5) |
| Fat mass index, kg/m$^2$ | 8.0 (2.6) | 11.0 (3.5) |
| Regional fat measures | | |
| Android fat mass, kg | 2.8 (1.0) | 2.5 (1.0) |
| Android fat percentage, %[a] | 40.1 (8.3) | 45.7 (8.9) |
| Gynoid fat mass, kg | 3.5 (1.1) | 4.8 (1.5) |
| Gynoid fat percentage, %[a] | 29.7 (6.1) | 44.1 (6.5) |

*Note*: Data are shown for non-imputed data and are presented as mean (standard deviation) for continuous variables and number (percentages) for categorical variables.

Abbreviations: *APOE*, apolipoprotein E; CES-D, Center for Epidemiologic Studies Depression Scale; MET, metabolic equivalent of task; N, number of participants.

[a]Calculated as android or gynoid fat mass divided by total mass in android or gynoid region times 100%.

**TABLE 2** Adiposity at baseline in association with the risk of dementia

| Adiposity measures | Hazard ratio per SD (95% confidence interval) | | |
|---|---|---|---|
| | Model 1 | Model 2 | Model 3 |
| **Men** (*n*/*N* = 293/3408) | | | |
| Body mass | 0.91 (0.78–1.06) | 0.89 (0.76–1.05) | 0.85 (0.72–1.01) |
| Fat mass | 0.89 (0.78–1.02) | 0.87 (0.75–1.00) | 0.84 (0.72–0.97) |
| Android fat mass | 0.86 (0.75–0.98) | 0.84 (0.73–0.97) | 0.80 (0.69–0.93) |
| Gynoid fat mass | 0.90 (0.79–1.04) | 0.88 (0.76–1.01) | 0.86 (0.74–1.00) |
| **Women** (n/N = 526/4563) | | | |
| Body mass | 0.89 (0.81–0.99) | 0.90 (0.82–1.00) | 0.89 (0.80–0.99) |
| Fat mass | 0.87 (0.79–0.97) | 0.88 (0.80–0.98) | 0.87 (0.78–0.97) |
| Android fat mass | 0.86 (0.78–0.96) | 0.87 (0.79–0.97) | 0.84 (0.75–0.95) |
| Gynoid fat mass | 0.83 (0.74–0.92) | 0.84 (0.75–0.93) | 0.84 (0.75–0.93) |

*Note*: Hazard ratios per standard deviation increase in adiposity measures (based on the first available DXA scan). Model 1 is adjusted for age, height, and education attainment. Model 2 is additionally adjusted for potential confounders (smoking status, alcohol intake, physical activity, depressive symptoms, and *APOE* ε4 status). Model 3 is additionally adjusted for potential confounders that may also act as mediators (diabetes, systolic blood pressure, diastolic blood pressure, total cholesterol, and high-density lipoprotein cholesterol).
Abbreviations: *APOE*, apolipoprotein E; DXA, dual-energy X-ray absorptiometry; *N*, participants at risk of dementia at baseline; *n*, participants with incident dementia; SD, standard deviation.

dementia-free controls (Figure S1). Matched cases had on average 1.6 adiposity measurements available (range 1–3), compared to 2.0 for controls (range 1–3). Cases were more often carriers of the *APOE* ε4 allele. Otherwise, no major differences in characteristics between cases and controls were observed (Table S4).

Overall, trajectories of adiposity measures for cases and controls were similar, in both men and women (Figure 2). However, men who developed dementia tended to have higher android and gynoid fat mass than controls 18 to 16 years before diagnosis, while women who developed dementia tended to have a slightly lower android and gynoid fat mass starting 4 years before diagnosis. Yet, these differences in trajectories were not statistically significant. Again, similar results were found when considering indices of the adiposity measures instead of crude measures (Figure S3 in supporting information).

## 4 | DISCUSSION

In this population-based study, higher body mass, fat mass, android fat mass, and gynoid fat mass were associated with a decreased risk of dementia in both men and women. After excluding the first 5 years of follow-up, only the association between gynoid fat mass and the risk of dementia among women remained statistically significant. Trajectories of all adiposity measures up to 18 years before diagnoses of dementia in patients were comparable to those of dementia-free controls.

Various studies have reported on the association between BMI and the risk of dementia and almost invariably have found that a higher BMI during mid-life—generally defined as 50 years or younger—was associated with an increased risk of dementia, while a higher BMI during late life was associated with a decreased risk of dementia.[3–5,9–12] This is in line with a phenomenon that is also seen with cardiovascular diseases and mortality, known as the "obesity paradox,"[32–34] and may in part be explained by failing to differentiate between fat mass and lean body mass.[35] However, studies that further investigated associations of different fat compartments with dementia in late life are scarce. One previous longitudinal study among 344 older adults of the Cardiovascular Health Study with a mean age of 78 years also used DXA scans to distinguish fat from fat-free mass.[36] They observed no statistically significant associations of total and truncal fat mass with the risk of dementia, possibly because of the smaller sample size, but the effect estimates were in the same direction as in the current study (HRs for the highest truncal fat quartile versus the lowest: 0.69 [95% CI 0.24–2.01] in men and 0.72 [0.37–1.39] in women). Previous studies have also highlighted the possibility of non-linear effects of weight on the risk of dementia as an explanation for the obesity paradox,[37,38] but our results did not provide evidence for such effects.

Biological underpinnings of a relation between adiposity during mid-life and an increased risk of dementia is thought to include metabolic dysfunction such as hypertension, insulin resistance, dyslipidemia, and inflammation. Dysregulation of adipokines, hormones released by adipose tissue, may also have a role.[39] At older age, adiposity likely confers similar metabolic consequences. Yet, we found a decreased risk of dementia in persons with a higher total or regional fat mass. Protective effects of adiposity in the older population on the risk of dementia have been suggested.[40] For instance, the adipokine leptin is thought to have neuroprotective effects by preventing neuronal death and improved cognitive performance in rodents.[41] High levels of leptin are seen in persons with adiposity, while their levels drop with weight loss. As such, decreased leptin levels in older adults due to weight loss may contribute to their increased risk of dementia.[42] Estrogen levels may further explain protective effects of adiposity among older women.[16] In fact, in postmenopausal women, adipose tissue is the primary source

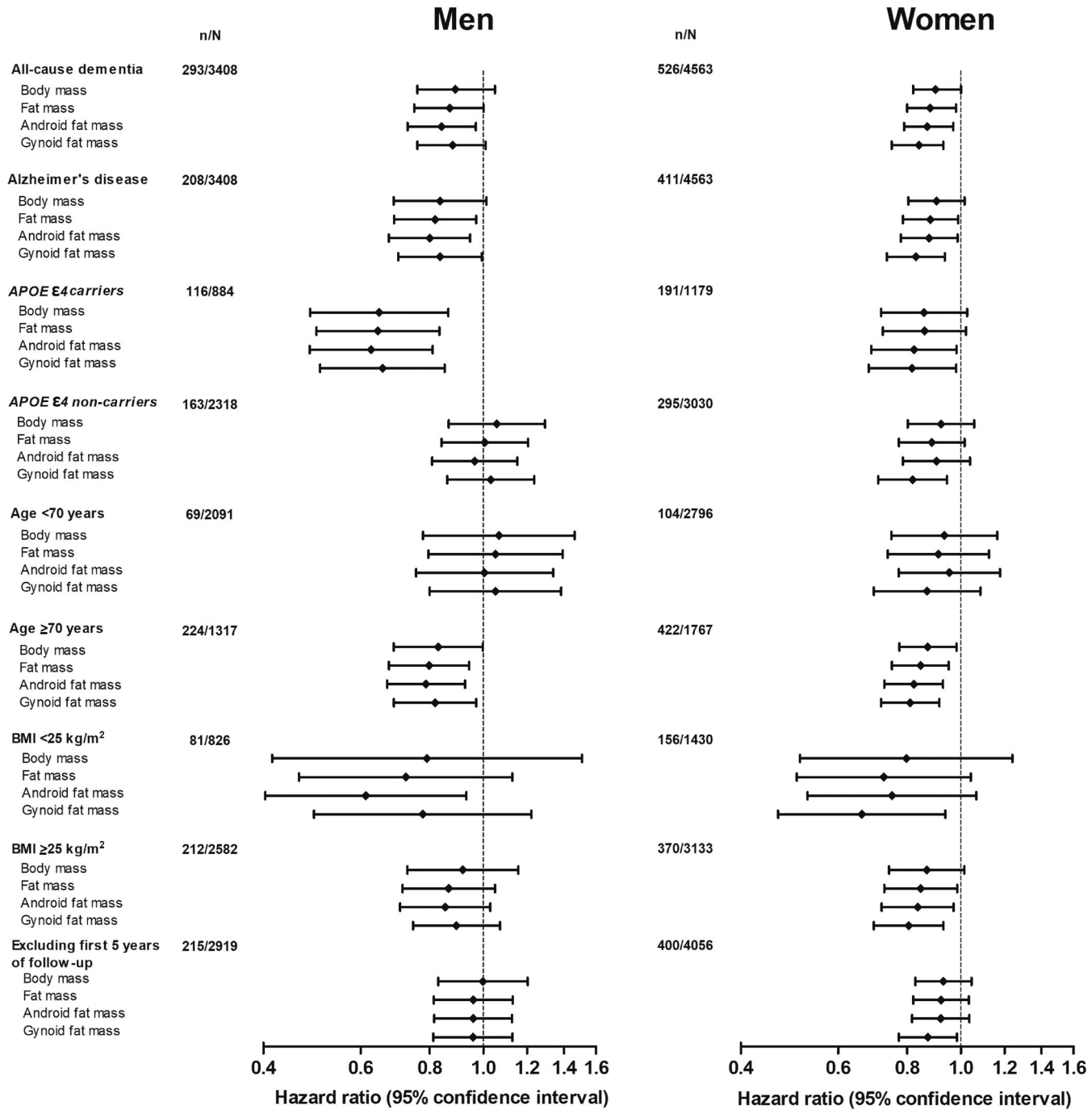


**FIGURE 1** Subgroup and sensitivity analyses for adiposity at baseline in association with the risk of dementia. Hazard ratios per standard deviation increase in adiposity measure (based on the first available DXA scan), adjusted for age, height, education attainment, smoking status, alcohol intake, physical activity, depressive symptoms, and *APOE* ε4 status. *APOE*, apolipoprotein E; BMI, body mass index; DXA, dual-energy X-ray absorptiometry; n, participants with incident dementia; *N*, participants at risk of dementia at baseline

of estrogen, which has been linked to brain health.[43] Potential alternative explanations for the association between higher adiposity markers and a decreased risk of dementia include reverse causality, that is, decreasing body (fat) mass due to preclinical dementia,[13] or mortality as competing event.

Given that most of our associations attenuated after excluding the first 5 years of follow-up, reverse causality likely explains at least part of the associations. We further provided insight into the potential role of reverse causality by visualizing trajectories of adiposity measures in persons with dementia before diagnosis and in dementia-free controls. Surprisingly, those only showed a small deviation in android and gynoid fat among women up to 4 years before diagnosis. Besides, the trajectories did not reveal the expected higher initial mass and later reduction in mass in persons with dementia, as was previously found

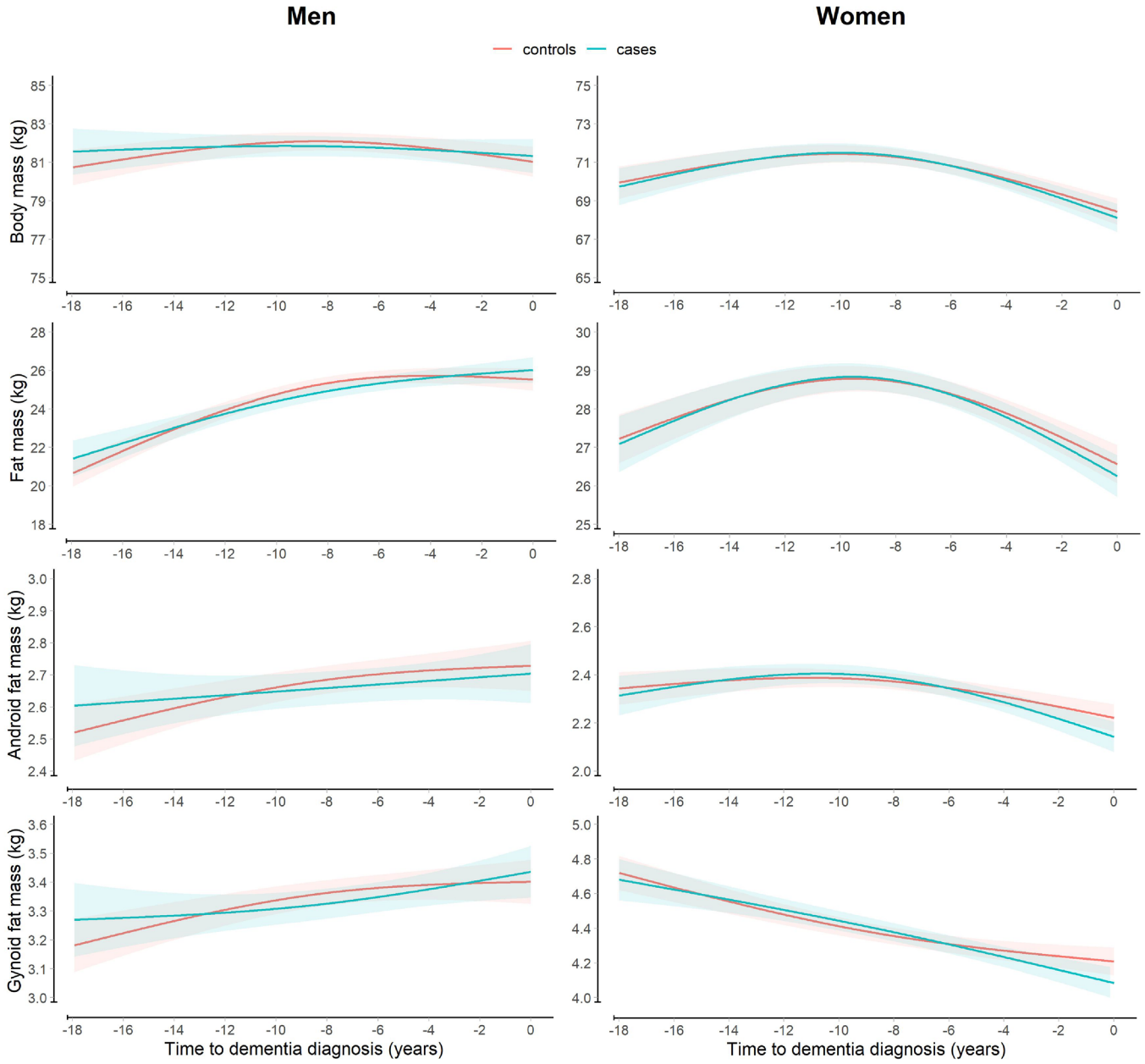


**FIGURE 2** Change in adiposity for cases before the diagnosis of dementia and for matched controls based on repeated measurements. Trajectories are shown for a man and woman of average age (77.0 years for men and 78.5 years for women) and height (174 cm for men and 160 cm for women). The numbers of observations per 2-year time interval are provided in Table S5 in supporting information

for BMI.[10,44,45] For instance, a decline in BMI was visible 7 years before dementia diagnosis (statistically significant 2.4 years before diagnosis) in the Three-City Study,[44] 6 years before dementia diagnosis in the Honolulu-Asia Aging Study,[45] and 8 years before diagnosis in the Whitehall II Study.[10] In the latter study, participants with dementia also had a higher BMI than dementia-free participants until 16 years before diagnosis. Such differences were not clearly seen in the current study, possibly due to the limited number of repeated measurements. For comparison, previous studies had up to six repeated measurements,[10,44,45] while the maximum in this study was three. There were particularly few DXA scan measurements available among cases in the period more than 14 years before their diagnosis.

Competing risks could also explain seemingly protective effects of adiposity, namely if a higher body or fat mass relates to a higher risk of mortality as a competing event, which subsequently precludes a dementia diagnosis. In this study, no pronounced associations between adiposity measures and mortality were found, making it unlikely that the associations between adiposity and the risk of dementia are due to competing risks of mortality. In women, lower gynoid fat mass was related to a somewhat lower survival as well as a lower dementia risk, making a protective effect of gynoid fat more plausible.

Results from the stratified analyses by *APOE* ε4 carrier status suggest that the *APOE* genotype modifies the association of adiposity with

dementia, particularly in men. Prior studies have described similar synergistic effects of *APOE* ε4 and adiposity,[29,30] for example as a result of their contributions to inflammation and metabolic disorders, although not all studies found this.[46] The stronger associations among *APOE* ε4 carriers could also be the result of weight loss in the preclinical dementia phase,[47] because carriers are more likely to develop dementia than non-carriers.

Strengths of this study are the data derived from DXA scans in a large community-based study population and the meticulous collection of dementia data, also among participants who no longer visited the research center. Limitations include the small number of repeated DXA measurements (≤3), that were mainly derived from persons of older age. More repeated measurements, starting from mid-life, may be needed to reveal differences in trajectories. Second, visceral fat mass was not available and instead android fat mass was used as a proxy, which also includes abdominal subcutaneous fat mass. Third, subgroup analyses should be interpreted with caution because of limited numbers of cases in subgroups. Last, body composition and the related disease risks differ with race,[48,49] thus translating these results derived from a predominantly White population to other populations should be done with caution.

In conclusion, higher total and regional fat mass were associated with a decreased risk of dementia. These results may be explained by reverse causality, although a protective effect of adipose tissue, particularly in the gynoid region among women, cannot be excluded. To further clarify the effect of adiposity on the risk of dementia, we encourage further studies to investigate total and regional adiposity at older age in light of early and mid-life adiposity. Future studies are also needed to explore associations in populations with different racial background and to clarify potential interactions of adiposity and *APOE* ε4.

## AUTHOR CONTRIBUTIONS

All authors have made substantial contributions to the design and conceptualization of the study (Sanne S. Mooldijk, Tosca O.E. de Crom, M. Kamran Ikram, M. Arfan Ikram, and Trudy Voortman); acquisition (Sanne S. Mooldijk, M. Kamran Ikram, M. Arfan Ikram, and Trudy Voortman), analysis (Sanne S. Mooldijk and Tosca O.E. de Crom), and interpretation of data (Sanne S. Mooldijk, Tosca O.E. de Crom, M. Kamran Ikram, M. Arfan Ikram, and Trudy Voortman); drafting the manuscript (Sanne S. Mooldijk and Tosca O.E. de Crom) or revising the manuscript critically for important intellectual content (M. Kamran Ikram, M. Arfan Ikram, and Trudy Voortman). All authors approved the final version of the manuscript for publication. Trudy Voortman 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.

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## CONFLICTS OF INTEREST

The authors report no conflicts of interest. Author disclosures are available in the supporting information.

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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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