Midlife overweight and obesity increase late-life dementia risk

A population-based twin study

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ABSTRACT

Objective: The relation of overweight to dementia is controversial. We aimed to examine the association of midlife overweight and obesity with dementia, Alzheimer disease (AD), and vascular dementia (VaD) in late life, and to verify the hypothesis that genetic and early-life environmental factors contribute to the observed association.

Methods: From the Swedish Twin Registry, 8,534 twin individuals aged ≥65 (mean age 74.4) were assessed to detect dementia cases (*DSM-IV* criteria). Height and weight at midlife (mean age 43.4) were available in the Registry. Data were analyzed as follows: 1) unmatched case-control analysis for all twins using generalized estimating equation (GEE) models and 2) cotwin matched case-control approach for dementia-discordant twin pairs by conditional logistic regression taking into account lifespan vascular disorders and diabetes.

Results: Among all participants, dementia was diagnosed in 350 subjects, and 114 persons had questionable dementia. Overweight (body mass index [BMI] >25–30) and obesity (BMI >30) at midlife were present in 2,541 (29.8%) individuals. In fully adjusted GEE models, compared with normal BMI (20–25), overweight and obesity at midlife were related to dementia with odds ratios (ORs) (95% CIs) of 1.71 (1.30–2.25) and 3.88 (2.12–7.11), respectively. Conditional logistic regression analysis in 137 dementia-discordant twin pairs led to an attenuated midlife BMI-dementia association. The difference in ORs from the GEE and the matched case-control analysis was statistically significant (*p* = 0.019).

Conclusions: Both overweight and obesity at midlife independently increase the risk of dementia, AD, and VaD. Genetic and early-life environmental factors may contribute to the midlife high adiposity–dementia association. ***Neurology*® 2011;76:1568-1574**

GLOSSARY

AD = Alzheimer disease; **BMI** = body mass index; **CERAD** = Consortium to Establish a Registry for Alzheimer's Disease; **CI** = confidence interval; ***DSM-IV*** = *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition; **DZ** = dizygotic; **GEE** = generalized estimating equation; **ICD** = International Classification of Diseases; **IDR** = Inpatient Discharge Registry; **MMSE** = Mini-Mental State Examination; **MZ** = monozygotic; **OR** = odds ratio; **VaD** = vascular dementia.

Body mass index (BMI) provides an indirect measure of adiposity, and is strongly correlated with total body fat tissue.[1] Adiposity may influence or be influenced by brain structures and functions, which may be involved in dementing processes.[2] In the last decade, many population-based longitudinal studies have evaluated the relationship between adiposity and dementia. Several reports have shown that midlife obesity increases the risk of dementia in late life[3-10]; however, the effect of midlife overweight on dementia is controversial.[3,5,7,9] Currently, the prevalence of overweight and obesity is over 50% among adults in the United States and Europe.[11]
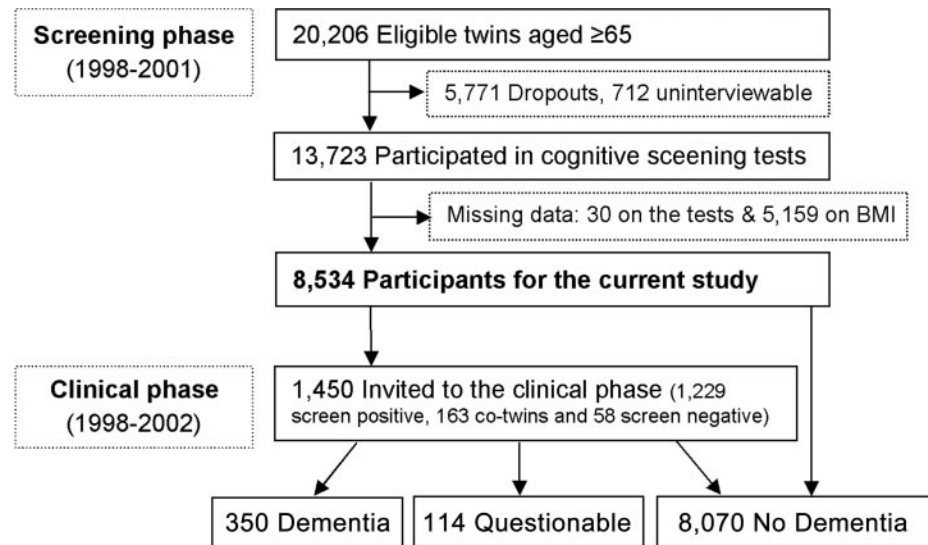
Although adiposity may be linked to dementia through several biologically plausible pathways,[12] our understanding of the mechanisms for such an association is still limited. Both

Figure 1 Flow chart of the study population

Screening phase (1998-2001)

20,206 Eligible twins aged ≥65

→ 5,771 Dropouts, 712 uninterviewable

13,723 Participated in cognitive sceening tests

→ Missing data: 30 on the tests & 5,159 on BMI

8,534 Participants for the current study

Clinical phase (1998-2002)

1,450 Invited to the clinical phase (1,229 screen positive, 163 co-twins and 58 screen negative)

350 Dementia | 114 Questionable | 8,070 No Dementia

BMI = body mass index.

obesity and dementia are complex genetic and lifestyle-related disorders. Evidence has shown that early-life environments (such as childhood socioeconomic situation) may affect the development of obesity and dementia.[13,14] The life course development of the adiposity-dementia association has been suggested,[15] but the contribution of genetics and early life environments to the relationship has not been investigated. In the present study, we sought to 1) verify the long-term effect of midlife overweight and obesity measured by BMI on the risk of dementia, Alzheimer disease (AD), and vascular dementia (VaD) taking into account diabetes and lifespan vascular disorders using unmatched case-control analysis; and 2) explore whether genetic and early-life environments could explain the observed association between midlife adiposity and dementia by cotwin matched case-control approach using data from the Swedish Twin Registry.

METHODS Participants and data collection. Participants were drawn from the nationwide Swedish Twin Registry.[16] In 1998–2001, all living twins in the registry who were born in 1935 and earlier (aged ≥65 years) were invited to participate in a telephone interview screening for most common diseases, which included a brief cognitive assessment.[17] In brief, a total of 20,206 individuals in the registry were eligible for screening. Of them, 13,693 twins completed the cognitive screening module, resulting in a participation rate of 67.8%. Information concerning demographic factors, education, current height and weight, health status and behavior, current and past diseases, and use of medications was also obtained during the interview. In addition,

self-report information on height and weight at midlife (mean age 43.4) was collected for all like-sexed twin pairs by the Registry in 1967, i.e., on average 30 years preceding the screening phase. Out of the 13,693 twins, 8,534 had data on height and weight at midlife available for the current analysis (figure 1).

Screening phase. The screening test included the TELE questionnaire for participants[18,19] and the Blessed Dementia Rating Scale for informants when participants performed poorly on the TELE.[19,20] The TELE and BDRS were combined into an ordinal scale with scores ranging from 0 (cognitively intact) to 3 (cognitive dysfunction). Participants who screened positive (i.e., scored 3) and their cotwins were invited to a clinical examination (n = 1,450).

Clinical phase and diagnosis. The full clinical workup consisted of a visit by an assessment team composed of a nurse and a physician using a protocol that generally followed the Consortium to Establish a Registry for Alzheimer's Disease (CERAD). The protocol included physical and neurologic examination, a review of medical history, informant interview, and a neuropsychological assessment. The neuropsychological battery included the Mini-Mental State Examination (MMSE), CERAD word list immediate and delayed recall, verbal fluency, block design, figure copying, judgment, information, symbol-digit, and prospective memory, as well as the Memory in Reality test.

The assessment team made an initial diagnosis of dementia and dementia subtypes following the *DSM-IV* criteria.[21] All protocols were reviewed by a diagnostic board, consisting of a neurologist and a neuropsychologist, who were blind to the assessment team's preliminary diagnosis, and verified the preliminary diagnosis. More details of the clinical examination and diagnostic procedure have been reported previously.[17] The cases completely fulfilling the *DSM-IV* criteria were diagnosed as "dementia," in contrast with a category of "questionable dementia," which was used for individuals who did not fulfill one of the first 3 *DSM-IV* diagnostic criteria, but did exhibit cognitive impairment or functional disability. Participants were first classified as no dementia, questionable, or dementia. A differential diagnosis

was then given for dementia subtype according to the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria for AD[22] and the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria for VaD.[23] Through the clinical workup, dementia was diagnosed in 350 subjects including 232 AD and 74 VaD cases, and 114 had questionable dementia. Among all participants, 8,070 did not have dementia.

Data on history of diabetes and vascular diseases obtained at the screening interview were integrated with data from the Inpatient Discharge Registry (IDR), which encompasses all hospital discharges in Sweden since 1969. All discharge diagnoses for participants who were hospitalized during 1969–2001 were obtained. Each record in the IDR included up to 8 discharge diagnoses according to the International Classification of Diseases, 8th revision (ICD-8) between 1969 and 1986 and 9th revision (ICD-9) since 1987. Medical conditions derived from the inpatient register database included diabetes (ICD-8, 9 code 250), hypertension (ICD-8 codes 400–404; ICD-9 codes 401–405), ischemic heart disease (ICD-8, 9 codes 410–414), cardiac dysrhythmia, heart failure or other myocardial insufficiency (ICD-8, 9 codes 427 and 428), and stroke (ICD-8, 9 codes 430–438). Diabetes and vascular diseases were deemed present if reported by self or informant, or if recorded in the inpatient registry. Survival status from midlife to the screening phase was obtained from the Cause of Death Register.

Validation of self-reported height and weight. A previous study indicated that the correlations between self-reported and measured height and weight were 0.97 for height and 0.95 for weight.[24] The mean differences (±SD) between self-reported and measured values were 1.2 ± 2.4 cm for height and 0.8 ± 4.0 kg for weight. In the present study, the correlation between self-reported height and weight at the screening phase and measured height and weight at the clinical phase were 0.91 ($p < 0.001$) and 0.93 ($p < 0.001$, n = 864), respectively. Pearson correlation coefficients were 0.87 ($p < 0.001$, n = 931) for the correlation between the height at midlife recorded in the twin registry and measured height at the clinical examination.

Standard protocol approvals. Informed consents were required from all participants during the telephone interview and again in the clinical phase. The data collection procedures were reviewed and approved by the Swedish Data Inspection Board, Stockholm Sweden, the Regional Ethics Committee at Karolinska Institutet, Stockholm, and the Institutional Review Board of the University of Southern California.

Statistical analysis. BMI was calculated as self-reported weight in kilograms divided by self-reported height in meters squared, and categorized into 4 groups: underweight (<20), normal weight (20–25), overweight (>25–30), and obese (>30).[25] Midlife BMI was used as both continuous and categorical variables in the analysis.

The characteristics of participants in different groups were compared using χ^2 tests for categorical variables, one-way analysis of variance for continuous variables. Multinomial logistic regression was first performed to estimate the odds ratios (OR) and 95% confidence intervals (CI) of dementia (350 dementia cases vs 8,070 controls) and questionable dementia (114 questionable dementia cases vs 8,070 controls) separately in relation to BMI. Further, 2 analytical strategies were applied to address the following aims: 1) unmatched case-control analyses was performed in all subjects (464 dementia and questionable dementia cases vs

8,070 controls) using generalized estimating equations (GEE) models, which are conceptually equivalent to logistic regression for the analysis of classic case-control design, but control for the clustering of twins within a pair; and 2) cotwin matched case-control analyses was carried out using conditional logistic regression models among the 137 dementia-discordant twin pairs after exclusion of 3,476 single twins, and 2,357 both no dementia and 35 both dementia twin pairs. The latter strategy allows matching for unmeasured familial factors, which could reflect genetic background or early life environment. Cases and controls are comparable with respect to genetic and early life environmental history (such as prenatal and postnatal nutritional status, and childhood socioeconomic status). If the association found in GEE analyses becomes attenuated in cotwin matched case-control analyses, genetic factors or familial environments or both are likely to contribute to the association. In contrast, if a significant association remains when using cotwin matched pairs, the influences of genetic or early environmental factors on the association are likely to be marginal.

Logistic regression was used to test the difference in ORs from GEE model and conditional logistic regression by examining the difference of overweight and obesity at midlife among unmatched vs cotwin controls. Age, sex, education, zygosity, diabetes, and vascular diseases were considered as confounders in all models. The statistical analyses were performed using SAS statistical software version 9.1 and Stata SE 10.

RESULTS Population characteristics. Among the 8,534 participants, 350 (4.1%) were dementia cases including 232 AD and 74 VaD, and 114 (1.3%) were diagnosed with questionable dementia. Among those included in the analysis, 6.0% of the females and 4.6% of the males had dementia or questionable dementia ($\chi^2 = 7.82$, $p = 0.005$).

Compared to participants without dementia, twins with dementia or questionable dementia were older, had a lower level of education and current BMI, had higher midlife BMI, and were more likely to have diabetes, stroke, and heart disease. A total of 2,541 twins (29.8%) were overweight or obese at midlife (table 1).

BMI in relation to questionable dementia and dementia. In the multinomial logistic analysis of the entire sample, midlife BMI as a continuous variable was significantly associated with an increased risk of dementia (OR 1.08, 95% CI 1.03–1.14) as well as questionable dementia (OR 1.07, 95% CI 1.04–1.11) after adjustment for potential confounders. Figure 2 shows the multi-adjusted ORs of dementia and questionable dementia related to BMI as categorical variable. As the midlife BMI-related ORs for dementia and questionable dementia were similar, these 2 categories were combined as an outcome of dementia in subsequent analyses.

Unmatched analysis. In GEE models, higher midlife BMI was associated with greater risk of all dementia, AD, and VaD using BMI as a continuous variable.

Table 1 Characteristics of the study participants (n = 8,435) by dementia diagnosis[a]

Characteristics	No dementia (n = 8,070)	Questionable dementia (n = 114)	Dementia (n = 350)	p Value
Age, y, mean (SD)	74.0 (6.7)	80.5 (7.1)	82.3 (6.5)	<0.001
Female sex	4,669 (57.9)	58 (50.9)	241 (68.9)	<0.001
Education, y, mean (SD)[b]	12.5 (62.3)	8.2 (2.9)	7.3 (2.5)	<0.001
Zygotic status				
Monozygotic	2,892 (35.8)	44 (38.6)	133 (38.0)	
Dizygotic	5,041 (62.5)	70 (61.4)	204 (58.3)	
Unknown	137 (1.7)	0	13 (3.7)	<0.001
Midlife BMI, mean (SD)	23.7 (2.9)	24.9 (4.9)	25.0 (3.1)	<0.001
Underweight (<20)	610 (7.5)	6 (5.3)	11 (3.1)	
Normal (20-25)	5,126 (63.5)	61 (53.5)	179 (51.1)	
Overweight (25-30)	2,120 (26.3)	41 (36.0)	136 (38.9)	
Obese (>30)	214 (2.7)	6 (5.3)	24 (6.9)	<0.001
Current BMI, mean (SD)	25.1 (3.7)	24.4 (3.6)	23.9 (4.7)	<0.001
Diabetes	805 (10.0)	22 (19.3)	84 (24.0)	<0.001
Stroke	621 (7.7)	35 (30.7)	103 (29.4)	<0.001
Heart disease	1,111 (13.8)	48 (42.1)	245 (70.0)	<0.001
Hypertension	2,727 (33.8)	42 (36.8)	126 (36.0)	>0.05

Abbreviation: BMI = body mass index.
[a] Values are n (%) of participants unless indicated otherwise.
[b] A total of 32 participants had missing value for education.

When BMI was analyzed as a categorical variable, compared with normal weight, overweight was associated with an increased risk of dementia and AD, while obesity increased the risk of dementia, AD, and VaD controlling for age, sex, and education. Further, the association was not attenuated by additional adjusting for diabetes and vascular diseases (table 2).

However, the statistical power was limited for the BMI-VaD association due to the few VaD cases.

Matched analysis. Among the 137 dementia discordant twin pairs, 44 were monozygotic (MZ), 90 were dizygotic (DZ), and 3 were unknown zygosity. In the cotwin matched case-control analyses, the association of midlife overweight and obesity (BMI >25) with dementia was attenuated, and no longer significant (table 3).

The difference between the ORs of dementia related to BMI >25 (overweight and obesity) from GEE model based on the entire sample (age- and sex-adjusted OR 1.56 [95% CI 1.28–1.91]) and from conditional logistic model based on dementia-discordant pairs (sex-adjusted OR 0.88 [95% CI 0.64–1.21]) was tested by comparing high BMI (>25) among the unmatched and matched controls. The difference was statistically significant (OR 1.62 [95% CI 1.12–2.66 $p = 0.019$]), indicating that genetic and family environmental factors may contribute to the high adiposity-dementia association.

Supplementary analyses. The dropout rate in the screening phase of this study was 32.2% (6,531/20,206) mainly due to refusal (74.8%) and to death (4.6%). Multivariable GEE model showed that being a dropout was associated with ORs of 1.05 (95% CI 1.02–1.06) for old age, 1.06 (95% CI 0.86–1.39) for female gender, 0.77 (95% CI 0.72–0.81) for education (per 1-year increase), 1.05 (95% CI 0.81–1.35) for stroke, 0.95 (95% CI 0.72–1.27) for diabetes, 0.79 (95% CI 0.63–1.03) for heart disease, and 0.98 (95% CI 0.74–1.29) for hypertension.

Figure 2 Odds ratio (OR) and 95% confidence interval (CI) of dementia and questionable dementia related to midlife body mass index (BMI), after adjustment for age, sex, education, zygosity, diabetes, stroke, hypertension, and heart disease (results from Multinomial Logistic Regression)
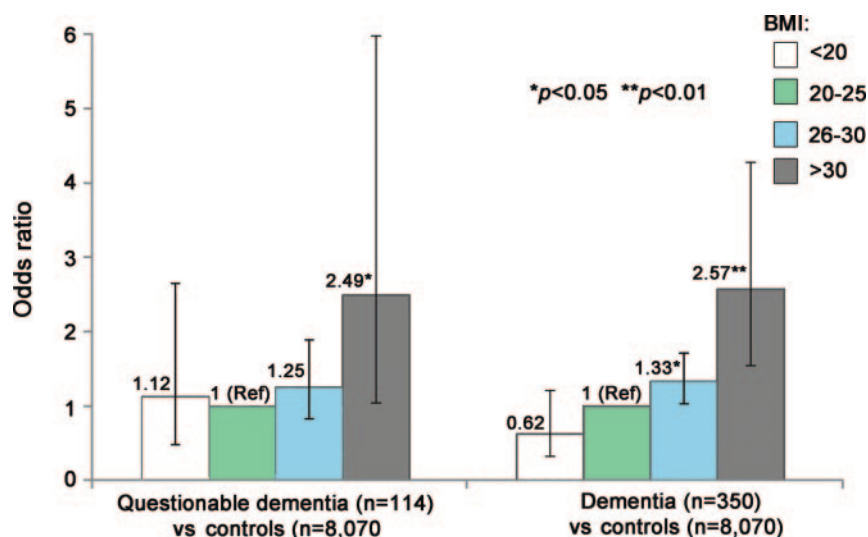
Table 2 Adjusted odds ratio (OR) and 95% confidence interval (CI) of dementia, Alzheimer disease, and vascular dementia related to midlife BMI (results from generalized estimating equation models)

Midlife BMI	No. of twins	All dementia			Alzheimer disease			Vascular dementia		
		No.	OR (95% CI)[a]	OR (95% CI)[b]	No.	OR (95% CI)[a]	OR (95% CI)[b]	No.	OR (95% CI)[a]	OR (95% CI)[b]
Continuous	8,534	464	1.09 (1.06-1.12)	1.06 (1.03-1.10)	232	1.09 (1.04-1.13)	1.06 (1.01-1.10)	74	1.14 (1.08-1.21)	1.11 (1.04-1.19)
Categorical										
<20	627	17	0.74 (0.44-1.25)	0.79 (0.45-1.38)	8	0.89 (0.64-1.23)	0.66 (0.31-1.41)	0	—	—
20-25	5,366	240	1 (Reference)	1 (Reference)	120	1 (Reference)	1 (Reference)	36	1 (Reference)	1 (Reference)
>25	2,541	207	1.50 (1.22-1.84)	1.80 (1.37-2.35)	104	1.52 (1.15-2.02)	1.98 (1.36-2.88)	38	1.62 (1.01-2.59)	1.35 (0.81-2.24)
25-30	2,297	177	1.37 (1.11-1.70)	1.71 (1.30-2.25)	90	1.41 (1.05-1.89)	1.91 (1.30-2.80)	31	1.39 (0.85-2.29)	1.17 (0.69-2.00)
>30	244	30	3.01 (1.95-4.64)	3.88 (2.12-7.11)	14	2.87 (1.57-5.26)	3.43 (1.49-7.90)	7	4.38 (1.89-10.14)	3.50 (1.36-8.99)

Abbreviations: BMI = body mass index; CI = confidence interval; OR = odds ratio.
[a] Adjusted for age, sex, and education.
[b] Adjusted for age, sex, education, diabetes, hypertension, stroke, and heart disease.

Further, we repeated the analysis of the BMI–dementia association leaving out the twins who scored 3 at cognitive screening but were diagnosed as no dementia or not referred to clinical workup (n = 655). This produced results similar to those from the initial analysis. Finally, we examined the effect of BMI >25 on mortality from midlife to late life (the screening phase). Among all like-sexed twins born before 1936, 4,825 died before the screening phase. In the GEE model, BMI >25 (overweight and obesity) at midlife was related to elevated risk of death with multiadjusted OR of 1.30 (95% CI 1.19–1.42).

DISCUSSION In this nationwide Swedish twin study, overweight and obesity at midlife increase the risk of all dementia, AD, and VaD, independently of lifespan diabetes and vascular diseases. Findings from the cotwin matched analyses suggest that familial factors (genetic factors and early life environments) contribute to the association between midlife high adiposity and dementia in late life.

Table 3 Midlife BMI in relation to dementia in dementia-discordant twin pairs (n = 137) (results from conditional logistic regression models)

Midlife BMI	No. of twins	Pairs	All dementia (n = 137)	
			OR (95% CI)[a]	OR (95% CI)[b]
Continuous	274	137	1.07 (0.97-1.21)	1.09 (0.95-1.26)
Categorical				
<20	15	8	1.19 (0.40-3.56)	1.07 (0.23-4.96)
20-25	154	73	1 (Reference)	1 (Reference)
>25	105	56	1.26 (0.77-2.67)	1.24 (0.71-2.87)
25-30	92	47	1.14 (0.71-2.32)	1.10 (0.68-3.30)
>30	13	9	2.24 (0.77-6.72)	1.62 (0.65-6.94)

Abbreviations: BMI = body mass index; CI = confidence interval; OR = odds ratio.
[a] Adjusted for sex and education.
[b] Adjusted for sex, education, diabetes, stroke, heart disease, and hypertension.

A growing body of evidence suggests that a high level of adiposity is associated with cognitive decline and dementia[10,26,27]; however, the relation between BMI and dementia among people aged over 65 is controversial.[28-30] Several population-based studies have reported an effect of obesity at middle age on dementia risk.[3,4,7,9] Only one study reported an increased dementia risk in people with overweight.[5] Despite the fact that high adiposity is associated with dementia, there remains a debate whether this concerns only AD or also VaD. Some prospective studies did find an association between obesity and increased risk of VaD,[7,29,31] while others did not.[9,32-34] In this Swedish twin cohort, we found that having dementia or AD was associated with more than a 70% higher odds of being overweight at midlife, while the odds of being obese at midlife were higher for those with AD as well as those with VaD. Although the effect of midlife overweight on dementia is not as substantial as that of obesity, its impact on public health and clinical practice is significant due to the fact that there are 1.6 billion overweight adults worldwide.[35]

Several potential biological mechanisms may explain the association between adiposity and dementia. First, higher BMI is associated with diabetes and vascular diseases, which are related to dementia risk.[12] Nonetheless, in our study, the association between midlife high BMI and dementia remained significant after controlling for lifespan vascular diseases, suggesting that nonvascular pathways might play an important role in the adiposity-dementia association. Second, higher adiposity at midlife may reflect a lifetime exposure to an altered metabolic and inflammatory state. Adiposity is one component of the metabolic syndrome which has been related to cognitive decline.[36] Further, adipose tissue is the largest endocrine organ and secretes inflammatory cytokines and growth hormones; some of them (such as

leptin, interleukin-6, and C-reactive protein) may affect cognitive functioning. Leptin is involved in deposition of amyloid β-42, and plays a role in neurodegenerative process.[37]

Twin studies involving a life-course approach may help to identify genetic and environmental influences on the development of chronic diseases, as twins provide naturally matched pairs, in which confounding effects of a large number of potentially causal factors (e.g., genetics and childhood environments) may be removed when comparisons are made within twin pairs. In cotwin control analyses, the association between higher midlife BMI and dementia was significantly attenuated, and thus may be attributed in part to genetic and early environmental factors such as childhood socioeconomic situation. However, twins may also experience similar exposures even at midlife and late life. Studies have reported that early life exposure to an imbalanced nutrition and disadvantaged economic status are related to a greater risk of obesity in adult life[38] and dementia in late life.[39] Our findings suggest that early-life environmental and genetic factors contribute to the link between adiposity and dementia.

Some limitations of the study should be mentioned. First, the use of prevalent dementia cases may have introduced some confounding effect due to differential survival among cases and controls. In addition, midlife obesity is associated with elevated mortality in our study, which would probably lead to an underestimation of the strength of the observed association. Second, compared to participants, the nonresponders were older, less educated, and more likely to be women, but did not differ from participants in terms of vascular risk factors. As old age, low education, and female sex are risk factors for dementia, possible selection bias could arise if the prevalence of dementia in this cohort differs from that in the general population. However, the prevalence of dementia in this study was comparable with several studies of dementia prevalence in Europe and the United States.[17] Third, midlife height and weight relied on self-reported information, which, however, were validated by a previous study. In addition, BMI alone might not be an ideal representation of body composition, although BMI has been widely used in population-based studies. Additional anthropometric measures, such as waist circumference, would be useful. Finally, both obesity and AD are genetically influenced disorders with substantial concordance in twins. Thus, the matched pairs could be regarded as overmatched, as twin pairs are similar on many aspects. Nevertheless, the comparison of the results from the entire sample and from matched pairs provides information about the potential role of genetic

and familial influences in the observed association. Finally, in the matched analysis, both MZ and DZ twins were included due to limited number of dementia-discordant MZ twin pairs. Hence, genetic effects were not perfectly controlled for.

Our results provide further support for the important role of high adiposity at midlife in the development of dementia, and highlight the need to control body weight as early as midlife for prevention of dementia in late life. These findings have relevant implications for public health, as the risk of dementia could be reduced by midlife weight loss.[40] Genetic and early-life environmental factors may contribute to the link of overweight and obesity to dementia, suggesting that the high adiposity-dementia association might develop across the lifespan.

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