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Overweight in Midlife and Risk of Dementia: A 40-Year Follow-up Study

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Abstract

Objective—This study examines if overweight in midlife increases dementia risk later in life.

Methods—In 1963 Body Mass Index was assessed in 1152 participants of The Swedish Twin Registry, then at the age of 45 to 65 years. These participants were later screened for dementia in a prospective study with up to 40 years follow-up. A total of 312 participants were diagnosed with dementia.

Results—Logistic regression analyses, adjusted for demographic factors, smoking and alcohol habits, indicated that men and women categorized as overweight in their midlife had an elevated risk of dementia (OR = 1.59; 95% CI: 1.21 to 2.07, $p = .002$), Alzheimer's disease (OR = 1.71; 95% CI: 1.24 to 2.35, $p = .003$), and vascular dementia (OR = 1.55; 95% CI: 0.98 to 2.47, $p = .059$). Further adjustments for diabetes and vascular diseases did not substantially affect the associations, except for vascular dementia (OR = 1.36; 95% CI: 0.82 to 2.56, $p = .116$), reflecting the significance of diabetes and vascular diseases in the aetiology of vascular dementia. There was no significant interaction between overweight and APOE $\epsilon 4$ status, indicating that having both risk factors does not have a multiplicative effect concerning dementia risk.

Conclusions—This study gives further support to the notion that overweight in midlife increases later risk of dementia. The risk is increased for both Alzheimer's disease and vascular dementia, and follows the same pattern for men and women.

Introduction

The long-term effects of overweight on physical health and survival are well known. Recent research is now even including potential negative effects on cognition in later life^{1–6}. In two recent systematic review articles^{7, 8} on overweight and risk of dementia it was proposed that high body mass index (BMI) is independently associated with risk of dementia.

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According to the reviews, the studies that reported significant associations had younger samples at baseline and longer follow-up periods.

Overweight should be measured in midlife in order to reveal the association to subsequent dementia because people often lose weight prior to diagnosis⁹ and early in the dementia phase¹⁰. This fact is bound to blur the association between overweight and dementia in older samples. Another reason is that BMI is a better measure of adiposity in younger samples as lean body mass is replaced by fat with increasing age¹¹. Thus, it is possible for old people to have relatively low BMI although they can have relatively high body fat. Finally, and most importantly, measuring overweight in midlife may reflect a more valid perspective on a persons' lifelong exposure to overweight, especially given the fact that most people tend to gain rather than lose weight in adulthood. Thus, when in the life course a risk factor for dementia is measured determines if and how the association is characterized^{12, 13}.

Studies that have addressed potential sex differences in the association between overweight and dementia risk indicate that overweight may be a stronger risk factor for women as compared to men^{3, 14}. Hayden et al.¹⁴ who used BMI in a sample of people aged 65 years and older to predict incident dementia, found an increased risk only for women, however, the authors reported a problem with low statistical power in the analyses of men. By using midlife assessment of BMI and skinfold thickness³, it was found that midlife BMI predicted dementia among women only, whereas midlife skinfold thickness predicted dementia in both sexes, suggesting that BMI is an inaccurate measure of adiposity in men.

A related question is if overweight is differentially associated with the most frequent types of dementia, that is, Alzheimer's disease (AD) and vascular dementia (VaD). This has only been examined in three studies^{1, 14, 15}. Two studies reported that overweight increases the risk of AD and not VaD in women^{1, 14}. In the study of Whitmer et al.¹⁵ overweight (BMI between 25 and 30) increased the risk of AD and VaD to the same extent (approximately a two- fold increased risk), whereas obesity (BMI ≥ 30) was more strongly related to VaD, indicating a five-fold risk, as compared to a three-fold risk of AD. In a recent study by the same group, midlife central obesity was found to predict dementia⁴.

In the investigation of the association between overweight and dementia it is important to include all covariates that are correlated with overweight and dementia and might affect the association, such as age, sex, lifestyle factors (education, smoking and alcohol consumption), diabetes, vascular diseases, and APOE $\epsilon 4$ carrier status. The majority of the studies addressing this issue include all relevant covariates, with the exception of APOE $\epsilon 4$ status.

The purpose of our study is to examine if overweight in midlife is related to increased risk of dementia in later life. We also examine if the risk is similar for men and women, and if overweight is differentially related to AD and VaD. Further, the potential effect of APOE $\epsilon 4$ allele will be examined.

Methods

Participants

Data on BMI come from the initial surveys that were administered to form the Swedish Twin Registry (STR). The STR was established in the late 1950s to study smoking and alcohol consumption in relation to potential risk of cancer and cardiovascular diseases^{16, 17}. In 1963 the twins answered questionnaires covering various environmental aspects including health and diseases, smoking habits, alcohol consumption and information on

weight and height. Almost 30 years later, two longitudinal studies on cognitive aging were conducted using the same twins who participated in the survey in the sixties, The Swedish Adoption/Twin Study of Aging¹⁸ (SATSA), starting in 1987, and Origins of Variance in the Old-Old¹⁹ (OCTO-Twin), starting in 1991. For the purpose of the present study information from the survey in the sixties and information from the SATSA and OCTO-Twin studies have been linked. All participants were informed about the study in accordance with the ethics committee of the Karolinska Institute, the Swedish Data Inspection Board, and the institutional board at the University of Southern California or the Pennsylvania State University.

The eligible participants for the current study were all individuals from the SATSA ($n = 767$) and the OCTO-Twin study ($n = 698$) who were at the age 45 to 65 at baseline in 1963 (born between 1898 – 1918) and who participated in the survey in 1963 ($N = 1465$). Out of these, all individuals were included who had valid data on all variables and who were screened for dementia (beginning in 1987 for SATSA, $n = 484$, and in 1991 for the OCTO-Twin study, $n = 668$) and tracked until 2005 or death. The total sample includes 1152 individuals (357 men and 795 women).

Overweight

Weight and height is based on information from the survey in 1963. BMI was calculated by dividing the weight in kilos by the height in square meters (kg/m^2). Overweight is normally defined as a BMI between 25 and 30, whereas obesity is defined as a BMI greater than 30. In our sample, however, less than 5% were obese according to this criterion. To gain statistical power, we therefore applied a slightly different categorization with BMI dichotomized into two categories with the top 25% of the distribution defined as overweight ($\text{BMI} \geq 26.5$; coded as 1) and all others defined as normal weight (coded as 0).

The information on heights and weights were self-reported, which is potentially a subject to bias. However, analyses completed in the SATSA comparing self-reported and measured information on heights and weights (within a one year period) resulted in a correlation of 0.97 for height and 0.95 for weight²⁰. The mean differences ($\pm$ SD) between self-reported and measured values were 1.2 ± 2.4 cm for height and 0.8 ± 4.0 kg for weight.

Dementia and vascular risk factors

The OCTO-Twin and the SATSA are longitudinal studies with repeated assessments at a 2, respectively 3-year time schedules. Thus, the participants have been evaluated continuously across the study period with respect to dementia and vascular risk factors. Clinical diagnoses of dementia followed the DSM-III-R criteria²¹. All individuals were assessed with a cognitive test battery during an in-person visit. Individuals suspected for dementia were given a diagnostic work-up, including an interview with an informant about memory and cognitive problems, review of in-person cognitive test protocols and medical records²². Findings were presented at a multidisciplinary consensus diagnosis conference, attended by the clinicians and chaired by a psychologist who had not met the participant. Subtypes of dementia were assigned following NINCDS/ADRDA criteria for Alzheimer's disease²³ and the NINDS-AIREN criteria for vascular dementia²⁴. All clinical diagnoses were completed without reference to neuroimaging. Prevalence rates of dementia in SATSA and OCTO-Twin have been found to resemble other similar studies such as the Kungsholmen study²⁵ in Sweden, and the Framingham study²⁶ in the U.S.

A total of 312 individuals received a dementia diagnosis: 181 were diagnosed with AD; 69 with VaD; and 62 with mixed, secondary or unspecified dementia. Mean age at recorded

dementia diagnosis was 83 years (range 62–96), and did not differ between the normal weight and the overweight groups.

The vascular risk factors of interest for the current study are smoking and alcohol habits, arterial hypertension, congestive heart failure, myocardial infarction, diabetes and stroke. The information on smoking and alcohol habits comes from the surveys in the sixties as well as from the longitudinal aging studies (SATSA and OCTO-Twin). The smoking variable was coded as 0 for non-smoker and 1 for current or previous smoker. The alcohol variable was coded as 0 for alcohol consumers and 1 for those who never use alcohol. Information on diabetes and vascular diseases was obtained through self-reports and through a review of medical records. If there was any notification of a disease or a history of self-report the person was coded as having the disease. The following diseases were included in the analyses: hypertension, congestive heart failure, myocardial infarction, diabetes, and stroke (0 = without the disease, 1 = with a disease).

APOE ϵ 4 carrier status was coded as 0 for non-carriers of the ϵ 4 allele and as 1 for those carrying 1 or 2 copies of the ϵ 4 allele. Information regarding APOE ϵ 4 carrier status was available for only 732 individuals. Therefore, APOE ϵ 4 status will not be included in the main analyses. However, it will be included in one complementary analysis in which potential interaction with overweight on dementia risk will be examined.

Data analyses

Group differences between the normal weight group and overweight group in background characteristics were analyzed with t-tests and chi square tests. Odds Ratio for dementia was calculated using an extension of the generalized linear model known as generalized linear mixed model (also known as hierarchical generalized linear model²⁷) to account for the hierarchical structure in the data while accounting for the dependency associated with twin pair status. Within this modeling procedure we analysed the logit function of the probability of an event of diagnosis of dementia as a conditional function of BMI, eight dummy coded covariates (i.e., gender, smoking, alcohol habit, hypertension, congestive heart failure, myocardial infarction, diabetes, and stroke), two continuous covariates (age and education,) and a random effect of the intercept reflecting estimated variability across the twin-pairs. The random effect was assumed to take a normal distribution with a mean of zero. Risk of dementia was first analysed for the total sample and then separately for men and women. In the next step, we examined if BMI was differentially related to AD and VaD: this was first analysed for the total sample, then separately for men and women. Two models were run in each case. Model I included age, gender, smoking, and alcohol habit as covariates. In Model II, diabetes and vascular diseases (hypertension, congestive heart failure, myocardial infarction, and stroke) were added along with the covariates included in Model I. The analyses were conducted using the GLIMMIX procedure in SAS version 9.1²⁸. The statistical analyses regarding the association between overweight and dementia were based on one-tailed tests using the conventional alpha level of 0.05.

Results

Sample characteristics

The sample characteristics are shown in Table 1. There were statistically significant differences between the normal weight group and the overweight group, such that the overweight group had fewer years of education, comprised more individuals who did not use alcohol, had more individuals with hypertension, congestive heart failure, and diabetes ($p < .05$).

Participant characteristics comparing controls with dementia cases are presented in Table 2. There were statistically significant differences between controls and cases, such that the dementia group had more women, were older, had fewer years of education, had shorter survival, comprised more individuals who did not use alcohol, had more prevalent congestive heart failure, stroke, and APOE $\epsilon 4$ carriers, and a higher BMI (p s < .05).

Risk of dementia in relation to midlife BMI

The results from the logistic regression analyses, that were all corrected for twin-ship, are presented in Table 3. Model I (adjusted for demographics, smoking, and alcohol use) showed that midlife overweight was associated with greater risk of dementia, such that those with a BMI above the third quartile had a 59% greater risk of getting dementia in old age as compared with those with lower BMI. Further adjustments for diabetes and vascular diseases in Model II did not substantially change this association. Among these covariates, only stroke came out as a significant covariate (OR = 1.59).

When BMI was examined in relation to AD the same pattern was found as with all dementia, although the association was stronger in terms of risk, OR = 1.71 in Model I, and OR = 1.68, in the fully adjusted model. None of the vascular risk factors were statistically significant. Concerning VaD, the risk associated with higher BMI fell short out of significance in Model I, (OR = 1.55; p = .059). However, the risk was substantially reduced in Model II by including diabetes and vascular diseases (OR = 1.36; p = .162), reflecting the significance of these factors in the aetiology of VaD. In this model, congestive heart failure (OR = 1.98), and stroke (OR = 6.97) were significantly related to risk of VaD (p s < .05), whereas diabetes was marginally significant (OR = 1.65; p = .067). The sex stratified analyses on BMI and dementia risk showed the same pattern among men and women, therefore, these results will not be presented separately.

A complementary analysis was conducted in which APOE $\epsilon 4$ carrier status was included in the analysis as a covariate as well as the interaction term between BMI and APOE $\epsilon 4$ status. As only 732 individuals had information regarding APOE $\epsilon 4$ status we first analysed BMI status in relation to all dementia in the subsample of 732 individuals not including APOE $\epsilon 4$ status. This analysis resulted in an OR of 1.62 (95% CI = 1.17 to 2.24, p = .008) for BMI status (as compared to OR of 1.59 for $N=1152$). When APOE $\epsilon 4$ status was included as a covariate, the association between BMI status and dementia was somewhat weaker, although still statistically significant (OR = 1.57, 95% CI = 1.13 to 2.20, p = .013). For APOE $\epsilon 4$ status the OR was 3.99 (95% CI = 2.96 to 5.38, p < .001), confirming the well established role of APOE $\epsilon 4$ as a risk factor for dementia. The interaction between BMI and APOE $\epsilon 4$ was not statistically significant (p = .781), indicating that having both risk factors does not have a multiplicative effect on dementia risk but rather an additive effect (see Table 4).

Discussion

The present study examined if overweight in midlife is related to risk of dementia in old age. Our results showed that midlife overweight significantly increased the risk of dementia in old age, even after controlling for known comorbid factors related to vascular risk. Further, the risk was increased for both AD and VaD. However, by controlling for diabetes and vascular diseases the association between BMI and VaD was reduced to a non-significant level. This was not the case for AD. Finally, the sex stratified analyses indicated the same pattern for men and women.

There are few studies that have examined the long term risk of overweight in relation to dementia. This is reasonable given the practical demands associated with studies requiring extensive follow-up time. Consequently, studies to date have often used medical records to

gain data on dementia diagnoses, a procedure that is unlikely to capture all cases and include information on dementia subtypes. In our study the dementia diagnoses were made through a thorough clinical procedure, resulting in a highly confident outcome diagnosis. On the other hand, the BMI measure is based on self reports on weight and height, leaving a potential risk for inaccuracy in report. However, correlational analyses conducted on SATSA²⁰, comparing self reported and measured data on heights and weights, resulted in correlation of 0.97 for height and 0.95 for weight, supporting a notion of valid and reliable self reported data. There are other measures of overweight that probably better reflect adiposity than BMI, such as hip-to-waist ratio and circumference, that we unfortunately did not have in our data. Another issue that needs to be highlighted when interpreting the results from the present study is the issue of potential survival bias. Included in our study are people aged 45 to 65 at baseline and who were alive at the start of the aging studies (SATSA and OCTO-Twin) on dementia. This implies that the participants were at the age of 69+ (for the SATSA) and 80+ (for the OCTO-Twin) at inclusion, meaning that the results can only be generalized to people who survive into that age. Another issue, related to the sample, is that it is constituted of twins which means that there is a dependency within twin pairs. This was, however, dealt with in the statistical analyses by using multilevel models that account for the dependency within pairs.

Generally, our results are in congruence with results from studies where overweight is measured in midlife and the follow up time for the dementia outcome is extensive^{2–4}. When we analysed the risk of dementia separately for the sexes the same pattern was found for men and women, a result that contradicts one study that reported greater risk for women¹⁴. Whitmer et al.³ found that the way adiposity is measured results in different dementia risk for the sexes, such that BMI predicted dementia only among women whereas skinfold thickness was a significant predictor for both sexes. Thus, there seem not to be any substantial differences between men and women in this matter.

Potential mechanisms by which overweight increases risk of compromised brain functioning in later life include vascular disease, diabetes, genetics, and inflammatory processes. Overweight increases the risk of hypertension, diabetes mellitus, and stroke, all three known risk factors for dementia. Our study, along with other studies show that even after controlling for these comorbid risk factors, overweight is still a significant risk factor of dementia. This does not, however, rule out the possibility that these diseases are of importance, especially given the fact that both hypertension and diabetes-related conditions are underdiagnosed and underreported in the general population. APOE ε4 carrier status is a known risk factor for vascular disease and dementia^{29, 30}. In our study there were somewhat more APOE ε4 carriers in the overweight group. In the analysis in which APOE ε4 status was included as a covariate, overweight remained a significant independent predictor for dementia. Most interestingly, however, was that overweight did not interact with APOE ε4 status on dementia risk in a multiplicative manner, supporting earlier findings from the Finish CAIDE study³¹. Another factor of importance is inflammation that has been shown to be associated with vascular disease³², obesity^{33, 34}, cognitive decline³⁵, and dementia³⁶. However, the direction of the associations between inflammation and the above conditions is controversial. In a recent study³⁵ it was demonstrated that the effects of the metabolic syndrome on cognitive decline were mediated by inflammation, such that those with high inflammation and the metabolic syndrome had a greater risk of cognitive decline compared with those with low inflammation but a metabolic syndrome.

To summarize, in congruence with the few studies that have assessed overweight in midlife and risk of dementia in later life, our study gives further support to the conclusion that overweight is a significant risk factor for dementia.

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Dr Hassing had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses. *Study concept and design:* Hassing, Dahl, Gatz, Pedersen, and Johansson. *Acquisition of data:* Berg, Gatz, Pedersen, and Johansson. *Analysis and interpretation of data:* Hassing, Dahl, Thorvaldsson, Gatz, and Johansson. *Drafting of the manuscript:* Hassing. *Critical revision of the manuscript for important intellectual content:* Hassing, Dahl, Thorvaldsson, Berg, Gatz, Pedersen, and Johansson. *Statistical analyses:* Hassing, Pedersen, and Thorvaldsson. *Obtained funding:* Hassing, Berg, Gatz, Pedersen, and Johansson. *Administrative, technical, and material support:* Berg and Gatz. *Study supervision:* Gatz and Johansson.

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Table 1

Participant Characteristics in Normal weight and Overweight Groups

	Normal weight	Overweight
N	864	288
Age in 1963, mean (SD)	52.5 (4.1)	52.5 (4.4)
Women, %	68	72
Years of education, mean (SD)	7.3 (2.3)	6.7 (2.0) *
Alive at the end of study, %	20	17
Years of survival after 1963, mean (SD)	37.2 (5.8)	35.3 (4.8)
Ever smoked, %	44	40
Ever used alcohol, %	68	62 *
Arterial hypertension, %	50	57 *
Congestive heart failure, %	23	29 *
Myocardial infarction, %	17	15
Diabetes, %	14	25 *
Stroke, %	16	18
APOE ε4 carrier ^a , %	30	35

Note. SD = Standard deviation.

*
p < .05.^a Available for 732 individuals.

Table 2

Participant Characteristics in the Normal Controls and Dementia Cases

	Cases			
	All	Controls	Dementia	VaD only
N	1152	840	312	69
Women, %	69	67	74*	64
Age in 1963, mean (SD)	52.5 (4.6)	52.1 (4.1)	53.6 (4.1)*	53.7 (4.3)*
Years of education, mean (SD)	7.2 (2.3)	7.3 (2.4)	6.9 (1.9)*	6.7 (2.2)
Alive at the end of study, %	19	38	22*	10*
Years of survival after 1963, mean (SD)	37.0 (5.5)	37.3 (5.8)	36.2 (4.5)*	35.3 (4.8)*
Ever smoked, %	43	43	43	52
Ever used alcohol, %	67	68	63*	65
Arterial hypertension, %	52	52	51	57
Congestive heart failure, %	25	23	29*	46*
Myocardial infarction, %	17	17	15	28*
Diabetes, %	17	17	19	25*
Stroke, %	17	15	22*	58*
APOE ε4 carrier [†] , %	31	22	50*	44*
BMI, mean (SD)	24.7 (3.0)	24.6 (2.9)	25.1 (3.2)*	25.2 (3.5)

Note. SD = Standard deviation.

* = p < .05 comparing controls with cases.

[†] Available for 732 individuals.

Table 3

Association Between Midlife Body Mass Index (highest quartile) and Risk of Dementia (N = 1152)

	Model I ^a		Model II ^b	
	OR (95% CI)	P Value	OR (95% CI)	P Value
All Dementia (n = 312)	1.59 (1.21 – 2.07)	.002	1.55 (1.18 – 2.04)	.004
Alzheimer's Disease (n = 181)	1.71 (1.24 – 2.35)	.003	1.68 (1.21 – 2.33)	.004
Vascular Dementia (n = 69)	1.55 (0.98 – 2.47)	.059	1.36 (0.82 – 2.56)	.162

Abbreviations: OR, Odds Ratio; CI, Confidence interval.

^aModel I is adjusted for age, sex, education, smoking- and alcohol habits.^bModel II is further adjusted for hypertension, congestive heart failure, myocardial infarction, diabetes, and stroke.

Table 4Prevalence of Dementia across Overweight and APOE ϵ 4 Carrier Status (N = 732)

	Non- APOE ϵ 4 Carriers		APOE ϵ 4 Carriers	
	Normal Weight	Overweight	Normal Weight	Overweight
N	402	103	172	55
Prevalence of Dementia	22%	31%	51%	62%

Abbreviation: APOE ϵ 4, apolipoprotein E allele 4.