Elevated body mass index, dementia risk, and post-mortem neuropathology

Patricia Vu

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Committee:

Walter Kukull

Christopher Keene

Luke Mease

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University of Washington

Abstract

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Patricia Vu

Chair of the Supervisory Committee:
Walter Kukull
Department of Epidemiology

BACKGROUND/SIGNIFICANCE: Over two-thirds of Americans aged 20 and over are considered overweight or obese. Compared to those who are within the healthy weight range as determined by body mass index (BMI), overweight and obese individuals are higher risk for poorer cognitive performance and structural brain pathology on neuroimaging studies. In addition, previous studies have shown a positive association between elevated BMI and the development of dementia later in life. In this study, we assessed for associations between overweight or obese BMI and dementia as well as for associations between overweight or obese BMI and neuropathology findings.

METHODS: Study participants were selected from a larger longitudinal dataset collected by the National Alzheimer's Coordinating Center. The inclusion criteria for this study included having records for BMI 10 to 15 years prior to death as well as neuropathology data. Individuals who were underweight were excluded. A cross-sectional study design was used to assess for associations between elevated BMI categories and dementia. To assess for associations between elevated BMI categories and severity of neuropathology findings, a cohort study design was

used. Logistic regression was used to determine odds ratios and their corresponding confidence intervals for all analyses.

RESULTS: There were no significant associations between individuals having overweight BMI or obese BMI and having a diagnosis of dementia. However, individuals who were overweight or obese had higher odds of having dementia when they carried an *APOE4* allele or completed less than a college-level education. There were no significant associations between elevated BMI categories and neuropathology findings, except for lower odds of hippocampus atrophy among obese individuals.

DISCUSSION: The lack of significant positive associations between elevated BMI categories and dementia may be due to the lower number of subjects with dementia who met the inclusion criteria for the study. The lack of significant positive associations between elevated BMI categories and more severe neuropathology findings may be due to the higher proportion of participants in this study having characteristics associated with higher socioeconomic status. Over 90% of subjects identified as white and over 60% of subjects completed at least a college-level education. This study did not account for the chronicity of exposure to elevated BMI nor other lifestyle factors such as physical activity, dietary intake, and substance use that affect brain health.

BACKGROUND & SIGNIFICANCE

Over two-thirds of Americans aged 20 and over are considered overweight or obese based on their measured body mass index (BMI) [1]. BMI is traditionally used to determine whether a person has a healthy weight (18.5-24.9), is underweight (<18.5), overweight (25.0-29.9), or obese (>30.0) based on their height and mass. Compared to healthy-weight individuals, those who are overweight or obese are at increased risk for mortality and chronic conditions that can reduce quality of life such as hypertension, type 2 diabetes, coronary heart disease, osteoarthritis, and poor mental health [2, 3]. Moreover, studies have shown that being overweight or obese is associated with poorer cognitive performance as well as structural pathology seen on brain imaging [4-10].

Studies utilizing magnetic resonance imaging (MRI) and computerized tomography have shown reduced gray matter volume in both individuals with elevated BMIs when compared to those with healthy BMIs [6-10]. An MRI study in adults ages 17 to 79 years old found negative correlations between BMI and whole brain volume as well as BMI and total gray matter volume after adjusting for age [8]. In a meta-analysis, consistent associations between obesity and lower gray matter volume on MRI in brain regions involved with executive functions in adults 18 years and older were noted [10]. Using computerized tomography in a longitudinal study, researchers reported women 70 years and older with temporal lobe atrophy had on average higher BMIs than those who did not have temporal lobe atrophy [11]. Differences in gray matter volume were also seen in obese children who were eight to ten years old when compared to non-obese children in areas associated with working memory [7].

Additionally, a study in adolescents 12 to 17 years old found a negative correlation between BMI and the integrity of white matter tracts that support working memory when they

combined cognitive testing with MRI findings [12]. Similar results were seen in a study assessing two large independent cohorts of adults ages 20 to 59. Researchers saw that higher BMI was associated with widespread reductions in fractional anisotropy even when controlling for conditions such as hypertension and diabetes [13]. Fractional anisotropy values have been used by researchers to evaluate the integrity of white matter tracts with lower values being indicative of impairment [12, 14, 15]. In a different study of adults 21 to 37 years old that combined diffusion tensor imaging with multiparameter mapping, the authors found that increasing BMI was associated with reduced myelin, increased water content, and altered iron content in white matter tracts that facilitate communication between the left and right brain hemispheres, the prefrontal cortex and thalamus, and among the frontal, occipital, parietal, and temporal lobes [15]. Evidence also supported that white matter in the frontal lobe may be particularly vulnerable to elevations in BMI [16, 17]. Based on their findings, the authors of these studies suggest that elevations in BMI may accelerate the normal decline in white matter integrity associated with aging, increasing the risk of dementia in persons who are overweight or obese [16, 17].

In a cohort study following adults who were initially nondemented from 70 to 88 years old, the authors found that women who developed dementia between 79 and 88 years of age were on average more overweight (as determined by BMI 1-3 units greater than 25 at ages 70, 75, and 79) than those who did not develop dementia [18]. In the same study, they saw that women who developed dementia earlier at 70, 75, and 79 had BMIs closer to the obese range compared to women who did not develop dementia [18]. Overall, the authors concluded the risk of developing dementia increased by 36% for every unit increase in BMI at 70 years old [18]. In a meta-analysis assessing the association between midlife (defined as 35 to 65 years old) BMI

and dementia, the authors found that midlife obesity increased the risk of developing dementia by 33% [19].

Elevated adiposity in individuals with high BMI may interact with genetic factors to mediate neurodegenerative processes. One of the most well-studied genetic risk factors for the development of Alzheimer's disease, the most common type of dementia, is the *ε4* allele of the Apolipoprotein E (*APOE*) gene [20]. The *APOE* gene is known to play a role in cholesterol transport, microglia activity, and inflammation and has two other major alleles: *ε2* and *ε3* [21-23]. Previous research supports that elevated body fat may act synergistically with the *APOE4* allele to result in poorer cognitive performance compared to when individuals only have one of these factors alone [24].

With the increasing prevalence of overweight and obese individuals in the United States, the military faces unique challenges with regards to recruitment, maintaining force readiness, and retention [25-28]. In addition, the increasing prevalence of overweight and obese individuals who are beneficiaries of the Military Health System pose a huge strain on resources allocated to healthcare for service members and their families. Furthermore, service members and their families are subjected to chronic stressors such as deployments and frequent moves that may increase their susceptibility to the effects of excess weight on brain health. While the current data supports that being overweight or obese may be detrimental to cognitive function secondary to its effects on gray and white matter structure, more studies are needed to assess for neuropathologic changes associated with elevated BMI. Currently, there are no known studies that assess for associations between overweight and obese BMI separately in late adulthood and post-mortem neuropathology findings in non-demented individuals a decade prior to death.

This study had two specific aims. The first specific aim was to assess for associations

between elevated BMI and presence of dementia as well as determine whether carrying an *APOE ε4* allele modifies any associations between BMI and dementia. The second aim was to assess for associations between overweight and obese BMI 10 to 15 years before death and severity of neuropathology outcomes to include brain atrophy, loss of white matter integrity, and pathologic markers associated with different forms of dementia in nondemented adults. We hypothesized that the odds of having dementia would be higher among subjects with elevated BMI (in the overweight or obese ranges). For subjects without dementia, we hypothesized that high BMI (overweight or obese BMI) would be associated with higher odds of more severe neuropathologic findings.

METHODS

Study design: This study employed a cross-sectional design and then a cohort design using longitudinal data previously collected by the National Alzheimer's Coordinating Center (NACC). First, a cross-sectional study design was used to determine the odds of dementia in overweight and obese subjects. Then a prospective cohort study design was used to assess for associations between having overweight or obese BMI 10 to 15 years prior to death and post-mortem neuropathology findings in non-demented individuals.

Study setting, and data collection: The data came from participants in the United States enrolled by the National Institute on Aging Alzheimer's Disease Research Centers (ADRCs) since 2005. The total dataset comprised participants who ranged from having normal cognition, to mildly impaired, to demented and includes data on individuals' demographics, medical history, as well as annual clinical follow-up information. Neuropathology data was available for

a subset of participants who have died and consented to autopsy. Genotypic data, which includes *APOE* genotype, was also available for approximately 75% of participants.

Study population: For this study, subjects were selected from the larger pool of NACC subjects who had BMI records (41,026 individuals). Of those with BMI records, 5841 individuals had died and undergone neuropathology evaluation by 18 October 2022 when the dataset was obtained from the NACC. The inclusion criteria for this study were subjects who had data for BMI 10 to 15 years prior to death as well as neuropathology data. Individuals who were underweight based on their BMI 10 to 15 years prior to death were excluded from the study due to conflicting data regarding the higher risk of underweight individuals developing dementia compared to individuals with healthy weights [19]. After applying the inclusion and exclusion criteria, 699 participants, who had both BMI records 10 to 15 years prior to death as well as neuropathology data, were included in this study (Fig. 1). Furthermore, for the cohort analysis for associations between BMI and neuropathology findings, subjects with a diagnosis of dementia were excluded due to the known effects of dementia on brain pathology and lack of data in this study regarding interval between diagnosis of dementia and death.

Exposure: For this study, the exposure of interest was average body mass index (BMI) 10 to 15 years prior to death in the overweight and obese weight ranges as defined by the Centers for Disease Control and Prevention. The subjects were thus categorized by BMI as healthy weight (18.5-24.9), overweight (25.0-29.9), or obese (30 and above).

Outcomes: The outcome of interest for the cross-sectional analysis was dementia. In this study, BMI data and carrying a diagnosis of dementia coincided. BMI prior to the diagnosis of dementia was not taken into consideration nor was the time between diagnosis of dementia and

death. Definitive dates of diagnosis for those who had dementia were not available for all NACC participants as some participants were enrolled in the original study after developing dementia.

As for the cohort study, the outcomes of interest were neuropathology findings, including cerebral cortex atrophy, hippocampus atrophy, white matter rarefaction, grade of Alzheimer's disease neuropathologic change (ADNC), Braak staging for neurofibrillary degeneration, CERAD semi-quantitative score for density of neuritic plaques, and Lewy body pathology. All autopsy data were scored previously by neuropathologists in categorical format. In this study, cerebral atrophy, hippocampal atrophy, and white matter rarefaction were reorganized as none to mild and moderate to severe. ADNC, also known as the ABC score, was categorized as none to low and intermediate to high. Braak stage was originally categorized from Stages 0 to VI and was reorganized into two categories: Stages 0 to IV and Stages V to VI [29]. The semi-quantitative CERAD neuritic plaque score was grouped as none to sparse diffuse plaques and moderate to frequent diffuse plaques. As for the presence of Lewy body pathology, the data was categorized as no Lewy body pathology and presence of Lewy body pathology.

Covariates: In assessing for associations between overweight and obese BMI and diagnosis of dementia, *APOE4* carrier status was considered as a potential effect modifier. *APOE* genotype was categorized as yes or no based on whether the individual carried at least one *ε4* allele. Highest level of education achieved (categorized as less than college and college and higher) and age greater 74 were also considered for their potential as effect modifiers.

Analysis: RStudio software version 4.1.1 was used for all analyses. First, descriptive statistics were performed separately for non-demented subjects and subjects with dementia to assess the demographic characteristics of the study population by their BMI category.

Descriptive statistics were also performed for the overall NACC population that had neuropathology data and any BMI data prior to death (Supplementary Table 1).

For the cross-sectional study, logistic regression was used to assess for associations between overweight or obese BMI and dementia. A cross-sectional design was used because the subjects carried a diagnosis of dementia at the time their BMI was obtained. To assess for confounding and effect modification, each covariate was included in the logistic regression model. A variable was considered a confounder if, compared to the unadjusted odds ratio (OR), the adjusted OR changed by 10% or more. A covariate was considered an effect modifier if significant interaction (p-value ≤ 0.05) existed between the variable and BMI. For the cohort study, logistic regression was also used to test for associations between overweight or obese BMI categories and higher severity of neuropathologic changes. For all analyses, ORs and CIs were calculated using those with healthy weight BMI as the reference group.

The use of existing de-identified data from the NACC in this study was exempted from the University of Washington Institutional Review Board review.

RESULTS

The total number of participants included in the cross-sectional analysis was 699. There were 518 participants without a diagnosis of dementia and 181 participants with a diagnosis of dementia. Among participants who were not diagnosed with dementia, the mean age at which BMI was assessed was 77.2 ± 8.4 years (this BMI was the average BMI participants had 10 to 15 years before death occurred). The mean age of death was 89.2 ± 8.4 years. Among participants with a diagnosis of dementia, the mean age at which BMI was assessed was 70.4 ± 9.9 years (again, this BMI was the average BMI participants had 10 to 15 years before death occurred).

The mean age of death in this group was 81.9 ± 10.0 years. Tables 1 and 2 show the demographic characteristics of the study participants who did not have dementia and participants diagnosed with dementia, respectively. The proportion of females in the healthy weight category was higher compared to the proportion of males in both the group without dementia and the group with dementia (67.3% and 64.2%, respectively). For those with BMI in the overweight range, the proportion of females and males were more similar: 52.3% were females in the group without dementia and 46.1% were females in the group with dementia. For those with BMI in the obese range, the proportion of females were higher than males: 65.2% were females in the group without dementia and 60.5% were females in the group with dementia. With regards to race, the majority of participants with and without dementia identified as Caucasian (>90%). As for highest level of education achieved among non-demented participants, 33.7% of participants with BMI in healthy category, 34% with BMI in the overweight category, and 33.6 % with BMI in the obese category earned less than a college degree. For participants with dementia, 40.3% of those in the healthy weight category, 59.2% of those in the overweight category, and 68.4% of those in the obese category earned less than a college degree.

In assessing for *APOE ε4* allele carrier status among non-demented participants, 41.8% of carriers had a healthy weight, 40.1% were overweight, and 18.1% were obese (Table 3). For participants who were diagnosed with dementia, the proportions of *ε4* allele carriers by BMI were as follows: 46.2% were healthy, 36.6% were overweight, and 17.2% were obese (Table 3). Results of logistic regression are shown in Table 4. The unadjusted odds of overweight participants having dementia were not significant (OR 1.15, 95% CI 0.78, 1.67). The unadjusted odds of obese participants having dementia were also not significant (OR 1.32, 95% CI 0.83, 2.10). No confounding by covariates was detected. *APOE ε4* carrier status and highest education

level completed were effect modifiers (Table 4). Carrying an *ε4* allele and completing less than a college education were effect modifiers. The odds of having dementia among overweight subjects were 2.06 times higher than the odds of having dementia in healthy weight subjects in those who carry an *APOE ε4* allele (95% CI 1.13, 3.77, p-value = 0.03). For obese individuals carrying an *APOE ε4* allele, the odds of having dementia were 2.53 times higher than the odds for heathy weight subjects (95% CI 1.25, 5.09, p-value = 0.03). The odds of having dementia among obese subjects were 3.20 times higher than the odds of having dementia among healthy weight subjects who completed less than a college education (95% CI 1.19, 8.59, p-value = 0.02).

Table 5 shows the results for the prospective cohort study. There was a significant association between obese BMI and moderate to severe hippocampal atrophy. The odds of developing moderate to severe hippocampal atrophy was 50% lower among obese subjects when compared to subjects with healthy weights (95% CI 0.29, 0.86). There were no other significant associations between high BMI categories and higher scores on neuropathology outcomes.

DISCUSSION

In this study, no significant associations were observed between high BMI categories and dementia in the cross-sectional analysis. Carrying an *APOE ε4* allele and completing less than a college education did modify the association between high BMI and dementia. The odds of dementia among subjects who were overweight or obese were higher when they carried an *APOE4* allele or completed less than a college-level education. The findings in this study were unexpected and may be due to the lower number of participants with dementia who met the inclusion criteria for the overall study, resulting in lack of statistical power. Multiple cohort and

longitudinal studies have found associations between high BMI and development of dementia [18, 19, 30-33]. Many of these studies, however, determined that high BMI in midlife (age ranging from 40 to 59 years old) rather than late-life BMI was associated with higher risk of developing dementia [30, 32, 33]. One study demonstrated that higher BMI at 50 years old was associated with a greater extent of Braak neurofibrillary tangles at autopsy in demented and non-demented individuals [34]. Associations between high BMI during late life (age 60 years and older) and developing dementia have been less clear and did not reach significance in several studies [32, 33, 35]. Only one study showed an increased risk of Alzheimer's disease, specifically, for women with higher BMIs from ages 70 to 79 [18]. This study used the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association Criteria in diagnosing Alzheimer's disease in their participants during life [18].

The neuropathology dataset from NACC utilized in this study lacked sufficient participants with BMI records during midlife to assess for associations between high BMI during midlife and dementia and high BMI during late life and dementia separately (Supplementary Table 1), which may have resulted in the null results. Furthermore, the cross-sectional nature of the analysis did not account for BMI as an exposure prior to diagnosis of dementia, any changes in BMI over the individuals' lifetime, or for the total duration of exposure to high BMI. Additionally, not all studies found positive associations between overweight or obese BMI and dementia [36, 37]. One study found that changes from high BMI from midlife to lower BMI in late-life were associated with higher risk of dementia, highlighting the non-static nature of BMI as an exposure for a complex outcome such as dementia [38].

When assessing for associations between overweight or obese BMI and brain pathology at autopsy in non-demented subjects in this study, the only significant association seen was the lower odds of hippocampus atrophy among obese subjects. There were no other significant associations between high BMI category and brain pathology, including cerebral cortex atrophy, white matter integrity, ADNC score, neurofibrillary degeneration, diffuse neuritic plaques, and Lewy body pathology. The lack of associations between high BMI and severity of brain pathology was unexpected and may be due to a variety of factors. Neuropathology findings such as cerebral cortex atrophy and white matter rarefaction are subjected to low interrater reliability due to lack of standardized metrics among neuropathologists and lack standardized, quantitative approaches to adequately compare with neuroimaging and other antemortem modalities. Additionally, the overall NACC study population is volunteer and referral-based and not a representative sample of the U.S. population, which may have resulted in selection bias. Greater than 90% of participants in the dataset identified as white. A higher proportion of NACC participants with neuropathology data and BMI data held at a college or advanced degree (>50%) compared to the general U.S. population (38%) [39]. Furthermore, greater than 60% of non-demented participants who met the inclusion criteria for this study (those who had BMI data 10 to 15 years prior death) held a college or advanced degree (Table 1). Race and educational attainment are important factors that contribute to socioeconomic status, which had been demonstrated to be associated with brain volume measures and development of neuropathology associated with dementia [40-42].

A study assessing late-life BMI and presence of moderate to severe neuritic plaques as well as Braak stages III-VI at autopsy found a negative association among participants who did not have dementia [43]. Their findings suggested a 7% decrease in odds of having Alzheimer's

disease neuropathology in those with higher BMI; however, the average age of the participants at which BMI was taken and average age of death differed by less than 5 years [43]. Assessing BMI closer to death may have confounded their results [44].

Similar to the cross-sectional analysis, the cohort analysis in this study only accounted for late-life BMI in assessing for associations between BMI and severity of neuropathology findings. Many studies, including this one, do not characterize whether there is a chronicity component to associations between being overweight or obese and neuropathology outcomes [8, 10, 11]. Furthermore, this study did not account for other lifestyle factors that may play a critical role in maintaining brain health and mitigating pathology such as physical activity, dietary intake, and substance use [45-47].

FIGURE 1. Study cohort selection from original National Alzheimer's Coordinating Center dataset

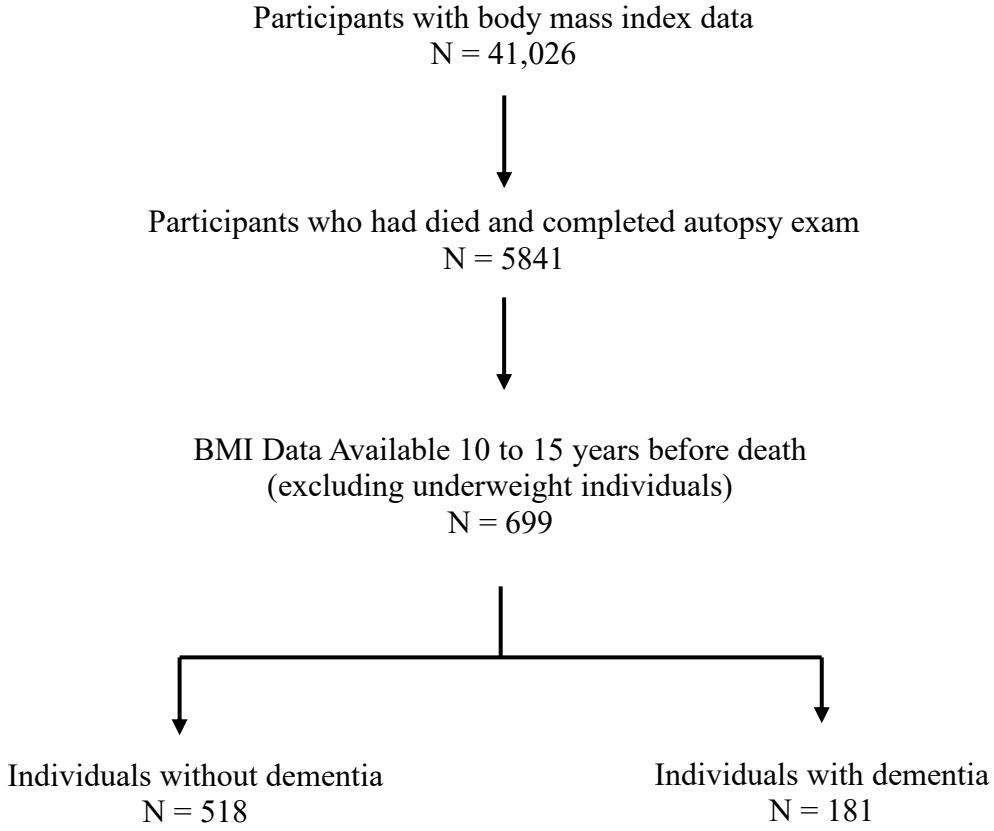

TABLE 1. Characteristics of study participants without dementia by body mass index category.

	Total N (%)	Healthy Weight n (%)	Overweight n (%)	Obese n (%)
Total	518 (100)	214 (100)	212 (100)	92 (100)
Sex				
Female	315 (60.8)	144 (67.3)	111 (52.3)	60 (65.2)
Male	203 (39.2)	70 (32.7)	101 (47.6)	32 (34.8)
Age (years)				
Less than 74	156 (30.1)	56 (26.2)	64 (30.2)	36 (39.1)
74 and older	362 (69.9)	158 (73.8)	148 (69.8)	56 (60.9)
Age at Death (years)				
< 60	3 (0.6)	2 (0.9)	1 (0.5)	0 (0)
60-69	8 (1.5)	3 (1.4)	5 (2.4)	0 (0)
70-79	41 (7.9)	18 (8.4)	12 (5.7)	11 (12.0)
80-89	191 (36.9)	68 (31.8)	77 (36.3)	46 (50.0)
90-99	234 (45.2)	100 (46.7)	103 (48.6)	31 (33.7)
100 and older	41 (7.9)	23 (10.7)	14 (6.6)	4 (4.3)
Race				
White	483 (93.2)	203 (94.9)	199 (93.9)	81 (88.0)
Black/African American	30 (5.8)	7 (3.3)	12 (5.7)	11 (12.0)
American Indian/Alaska Native	0 (0)	0 (0)	0 (0)	0 (0)
Native Hawaiian/Pacific Islander	0 (0)	0 (0)	0 (0)	0 (0)
Asian	3 (0.6)	2 (0.9)	1 (0.5)	0 (0)
Other	1 (0.2)	1 (0.5)	0 (0)	0 (0)
Unknown	1 (0.2)	1 (0.5)	0 (0)	0 (0)
Highest Level of Education Achieved				
Less than high school	20 (3.9)	4 (1.9)	12 (5.7)	4 (4.3)
High School Graduate	60 (11.6)	27 (12.6)	20 (9.4)	13 (14.1)
Some college or Technical training	95 (18.3)	41 (19.2)	40 (18.9)	14 (15.2)
College Graduate	130 (25.1)	68 (31.8)	44 (20.8)	18 (19.6)
Graduate Training	211 (40.7)	73 (34.1)	96 (45.3)	42 (45.7)
Unknown	2 (0.4)	1 (0.5)	0 (0)	1 (1.1)

TABLE 2. Characteristics of study population with dementia by body mass index category.

	Total N (%)	Healthy Weight n (%)	Overweight n (%)	Obese n (%)
Total	181 (100)	67 (100)	76 (100)	38 (100)
Sex				
Female	101 (55.8)	43 (64.2)	35 (46.1)	23 (60.5)
Male	80 (44.2)	24 (35.8	41 (53.9)	15 (39.5)
Age (years)				
Less than 74	105 (58.0)	35 (52.2)	47 (61.8)	23 (60.1)
74 and older	76 (42.0)	32 (47.8)	29 (38.2)	15 (39.5)
Age at Death (years)				
< 60	2 (1.1)	0 (0)	1 (1.3)	1 (2.6)
60-69	23 (12.7)	4 (6.0)	15 (19.7)	4 (10.5)
70-79	55 (30.4)	22 (32.8)	20 (26.3)	13 (34.2)
80-89	60 (33.1)	26 (38.8)	21 (27.6)	13 (34.2)
90-99	40 (22.1)	14 (20.9)	19 (25.0)	7 (18.4)
100 and older	1 (0.6)	1 (1.5)	0 (0)	0 (0)
Race				
White	168 (92.8)	62 (92.5)	73 (96.1)	33 (86.6)
Black/African American	7 (3.9)	2 (3.0)	2 (2.6)	3 (7.9)
American Indian/Alaska Native	0 (0)	0 (0)	0 (0)	0 (0)
Native Hawaiian/Pacific Islander	0 (0)	0 (0)	0 (0)	0 (0)
Asian	3 (1.7)	2 (3.0)	1 (1.3)	0 (0)
Other	1 (0.6)	1 (1.5)	0 (0)	0 (0)
Unknown	2 (1.1)	0 (0)	0 (0)	2 (5.3)
Highest Level of Education Achieved				
Less than high school	13 (7.2)	3 (4.5)	5 (6.6)	5 (13.2)
High School Graduate	47 (26.0)	12 (17.9)	21 (27.6)	14 (36.8)
Some college or Technical training	38 (21.0)	12 (17.9)	19 (25.0)	7 (18.4)
College Graduate	29 (16.0)	11 (16.4)	14 (18.4)	4 (10.5)
Graduate Training	53 (29.3)	29 (43.3)	16 (21.1)	8 (21.1)
Unknown	1 (0.6)	0 (0)	1 (1.3)	0 (0)

TABLE 3. *APOE4* allele carrier status by body mass index category and dementia status

		Non-Demented, N = 518		
	Total	*APOE ε4* Carrier	Not *APOE ε4* Carrier	Unknown
BMI Category	n (%)	n (%)	n (%)	n
Healthy Weight	214	74 (41.8)	132 (41.9)	8
Overweight	212	71 (40.1)	128 (40.6)	13
Obese	92	32 (18.1)	55 (17.5)	5
		Demented, N = 181		
	Total	*APOE ε4* Carrier	Not *APOE ε4* Carrier	Unknown
BMI Category	n (%)	n (%)	n (%)	n
Healthy Weight	67	43 (46.2)	19 (24.7)	5
Overweight	76	34 (36.6)	38 (49.4)	4
Obese	38	16 (17.2)	20 (26.0)	2

TABLE 4. Associations between high BMI and dementia and effect modifiers.

	BMI Category	OR (CI)	p-values
Dementia Diagnosis	Healthy Weight	Ref	
	Overweight	1.15 (0.78, 1.67)	0.48
	Obese	1.32 (0.83, 2.10)	0.25
Dementia & *APOE ε4* Carrier Interaction	Healthy Weight	Ref	
	Overweight	2.06 (1.13, 3.77)	0.03
	Obese	2.53 (1.25, 5.09)	0.03
Dementia & Level of Education	Healthy Weight	Ref	
	Overweight	2.12 (0.97, 4.63)	0.06
	Obese	3.20 (1.19, 8.59)	0.02
Dementia & Age $\geq$ 74	Healthy Weight		
	Overweight	0.82 (0.37, 1.81)	0.62
	Obese	1.29 (0.50, 3.38)	0.60

TABLE 5. Associations between high body max index and neuropathology outcomes from autopsy in participants without dementia

	BMI Category	OR (CI)	p-values
Cerebral Atrophy	Healthy Weight	Ref	
	Overweight	1.05 (0.71, 1.56)	0.81
	Obese	0.66 (0.38, 1.15)	0.14
Hippocampus Atrophy	Healthy Weight	Ref	
	Overweight	0.88 (0.60, 1.30)	0.53
	Obese	0.50 (0.29, 0.86)	0.01
White Matter Rarefaction	Healthy Weight	Ref	
	Overweight	0.98 (0.65, 1.49)	0.93
	Obese	0.93 (0.54, 1.60)	0.80
ADNC	Healthy Weight	Ref	
	Overweight	0.91 (0.41, 1.14)	0.65
	Obese	0.68 (0.61, 1.37)	0.14
Neurofibrillary Degeneration	Healthy Weight	Ref	
	Overweight	0.81 (0.24, 2.69)	0.73
	Obese	1.07 (0.20, 5.64)	0.93
Diffuse Plaques	Healthy Weight	Ref	
	Overweight	0.83 (0.54, 1.26)	0.38
	Obese	0.74 (0.44, 1.26)	0.27
Lewy Bodies	Healthy Weight	Ref	
	Overweight	1.25 (0.84, 1.86)	0.28
	Obese	0.92 (0.54, 1.56)	0.76

SUPPLEMENTARY TABLE 1. Characteristics of all participants in the original National Alzheimer's Coordinating Center dataset who had neuropathology data as well as data on body mass index

	Underweight n (%)	Healthy Weight n (%)	Overweight n (%)	Obese n (%)
Total	120	2375	2254	1092
Sex				
Female	101 (84)	1240 (52)	827 (37)	497 (46)
Male	19 (16)	1135 (48)	1427 (63)	595 (54)
Age (years)				
Less than 40	1 (0.8)	13 (0.5)	7 (0.3)	5 (0.5)
40 to 59	8 (6.7)	178 (7.5)	206 (9.1)	139 (13)
60 and older	111 (93)	2184 (92)	2041 (91)	948 (87)
Age at Death (years)				
< 60	8 (6.7)	97 (4.1)	81 (3.6)	68 (6.2)
60-69	15 (13)	299 (13)	338 (15)	189 (17)
70-79	27 (23)	531 (22)	534 (24)	324 (30)
80-89	34 (28)	852 (36)	796 (35)	350 (32)
90-99	33 (28)	537 (36)	796 (35)	350 (32)
100 and older	3 (2.5)	59 (2.5)	52 (2.3)	5 (0.5)
Race				
White	108 (90)	2236 (94)	2136 (95)	1019 (93)
Black/African American	4 (3.3)	87 (3.7)	83 (3.7)	60 (5.5)
American Indian/Alaska Native	1 (0.8)	3 (0.1)	5 (0.2)	1 (<0.1)
Native Hawaiian/Pacific Islander	0 (0)	1 (<0.1)	1 (<0.1)	2 (0.2)
Asian	7 (5.8)	35 (1.5)	14 (0.6)	3 (0.3)
Other	0 (0)	4 (0.2)	9 (0.4)	2 (0.2)
Unknown	0 (0)	9 (0.4)	6 (0.3)	5 (0.5)
Highest Level of Education Achieved				
Less than high school	5 (4.2)	102 (4.3)	101 (4.5)	78 (7.2)
High School Graduate	27 (23)	379 (16)	438 (20)	222 (21)
Some college or Technical training	19 (16)	414 (18)	382 (17)	231 (21)
College Graduate	36 (30)	640 (27)	565 (25)	233 (22)
Graduate Training	32 (27)	824 (35)	747 (33)	318 (29)
Unknown	1 (<0.1)	16 (<0.1)	21 (<0.1)	10 (<0.1)

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