**APOE genotypes modify the obesity paradox in dementia**

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**ABSTRACT**

**Background** While obesity in midlife is a risk factor for dementia, several studies suggested that obesity also protected against dementia, hence so-called obesity paradox. The current study aims to address the relationship between apolipoprotein E (APOE) genotype and obesity in dementia.

**Methods** Clinical and neuropathological records of the National Alzheimer’s Coordinating Center (NACC) in the USA, which longitudinally followed approximately 20,000 subjects with different cognitive statuses, APOE genotype and obesity status were reviewed.

**Results** Obesity was associated with cognitive decline in early elderly cognitively normal individuals without APOE4, especially those with APOE2. Neuropathological analyses adjusted for dementia status showed that APOE2 carriers tended to have more microinfarcts and haemorrhages due to obesity. On the other hand, obesity was associated with a lower frequency of dementia and less cognitive impairment in individuals with mild cognitive impairment or dementia. Such trends were particularly strong in APOE4 carriers. Obesity was associated with fewer Alzheimer’s pathologies in individuals with dementia.

**Conclusions** Obesity may accelerate cognitive decline in middle to early elderly cognitively normal individuals without APOE4 likely by provoking vascular impairments. On the other hand, obesity may ease cognitive impairment in both individuals with dementia and individuals at the predementia stage, especially those with APOE4, through protecting against Alzheimer’s pathologies. These results support that APOE genotype modifies the obesity paradox in dementia.

**BACKGROUND**

The prevalence of obesity is increasing worldwide, and >650 million adults were obese in 2016. Obesity is defined as abnormal or excessive fat accumulation that may impair health. Obesity is also a condition of prediabetes and is related to vascular diseases. On the other hand, the number of people in the world with dementia was 57.4 million in 2019, which will increase approximately 2.5-fold by 2050. Dementia is a syndrome in which there is a deterioration of cognitive function beyond what might be expected owing to the usual consequences of biological ageing, enough to interfere with independence in everyday activities, where at a minimum, assistance is required for complex instrumental activities of daily living, such as paying bills or managing medications. The effects of obesity on cognitive decline and incident dementia have been previously reported and discussed. Obesity in midlife was associated with the progression of vascular injury and atrophy in the brain and incident dementia in later life. On the other hand, obesity in late life reduced the risk of dementia compared with those with a normal body mass index (BMI). A meta-analysis showed a positive

**WHAT IS ALREADY KNOWN ON THIS TOPIC**

⇒ Although there are some controversial results, some studies reported that obesity in midlife was associated with the incident dementia, while other studies reported that obesity in late life reduced the risk of dementia, which is also supported by a meta-analysis.

⇒ These results indicate the existence of the obesity paradox in dementia.

⇒ Meanwhile, the relationship between apolipoprotein E (APOE) and obesity paradox in dementia has been scarcely studied.

⇒ Understanding of their relationship might further clarify the role of obesity in dementia.

**WHAT THIS STUDY ADDS**

⇒ This study for the first time revealed the relationship between APOE genotype and obesity paradox in dementia, where the harmful effects of obesity on cognitive decline in midlife to early elderly people is observed in non-APOE4 carriers, especially in APOE2 carriers, while the protective effects of obesity on dementia is remarkable in APOE4 carriers.

⇒ These results may explain the discrepancies in results reported in previous studies.

⇒ Moreover, this study revealed the underlying mechanisms; the harmful effects of obesity on cognitive decline is associated with vascular impairments, while the protective effects of obesity on dementia is associated with reduction of Alzheimer’s pathologies, to which APOE4 carriers are intrinsically vulnerable.

**HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY**

⇒ Obesity can work as a risk and protective factor for dementia depending on APOE genotype.

⇒ Thus, it would be important to determine the APOE genotype in clinical practice; especially, APOE4 carriers could have more benefits from obesity to reduce their own risk of dementia.

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association between obesity in midlife and later dementia, but the opposite was true in late life.\textsuperscript{14} An analysis of data from 1.3 million individuals also indicated that higher BMI has a harmful effect in long-term follow-up and a protective effect in the short-term follow-up before dementia diagnosis.\textsuperscript{15} The findings from these reports support the obesity paradox in dementia. The term obesity paradox was initially proposed for heart failure, where patients with obesity had a lower risk of death than those with a normal BMI,\textsuperscript{20,21} despite the fact that obesity increases the risks of vascular diseases.\textsuperscript{4,5} On the other hand, another systematic literature review and another report failed to support a paradox on the beneficial impacts of obesity in late life on incident dementia,\textsuperscript{16-17} suggesting that the concept of the obesity paradox in dementia is still controversial.

Apolipoprotein E (APOE) is the strongest genetic risk factor for Alzheimer’s disease (AD).\textsuperscript{22-26} Recently, by reviewing the database of National Alzheimer’s Coordinating Center (NACC), we analysed the effects of APOE on cognitive decline as well as the interaction between diabetes and the APOE genotype.\textsuperscript{27,28} In the latter study, we showed that diabetes affects cognitive decline in non-APOE4 carriers, but not in APOE4 carriers.\textsuperscript{28} The NACC database contains a prospective standardised, longitudinal clinical evaluation of a large number of patients in the National Institute on Aging’s Alzheimer’s Disease Research Center (ADC) programme across the USA with available autopsy data for a subset of patients. In the current study, by using this database, we investigated whether obesity is associated with cognitive decline, incident dementia and neuropathological changes, depending on the APOE genotype, hypothesising that the obesity paradox could be affected in an APOE genotype-dependent manner.

METHODS
Data acquisition
The clinical data in the NACC database, which were collected by the ADC from September 2005 to September 2018 as the longitudinal Uniform Data Set (UDS),\textsuperscript{29,30} were assessed in this study. NACC participants are regarded as a referral-based or volunteer case series, and the majority of the subjects are Caucasians, followed by black or African-Americans, including both individuals with dementia and without dementia. To examine the effects of obesity on cognitive decline during ageing, and simplify its relationship with APOE genotype, we restricted our analysis to subjects whose APOE genotype information (other than the APOE ε2/ε4 genotype) was available and who were recruited at an age ≥60 years of age (selection diagram is shown in online supplemental figure 1). APOE genotype status was defined as APOE2 carriers (ε2/ε2 or ε2/ε3), APOE3 homozygote individuals (ε3/ε3) and APOE4 carriers (ε3/ε4 or ε4/ε4), and treated as a nominal variable with three values (ie, ε2, ε3 and ε4), as we did previously.\textsuperscript{27,28,31-33} Subjects with APOE ε2/ε4 genotype (n=550) were excluded due to the mutually exclusive effects of APOE2 and APOE4 on cognitive decline during ageing.\textsuperscript{27,28,34} To assess obesity status, we calculated BMI based on the subject’s weight and height, according to the formula.\textsuperscript{35} We removed subjects whose BMI was <20 at any visit (n=710) and subjects whose BMI status changed between obese and non-obese during visits (n=957). If a subject showed BMI >30 at all visits, we classified them as obese (n=3932). As the control group for comparison, we defined the non-obese group. If a subject showed BMI between 20 and 30 at all visits, we classified them as non-obese (n=16 116, table 1). As an alternative control, we also defined the normal group whose BMI was between 20 and 25 at all visits (n=6793, online supplemental table 1). Diabetes and non-diabetes were defined as we previously reported.\textsuperscript{28,32} To define the dementia status of each subject, we used ‘NACCUDSD’ in the UDS,\textsuperscript{30} which described cognitive status (cognitively normal, dementia, mild cognitive impairment (MCI) or impaired but not MCI (other), table 1). We also used the neuropathological data of a subset of participants (table 2), recorded as the NACC neuropathology data collection form, which collected several age-related neuropathological changes related to AD, cerebrovascular diseases, Lewy body diseases and others.\textsuperscript{34} In some analyses, we also adjusted for hypertension and hyperlipidaemia status, defined as any/no history of hypertension/ hypercholesterolaemia from the subject’s health history form, stored as variables ‘HYPERTEN’ and ‘HYPERCHO’, respectively, in the UDS.\textsuperscript{30}

Statistical analysis
To assess the risk of cognitive decline during ageing in the NACC cohort, we conducted similar analyses as we addressed the effects of the APOE genotype status and its relationship with diabetes.\textsuperscript{28} In brief, we used the variable ‘DECAGE’ in the UDS\textsuperscript{30} to define the age of onset of cognitive decline, which was determined by clinicians after consulting with medical records, direct observation and subject/informant reports. We used a Cox proportional hazard model with sex, race, years of education, obesity, diabetes and APOE genotype status as covariates; the date of birth as the time of origin and the age of the onset of cognitive decline as the time of event. Subjects who did not show any cognitive decline at their last visit were right-censored (36.8% of total subjects). HRs, 95% CIs of the HRs and associated p values were reported.

The effects of obesity on the Clinical Dementia Rating (CDR Dementia Staging instrument) scores\textsuperscript{35} were analysed using a multivariable linear regression model adjusted for sex, race, years of education, age at the cognitive test, diabetes and APOE genotype status with/without considering the interaction between obesity and APOE genotype status. The effects of obesity on the risk of dementia were analysed using a multivariable logistic regression model adjusted for sex, race, age, years of education, diabetes and APOE genotype status with/without considering the interaction between obesity and APOE genotype status. The effects of obesity on the neuropathological scores in total subjects were analysed using a multivariable linear regression model adjusted for sex, race, age at death, dementia status, diabetes and APOE genotype status with/without considering the interaction between obesity and APOE.

We first constructed each model with these co-variants without including the interaction between obesity and APOE, and estimated the effects of obesity. We next added the interaction between obesity and APOE to each model, and when there was a trend in their interaction, we proceeded to analysing the effects of obesity in each APOE genotype status. When there was no significant interaction between obesity and the APOE genotype status, we treated such results for reference purposes. To decrease type I error, we introduced Bonferroni adjustment when analysing each APOE genotype status. P values <0.05 were considered to be significant, where statistical analyses were performed using JMP Pro software (V.13, SAS Institute).
RESULTS

Obesity is associated with cognitive decline in early elderly cognitively normal individuals without APOE4, especially those with APOE2

To assess the effects of obesity on cognitive decline, we first analysed the NACC variable 'DECAGE', which indicates the age at which cognitive decline begins. By using this variable, we successfully analysed the effects of APOE on cognitive decline as well as the interaction between diabetes and APOE genotype. Figure 1A). Moreover, we observed a significant interaction between obesity and APOE genotype status (p=0.0269). Thus, we stratified by each APOE genotype status, and observed that obesity was associated with earlier cognitive decline in APOE2 carriers (HR 1.42, 95% CI 1.21 to 1.66, p<0.001, figure 1B) and APOE3 homozygote individuals (HR 1.24, 95% CI 1.16 to 1.32, p<0.001, figure 1C) but not in APOE4 carriers (HR 1.06, 95% CI 0.99 to 1.14, p=0.350, figure 1D). When we used the normal group rather than the non-obese group as a control, or adjusted for hypertension and hyperlipidaemia status, we still observed similar effects of obesity depending on the APOE genotype status (online supplemental figure 2). Notably, we noticed that decline curve of the obesity group became milder after 80 years of age and eventually intersected with that of the control group over 90 years of age, suggesting an age-dependent difference in obesity effects on cognitive decline. To confirm these results, we analysed CDR scores in cognitively normal individuals. Consistently, while no effects were observed in late elderly (≥80 years old) individuals, obesity was associated with worse CDR sum of boxes scores and with some individual items, including community affairs, home and hobbies and personal care (although this...
was not significant) in early elderly (60–79 years old) people (figure 2 and online supplemental table 2). Similar results were obtained when limited to their age <75 years old. But, when analysed across all ages, the effects of obesity became milder and not significant (data not shown). Notably, a trend in the interaction between obesity and APOE genotype existed in the CDR home and hobbies (p=0.0823, figure 2B) and CDR sum of boxes (p=0.0823, figure 2C) scores of these early elderly individuals. Indeed, obesity was associated with worse CDR scores only in APOE2 carriers (figure 2D,E). Consistently, when we used the normal group as a control, similar effects of obesity adjusting for dementia status. In this analysis, there was only one interaction between obesity and APOE, that is, the existence of microinfarcts (p=0.0185, online supplemental table 4). We indeed observed that obesity was associated with the existence of microinfarcts only in APOE2 carriers (p=0.0281) but not in APOE3 homozygote individuals (while some trend existed: p=0.119) or APOE4 carriers (figure 2F). Such trends were almost similar even when adjusted for hyperlipidaemia and hypertension (figure 2G). In an exploratory analysis separating APOE genotype status, we observed that the severity of arteriosclerosis and the presence of haemorrhages are also significantly associated with obesity only in APOE2 carriers (online supplemental table 4). As the vascular system plays important roles in maintaining cognitive function, these results may suggest that obesity accelerates cognitive decline in APOE2 carriers by provoking vascular impairments.

### Table 2 Demographic characteristics of pathologically assessed subjects with or without obesity categorised by APOE genotype status in the NACC database

<table>
<thead>
<tr>
<th>No.</th>
<th>Total</th>
<th>Non-obese</th>
<th>Obese</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M:F)</td>
<td>3171</td>
<td>2737</td>
<td>434</td>
<td>–</td>
</tr>
<tr>
<td>Age at death (years)</td>
<td>1779:1392</td>
<td>1536:1201</td>
<td>243:191</td>
<td>0.9599</td>
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<tr>
<td>White:Black:Other</td>
<td>82.6±9.4</td>
<td>82.9±9.3</td>
<td>79.3±8.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes:Non-diabetes</td>
<td>3024:114:33</td>
<td>2616:93:28</td>
<td>408:21:5</td>
<td>0.343</td>
</tr>
</tbody>
</table>

**By APOE genotype status**

**APOE2 carriers (ε2/ε2 or ε2/ε3)**

<table>
<thead>
<tr>
<th>No.</th>
<th>Total</th>
<th>Non-obese</th>
<th>Obese</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M:F)</td>
<td>274</td>
<td>222</td>
<td>52</td>
<td>–</td>
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<tr>
<td>Age at death (years)</td>
<td>139:135</td>
<td>111:111</td>
<td>28:24</td>
<td>0.6174</td>
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<tr>
<td>White:Black:Other</td>
<td>84.1±10.4</td>
<td>85.2±10.4</td>
<td>79.5±9.2</td>
<td>0.0002</td>
</tr>
<tr>
<td>Diabetes:Non-diabetes</td>
<td>259:13:2</td>
<td>211:9:2</td>
<td>48:4:0</td>
<td>0.3848</td>
</tr>
<tr>
<td>Dementia:MCI:Cognitive normal:Other</td>
<td>158:41:68:7</td>
<td>126:33:67:12:0</td>
<td>32:8:12:0</td>
<td>0.3621</td>
</tr>
</tbody>
</table>

**APOE3 homozygotes**

<table>
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<tr>
<th>No.</th>
<th>Total</th>
<th>Non-obese</th>
<th>Obese</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M:F)</td>
<td>1509</td>
<td>1298</td>
<td>211</td>
<td>–</td>
</tr>
<tr>
<td>Age at death (years)</td>
<td>827:682</td>
<td>704:594</td>
<td>123:88</td>
<td>0.2711</td>
</tr>
<tr>
<td>White:Black:Other</td>
<td>83.6±9.5</td>
<td>84.4±9.4</td>
<td>79.2±8.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes:Non-diabetes</td>
<td>1466:41:22</td>
<td>1247:34:17</td>
<td>199:7:5</td>
<td>0.4541</td>
</tr>
</tbody>
</table>

**APOE4 carriers (ε3/ε4 or ε4/ε4)**

<table>
<thead>
<tr>
<th>No.</th>
<th>Total</th>
<th>Non-obese</th>
<th>Obese</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M:F)</td>
<td>1388</td>
<td>1217</td>
<td>171</td>
<td>–</td>
</tr>
<tr>
<td>Age at death (years)</td>
<td>813:575</td>
<td>721:496</td>
<td>92:79</td>
<td>0.1778</td>
</tr>
<tr>
<td>White:Black:Other</td>
<td>80.8±8.5</td>
<td>81.0±8.4</td>
<td>79.2±8.4</td>
<td>0.0116</td>
</tr>
<tr>
<td>Diabetes:Non-diabetes</td>
<td>1319:60:9</td>
<td>1158:50:9</td>
<td>161:10:0</td>
<td>0.1881</td>
</tr>
</tbody>
</table>

For continuous data, values are the mean±SD. P values are from one-way analysis of variance (continuous data) or the χ² test (categorical value).

APOE, apolipoprotein E; F, female; M, male; MCI, mild cognitive impairment; NACC, National Alzheimer’s Coordinating Center.

Obesity is associated with microinfarcts and other vascular impairments in APOE2 carriers

To address the mechanism by which obesity is associated with worse cognitive decline in subjects without APOE4, especially APOE2 carriers, we analysed neuropathology records. To overcome the statistical power of the small number of APOE2 carriers who had pathological records available, especially when separated by dementia status, we analysed all subjects by adjusting for dementia status. In this analysis, there was only one significant interaction between obesity and APOE, that is, the existence of microinfarcts (p=0.0185, online supplemental table 4). We indeed observed that obesity was associated with the existence of microinfarcts only in APOE2 carriers (p=0.0281) but not in APOE3 homozygote individuals (while some trend existed: p=0.119) or APOE4 carriers (figure 2F). Such trends were almost similar even when adjusted for hyperlipidaemia and hypertension (figure 2G). In an exploratory analysis separating APOE genotype status, we observed that the severity of arteriosclerosis and the presence of haemorrhages are also significantly associated with obesity only in APOE2 carriers (online supplemental table 4). As the vascular system plays important roles in maintaining cognitive function, these results may suggest that obesity accelerates cognitive decline in APOE2 carriers by provoking vascular impairments.
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group (table 1 and online supplemental table 1). Indeed, the OR of dementia by obesity adjusted for age, sex, race, education, diabetes and APOE was significantly <1.0 (OR 0.710, 95% CI 0.66 to 0.77, p<0.0001), compared with the non-obese group (figure 3A). Moreover, there was a significant interaction between obesity and the APOE genotype status (p=0.0074), where the effects of obesity tended to be stronger in APOE4 carriers (OR 0.648, 95% CI 0.57 to 0.73, p<0.001), than in APOE3 homozygote individuals (OR 0.722, 95% CI 0.65 to 0.81, p<0.001) or APOE2 carriers (OR 0.910, 95% CI 0.71 to 1.17, p=1.00) (figure 3B).

These results suggest somewhat protective effects of obesity on dementia, which would be stronger in APOE4 carriers. To confirm these results, we analysed CDR scores in subjects with MCI and dementia. Indeed, obesity was associated with better scores of CDR memory and orientation in both subjects with MCI and dementia (figure 3C,D). Moreover, while there was no significant difference, there was a trend of better CDR sum of boxes scores by obesity (figure 3E). When compared with the normal group, obesity was associated with a better CDR sum of boxes score in subjects with MCI (figure 3F). More detailed results are described in online supplemental tables 5 and 6. Notably, there was a significant interaction between obesity and the APOE genotype in the CDR memory score in subjects with MCI, where obesity was associated with a better score only in APOE4 carriers (figure 3G). In the exploratory analysis for each APOE genotype status, we observed that obesity was associated with better scores of some of the other CDR evaluations in APOE4 carriers or APOE3 homozygote individuals in subjects with MCI and dementia (online supplemental tables 5 and 6). These results indicate that obesity is associated with less cognitive impairment in subjects with MCI and dementia, especially those with the APOE4 genotype, supporting an APOE genotype-dependent protective effect of obesity on risk of dementia.

Obesity is associated with fewer Alzheimer’s pathologies in subjects with dementia

To further address the mechanism by which obesity protects against cognitive impairment in patients with dementia, especially those with the APOE4 genotype, we analysed the neuropathological records of subjects with dementia. Indeed, obesity was associated with fewer AD-related pathologies, including diffuse plaques, neuritic plaques and neurofibrillary tangles (figure 4A–C and online supplemental table 7). In particular, the effects of obesity on neuritic plaques and neurofibrillary tangles were strong (p<0.001), which were still significant when limited to patients with AD (data not shown). While there was no significant interaction between obesity and the APOE genotype, our exploratory analyses separating individuals by APOE genotype.
Figure 2. Obesity is associated with worse Clinical Dementia Rating (CDR) scores in early elderly cognitively normal individuals, especially those with APOE2. Effects of obesity on the CDR community affairs score (A), home and hobbies score (B) and sum of boxes score (C) in cognitively normal subjects, stratified by age (<80 and ≥80 years old), by adjusting for sex, race, years of education, age at cognitive test, diabetes and apolipoprotein E (APOE) genotype status. Effects of obesity on CDR home and hobbies (D) and CDR sum of boxes (E) in middle to early elderly cognitively normal people stratified by APOE genotype status, adjusted for sex, race, age, years of education and diabetes. Effects of obesity on microinfarcts in total subjects, stratified by APOE genotype status, adjusted for sex, race, age at death, diabetes and dementia status (F) or adjusted for sex, race, age at death, diabetes, hyperlipidaemia, hypertension and dementia status (G). Data are presented as the adjusted mean±SEM. The degree (p value) of interaction between obesity and APOE genotype status is shown at the bottom of each figure (A–C). *P<0.05 ; by Student’s t-test (A–C) with Bonferroni adjustments (D–G). N.S., not significant; NC, normal cognition.
Figure 3  Obesity is associated with lower frequency of dementia (DEM) and less cognitive decline in subjects with mild cognitive impairment (MCI) and dementia, especially those with APOE4. OR with 95% CIs of DEM by obese, compared with non-obese group, across total subjects (A) or in each apolipoprotein E (APOE) carrier (B) as calculated by logistic regression models that were adjusted for sex, age, race, education, diabetes and APOE genotype status. The p value in (A) refers to the significant interaction between obesity and APOE genotype. Effects of obesity on the Clinical Dementia Rating (CDR) memory score (C), orientation score (D) and sum of boxes score (E and F) in subjects with MCI and DEM, compared with the non-obese group (C–E) or normal group (F), by adjusting for sex, race, years of education, age, diabetes and APOE genotype status. The degree (p value) of interaction between obesity and APOE genotype status is shown at the bottom of each figure. (G) Effects of obesity on the CDR memory score in each APOE carrier with MCI, compared with non-obese group, by adjusting for sex, race, years of education, age and diabetes. Data are presented as the adjusted mean±SEM. *P<0.05, **P<0.01 and ***P<0.001; by Student’s t-test (C–F) with Bonferroni adjustments (G). N.S., not significant.
status observed that obesity was associated with fewer neurofibrillary tangles in both APOE3 homozygote individuals and APOE4 carriers, while APOE4 carriers themselves were more vulnerable to neurofibrillary tangles (figure 4D,E). These results suggest that obesity could ease cognitive impairment in both people with dementia and people at the predementia stage, especially those with the APOE4 genotype, through protection from AD-related pathologies.

**DISCUSSION**

In the present study analysing NACC participants, we observed that obesity was significantly associated with earlier cognitive decline across all subjects (figure 1A). Notably, we noticed that the cognitive decline curve of the obesity group became milder after 80 years of age, and eventually intersected with that of the control group over 90 years of age, suggesting an age-dependent difference in obesity effects on cognitive decline. Consistent with this notion, when separated by age status, we observed harmful effects of obesity on some CDR scores in only middle to early elderly people (figure 2). Despite these results, the OR of dementia by obesity adjusted for age, sex, race, education, diabetes and APOE genotype was significantly <1.0 compared with the non-obese group (figure 3A). Taken together with the results of CDR scores suggesting beneficial effects of obesity in people with MCI and dementia (figure 3C–F), these results support the obesity paradox in dementia, which has been indicated by other studies.13–15

More interesting, by considering the effects of APOE genotype status, we observed that this obesity paradox in dementia is APOE genotype dependent. In APOE2 carriers, obesity was associated with cognitive decline in early elderly cognitively normal people (figure 1B) but not with a lower frequency of dementia (figure 4B). In APOE3 homozygotes, obesity was associated with cognitive decline in early elderly cognitively normal individuals...
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(figure 1C) and with a lower frequency of dementia (figure 3B). Therefore, the obesity paradox was observed in APOE3 homozygotes, but not in APOE2 carriers. Interestingly, in APOE4 carriers, obesity was not associated with cognitive decline in early elderly cognitively normal people (figure 1D); however, there was a lower fewer frequency of dementia (figure 3B) and less cognitive decline in subjects with MCI and dementia (figure 3G and online supplemental tables 5 and 6). Thus, the obesity paradox in dementia was observed in subjects with APOE3 and partially in those with APOE4, but it was not observed in those with APOE2. This APOE genotype dependency of the obesity paradox may partially explain the discrepancies in results reported in previous studies, in addition to the differences in ethnicity, race, age, sex and other confounding factors.33-36

Neuropathological analyses adjusting for dementia status showed that APOE2 carriers tended to have more microinfarcts due to obesity. Obesity has been reported to be associated with a significantly increased risk of stroke.3 Consistent with this, obesity is associated with the presence of infarcts, lacunes and haemorrhages (online supplemental table 4). We observed the interaction of the APOE genotype and obesity on the presence of microinfarcts (online supplemental table 4) with no association in APOE4 carriers (figure 2F,G). The fact that cerebral amyloid angiopathy tended to be decreased by obesity (online supplemental table 4) may explain why the presence of microinfarcts was comparable between obesity and non-obesity in APOE4 carriers, although APOE4 carriers have more cerebral amyloid angiopathy.35

Of interest, obesity is associated with fewer Alzheimer’s pathologies in subjects with dementia (figure 4). This is consistent with a previous report, which showed that higher BMI was associated with lower cortical amyloid burden in late life.38 Conversely, lower BMI in late life is reported to be associated with greater amyloid burden in clinically normal individuals49 and both amyloid and tau burden in cognitively normal individuals and individuals with MCI.40 A study using cerebrospinal fluid biomarkers also showed that total tau protein and phosphorylated tau protein were lower in participants with obesity than in participants without obesity.45 In animal models, we observed less amyloid burden in APP (amyloid precursor protein) transgenic mice with obesity42 and APP knockin mice with obesity (unpublished results). Therefore, one of the underlying mechanisms of the obesity paradox in dementia may be the reduction in Alzheimer’s pathologies by obesity. It would be reasonable to consider that such effects are more prominent for APOE4 carriers, who are intrinsically vulnerable to AD pathologies.24

There have been intense debates regarding the genetic testing of APOE genotype status in clinical practice. Rationale against genetic testing is driven by the lack of effective treatments and its insufficiency for improved diagnosis and prediction, while having potentially emotional and behavioural impacts to APOE4 carriers.43 44 Recent approvals of anti-amyloid treatments may change such recommendations, because the results of APOE genetic testing can offer insights into both clinical benefits and also potential risks of developing amyloid-related imaging abnormalities.45 However, it is still unclear whether APOE genotyping should be widely used in clinical practice, considering the limited therapeutic efficacy and high cost of these treatments.46 47 On the other hand, the current results provide additional rationale for the APOE genetic testing as APOE4 carriers could have greater benefits from obesity to reduce their risk of dementia. The current results likely suggest that elderly APOE4 carriers with obesity does not need to aim normal weight, while it is not clear whether APOE4 carriers are recommended to gain weight to reduce their risk of dementia. Conversely, such potential benefits should be further validated and clarified in detail when genetic tests of APOE allele are widely used in clinical practice. Nonetheless, the risk and benefit of obesity should be appropriately managed in terms of general health for each individual.

There are several limitations in this study. First, we classified subjects who had BMI >30 at all visits as obese. Although obesity is defined as abnormal or excessive fat accumulation that may impair health,4 in this study, neither the extent of fat nor the presence of health impairment were accessed. For adults, WHO defines obesity as a BMI ≥30 and mentions that BMI provides the most useful population-level measure of obesity, as it is the same for both sexes and for all ages of adults, although it should be considered a rough guide because it may not correspond to the same degree of fatness in different individuals.4 The evaluation of fat accumulation and health impairment should be added in future studies. Second, the subjects of this study were participants in the National Institute on Aging’s ADC programme across the USA; therefore, our analysis was not population based. Third, the obesity paradox in dementia might be attributed to secondary weight loss due to dementia because a decline in weight is observed in individuals with dementia,47 48 MCI49 and the preclinical stage of AD.50 A recent study also reported that weight loss due to dementia negatively confounded the association between obesity in late life and brain atrophy, as demonstrated by an MRI study,51 suggesting that the obesity paradox in dementia might be explained by reverse causation. Although such limitations would not affect our results regarding the APOE genotype-dependent obesity paradox in dementia, future studies resolving these limitations might address more precise effects on how obesity interacts with the APOE genotype when contributing to cognitive decline and the risk of dementia.

In summary, using the NACC database, we observed that (1) obesity was associated with cognitive decline in early elderly cognitively normal people without the APOE4 genotype, especially those with the APOE2 genotype, and that obesity was associated with microinfarcts and other vascular impairments in APOE2 carriers; (2) obesity was associated with a lower frequency of dementia and less cognitive decline in subjects with MCI and dementia, especially in those with the APOE4 genotype, and that obesity was associated with fewer Alzheimer’s pathologies in subjects with dementia. These results indicate that the obesity paradox in dementia depends on APOE genotype status. A further understanding of how obesity can reduce Alzheimer’s pathologies would provide clues on how to manage such abundant neurodegenerative diseases in our ageing society.

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General neurology


