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Apolipoprotein Epsilon 4 Allele Modifies Waist-to-Hip Ratio Effects on Cognition and Brain Structure

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Abstract

This study aimed to determine whether relationships between obesity, as measured by waist-to-hip ratio (WHR), and cognition and brain structure were modified by the apolipoprotein epsilon 4 allele (apoE4). The sample included 1,969 stroke and dementia-free participants from the Framingham Offspring Cohort who underwent neuropsychological (NP) testing and structural Magnetic Resonance Imaging (MRI) between 1999–2002. WHR was categorized into sex-specific quartiles with those in Q4 representing central obesity. Multivariate linear regression estimated the relationships between Q4-WHR, cognitive and MRI measures; interaction terms examined modification of these relationships by the presence of apoE4. All analyses were cross sectional.

ApoE4 status significantly modified a number of associations. Specifically, we observed a significant negative relationship between Q4-WHR and a measure of executive function in the apoE4+ group but not in the apoE4− group. Similarly, we observed a stronger negative relationship between Q4-WHR and a measure of memory function for those in the apoE4+ group compared to those in the apoE4− group. Additionally, apoE4 status modified the relationship between Q4-WHR and two measures of structural brain integrity. First, a paradoxical finding of a negative association between WHR and frontal brain volume that was significant only for those in the apoE4- group, and a second finding that WHR was significantly associated with greater white matter hyperintensity volume only in the apoE4+ group.

These findings suggest that associations between central adiposity and both neuropsychological performance and underlying brain structure are highly complex and must be considered in the context of possible modifying genetic influences.

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Keywords

waist-to-hip ratio; apoE4; metabolic syndrome; obesity; Alzheimer's disease

Introduction

Body mass index (BMI) is a commonly used metric of obesity that has been related to cognitive impairment [1–3]. Further, adiposity during mid-life is linked to risk of later life dementia [2, 4, 5]. However, there is growing evidence suggesting that it is the physical *distribution* of mid-life body fat and not overall adiposity that may be the strongest predictor of dementia risk and other later-life health consequences. Waist-hip ratio (WHR) is a non-invasive method for assessing the distribution of body fat and has been shown to be more strongly related to a variety of health outcome measures when compared to BMI or waist circumference [6].

Recent evidence suggests that increasing levels of central obesity may be associated with poorer performance on measures of executive function and visuomotor skills in otherwise healthy adults [7, 8]. However, the relationship between WHR and cognition is complex, as Kerwin [9] recently found that higher WHR may be a protective factor against cognitive loss, whereas additional research suggests that central obesity in middle age may be a predictor of both AD [10–13] and other types of dementia in later life [5]. The lack of consensus regarding the significance of WHR necessitates further research into this area.

While apolipoprotein e4 (apoE4) is a well-recognized independent risk factor for AD, there are only a few studies that demonstrate that genetic factors impact the relationship between vascular health status and cognition [14]. Data from the Framingham Heart Study (FHS) recently demonstrated that the presence of the apoE4 allele modified the relationship of cerebrovascular disease (CVD) risk, as indexed by the Framingham Stroke Risk Profile ([FSRP], a composite measure of stroke risk), brain volume (i.e., lateral ventricular volume) and cognition (i.e., Logical Memory-delayed recall, Paired Associates-delayed recall, Visual Reproductions-delayed recall) in otherwise healthy adults [15].

The current study investigates how the presence of the apoE4 allele modifies the relationships among mid-life adiposity, cognition and brain morphology using WHR as a measure of central obesity.

Methods

The Framingham Heart Study (FHS) was established in 1948 with an original cohort of 5,209 men and women between the ages of 30 and 62, recruited from the town of Framingham, Massachusetts. Briefly, from 1971 to 1975, 5124 participants (who were children of the original FHS cohort) were recruited for the Offspring Cohort and have been examined approximately every 4 years. The specific design and selection criteria for this cohort have been previously described in other FHS papers [16]. Our sample is a subset of the 3,091 Offspring participants, ages 40–79 (mean age 61 ± 9 years) who had completed their seventh exam (1998–2001) and have available measurements of WHR and apoE genotyping. Of this subset, 2,028 participants had both magnetic resonance and neuropsychological data. An additional 59 participants were excluded due to the presence of stroke, dementia or another neurological disorder, resulting in a final sample of 1,969. The mean WHR of those participants with both neuropsychological (NP) and magnetic resonance imaging (MRI) data was lower relative to those participants who did not have both NP and MRI data (0.945 vs. 0.953, p=0.011). Frequency of apoE4 was not significantly

different between those participants who had both NP and MR data (21%) versus those who did not (20%).

The Boston University Institutional Review Board approved the study protocol and all participants provided written informed consent.

The MRI variables, which have previously been described [17], were as follows: total brain volume, white matter hyperintensities, frontal brain volume, temporal horn volume, and lateral ventricular volume; each was expressed as a percentage of total cranial volume and log-transformed as necessary to normalize its distribution. Hippocampal volume was measured using previously reported methods [17].

Participants who consented to MRI scanning were imaged primarily on a Siemens Magnetom 1 T field strength magnetic resonance machine using a T2-weighted double spin-echo coronal imaging sequence of 4mm contiguous slices from nasion to occiput with a repetition time (TR) of 2420 ms, echo time (TE) of TE1 20/TE2 90 ms; echo train length 8 ms; field of view (FOV) 22 cm and an acquisition matrix of 182 × 256 interpolated to a 256 × 256 with one excitation.

The NP tests were administered by trained psychometricians using standard test instruction. The cognitive domains included: verbal memory (as measured by Wechsler Memory Scale (WMS) Logical Memory-delayed recall); verbal learning (as measured by WMS Paired Associates-delayed recall); nonverbal memory (as measured by WMS Visual Reproductions-delayed recall); processing speed (as measured by Trail Making Test-A); set shifting and complex attention (as measured by Trail Making Test-B); abstract reasoning (as measured by Wechsler Adult Intelligence Scale - Revised (WAIS-R) Similarities); and visuoperceptual skills (as measured by the Hooper Visual Organization Test) [18]. NP measures were log-transformed when necessary, adjusted for age and education within gender, and then standardized within gender.

WHR measure was divided by gender and then subdivided into quartiles with Q1 representing the lowest 25% and Q4 the highest. Our primary analyses used the top sex-specific quartile (n=494) of WHR (Q4-WHR) as a measure of central obesity (i.e., the quartile with the highest WHR). We chose to focus specifically on the relationship between Q4 and both NP and MRI measures because we are interested in the impact of relatively higher levels of obesity on cognitive ability and neuroanatomical variations. Previous analyses have indicated that there may be a threshold effect in which lower levels of obesity were not linked to the measures of interest. Thus, using continuous measures or less severe levels of obesity would potentially result in less than significant results regarding the relationships between cognitive performance or MRI measures at the threshold level (e.g., Q4).

Multivariate linear regression was used to assess the relationships between Q4-WHR on the NP and MRI variables; interaction terms were included to examine modification of these relationships by the presence of the apoE4 allele. We used a cutoff of $p<0.10$ to determine significant interaction. All other analyses were performed using 5% levels of significance. We conducted additional analyses to determine how the relationship between Q4-WHR and the NP/MRI measures differed for those who were apoE4+ versus apoE4−. NP variables were pre-adjusted for age, gender and education as described above; analyses of MRI outcomes were adjusted for age and gender.

Finally, to better assess the degree to which the modifying effects of apoE4 are unique to the relationship between central adiposity to NP and anatomical variation as opposed to overall body mass, we conducted a separate analysis evaluating how apoE4 impacted the

relationship between the top quartile of BMI and both NP performance and neuroanatomical variation.

Results

Table 1 presents the summary statistics for our variables including a breakdown of major demographic variables and both neuropsychological and neuroanatomical measures, by apoE status.

Table 2 presents the adjusted difference in means of NP measures that examines whether there is a significant relationship with cognition among those who are obese (Q4-WHR). Table 2 further presents whether apoE4 status modifies the effect of these Q4-WHR-NP associations.

As had been found previously, Q4-WHR was significantly associated with many of the cognitive measures. Specifically, we found negative relationships between Q4-WHR and performance on Paired Associates-delayed recall ($p<0.001$), Visual Reproductions-delayed recall ($p<0.001$), Trail Making Test-A ($p<0.001$), Trail Making Test-B ($p<0.001$), and Similarities ($p<0.001$).

ApoE4 status modified the overall association between Q4-WHR and Trail Making Test-B ($p=0.092$), such that the negative relationship was stronger in the apoE4 positive group. In addition, while there was no overall association between Q4-WHR and performance on the Logical Memory-delayed recall task, there was a significant interaction ($p=0.027$); and although it did not reach the 5% significant level, there is a borderline negative association only in the apoE4 positive group ($p=0.052$).

Table 3 presents the results determining whether there was a relationship between central obesity (Q4-WHR) to the MRI measures, as well as whether apoE4 status on those associations modified these relationships. As has been found previously, Q4-WHR was negatively associated with total brain volume ($p<0.001$) and frontal brain volume ($p<0.001$). Q4-WHR was positively associated with lateral ventricular volume ($p<0.001$) and temporal horn volume ($p<0.01$). There were no significant associations between Q4-WHR and either white matter hyperintensities or hippocampal volume.

ApoE4 status was found to modify the overall relationship between Q4-WHR and frontal brain volume ($p=0.047$), such that the negative association was significant only for those in the apoE4 negative group ($p<0.001$).

While the overall relationship between Q4-WHR and white matter hyperintensity volume was not significant, the interaction with apoE4 status was significant ($p=0.033$), such that there was a significant positive association between Q4-WHR and white matter hyperintensities only in the apoE4 present group ($p<0.05$).

Table 4 presents the adjusted difference in means of neuropsychological measures to examine whether those in the top sex-specific quartile for Body Mass Index (Q4-BMI), another commonly used measure of obesity, was related to NP outcomes. Table 4 further presents significance levels for the modifying effect of apoE4 status on those associations. Q4-BMI was negatively associated with performance on Trail Making Test B ($p<0.05$) overall, but as indicated by a significant interaction ($p=0.010$), this relationship was only significant for the apoE4 group ($p<0.01$). No other relationships were significant between Q4-BMI and NP.

Table 5 presents the results of whether the top quartile (Q4-BMI) was related to MRI measures, as well as the modifying effect of apoE4 status on those associations. Q4-BMI was negatively associated with total brain volume ($p<0.001$), white matter hyperintensities ($p<0.05$), and frontal lobe volume ($p<0.001$). Additionally, apoE4 modified the relationship between Q4-BMI and lateral ventricular volume ($p=0.046$) such that there was a positive association ($p<0.05$) in the apoE4 present group only.

Discussion

Results from this study confirmed previous findings from the Framingham Heart Study of a relationship between central obesity and morphometric and cognitive measures. Q4-WHR, a proxy for central adiposity, predicted poorer performance on Paired Associates-delayed recall, a measure of verbal learning; Visual Reproductions-D.R., a measure of long term nonverbal memory; Similarities, a measure of verbal abstract reasoning; and Trail Making Tests A and B, measures of processing speed and complex attention, respectively.

Central to this study was the finding that there was a modifying effect of apoE4 status on the relationship between obesity and two NP measures. First, the negative association between Q4-WHR and Trailmaking Test B was much stronger in the apoE4 positive group compared to the apoE4 negative group. Second, although there was no significant relationship between Q4-WHR and Logical Memory-D.R. overall, the presence of a significant interaction suggests that apoE4 status had a modifying impact on this relationship, where central adiposity may negatively impact delayed verbal recall among persons who are apoE4 positive but have little impact on persons who are apoE4 negative.

Critical to this study, we found that the overall negative association between Q4-WHR and frontal brain volume was significant only for those in the apoE4 negative group. This finding is paradoxical in that it suggests that the relationship of obesity and frontal lobe volume only applied to those without the apoE4 allele, and that among those who were apoE4 positive, frontal lobe volumes were not related to obesity. In contrast, despite no overall significant relationship between Q4-WHR and white matter hyperintensity volume, for those with the apoE4 allele, obesity was significantly associated with greater white matter hyperintensity volume. This finding is more in line with expectations and suggests that among those with the apoE4 allele, obesity has a deleterious effect on white matter integrity. Taken together, these two findings raise the intriguing possibility that the modifying effect of apoE4 on the WHR-MRI relationship is different for white and grey matter measures.

Our findings confirm previous results from Wolf et al. [7] linking central obesity to cognitive performance, and Debette et al. [19] linking adiposity to brain structure (however, see Kerwin et al. [9]) The current study contributes the observation that apoE4 (a well established genetic risk factor for AD) may modify the effects that central obesity has on both function and structure.

In a secondary analysis we examined whether apoE4 status similarly modifies the relationship of obesity, as measured by Q4-BMI, to our measures of neuropsychological function and structural brain integrity. Similar to Q4-WHR, the relationship between Trail Making Test B and Q4-BMI was significant only for the apoE4 positive group. Additionally, the relationship between lateral ventricular volume and Q4-BMI was significantly greater for the apoE4 positive group. In general, these findings are in concert with those from our Q4-WHR analyses and support the claim that the presence of apoE4 imparts significant risk on brain function and structure.

Future Investigations

Investigators have proposed that co-occurrence of central obesity as well as various other CVD risk factors may signal an underlying, often age-related, insulin resistance-based dysregulation of metabolism (MD) that results from development of insulin resistance [20–22]. The evidence that central obesity and apoE4 interact to affect brain and cognition in dementia-free adults raises two possible explanations for the association of middle aged central obesity and later life dementia. First, it is possible that MD may directly affect neural structure and function in a manner that is similar to the effect of apoE4. The second possibility is that the presence of central adiposity itself is, in part, a reflection of underlying genetically determined alterations in neural regulation, and is simply an early sign of a disease state that will manifest as a dementing illness later in life. While we offer the above hypotheses as two possible explanations for the association between middle aged central obesity and later life dementia, further investigation is needed to address these possibilities.

Strengths and Limitations

The strengths of this investigation are the large community-based sample and the availability of midlife measure of WHR to relate to prospectively ascertained total and regional brain volumes and NP tests. This study also has several limitations, however. First, our participants are of predominantly European decent, which restricts the generalizability of results to other ethnicities/races. Second, while WHR may be an effective predictor of NP performance, it does not distinguish between visceral and subcutaneous fat, which carry different degrees of risk [23]. Third, the mean WHR of those participants with both NP and MRI data was lower relative to those participants who did not have both NP and MRI data (0.945 vs. 0.953, p=0.011), suggesting that the healthier participants were able to complete both measures. Finally, the small number of apoE4/4 (n=34) did not allow sufficient power to determine whether E4 homogeneity or heterogeneity was a significant factor.

While the issues discussed above reflect limitations, this research provides preliminary insight toward a more comprehensive understanding of how mid-life risk factors may increase risk for cognitive impairment in later life. Understanding these factors will facilitate earlier intervention and encourage preventative health behaviors, potentially allowing geriatric populations to extend functional independence.

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Table 1

Participant characteristics.

Variables	Overall	ApoE4† Absent (2/2, 2/3, 3/3)	ApoE4† Present (3/4, 4/4)
N	1969	1550	419
Age [Mean ± SD]	61 ± 9	61 ± 9	61 ± 9
Male (%)	47%	47%	45%
Waist-to-Hip Ratio [Mean ± SD]	0.94 ± 0.08	0.94 ± 0.08	0.94 ± 0.08
Neuroanatomical Measures ††			
Total Brain Volume [Mean ± SD]	79 ± 3	79 ± 3	79 ± 4
White Matter Hyperintensities[Median (Range)]†††	0.05 (0–4.77)	0.05 (0–4.77)	0.05 (0–1.84)
Frontal Lobe Volume [Mean ± SD]	36 ± 3	36 ± 3	37 ± 3
Temporal Lobe Volume [Mean ± SD]†††	11 ± 1	11 ± 1	11 ± 1
Temporal Horn Volume [Median (Range)]	0.04 (0–0.42)	0.04 (0–0.38)	0.04 (0–0.42)
Lateral Ventricular Volume [Mean ± SD]	1.8 ± 1.2	1.8 ± 1.2	1.8 ± 1.1
Hippocampal Volume [Mean ± SD]	0.34 ± 0.05	0.34 ± 0.05	0.34 ± 0.06
Neuropsychological Measures			
Logical Memory- Delayed Recall (D.R.) [Mean ± SD]	10.5 ± 3.6	10.5 ± 3.6	10.4 ± 3.9
Paired Associates- D.R. [Mean ± SD]	8.3 ± 1.5	8.3 ± 1.5	8.3 ± 1.6
Visual Reproduction–D.R. [Mean ± SD]	8.2 ± 3.4	8.2 ± 3.4	8.3 ± 3.4
Trails A [Median (Range)] (Minutes)†††	0.5 (0.2–5.8)	0.5 (0.2–5.8)	0.5 (0.2–3.6)
Trails B [Median (Range)] (Minutes)†††	1.2 (0.4–10)	1.2 (0.4–10)	1.2 (0.4–10)
Similarities [Mean ± SD]	16.8 ± 3.6	16.7 ± 3.6	17.0 ± 3.6
Hooper Visual Organization Test [Median (Range)]†††	26 (3–30)	26 (6–30)	26 (3–30)

Note.

†ApoE4 = apolipoprotein E;

††Neuroanatomical measures were analyzed as a percentage of total cranial volume; the units listed are percentages;

†††For Hooper Visual Organization Test, Trails A, Trails B, white matter hyperintensities and temporal horn volume, variables were log transformed.

Table 2

Moderating effect of apolipoprotein E (apoE4) status on the relationship between top sex-specific quartile of waist-to-hip ratio (Q4) and cognitive tests.

	Overall (Beta ± SE)[+]	P-Value for Interaction with ApoE4	ApoE4 Absent (2/2, 2/3, 3/3) (Beta ± SE)[+]
N	**1969**		**1550**
Logical memory-D.R.[†]	−0.013±0.054	0.027	0.055±0.061
Paired associates-D.R.	−0.187±0.054***	0.776	−0.179±0.061**
Visual Reproductions-D.R.	−0.195±0.053***	0.180	−0.155±0.061*
Trails A	−0.196±0.054***	0.358	−0.169±0.060**
Trails B	−0.195±0.053***	0.092	−0.144±0.058*
Similarities	−0.182±0.054***	0.668	−0.171±0.061**
Hooper Visual Organization Test	−0.045±0.054	0.895	−0.050±0.062

Note.

[†] D.R.=Delayed Recall;

* p<0.05;

** p<0.01;

*** p<0.001;

[+] adjusted difference in means comparing participants in Q4 to those in Q1–Q3

Table 3

Moderating effect of apolipoprotein E (apoE4) status on the relationship between top sex-specific quartile of waist-to-hip ratio (Q4) and brain volume.

	Overall (Beta ± SE)[+]	P-value for Interaction with ApoE4	ApoE4 Absent (2/2, 2/3, 3/3) (Beta ± SE)[+]	ApoE4 Present (3/4, 4/4) (Beta ± SE)[+]
Total Brain Volume	−0.197±0.045***	0.892	−0.203±0.050***	−0.189±0.096
White Matter Hyperintensities	0.018±0.047	0.033	−0.038±0.054	0.199±0.095*
Frontal Lobe Volume	−0.258±0.046***	0.047	−0.313±0.052***	−0.097±0.095
Temporal Lobe Volume	−0.095±0.051	0.817	−0.092±0.059	−0.120±0.101
Temporal Horn Volume	0.130±0.049**	0.612	0.142±0.056*	0.083±0.101
Lateral Ventricular Volume	0.141±0.048**	0.162	0.108±0.056	0.267±0.090**
Hippocampal Volume	−0.029±0.054	0.148	−0.075±0.062	0.109±0.108

Note.

*p<0.05;

**p<0.01;

***p<0.001;

+adjusted difference in means comparing participants in Q4 to those in Q1–Q3

Table 4

Moderating effect of apolipoprotein E (apoE4) status on the relationship between top sex-specific quartile of BMI (Q4) and cognitive tests.

	Overall (Beta ± SE)[+]	P-Value for Interaction with ApoE4	ApoE4 Absent (2/2, 2/3, 3/3) (Beta ± SE)[+]	ApoE4 Present (3/4, 4/4) (Beta ± SE)[+]
Logical memory-D.R.[†]	0.073±0.053	0.978	0.073±0.059	0.069±0.121
Paired associates-D.R.	−0.077±0.053	0.227	−0.044±0.059	−0.203±0.124
Visual Reproductions-D.R.	−0.007±0.053	0.629	0.005±0.059	−0.058±0.115
Trails A	−0.041±0.053	0.308	−0.014±0.058	−0.147±0.126
Trails B	−0.119±0.052[*]	0.010	−0.052±0.056	−0.385±0.130[**]
Similarities	−0.089±0.053	0.304	−0.061±0.059	−0.195±0.119
Hooper Visual Organization Test	0.016±0.053	0.247	0.047±0.060	−0.106±0.117

Note.

[†] D.R.=Delayed Recall;

[*] p<0.05;

[**] p<0.01;

[***] p<0.001;

[+] adjusted difference in means comparing participants in Q4 to those in Q1–Q3

Table 5

Moderating effect of apolipoprotein E (apoE4) status on the relationship between top sex-specific quartile of BMI (Q4) and brain volume.

	Overall (Beta ± SE)[+]	P-value for Interaction with ApoE4	ApoE4 Absent (2/2, 2/3, 3/3) (Beta ± SE)[+]	ApoE4 Present (3/4, 4/4) (Beta ± SE)[+]
Total Brain Volume	−0.152±0.043***	0.142	−0.119±0.048*	−0.277±0.099**
White Matter Hyperintensities	−0.115±0.046*	0.133	−0.150±0.051	0.020±0.099
Frontal Lobe Volume	−0.329±0.044***	0.704	−0.358±0.050***	−0.316±0.097**
Temporal Lobe Volume	−0.096±0.049	0.686	−0.088±0.056	−0.137±0.104
Temporal Horn Volume	0.068±0.048	0.296	0.043±0.054	0.167±0.104
Lateral Ventricular Volume	0.044±0.047	0.046	−0.001±0.053	0.229±0.093*
Hippocampal Volume	0.006±0.052	0.489	0.025±0.059	−0.064±0.111

Note.

* p<0.05;

** p<0.01;

*** p<0.001;

+ adjusted difference in means comparing participants in Q4 to those in Q1–Q3