

Obesity, diabetes and cognitive deficit: The Framingham Heart Study

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Abstract

Objective:: To determine the independent effects of obesity on cognitive performance and to examine interactions between obesity and non-insulin dependent diabetes mellitus (NIDDM).

Methods:: Using a prospective design, male ($n = 551$) and female ($n = 872$) participants of the Framingham Heart Study were classified as obese (yes/no), diabetic (yes/no), and the number of diabetes-years was determined by data collected over an 18-year surveillance period. All subjects were free from dementia, stroke, and clinically diagnosed cardiovascular disease up to the time of cognitive testing. Statistical models were adjusted for age, education, occupation, native language, and cardiovascular disease risk factors. Body mass index status (non-obese or obese) and NIDDM status (diabetic/non-diabetic) were related to cognitive performance on multiple cognitive measures.

Results:: Adverse effects of obesity on cognitive performance were observed for men only. Diabetes-years related to poorer cognitive performance, but only when men and women were combined for analyses. Neither diabetes nor diabetes-years by obesity interactions were observed.

Conclusions:: The gender-specific results for obesity, but not for diabetes, suggests that the underlying mechanisms linking them to cognition may be different.

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1. Background

The Framingham Heart Study (FHS) has made it possible for us to characterize relations among obesity, diabetes and cognitive functioning for a large-community based sample. We summarize these studies [2,3] and present several new analyses designed to better understand these relations. The prevalence of type II diabetes mellitus and obesity increase with age and both are risk factors for cognitive deficit [2,3,14]. The average age in the present study was 67 years (range = 55–88). Thus, we present data for persons at a vulnerable age with respect to diabetes, obesity, and cognitive deficit.

1.1. Few studies relate obesity to cognition

Reviews of the literature [14] generally support the hypothesis that there is an association between non-insulin dependent diabetes and lowered cognitive performance, although negative findings have been reported. Indeed, we have reported inverse associations between the number of years our participants were diagnosed as non-insulin dependent diabetics (NIDDM) (diabetes-years) and level of cognitive performance [3]. The presence of hypertension and diabetes together was associated with lower levels of performance than either diabetes or hypertension alone.

Consequently, it is surprising to find that there are so few studies relating obesity, an important cofactor in diabetes, to cognitive performance. Obesity and even overweight have been found to be independent risk factors for CVD in a

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number of epidemiological studies [9], including the FHS [5]. This paucity of work on obesity and diabetes may reflect a general assumption that obesity is not a primary risk factor for poor cognitive performance, but merely predisposes to, or exacerbates, the effect of other risk factors for CVD on cognition, e.g., hypertension, diabetes, high cholesterol, and cigarette smoking.

We are aware of only two previous studies associating obesity with lowered cognitive functioning [8,15]. Neither study included women or asked whether obesity was related to cognitive performance independent of its relationship to hypertension, diabetes, cholesterol level, and smoking. The FHS, by virtue of physician assessment of cardiovascular risk factors and CVD over many years prior to the administration of a neuropsychological battery, provided an opportunity to correct these deficits in the literature.

1.2. Framingham investigation of obesity and cognitive function

We raise three major questions: (1) does obesity relate to cognitive functioning independently of diabetes, total cholesterol, alcohol consumption, cigarette smoking, hypertension, stroke, and CVD; (2) do obesity and gender interact; (3) do obesity and diabetes or diabetes-years interact such that there is greater cognitive deficit in the presence of both than in the presence of one or the other?

2. Methods

Methods have been described previously [2,3]. The FHS is an ongoing, population-based, longitudinal study. Participants were recruited from the community of Framingham, Massachusetts, beginning in 1948 (Examination 1). Neuropsychological test data were obtained from 2123 participants, aged 55–88, using the Kaplan–Albert neuropsychological test battery [9] during their 14th or 15th biennial examination (1974–1978). Prevalent and incident CVD risk factors and events were evaluated by physician examination and clinical diagnosis on a biennial schedule from 1948 to the time of neuropsychological testing. The design was prospective. The risk surveillance period was biennial Exams 4 through 12 (1954–1970), and thus preceded neuropsychological testing (1974–1978) by four to eight years. In a secondary analysis, the surveillance period was redefined as Exams 4 through 14/15, thus allowing for an examination of the effects of risk factors and covariate control up to, and including, the time of cognitive testing. Findings were the same for both surveillance windows.

Following exclusions for missing data ($n=123$), completed stroke ($n=78$), diagnosis of dementia ($n=28$), CVD, including myocardial infarction, angina pectoris, congestive heart failure, intermittent claudication, or coronary insufficiency ($n=356$), the final sample included 551 men and 872 women.

2.1. Design

The following variables were obtained from the surveillance window (Exams 4–12): (1) diastolic (DBP, in mmHg) and systolic (SBP, in mmHg) blood pressures; (2) body mass index (BMI [weight (kg)/height (m²)]); (3) casual glucose (in mmol/L); (4) self-reported number of cigarettes smoked per day; (5) total serum cholesterol (in mm/dL); (6) self-reported number of alcoholic beverages per week, converted to ounces of alcohol consumed per week. A mean score for each risk factor was then calculated by summing the values for each measure across Exams 4 through 12 and dividing by the number of examinations attended (minimum of six examinations). Hypertension was defined as diastolic BP ≥ 90 and/or systolic BP ≥ 140 [10]. Presence of NIDDM was determined by the following criteria: (1) age greater than 30 years at the time of diagnosis, (2) treatment with insulin or oral hypoglycemic agents, or (3) a casual blood glucose level >8.3 mmol/L as determined at biennial examinations. A person was defined as diabetic if these criteria were met at any examination during the surveillance period. Additional covariates included age, occupation, and education level at neuropsychological testing, and whether or not English was the individual's native language (yes/no).

2.2. Independent variables

Using mean values obtained over the surveillance period, three BMI groups were defined on the basis of criteria established by the National Heart, Lung, and Blood Institute, Obesity Education Initiative [12]: normal weight (<25 kg/m²); overweight (25–29.9 kg/m²), and obese (≥ 30 kg/m²). The three BMI groups were used in preliminary analyses. The primary analyses involved comparisons of the obese and non-obese (normal weight + overweight) groups. Diabetes (yes/no) and diabetes-years, the number of years an individual carried a diagnosis of NIDDM, were employed in secondary analyses.

2.3. Neuropsychological test battery

A detailed description is presented elsewhere [2,3]. Eight sub-tests taken from the Wechsler adult intelligence scale (WAIS), the Wechsler memory scale, and the multilingual aphasia examination were presented in the following standardized sequence: logical memory-immediate recall, visual reproductions, paired associates learning, digit span forward, digit span backward, word fluency (Controlled Oral Word Associations), similarities, and logical memory-delayed recall.

3. Results

Our presentation of findings differs from our original paper on obesity [2] in three ways: (1) we feature multiple

Table 1
Demographic and health characteristics of the FHS sample [2]^a

| | Men (<i>n</i> = 551) | | | | Women (<i>n</i> = 872) | | | | <i>P</i> < ^c |
|----------------------------|-----------------------|-------------------|----------|---------|-------------------------|-------------------|----------|---------|-------------------------|
| | Mean | S.D. ^b | <i>N</i> | Percent | Mean | S.D. ^b | <i>N</i> | Percent | |
| Body mass index | 26.3 | 3.2 | | | 25.3 | 3.8 | | | 0.01 |
| Normal | 23.1 | 1.6 | 190 | 34.5 | 22.6 | 1.6 | 482 | 55.3 | |
| Overweight | 27.2 | 1.4 | 300 | 54.4 | 27.0 | 1.4 | 295 | 33.8 | |
| Obese | 32.3 | 2.2 | 61 | 11.1 | 33.2 | 3.0 | 95 | 10.9 | |
| Age | 65.7 | 6.9 | | | 67.2 | 7.3 | | | 0.01 |
| Educational level | 4.9 | 1.5 | | | 4.8 | 1.6 | | | NS |
| Occupational level | 4.1 | 1.6 | | | 4.0 | 1.6 | | | NS |
| Native English language | | | 453 | 75.6 | | | 726 | 77.8 | NS |
| Hypertensive | | | 161 | 29.2 | | | 250 | 28.7 | NS |
| Alcohol consumption | 5.9 | 6.6 | | | 2.5 | 3.4 | | | 0.01 |
| Cigarettes/day | 10.7 | 12.5 | | | 5.5 | 8.8 | | | 0.01 |
| Total cholesterol | 233.0 | 35.4 | | | 244.3 | 39.1 | | | 0.01 |
| Type II diabetes | | | 44 | 8.0 | | | 52 | 6.0 | NS |
| Diabetes-years (diabetics) | 5.3 | 5.7 | | | 6.6 | 6.8 | | | NS |

^a See text of this article or [2] for definitions of the covariables.

^b Standard deviation.

^c *t*-Tests for continuous variables; χ^2 tests for categorical variables; NS = non-significant.

regression analyses; (2) we add English as the first (native) language (yes/no) to the covariate set; (3) we relate diabetes [3] to obesity.

Table 1 summarizes the demographic and health characteristics of the sample. Women were older and exhibited significantly lower levels of alcohol consumption and smoking, but higher levels of total cholesterol. Men were more highly educated and had higher occupation levels. Men and women did not differ with respect to the proportion for whom English was the first language spoken. The prevalence data for type II diabetes and obesity, determined after exclusions (Table 1), were based on data obtained between 1954 and 1970 (Exams 4–12). There have been progressive increases in the prevalence of these risk factors since then.

3.1. Preliminary analyses

The relationship between obesity and cognitive performance was unchanged whether ever diabetic (yes/no) or diabetes-years was employed in the model. Normal weight and overweight cohorts did not differ for any of the cognitive measures for males or females (*ps* = 0.14–0.86). Consequently, a single non-obese group was used for all further analyses.

3.2. Obesity results

A significant (all *p* values < 0.05) obesity (yes/no) by gender interaction was obtained for the global composite score and five of the individual test scores. Thus, we stratified by gender for further analyses.

The regression coefficients shown in Table 2 indicate related performance level (in units of S.D.) to presence of

obesity. Thus, for example, with adjustment for age, there was a 0.38S.D. lowering of the global composite for obese versus non-obese men. For men, with adjustment for age, obesity was associated with decrements in cognitive performance for every cognitive test measure but paired associates learning. For women, obesity was related to cognitive performance for every cognitive outcome measure.

When the risk factor covariate set (hypertension, diabetes, BMI, total cholesterol, cigarette smoking) was added to age, fewer significant associations between obesity and cognitive performance were observed but some remained statistically significant, including the global composite score. However, when education, occupation, and English as the native language were added to the age and risk factor covariate set, fewer significant associations between obesity and cognitive performance were observed for men and the magnitude of association was reduced. For women, covariate-adjusted associations were not only greatly attenuated, but also non-significant for every cognitive test. The order in which the sets of covariates analyses were performed made no difference. Moreover, adjustment for education, and native English in separate steps negated significant and meaningful associations between obesity and cognitive performance for women. Moreover, the gender \times obesity interactions remained despite additional statistical adjustment for treatment with antihypertensive medications (270 women and 173 men) and use of tranquilizing medications (84 women and 33 men).

3.3. Education, occupation, and language

Analyses, stratifying by male and female gender, were performed in order to determine why the education, occupation and native language covariates had a greater impact

Table 2

Regression coefficients showing decrements in performance in units of S.D. in relation to the presence of obesity vs. non-obesity for men and women

| Cognitive test | Model covariates | | |
|---------------------------------|------------------|-------------------------------------|--|
| | Age ^a | Age + CVD risk factors ^b | Age + CVD risk factors + education + occupation + native language ^c |
| Men | | | |
| Logical memory-immediate recall | −0.38** | −0.35* | −0.18 |
| Visual reproductions | −0.36** | −0.35** | −0.23* |
| Paired associates | −0.18 | −0.17 | −0.07 |
| Digit span forward | −0.22 | −0.23* | −0.12 |
| Digit span backward | −0.44*** | −0.46*** | −0.31** |
| Logical memory-delayed recall | −0.35** | −0.31* | −0.15 |
| Similarities | −0.32** | −0.34** | −0.13 |
| Word fluency | −0.31** | −0.35** | −0.15 |
| Global composite | −0.46*** | −0.46**** | −0.25** |
| Women | | | |
| Logical memory-immediate recall | −0.25** | −0.16 | 0.11 |
| Visual reproductions | −0.22* | −0.18* | 0.01 |
| Paired associates | −0.22* | −0.16 | 0.01 |
| Digit span forward | −0.24* | −0.19* | 0.01 |
| Digit span backward | −0.21* | −0.16 | 0.07 |
| Logical memory-delayed recall | −0.25** | −0.16 | 0.07 |
| Similarities | −0.34** | −0.29** | 0.10 |
| Word fluency | −0.40*** | −0.31** | 0.00 |
| Global composite | −0.37*** | −0.28** | 0.09 |

^a Model: age, obesity; S.E.s ranged from 0.09 to 0.12.

^b Model: age, obesity, hypertension, total cholesterol, alcohol consumption, cigarettes/day; S.E.s ranged from 0.09 to 0.12.

^c Model: age, obesity, hypertension, total cholesterol, alcohol consumption, cigarettes/day, education level, occupation level, native English language; S.E.s ranged from 0.08 to 0.12.

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.001$.

**** $p < 0.0001$.

on relations between obesity and cognitive performance in woman than men. For the entire sample, males and females did not differ with respect to education, occupation, or native language (see Table 1). Highly similar correlations between each of these covariates and cognitive performance were observed for men and women and also for non-obese men and women. However, in obese women, education was more highly correlated with the global composite test score ($r = 0.78$) than in obese men ($r = 0.49$).

3.4. Diabetes and diabetes-years

Diabetes (yes/no) did not interact with gender or obesity. Using the extended-surveillance window (Exams 4–14/15), thus allowing for the greatest possible range of scores for the diabetes-years variable, we substituted diabetes-years in the regression models. Diabetes-years did not interact with obesity. Moreover, unlike obesity, diabetes-years did not interact significantly with gender. However, regardless of the covariate model, combining men and women, diabetes-years was related to logical memory-immediate recall ($\beta = -0.04$, $p < 0.001$), similarities ($\beta = -0.02$, $p < 0.03$), word fluency ($\beta = -0.03$, $p < 0.02$), logical memory-delayed recall ($\beta = -0.02$, $p < 0.05$), and the global composite score ($\beta = -0.02$, $p < 0.02$).

4. Discussion

4.1. Obesity

Obesity was related to cognitive performance in men but not women. These results were obtained in the context of several important design features: (1) a prospective design with a community-based sample; (2) adjustment for age, education, occupation, native English language, alcohol consumption, cigarette smoking, total cholesterol, NIDDM (or diabetes-years) and hypertension; (3) exclusion of individuals who had experienced stroke, dementia, or any cardiovascular disease event prior to cognitive testing.

Our findings are consistent with two previous studies [8,15]. Neither included women in the sample, nor did they feature the cardiovascular risk factor controls employed in the present investigation.

As expected, adjustment for education, occupation, and native English, attenuated associations between obesity and cognition for men. However, it negated associations in women. One possible reason is that education was positively and more highly correlated with cognitive performance in obese women than in obese men.

Given the data available to us, we cannot rule out the possibility that obesity is simply a proxy for uncontrolled

psychosocial variables more strongly influencing men than women, e.g., nutrition, activity level, exercise, and depressed mood. Unfortunately, either these data were not collected until after the neuropsychological examination, were available for too few subjects, or were collected too early in the series of examinations to be used as meaningful covariates. Clearly they are important ingredients of planned investigations and should be included in future investigations.

It is also possible that relations between obesity and cognition survived in men because they were stronger in men prior to statistical adjustment, albeit very modestly so. This observation fits with the literature. In general, men are more vulnerable to CVD risk factors. While obesity is a prospective predictor of CVD incidence among women and men [5,9], obese men are at higher risk for CVD mortality [16]. Several large epidemiological investigations in late middle-aged and elderly persons [4,9], including the FHS [7,16] indicate that obesity is an independent risk factor for cardiovascular disease in men, but not women. Further, for older persons [10], male gender appears to exacerbate cerebral degenerative changes. It is widely recognized that women, compared to men of the same age, are protected from the adverse influence of CVD risk factors on morbidity and mortality; they occur later and with less frequency among women [11,13].

Central adiposity (CA) may also explain the gender by obesity interaction. The prevalence of central adiposity in men exceeds that of women [1] and there is greater CVD risk associated with CA than with excess body fat in general [1], and abdominal obesity has been related to cognitive performance in a recent study of South Korean individuals over 65 years of age [6]. Unfortunately, data on CA were obtained too many years prior to neuropsychological test performance to be used as a meaningful covariate. It is important to incorporate CA, or more contemporary measures of regional body fat, into the design of new studies.

4.2. Diabetes

Metabolic disorder has been identified as potentially important explanatory mechanism with respect to diabetes and cognition [14]. We found a modest association between diabetes-years and cognitive performance, but diabetes-years did not interact with gender or obesity. Absence of these interactions might possibly be interpreted as indicating that mechanisms linking obesity to cognition are different from those linking diabetes and cognition, even though metabolic disorder plays a role in each [14].

Ryan [14] concludes that the mechanisms intervening between diabetes and cognition are poorly understood. The link between obesity and cognition is even less well understood. There are several important future areas of research on mechanisms linking obesity and cognition: (1) investigation of nutritional, exercise, activity, mood state, and socioeconomic factors; (2) examination of the mediating role

of metabolic disorders; (3) investigation of the role of sub-clinical vascular diseases using imaging techniques. Longitudinal studies are essential.

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