

PAPER

Lower cognitive function in the presence of obesity and hypertension: the Framingham heart study

MF Elias^{1,2,*}, PK Elias¹, LM Sullivan³, PA Wolf⁴ and RB D'Agostino¹

¹Department of Mathematics and Statistics, Statistics and Consulting Unit, Boston University, Boston, MA, USA; ²Department of Psychology, University of Maine, Orono, ME, USA; ³Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA; and ⁴Department of Neurology, Boston University School of Medicine, Boston, MA, USA

OBJECTIVE: To determine the independent effects of obesity and hypertension on cognitive functioning.

METHODS: Using a prospective design, male ($n=551$) and female ($n=872$) participants of the Framingham Heart Study were classified by presence or absence of obesity and hypertension based on data collected over an 18-y 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, cigarette smoking, alcohol consumption, total cholesterol, and a diagnosis of type II diabetes. Body mass index status (nonobese or obese) and blood pressure status (normotensive or hypertensive) were then related to cognitive performance (learning, memory, executive functioning, and abstract reasoning) on tests administered 4–6 y later.

RESULTS: Adverse effects of obesity and hypertension on cognitive performance were observed for men only. Obese and hypertensive men performed more poorly than men classified as either obese or hypertensive, and the best performance was observed in nonobese, normotensive men.

CONCLUSIONS: The adverse effects of obesity and hypertension in men are independent and cumulative with respect to cognitive deficit.

International Journal of Obesity (2003) 27, 260–268. doi:10.1038/sj.ijo.802225

Keywords: obesity; hypertension; men; women; cognitive functioning

Introduction

The purpose of this study was to examine the combined effects of obesity and hypertension on cognitive functioning among community-dwelling older adults who had not experienced clinical stroke, dementia, or cardiovascular disease (CVD). Obesity and hypertension are well-established risk factors for CVD in the general population.

Hypertension is also a risk factor for lowered cognitive function in persons free from clinically diagnosed stroke and dementia.^{1–6} Models linking blood pressure to cognitive functioning indicate that possible pathways between risk and cognitive deficit may be metabolic imbalance, clinically silent stroke, atherogenesis,^{1,5–7} altered distribution of cerebral blood flow,⁸ or demyelination or microinfarction

in the cerebral white matter.⁴ Many of these pathophysiological sequelae are also found in association with obesity, although it is often assumed that obesity is a risk factor for CVD simply by virtue of its association with other risk factors. However, obesity and even overweight have been found to be independent risk factors for CVD in a number of studies,⁹ including the Framingham Heart Study.¹⁰

There have been few studies of obesity and cognitive functioning,¹ possibly because of the general assumption that it is not a primary risk factor for poor cognitive performance, but merely predisposes or exacerbates other risk factors for CVD such as hypertension, diabetes, high cholesterol, and cigarette smoking. Only two studies have provided some evidence that obesity *per se* is associated with lowered cognitive functioning in men.^{11,12} However, these studies failed to address whether obesity was associated with cognitive performance independently of the effects of diabetes, hypertension, cholesterol levels, and cigarette smoking. Moreover, they did not include controls for cardiovascular diseases and events that may have been correlated with overweight or obesity.

*Correspondence: Dr MF Elias, Department of Mathematics and Statistics, Statistics and Consulting Unit, Boston University, 111 Cummington St., Boston University, Boston, MA 02215, USA.

E-mail: mfelias@aol.com

Received 21 April 2002; revised 7 August 2002;
accepted 7 October 2002

There is a linear relationship between body mass index (BMI) and blood pressure (BP) even among persons who are not overweight.¹³ Clearly, obesity and even body weight within the normal range play an important role in elevated BP.¹³ Thus it is surprising that few, if any, studies employing cognitive outcome variables have examined the interactive effects of obesity and hypertension on cognitive functioning.

We raised three major questions in the present study: (1) are the effects of obesity and hypertension on cognitive functioning similar for men and women; (2) does obesity and/or hypertension have an adverse effect on cognitive functioning independent of diabetes, total cholesterol, alcohol consumption, and cigarette smoking; (3) if so, are the effects of obesity and hypertension cumulative with respect to level of cognitive performance? In other words, is there an inverse association between the number of target risk factors present, 0 (neither hypertension *nor* obesity), 1 (hypertension *or* obesity), and 2 (hypertension *and* obesity) and the level of cognitive performance?

The importance of excluding persons with cardiovascular comorbidity in studies of risk factors and cognitive functioning has been strongly emphasized in the literature.^{1,14} This is particularly important because persons may intensify efforts to modify risk in response to cardiovascular or cerebrovascular events.¹⁵ Consequently, the present study was designed to examine relationships among obesity, hypertension, and cognitive functioning in persons free from completed stroke, dementia, and cardiovascular disease.

Methods

Subjects

The Framingham Heart Study is an ongoing, population-based, longitudinal investigation as distinct from a case-control study of patients entering the study with disease. Subjects were recruited from the community of Framingham, MA, beginning in 1948, and have been followed with respect to cardiovascular risk factors and events every 2 y up to the present. Our analyses employed neuropsychological data that were collected at Examinations 14 and 15. Data were obtained from 2123 participants of the Framingham Heart Study, aged 55–88, who were administered the Kaplan–Albert neuropsychological test battery¹⁶ during their 14th or 15th biennial examination (1974–1978). Prevalent and incident CVD risk factors and disease 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 Examinations 4–12 (1954–1970), and thus preceded neuropsychological testing (1974–1978) by 4–8 y. In a secondary analysis, the surveillance period was redefined as Examinations 4–14/15, thus allowing for an examination of the effects of risk factors and covariate control up to, and including, the time of cognitive testing.

Of the 2123 eligible participants, 700 persons were excluded based on the following criteria, as determined at the time of cognitive testing: (1) nonattendance at baseline Examination 4 (to assure that the earliest measures of the predictors and covariates were included in the surveillance window), $n=87$; (2) attendance at fewer than six examinations (to assure an adequate sampling of predictor and covariate measures within the surveillance window), $n=36$; (3) history of completed stroke, $n=78$; (4) history of dementia, $n=28$; (5) history of cardiovascular disease or event, including myocardial infarction, angina pectoris, congestive heart failure, intermittent claudication, or coronary insufficiency, $n=356$; (6) failure to complete the entire neuropsychological test battery (to allow for statistical analyses using multivariate analysis of covariance), $n=115$. Demographic data for the final sample used in the primary analyses (551 men and 872 women) are shown in Table 1.

Design

The following data on CVD risk factors were obtained at each examination during the surveillance window: (1) diastolic (DBP, mmHg) and systolic (SBP, mmHg) blood pressures (two physician measurements at each examination); (2) body mass index (BMI (weight (kg)/height (m)²)); (3) casual glucose (mmol/l); (4) self-reported number of cigarettes smoked per day; (5) total serum cholesterol (mm/dL); and (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 Examinations 4–12 and dividing by the number of examinations attended (minimum of six examinations).

Independent variables Using mean values for BMI 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:¹⁷ normal weight (<25 kg/m²); overweight (25–29.9 kg/m²), and obese (≥ 30 kg/m²).

Hypertensive and normotensive groups were identified on the basis of mean systolic and diastolic BP values computed over the surveillance period. Using guidelines established by the Sixth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure,¹⁸ hypertension was defined as diastolic BP ≥ 90 and/or systolic BP ≥ 140 . The assignment of persons with hypertensive BP stages I–III into one group was done to assure adequate size for analyses in which the combined effects of hypertension and obesity were examined.

Covariates Covariates included age at neuropsychological testing, maximum educational level reached at time of neuropsychological testing (coded on a nine-point scale ranging from 0 (no formal education) to 8 (postcollege courses, including graduate or professional degrees)), highest

Table 1 Demographic characteristics of men and women in the Framingham Heart Study who participated in the study of obesity, hypertension, and cognitive performance

	Men (n=551)				Women (n=872)				P < ^a
	Mean	s.d.	n	Percent	Mean	s.d.	n	Percent	
CVD risk factor^b									
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	
Blood pressure (BP)									
Systolic BP	131.4	14.6			131.7	16.9			NS
Diastolic BP	82.7	8.3			80.1	8.4			0.01
Normotensive			390	70.8			622	71.3	NS
Hypertensive			161	29.2			250	28.7	NS
Covariates^c									
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
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

^aSignificance levels for differences between men and women; *t*-tests for continuous variables; χ^2 tests for categorical variables; NS = nonsignificant.

^bCVD risk factors defined as follows: BMI, mean values (kg/m²) from Examinations 4–12; normal, <25, overweight, 25–29.9, obese, ≥ 30 ; systolic and diastolic BP, mean values (mm/Hg) from Examinations 4–12; normotensive, diastolic BP <90 and systolic BP <140; hypertensive, diastolic BP ≥ 90 and/or systolic BP ≥ 140 .

^cCovariates defined as follows: age (in y) at time of neuropsychological testing; highest educational level achieved, scores 0–8, where 0 = no education, 1 = grades 1–3, 2 = grades 4–7, 3 = completed grade 8, 4 = attended high school, 5 = high school graduate, 6 = attended college, 7 = college graduate, 8 = post-graduate school or courses; highest occupational level achieved, scores 1–7, where 1 = executive/professional, 2 = managerial, 3 = administrative personnel, 4 = clerical/sales, 5 = skilled manual labor, 6 = semiskilled manual labor, 7 = unskilled labor; alcohol consumption, mean values (in oz/wk) from Examinations 4–12; cigarettes/day, mean cigarettes smoked per day from Examinations 4–12; total cholesterol, mean nonfasting levels (in mg/dL from exams 4–12; type II diabetes, age greater than 30 at time of diagnosis and treatment with insulin or oral hypoglycemic agents or casual blood glucose >8.3 mmol/l.

level of occupation achieved at time of neuropsychological testing (coded on a seven-point scale ranging from 1 (professional) to 7 (unskilled labor)), and four CVD risk factors defined by data collected during the surveillance window (mean alcohol consumption, mean cigarettes/day, mean total cholesterol level, and type II diabetes. The presence or absence of type II diabetes was determined by the following criteria: (1) age greater than 30 y 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.

Neuropsychological test battery and procedure Two experienced neuropsychological examiners, who were trained and supervised by a senior (PhD level) neuropsychologist, tested the participants. The examiners were blind to the health status of the participants.

Cognitive performance was measured with the Kaplan–Albert Neuropsychological Test Battery.¹⁶ It consisted of eight subtests taken from the Wechsler Adult Intelligence

Scale (WAIS), the Wechsler Memory Scale, and the Multilingual Aphasia Examination. Individual tests from this battery, as well as a composite score, have been associated with diabetes and hypertension in previous studies (eg, Elias et al^{2,3}). The subtests measure long-term visual memory, verbal learning, visual organization, visual memory, attention and concentration, abstract reasoning, and concept formation.¹⁹ Subtests 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. Administration time for the battery is 30–45 min.

In addition to the individual test scores, a Total Test score was derived by obtaining standardized (*z*) scores for each subtest (based on the full sample of men and women prior to exclusions), adding the *z* scores, dividing by the number of tests, and then expressing the resultant composite score as a *z* score. Thus a person scoring at the mean of the sample and another person scoring a s.d. above the mean would have *z* scores of 0 and 1, respectively.

Statistical methods

Multivariate (MANCOVA) and univariate (ANCOVA) analyses of covariance were employed²⁰ (pp. 1–38). Consistent with its use as a protection scheme, the multivariate test (*F* approximation of Wilks Lambda criterion) was used as an omnibus test with respect to the separate ANCOVAs performed for each cognitive measure²⁰ (pp. 1–38). The MANCOVA analyses required equal numbers of subjects and, consequently, only persons who completed every subtest in the battery could be included (see exclusions in the Methods section). With exceptions noted later, obesity and hypertension (the predictor variables) were included in the models together (ie, adjusted for each other), along with the covariates: age, education level, occupation level, mean alcohol consumption, mean cigarette smoking, mean total cholesterol, and type II diabetes. Interaction terms were added to this model as described below.

First, tests of Sex × Obesity and Sex × Hypertension interactions with MANCOVA and ANCOVA analyses were done. Based on these results, analyses were done after stratification by sex. These include preliminary tests of the Obesity × Hypertension interaction. A final set of multiple linear regression analyses was employed in order to determine the association between the number of predictor risk factors present (0, 1, or 2) and cognitive functioning.

Results

Description of the sample

Table 1 summarizes the descriptive measures of the target CVD risk factors and covariates for men and women. Significant sex differences were found for many of the risk factor categories, although in most cases the differences would not be considered clinically significant. With regard to covariate measures, it should be noted that women were older and exhibited significantly lower levels of alcohol consumption and smoking, and higher levels of total cholesterol.

Table 2 displays the means, s.e.m., and the range of cognitive scores for males and females. As may be seen, the

women performed better on Paired Associates Learning, Digit Span Backward (marginally), and Word Fluency, and more poorly on Logical Memory–Delayed.

Preliminary tests: BMI

Prior to analyses comparing obese and nonobese individuals, multivariate and univariate analyses were undertaken in order to determine whether normal weight and nonobese, but overweight persons differed from each other for any of the subtest scores. Separate analyses were conducted for men and women. The MANCOVA results were not significant for either men ($P=0.65$) or women ($P=0.72$). ANCOVA results confirmed that the normal weight and overweight groups did not differ for any of the individual cognitive measures: males, $P=0.14–0.86$; females, $P=0.17–0.84$. Consequently, the normal weight and overweight groups were combined into a single nonobese group for all further analyses.

Interaction tests

Tests of the Sex × Hypertension × Obesity interactions were not significant. The Hypertension × Sex interaction did not reach significance in the multivariate model ($P<0.06$). However, the Obesity × Sex interaction was significant in the multivariate model ($P<0.02$), and it also reached significance in the univariate models for the following independent variables: Logical Memory ($P<0.02$), Visual Reproductions ($P<0.004$), Digit Span Backward ($P<0.002$), Similarities ($P<0.04$), and Logical Memory—Delayed Recall ($P<0.01$).

Given the significance levels for the Obesity × Sex interactions ($P<0.05$), all subsequent analyses were done with stratification by sex. In the sex-specific models, Obesity × Hypertension interactions were tested first. For both the multivariate and univariate models, they were nonsignificant ($P=0.28–0.91$) for both sexes, and thus were deleted from the models for the remaining analyses.

Table 2 Means, standard deviations, and ranges for the cognitive tests by gender^a

Test	Men (n = 551)			Women (n = 872)			P < ^b
	Mean	s.d.	Range	Mean	s.d.	Range	
Logical Memory	7.15	3.39	0–20	7.01	3.41	0–20	NS
Visual Reproductions	6.14	3.20	0–14	5.96	3.05	0–14	NS
Paired Associates	11.56	3.38	2–21	12.87	3.41	0–21	0.0001
Digit Span Forward	5.98	1.27	0–8	5.90	1.26	0–8	NS
Digit Span Backward	4.08	1.27	2–8	4.21	1.21	0–8	0.06
Similarities	11.78	5.44	0–24.5	11.94	5.68	0–24.5	NS
Word Fluency	30.81	12.12	2–65	32.93	12.70	0–74	0.002
Delayed Memory	6.12	3.52	0–18	5.56	3.34	0–17	0.003

^aStatistical analyses performed using the SAS GLM procedure; ANOVA d.f.=1, 1421.

^bP-values for ANOVAS comparing men and women.

Main effects tests within sex

All analyses involved obesity and hypertension as the predictor variables (in the models together), along with the full covariate set, unless otherwise specified below. All analyses were done separately for men and women.

Table 3 summarizes findings for nonobese and obese men and women separately in terms of means, s.e.m., and *P*-values. There was a significant multivariate effect of Obesity for the men ($P < 0.002$), but not for the women ($P = 0.91$). With all the covariates in the model, obese men performed significantly more poorly than nonobese men for the Logical Memory—Immediate Recall, Visual Reproductions, Digit Span Backward, Word Fluency, and Logical Memory—Delayed Recall tests ($P < 0.03$), and a marginal effect was seen for Similarities ($P < 0.07$). There were no significant Obesity effects for women ($P = 0.14$ – 0.97).

For the MANCOVA model, the test of Hypertension was statistically significant for the men ($P < 0.05$), but not for the women ($P = 0.83$). There were three significant mean differences between normotensive and hypertensive men for the ANCOVA tests: Logical Memory—Immediate Recall (6.99 ± 0.24 vs 6.31 ± 0.29 , $P < 0.01$), Visual Reproductions (5.80 ± 0.21 vs 5.10 ± 0.26 , $P < 0.003$), and Logical Memory—Delayed Recall (5.90 ± 0.24 vs 5.30 ± 0.30 , $P < 0.05$). Hypertensive and

normotensive women did not differ with respect to any of the cognitive measures ($P = 0.14$ – 0.97).

The Total Test score was analyzed with ANCOVA because it was based on a linear composite of *z* scores derived from each cognitive test. The pattern of preliminary findings, including tests of interactions, was the same as that for the multivariate tests of cognitive measures. Thus, findings are summarized only for the analyses involving stratification by sex. Table 4 summarizes the *P*-values for ANCOVA and the means and s.e. of the mean for the Total Score expressed in units of s.d. of the *z* scores. Obese men performed at a level of 0.44 s.d. below the level of nonobese men ($P < 0.0001$). The difference between hypertensive and normotensive men was smaller (-0.16 s.d.), but also significant ($P < 0.04$). In contrast, tests of obese vs nonobese women and hypertensive vs normotensive women showed no differences with respect to the Total Test score ($P = 0.23$ and 0.88 , respectively).

Combined effects of hypertension and obesity

The final set of analyses employed multiple linear regression analyses to examine the combined effects of obesity and hypertension on the cognitive measures for which significant effects were obtained for both predictor variables:

Table 3 Cognitive test raw score adjusted means and standard errors of the mean for nonobese and obese men and women^a

Cognitive Test Measure	Men (n=551)			Women (n=872)		
	Mean	s.e. ^b	<i>P</i> < ^c	Mean	s.e. ^b	<i>P</i> < ^c
Logical Memory—Immediate Recall						
Nonobese	7.13	0.16		6.92	0.12	
Obese	6.14	0.14	0.02	7.31	0.23	0.24
Visual Reproductions						
Nonobese	6.14	0.14		5.99	0.12	
Obese	4.76	0.23	0.0004	5.98	0.29	0.97
Paired Associate Learning						
Nonobese	11.62	0.16		12.85	0.13	
Obese	11.01	0.41	0.16	13.13	0.34	0.45
Digit Span Forward						
Nonobese	5.99	0.06		5.89	0.05	
Obese	5.72	0.16	0.11	5.92	0.12	0.87
Digit Span Backward						
Nonobese	4.12	0.06		4.21	0.05	
Obese	3.49	0.16	0.0002	4.28	0.11	0.60
Similarities						
Nonobese	11.80	0.22		11.90	0.18	
Obese	10.68	0.59	0.07	12.60	0.45	0.14
Word Fluency						
Nonobese	31.28	1.38		32.70	0.44	
Obese	27.98	1.38	0.03	33.26	1.13	0.64
Logical Memory—Delayed Recall						
Nonobese	6.10	0.16		5.47	0.12	
Obese	5.11	0.42	0.03	5.88	0.32	0.24

^aMeans are adjusted for age, education, occupation, cigarettes/day, alcohol consumption, total cholesterol, type II diabetes, and normotensive/hypertensive status; statistical analyses performed using the SAS GLM procedure; MANCOVA d.f., men (8, 532), women (8, 849); ANCOVA d.f., men (1, 540), women (1, 856).

^bStandard error of the mean.

^c*P*-values for ANCOVAs comparing obese and nonobese groups within sex.

Table 4 Adjusted means of the standardized scores (*z*) and standard errors of the mean for the Total Test score for the blood pressure and body mass index categories by gender^a

	Men (n = 551)			Women (n = 872)		
	Mean	s.e. ^b	P < ^c	Mean	s.e. ^b	P < ^c
BP Category						
Normotensive	-0.09	0.06		0.15	0.05	
Hypertensive	-0.25	0.07	0.04	0.14	0.05	0.88
BMI Category						
Nonobese	0.05	0.04		0.10	0.02	
Obese	-0.39	0.10	0.0001	0.19	0.08	0.23

^aMeans are adjusted for age, education, occupation, cigarettes/day, alcohol consumption, total cholesterol, type II diabetes, and blood pressure group or body mass index group; statistical analyses performed using the SAS GLM procedure; ANCOVA d.f., men (1, 540), women (1, 856).

^bStandard error of the mean.

^cP-values are for ANCOVAs comparing normotensive and hypertensive groups or nonobese and obese groups within sex.

Logical Memory—Immediate Recall, Visual Reproductions, and Logical Memory—Delayed Recall. These analyses were conducted only for men because no significant results were obtained with either predictor for the women. Men were assigned a Risk Factor score of 0, 1, or 2 as follows: 0 if neither obesity nor hypertension were present; 1 if either obesity or hypertension were present; 2 if both obesity and hypertension were present. Multiple linear regression analyses were done with the risk factor score as the predictor variable and with the same covariate set used in the MANCOVA and ANCOVA analyses reported above.

The results for the raw score trends for these analyses are shown in Figure 1. For all three cognitive measures, planned comparisons indicated that the presence of both hypertension and obesity resulted in significantly poorer performance than did the absence of both risk factors. However, as is clear from Figure 1, the presence of either obesity or hypertension resulted in a cognitive performance level between the performance levels for 0 or 2 risk factors, and, for Logical Memory—Immediate Recall and Visual Reproductions, the trend was nearly linear. For Logical Memory—Immediate Recall, all three Risk Factor scores differed significantly from each other ($P < 0.05$). For Visual Reproductions, a Risk Factor score of 1 or 2 was associated with poorer performance than a Risk Factor score of 0 ($P < 0.002$). For Logical Memory—Delayed Recall, a Risk Factor score of 2 was associated with poorer performance than a Risk Factor score of either 0 or 1 ($P < 0.03$).

Secondary analyses

Since MANCOVA and ANCOVA analyses were employed together, persons who did not complete all tests in the battery were excluded from the statistical analyses. When these persons were included and the analyses were repeated, the pattern of significant results was the same for all ANCOVAs performed.

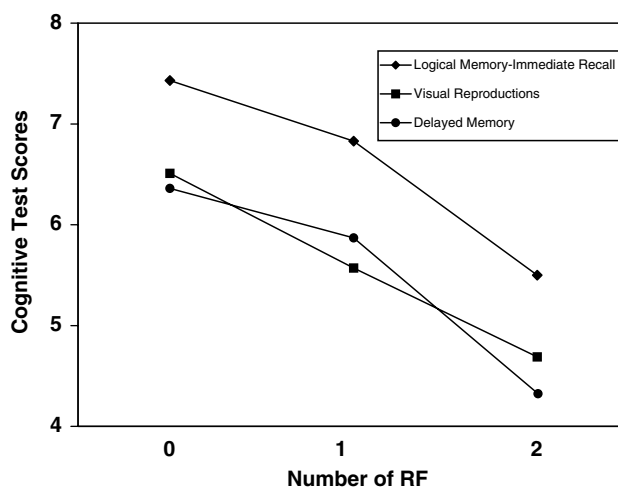


Figure 1 Relation of number of CVD risk factors (0 = none; 1 = either obesity or hypertension present; 2 = both obesity and hypertension present) to cognitive test performance in men.

The study employed a prospective design in which Examinations 4–12 constituted the surveillance period and cognitive test performance was measured at Examination 14 or 15. However, a question can be raised as to whether results would have been the same with extension of the surveillance period to overlap with the cognitive assessments (Examinations 4–14/15). Values for this overlapping surveillance period were determined, and all analyses were repeated and replicated, that is, results were exactly the same as when Examinations 4–12 constituted the surveillance period.

At the time of neuropsychological testing, 84 women and 33 men were being treated with tranquilizing medications; 279 women and 137 men were being treated with anti-hypertensive medications. Both of these variables were coded as presence (1) or absence (0) of treatment and were added to the covariate set. Neither tranquilizer use nor

treatment for hypertension were related to any of the cognitive test scores ($P=0.16-0.98$), and all associations among obesity, hypertension, and cognitive performance were unchanged.

Discussion

There were four important findings in this study: (1) significant effects of hypertension and obesity on tests of learning and memory were observed for men, but not for women; (2) obesity and hypertension were associated with lower cognitive functioning in late middle-aged and elderly men, independent of other common CVD risk factors; (3) obesity and hypertension had common effects on specific tests of memory, thus suggesting that pathophysiological mechanisms by which they affect cognition may be similar; (4) among men, the adverse effects of obesity and hypertension are cumulative with respect to deficit; the presence of both risk factors results in more cognitive deficit than the presence of either or none. The latter relation is of clinical importance because obesity is characteristic of many hypertensive patients and, in fact, may be a common cause of hypertension.¹³

These results were obtained in the context of several important design features: (1) a prospective design was employed using a community-based population; (2) obesity and hypertension effects were adjusted for age, education, occupation, alcohol consumption, cigarette smoking, total cholesterol, and type II diabetes; (3) individuals who had experienced stroke, dementia, or any CVD event prior to cognitive testing were excluded. It is particularly important to relate CVD risk factors, such as obesity and hypertension, to cognitive functioning among individuals who have not experienced frank cerebrovascular or cardiovascular disease and thus have not modified their risk behavior in relation to that event.

The sex-specific effect of hypertension on cognitive functioning may be related to the fact that women are more likely to have their hypertension treated and controlled at all age levels.²¹ Indeed, for the Framingham Study participants used in our analyses, all of whom were free of cardiovascular disease, 15% of the women, but only 7% of the men, were treated with antihypertensive medication during the surveillance window, and indeed, women did have slightly lower diastolic blood pressures (see Table 1). Similarly, 32% of the women, but only 24% of the men, were treated for hypertension at the time of cognitive testing. However, inclusion of this treatment variable in the statistical models did not alter the sex-specific effects. Moreover, there is evidence that male gender potentiates both cerebral-degenerative and cognitive changes related to hypertension in older adult subjects.²²

Our findings with respect to obesity are consistent with the two studies that have reported adverse effects of obesity on cognitive functioning in males,^{11,12} but neither study

included women in the samples. Sex differences in sample size do not explain our finding. The proportion of obese men and women was similar (11.1 and 10.9%, respectively) and the sample of women was larger than the sample of men, thus allowing for more power with respect to statistical tests. Further, while there were gender differences in performance on the various tests, there was no consistent pattern across tests (eg, women performing consistently better than men). Thus, differences in task difficulty do not explain the unique adverse effects of obesity on cognitive functioning among men.

The sex-specific effect of obesity is consistent, however, with current models used to explain the adverse effects of CVD risk factors on cognitive function. These models generally postulate a mediating variable of subclinical cardiovascular disease.^{1,5,23} Support for this model comes from studies of sex-specific relations between obesity and CVD outcomes. Thus, while obesity is a long-term predictor of CVD incidence among women as well as men,¹⁰ obese men have been found to be at higher risk for cardiovascular mortality than obese women.²⁴ Several large epidemiological studies of late middle-aged and elderly persons,^{9,25} including early reports for the Framingham Cohort,^{26,27} indicate that obesity is an independent risk factor for cardiovascular disease in men, but not in women. Further, there is evidence that male gender potentiates cerebral degenerative changes with consequent effects on cognitive function in the presence of CVD risk factors among older persons.²² It is widely recognized that women, relative to men of the same age, are protected from the adverse effects of all CVD risk factors on morbidity and mortality; they occur later and with less frequency among women.^{28,29}

We did not have data on some additional variables that would have allowed consideration of alternative explanations for the sex-specific effects of obesity. These variables include nutritional and exercise information, psychosocial variables, such as depression, and measurement of central adiposity, which has been shown to carry greater risk for CVD than does excess body fat.³⁰ However, either these variables were not collected at each Framingham Heart Study examination throughout the surveillance period of the present study or they were obtained so early in the surveillance period that relating them to cognitive functioning at Examinations 14/15 was not meaningful.

It is certainly possible that the obese men were more prone to central adiposity than the obese women in our study. Thus, the greater CVD risk associated with central adiposity, rather than obesity *per se*, might explain the sex-specific effects of obesity on measures of cognition. Similarly, depression and depressive symptoms have been related to CVD and cognitive performance.³¹⁻³⁴ However, the use of depression as an explanatory concept for the gender-specific results of the present study is weakened by the fact that, among the Framingham Offspring, men exhibited lower levels of depressed mood than did women, and neither

obesity nor blood pressure were related to depression in men.³⁵

Obese individuals are more likely to be found among lower socioeconomic groups.^{36–39} Unfortunately, a direct measure of socioeconomic status was not available to us at any time during the study period. However, education and occupation levels are strong correlates of socioeconomic status,^{39,40} and both of these variables were employed as statistical controls in the present study.

In summary, because obesity and hypertension are independent risk factors for CVD, we expected that they would be independently related to cognitive performance. This hypothesis was confirmed. The significant associations of obesity and hypertension with cognitive functioning were not affected by statistical control for each other or by statistical control for coexisting CVD risk factors. Further, adverse cognitive effects of obesity and hypertension were observed for men, but not for women. Our data strongly suggest that earlier-onset, long-term obesity and hypertension may adversely affect later cognitive performance and, hopefully, will stimulate studies leading to a better understanding of the mechanisms underlying their differential effects on cognition in men and women.

Acknowledgements

This research was supported, in part, by research grants from the National Institutes of Health: 1-R01-HL65177-03 (National Lung, Blood and Heart Institute and the National Institute on Aging); 1-R01-NS17950-21 (National Institute of Neurological Diseases and Stroke); 1-R01-AG16495-04 (National Institute on Aging); and 3-R01 AG08122-12 (National Institute on Aging) and CONTRACT NO1-HC-25195 (NIH/NHLBI).

We extend our sincere appreciation to Dr Michael A Robbins, Kristin A Swenson, Gregory A Dore, and Barbara A Hermann, University of Maine, for their assistance in the preparation of the manuscript.

References

- 1 Elias MF, Elias PK, Robbins MA, Wolf PA, D'Agostino RB. Cardiovascular risk factors and cognitive functioning: an epidemiological perspective. In: Waldstein SR, Elias MF (eds). *Neuropsychology of cardiovascular disease*. Lawrence Erlbaum: Mahwah, NJ; 2001. pp 83–104.
- 2 Elias MF, Wolf PA, D'Agostino RB, Cobb J, White LR. Untreated blood pressure is inversely related to cognitive functioning: The Framingham Study. *Am J Epidemiol* 1993; **138**: 353–364.
- 3 Elias PK, Elias MF, D'Agostino RB, Cupples LA, Wilson PW, Silbershatz H, Wolf PA. NIDDM and blood pressure as risk factors for poor cognitive performance. *Diabetes Care* 1997; **20**: 1388–1395.
- 4 Knopman D, Boland LL, Mosely T, Howard G, Liao D, Szklo M, McGovern P, Folsom AR, for the Atherosclerosis Risk in Communities (ARIC) Study Investigators. Cardiovascular risk factors and cognitive decline in middle-aged adults. *Neurology* 2001; **56**: 42–48.
- 5 Waldstein SR. Hypertension and neuropsychological function: a lifespan perspective. *Exp Aging Res* 1995; **21**: 321–352.
- 6 Waldstein SR, Katzel LI. Hypertension and cognitive functioning. In: Waldstein SR, Elias MF (eds). *Neuropsychology of cardiovascular disease*. Lawrence Erlbaum: Mahwah, NJ; 2001. pp 15–36.
- 7 Desmond DW, Tatemichi TK, Paik M, Stern Y. Risk factors for cerebrovascular disease as correlates of cognitive function in a stroke-free cohort. *Arch Neurol* 1993; **50**: 162–166.
- 8 Jennings JR, Muldoon MF, Ryan CM, Mintun MA, Meltzer CC, Townsend DW, Sutton-Tyrrell K, Shapiro AP, Manuck SB. Cerebral blood flow in hypertensive patients. An initial report of reduced and compensatory blood flow responses during performance of two cognitive tasks. *Hypertension* 1998; **31**: 1216–1222.
- 9 Kuller LH. Epidemiology of obesity in adults in relationship to cardiovascular disease. In: Fletcher GF, Grundy SM, Hayman L (eds). *Obesity: impact on cardiovascular disease*. Futura Publishing Company: Armonk, NY; 1999. pp 3–29.
- 10 Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation* 1983; **67**: 968–977.
- 11 Kilander L, Nyman H, Boberg M, Lithell H. Cognitive function, vascular risk factors and education: a cross-sectional study based on a cohort of 70-year-old men. *J Intern Med* 1997; **242**: 313–321.
- 12 Sorensen TI, Sonne-Holm S, Christensen U, Kreiner S. Reduced intellectual performance in extreme overweight. *Hum Biol* 1982; **54**: 765–775.
- 13 Hall JE, Brands MW, Jones DW, Shek EW, Henegar J. Mechanisms of obesity hypertension and relevance to essential hypertension. In: Fletcher GF, Grundy SM, Hayman L (eds). *Obesity: impact on cardiovascular disease*. Futura Publishing Company: Armonk, NY; 1999. pp 133–154.
- 14 Lowe LP, Tranel D, Wallace RB, Welty TK. Type II diabetes and cognitive function. A population-based study of Native Americans. *Diabetes Care* 1994; **17**: 891–896.
- 15 Siegler IC, Bosworth HB, Elias MF. Adult development and aging in health psychology. In: Nezu AM, Nezu CM, Geller PA (eds). *Comprehensive handbook of psychology. Health psychology*, Vol 9. Wiley: New York; 2003. pp 487–510.
- 16 Elias MF, Elias PK, D'Agostino RB, Silbershatz H, Wolf PA. Role of age, education and gender on cognitive performance in the Framingham Heart Study: community-based norms. *Exp Aging Res* 1997; **23**: 201–235.
- 17 NHLBI Obesity Education Initiative Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. *The practical guide: identification, evaluation, and treatment of overweight and obesity*. NIH Publication No. 00-4084. National Institutes of Health: Washington, DC; 2000.
- 18 Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. The sixth report of the Joint National committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. *Arch Intern Med* 1997; **157**: 2413–2446.
- 19 Lezak MD. *Neuropsychological assessment*, 3rd edn. Oxford University Press: New York; 1995, p 549.
- 20 Harris RJ. *A primer of multivariate statistics*. Academic Press: New York; 1985.
- 21 LaCroix AZ. Gender effects and hypertension in women. In: Izzo Jr JL, Black HR (eds). *Hypertension primer*. American Heart Association: Dallas, TX; 1993. pp 150–152.
- 22 Meyer JS, Rauch GM, Crawford K, Rauch RA, Konno S, Akiyama H, Terayama Y, Haque A. Risk factors accelerating cerebral degenerative changes, cognitive decline and dementia. *Int J Geriatr Psychiatry* 1999; **14**: 1050–1061.
- 23 Ryan CM. Diabetes-associated cognitive dysfunction. In: Waldstein SR, Elias MF (eds). *Neuropsychology of cardiovascular disease*. Lawrence Erlbaum: Mahwah, NJ; 2001. pp 61–82.

- 24 Wilcosky T, Hyde J, Anderson JJ, Bangdiwala S, Duncan B. Obesity and mortality in the Lipid Research Clinics Program Follow-up Study. *J Clin Epidemiol* 1990; **43**: 743–752.
- 25 Gillum RF, Mussolino ME, Madans JH. Body fat distribution, obesity, overweight, and stroke incidence in women and men: the NHANES I. *Int J Obes Relat Metab Disord* 2001; **25**: 628–638.
- 26 Truett J, Cornfield J, Kannel WB. A multivariate analysis of risk of coronary heart disease in Framingham. *J Chronic Dis* 1967; **20**: 511–524.
- 27 Kannel WB, Gordon T. Obesity and cardiovascular disease. The Framingham study. In: Burland LW, Samuel RD, Uudkin J (eds). *Obesity*. Churchill-Livingstone: Edinburgh; 1974. pp 24–51.
- 28 Murabito JM. Women and cardiovascular disease: contributions from the Framingham Heart Study. *J Am Med Womens Assoc* 1995; **50**: 35–39.
- 29 Rossouw JE. Hormones, genetic factors, and gender differences in cardiovascular disease. *Cardiovasc Res* 2002; **53**: 550–557.
- 30 Brownell KD, Wadden TA. Etiology and treatment of obesity: understanding a serious, prevalent, and refractory disorder. *J Consult Clin Psychol* 1992; **60**: 505–517.
- 31 Horsten M, Mittleman MA, Wamala SP, Schenck-Gustafsson K, Orth-Gomer K. Depressive symptoms and lack of social integration in relation to prognosis of CHD in middle-aged women. The Stockholm Female Coronary Risk Study. *Eur Heart J* 2000; **21**: 1072–1080.
- 32 Musselman DL, Evans DL, Nemeroff CB. The relationship of depression to cardiovascular disease: epidemiology, biology and treatment. *Arch Gen Psychiatry* 1998; **55**: 580–592.
- 33 Takemura Y, Kikuchi S, Takagi H, Inaba Y, Nakagawa K. A cross-sectional study on the relationship between depression and left ventricular hypertrophy. *Prev Med* 1998; **27**: 787–791.
- 34 Jorm AF. Is depression a risk factor for dementia or cognitive decline? A review. *Gerontology* 2000; **46**: 219–227.
- 35 Elias MF, Sullivan LM, Elias PK, Wolf PA, Robbins MA, D'Agostino RB. Obesity predisposes to depression in younger but not older women: The Framingham Offspring Study. Abstract 347. *Psychosom Med* 2002; **64**: 171.
- 36 Moore ME, Stunkard AJ, Srole L. Obesity, social class, and mental illness. *J Am Med Assoc* 1962; **181**: 962–966.
- 37 Stunkard AJ. Obesity and the social environment: current status, future prospects. *Ann NY Acad Sci* 1977; **300**: 298–320.
- 38 Whitelaw AG. Association of social class and sibling number with skinfold thickness in London school boys. *Hum Biol* 1971; **43**: 414–420.
- 39 Cagney KA, Lauderdale DS. Education, wealth, and cognitive function in later life. *J Geront B Psychol Sci Soc Sci* 2002; **57B**(2), P163–P172.
- 40 Wechsler D. *The measurement and appraisal of adult intelligence*, 4th edn. Williams and Wilkins: Baltimore; 1958. p 137.