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Adiposity, Adipokines, and Risk of Incident Stroke in Older Men

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Background and Purpose—The association between adiposity and adipocytes and risk of stroke in older adults is uncertain. We have examined the association between adiposity measures and adipocytes (adiponectin and leptin) with incident stroke events in older men.

Methods—Prospective study of 3411 men aged 60 to 79 years with no previous diagnosis of myocardial infarction, heart failure, or stroke followed-up for an average of 9 years, during which there were 192 incident major stroke events.

Results—In age-adjusted analyses, body mass index and waist circumference were not significantly associated with risk of stroke in older men, although obese men (body mass index >30 kg/m²) showed the lowest risk of stroke. Despite the strong positive correlation between leptin and body mass index and waist circumference, risk of stroke was significantly increased in those in the top quartile of the leptin distribution. The increased risk remained after adjustment for potential confounders, including systolic blood pressure (adjusted hazard ratios top quartile versus bottom quartile: 2.03; confidence interval, 1.27–3.27). Further adjustment for markers of inflammation (C-reactive protein), endothelial dysfunction (von Willebrand factor), fibrinolytic activity (d-dimer), and γ -glutamyl transferase attenuated the increased risk, but risk remained significantly increased (adjusted hazard ratios, 1.73; confidence interval, 1.06–2.83). By contrast, no association was seen between adiponectin and risk of stroke.

Conclusions—Conventional adiposity measures were not associated with increased stroke risk in older men. However, leptin (a good marker of percent fat mass), but not adiponectin, predicted stroke, suggesting a link between fat mass and stroke risk. (*Stroke*. 2013;44:3-8.)

Key Words: adipocytes ■ adiposity ■ cerebrovascular disease ■ epidemiology risk factors

Obesity is associated with increased risk of atherosclerotic vascular disease, including myocardial infarction (MI) and stroke,^{1,2} although the association between adiposity and stroke in older adults is uncertain.³⁻⁵ Adipose tissue, in addition to being a fat store, secretes a number of hormones such as adiponectin and leptin, which have been variably linked to the development of coronary heart disease^{6,7} and may be involved in the underlying biological mechanisms linking obesity to stroke. However, their role in stroke has been less studied. Although a number of cross-sectional and retrospective case-control studies suggest that leptin and low adiponectin are associated with increased stroke risk,⁸⁻¹³ prospective data on their association with stroke are limited and conflicting.⁸ Whereas 1 prospective study suggested that leptin was a risk factor for stroke,¹⁴ 2 recent prospective and nested case-control studies showed no association between leptin and stroke.^{15,16} Two prospective nested case-control studies have reported an association between low adiponectin and increased risk of stroke,^{16,17} but other prospective studies have reported no association between adiponectin and stroke.^{14,15,18,19} We have examined the

relationship between adiposity (body mass index [BMI], waist circumference [WC]) and the adipose-derived proteins leptin and adiponectin with risk of incident stroke in a prospective cohort of older men aged 60 to 79 years.

Subjects and Methods

The British Regional Heart Study is a prospective study of cardiovascular disease (CVD) involving 7735 men, aged 40 to 59 years, drawn from general practice in each of 24 British towns, who were screened between 1978 and 1980.²⁰ The population studied was socioeconomically representative of British men but comprised predominantly white Europeans (>99%). In 1998 to 2000, all surviving men, now aged 60 to 79 years (mean age, 68.7 years), were invited for a 20-year follow-up examination. The men completed a questionnaire that included questions on their medical history and lifestyle behavior. They were requested to fast for a minimum of 6 hours, during which time they were instructed to drink only water and to attend for measurement at a prespecified time between 0800 and 1800 hours. All men were asked to provide a blood sample, collected using the Sarstedt Monovette system. The samples were frozen and stored at -20°C on the day of collection and transferred in batches for storage at -70°C until analysis, performed after no more than 1 freeze-thaw cycle.

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Twelve-lead ECGs were recorded using a Siemens Sicard 460 instrument and were analyzed and coded in accordance with Minnesota Coding definitions at the University of Glasgow ECG core laboratory based at Glasgow Royal Infirmary.²¹ Atrial fibrillation was defined according to Minnesota codes 8.3.1 and 8.3.3. A total of 4252 men (77% of survivors) reported for examination. The men were asked whether a doctor had ever told them that they had angina or MI (heart attack, coronary thrombosis) or stroke, and to bring their medication to the examination session. A total of 4094 men provided blood samples. We excluded men with a recall of a diagnosis of MI, stroke, or heart failure (n=678), and we excluded 5 additional men with no adiposity measures, leaving 3411 men for analysis.

Cardiovascular Risk Factors

Anthropometric measurements including body weight, height, and WC were performed. Details of measurements and classification methods for smoking status, physical activity, BMI, WC, social class, forced expiratory volume in 1 second, blood pressure, renal dysfunction, and lipids have been described.^{22–25} Men with a doctor's diagnosis of diabetes mellitus or those with a fasting glucose of >7 mmol/L (World Health Organization criteria) were considered to have prevalent diabetes mellitus.

Hemostatic and Inflammatory Biomarkers

At the 20-year examination, D-dimer was measured with ELISA (Biopool AB), as was von Willebrand factor (vWF) antigen (DAKO). C-reactive protein (CRP) was assayed by ultrasensitive nephelometry (Dade Behring). Interleukin-6 (IL-6) was assayed using a high-sensitivity ELISA (R&D Systems).

Adiponectin and Leptin

Plasma adiponectin concentrations were determined using ELISA (R&D Systems). The intra-assay and the interassay coefficients of variability were each 7.5%. We previously have shown this method to correlate well with a radioimmunoassay method for adiponectin measurement.⁶ Plasma leptin was measured by an in-house radioimmunoassay carefully validated against the commercially available Lingo assay, as previously described.⁷ The intra-assay and interassay coefficients of variation were <7% and <10%, respectively, over the sample concentration range. The detection limit of the assay was 0.5 ng/mL, which is superior to commercial assays. Within-person variation of leptin values over 4 years was high (correlation coefficient, 0.79; 95% confidence interval, 0.73–0.83,⁷ and for adiponectin the correlation coefficient was 0.58 and 95% confidence interval was 0.49–0.66.⁶ Data on adiponectin were available for 3372 men and were available for leptin for 3218 men. Men with missing data were excluded from analysis.

Follow-up

All men had been followed-up from initial examination (1978–1980) for cardiovascular morbidity and follow-up had been achieved for 99% of the cohort.²⁶ In the present analyses, all-cause mortality and morbidity events were based on follow-up from rescreening in 1998 to 2000 at mean age of 60 to 79 years to July 2008, which is a mean follow-up period of 9 years (range, 8–10 years). Information on death was collected through the established tagging procedures provided by the National Health Service registers. Fatal stroke episodes were those coded on the death certificate as International Classification of Diseases 430–438. Nonfatal stroke events were those that produced a neurological deficit that was present for >24 hours. Evidence regarding nonfatal stroke was obtained by ongoing reports from general practitioners, by biennial reviews of the patients' practice records (including hospital and clinic correspondence) through to the end of the study period, and from repeated personal questionnaires to surviving subjects after initial examination. Supplementary information on computerized tomography/MRI scans were only available for 100 (52%) of the 192 stroke cases. Of these, 62 (62%) were ischemic stroke, 9 (0.9%) were hemorrhagic strokes, and 29 (29%) were indeterminate.

Statistical Methods

The distribution of leptin and adiponectin was skewed and log transformation was used. Cox proportional hazards model was used to assess the multivariate-adjusted hazards ratio (relative risk) in a comparison of quartiles of leptin and adiponectin. To assess the association between BMI and stroke, we considered BMI as a categorical variable based on World Health Organization cut-offs (normal weight, BMI 18.5–24.9 kg/m²; overweight, BMI 25.0–29.9 kg/m²; and obese, BMI >30 kg/m²). Similarly we considered WC as a categorical variable using 3 categories: <94 cm; 94 to 101 cm; and >102 cm. In multivariate analyses, smoking (never, long-term ex-smokers [>15 years], recent ex-smokers [<15 years], and current smokers), social class (manual vs nonmanual), physical activity (4 groups), alcohol intake (5 groups), diabetes mellitus (yes or no), and angina (yes or no) were fitted as categorical variables; forced expiratory volume in 1 second, CRP, IL-6, vWF, γ -glutamyl transferase, and D-dimer were fitted as continuous variables. $P < 0.05$ was used for statistical significance.

Results

During the mean follow-up period of 9 years, there were 192 incident stroke cases (5.9/1000 person-years) in the 3411 men with no history of stroke, MI, or heart failure. Table 1 shows baseline characteristics in the men who had development of stroke and in those who remained free of stroke. Men who had development of stroke showed higher rates of blood pressure treatment and higher mean levels of systolic and diastolic blood pressure, CRP, and IL-6, and lower levels of forced expiratory volume in 1 second. Leptin levels were higher in stroke cases ($P=0.07$). Little difference was seen between stroke and adiponectin levels ($P=0.55$).

There was no significant association between measures of adiposity (WC or BMI) and risk of stroke (Table 2) in age-adjusted analysis. Adjustment for potential confounders including blood pressure reduced the risk in obese men further, and the lower risk in obese men compared with those with BMI <25 kg/m² was significant ($P=0.04$). Exclusion of men with renal dysfunction (estimated glomerular filtration rate <60 mL/min per 1.73 m²) or history of cancer did not alter the findings.

Leptin was associated with many risk factors, including blood pressure, γ -glutamyl transferase, markers of inflammation (CRP and IL-6), vWF, and D-dimer, although the association with blood pressure was abolished after adjustment for age and BMI (Table 3). Adiponectin showed little association with blood pressure and the associations with markers of inflammation, γ -glutamyl transferase, and vWF were attenuated after adjustment for age and BMI. Increased leptin was associated with significantly increased risk of stroke after adjustment for age and BMI (Table 4). Adjustment for potential confounders and blood pressure caused minor differences in the association. Further adjustment for CRP, vWF, γ -glutamyl transferase, and D-dimer attenuated the association but risk remained significantly increased in those with increased leptin. Adjusting for IL-6 instead of CRP yielded similar results. By contrast, no consistent association was seen between adiponectin and risk of stroke.

We also conducted a sensitivity analysis restricting incident cases to confirmed ischemic strokes (n=62 cases). Elevated leptin was significantly associated with ischemic stroke after adjustment for factors in model 1 in Table 4 (adjusted

Table 1. Baseline Characteristics (1998–2000) in 3411 Men Without Preexisting Myocardial Infarction, Stroke, or Heart Failure According to Incident Stroke Status

	No Stroke (n=3219)	Developed Stroke (n=192)	P Difference
Age, y	68.24 (5.40)	71.16 (5.38)	<0.0001
BMI, kg/m ²	26.80 (3.59)	26.58 (3.45)	0.42
WC, cm	96.84 (10.2)	96.87 (10.0)	0.97
Inactive, %	31.8	38.2	0.07
Current smokers, %	5.6	6.3	0.59
Manual, %	53.2	56.1	0.50
Moderate/heavy drinkers, %	19.2	21.1	0.53
Using blood pressure treatment, %	5.3	7.3	0.04
Angina, %	5.6	7.0	0.31
Diabetes mellitus, %	5.7	5.9	0.89
Atrial fibrillation, %	2.8	4.2	0.29
SBP, mm Hg	149.4 (23.7)	157.1 (25.3)	<0.0001
DBP, mm Hg	85.51 (10.9)	87.35 (12.3)	0.02
Cholesterol, mmol/L	6.05 (1.06)	6.09 (1.16)	0.63
HDL cholesterol, mmol/L	1.33 (0.34)	1.33 (0.36)	0.91
FEV ₁ , L	2.64 (0.65)	2.45 (0.66)	0.0002
Glucose, mmol/L*	5.81 (5.25–6.08)	5.93 (5.23–6.16)	0.30
HOMA-IR	0.78 (0.33–1.14)	0.83 (0.34–1.08)	0.35
GGT, U/L	28.22 (19–38)	30.87 (19–46)	0.04
CRP, mg/L*	1.63 (0.78–3.21)	2.11 (1.05–3.90)	0.002
IL-6, pg/mL*	2.34 (1.52–3.31)	2.94 (1.77–4.25)	<0.0001
vWF, IU/dL	136.8 (45.1)	150.2 (50.1)	<0.0001
D-dimer, ng/mL*	79.0 (47–117)	102.5 (60.5–156.5)	<0.0001
Adiponectin, μg/mL*	6.75 (4.36–10.84)	7.03 (4.29–10.71)	0.55
Leptin, ng/mL*	8.93 (5.6–13.9)	9.87 (6.0–16.4)	0.07

BMI indicates body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; FEV₁, forced expiratory volume in 1 second; GGT, γ -glutamyl transferase; HDL, high-density lipoprotein; HOMA-IR, homeostasis model of assessment of insulin resistance; IL, interleukin; SBP, systolic blood pressure; SD, standard deviation; vWF, von Willebrand factor. WC, waist circumference. Data are mean (SD) unless specified.

*Geometric mean and interquartile range.

hazard ratio, quartile 4 vs quartile 1 2.31; confidence interval, 1.03–5.17).

Discussion

In this large population study of British men aged 60 to 79 years, increased adiposity was not associated with increased stroke incidence. WC showed no association with stroke risk at all; however obese men (BMI >30 kg/m²) tended to have the lowest risk, in contrast to the leptin results. However, we have confirmed the findings of some previous prospective studies that leptin,¹⁴ but not adiponectin,^{14,15,18,19} is associated with incident stroke after adjusting for BMI and established risk factors for stroke. Our findings extend those of other studies on adipocytes and risk of stroke by examining the association in a population at high risk for stroke and by assessing a wide range of potential mediators and mechanisms, including inflammation, metabolic risk factors, endothelial dysfunction (vWF), and fibrinolytic factors (D-dimer).

Despite leptin being a strong correlate of adiposity, BMI and WC were not associated with increased risk of stroke in older men in age-adjusted analyses. Our null findings are consistent with 2 other population studies that have shown no association

between adiposity and stroke in older men.^{4,5} The lack of positive association between WC and BMI and stroke, in contrast to the positive association of leptin, may reflect the weaker associations between WC, BMI, and the true percentage of adipose tissue in older people. Alternatively, the paradoxical finding of a null relationship between WC and CVD risk and an inverse association between BMI and CVD seen even after exclusion of men with preexisting cancer and low renal function may reflect what is often seen in those with established CVD, commonly referred to as the obesity paradox.²⁷ Although men with established CVD and stroke were excluded, it is possible that many of these older men have subclinical CVD or pulmonary disease conditions in which the obesity paradox is often reported. Thus, subclinical disease in a proportion of men is likely leading to weight loss, particularly lean body mass, and so these men have low current BMI, whereas fat mass (and therefore leptin concentration) is less affected.

A significant positive association was observed between increased leptin and stroke in these older men independent of BMI and established stroke risk factors, including smoking and systolic blood pressure. Leptin exerts many potentially atherogenic effects, such as induction of endothelial

Table 2. Incidence Rates Per 1000 Person-Years and Adjusted Relative Hazard Ratios and 95% Confidence Intervals for Incident Stroke in Men by Levels of Body Mass Index and Waist Circumference in Those With No Preexisting Stroke, Myocardial Infarction, or Heart Failure

	BMI, kg/m ²			<i>P</i> Trend Across the Groups
	<25.0	25.0–29.9	>30.0	
N of men (cases)	1067 (67)	1797 (103)	540 (21)	
Rate/1000 person-years	7.9	7.0	5.0	
Age-adjusted HR	1.00	0.94 (0.69–1.28)	0.69 (0.42–1.13)	0.19
Model 1	1.00	0.88 (0.64–1.21)	0.60 (0.36–0.98)*	0.07
	WC, cm			<i>P</i> Trend Across the Groups
	<94	94–102	>102	
N of men (cases)	1324 (74)	1122 (68)	951 (50)	
Rate/1000 person-years	6.8	7.3	6.6	
Age-adjusted HR	1.00	1.12 (0.81–1.55)	1.00 (0.70–1.43)	0.95
Model 1	1.00	1.04 (0.75–1.46)	0.85 (0.58–1.24)	0.50

BMI indicates body mass index; HR, hazard ratio.

Model 1: adjusted for age, diabetes mellitus, angina, atrial fibrillation, smoking, social class, alcohol intake, physical activity, lung function, systolic blood pressure, and use of antihypertensive drugs.

*Test difference between BMI >30 vs <25.0 group. *P*=0.04.

dysfunction, stimulation of inflammatory reaction, and influence on coagulation/fibrinolysis balance,^{28,29} which may contribute to stroke development. However, the association between leptin and stroke was not explained by inflammation (CRP or IL-6), vWF (a marker of endothelial dysfunction), or D-dimer (marker of fibrinolytic activity).

Other potential mechanisms by which leptin may contribute to stroke risk may be through its direct proatherogenic effect on oxidative stress, platelet aggregation, and proliferation of vascular smooth muscle cells, which play a vital role in arterial intima thickening.^{28,29} In population studies, hyperleptinemia has been associated with increased intima-media thickness of the common carotid artery,³⁰ which has been more strongly linked to incident stroke than to MI.³¹ This would be consistent with the finding that leptin predicted incident stroke but has not been shown to be associated with

coronary heart disease in this study.²⁵ Thus, leptin may have a direct atherogenic effect on the carotid artery wall, which may be the pathway by which leptin contributes to development of stroke.

Of course, it is possible that leptin, being a strong correlate to percent fat mass,³² is better at identifying older men with more total fat load (and, by association, less muscle mass). Thus leptin, rather than exerting a direct toxic effect, may signal changes in body morphology not available via conventional adiposity measures but that are linked to stroke risk. This hypothesis is speculative and requires future study.

Our study is not without some limitations. It was based on an older, predominantly white male population, so that the results cannot be generalized directly to women, younger men, or other ethnic groups. In a recent report in women and in middle-aged men, leptin was not shown to be associated

Table 3. Correlation Coefficients Relating Leptin and Adiponectin to Biological Cardiovascular Risk Factors

	Leptin		Adiponectin	
	Unadjusted	Age- and BMI-Adjusted	Unadjusted	Age- and BMI-Adjusted
Age	0.02		0.16	
BMI	0.57*		−0.15	
WC	0.57*		−0.16	
Adiponectin	−0.09*	−0.004		
Systolic blood pressure	0.06†	0.01	0.03	0.02
Diastolic blood pressure	0.06†	0.01	0.03	0.05†
FEV ₁	−0.08*	−0.09*	−0.07*	−0.02
GGT	0.20*	0.11*	−0.08*	−0.03
CRP	0.21*	0.12*	−0.06*	−0.06†
IL-6	0.14*	0.07*	−0.01	−0.03
vWF	0.13*	0.14*	0.04‡	0.01
d-dimer	0.08†	0.07†	0.02	−0.03

BMI indicates body mass index; CRP, C-reactive protein; FEV₁, forced expiratory volume in 1 second; GGT, γ -glutamyl transferase; IL, interleukin; vWF, von Willebrand factor; WC, waist circumference.

**P*<0.0001; †*P*<0.01; ‡*P*<0.05

Table 4. Incidence Rates Per 1000 Person-Years and Adjusted Relative Hazard Ratios and 95% Confidence Intervals for Major Stroke Events by Quartiles of Leptin and Adiponectin in Men With No Preexisting Stroke, Myocardial Infarction, or Heart Failure

	Quartiles (ng/mL), Leptin				P for Trend
	1 (<1.74)	2 (1.74–2.20)	3 (2.20–2.63)	4 (>2.64)	
N (cases)	812 (37)	792 (49)	810 (39)	804 (57)	
Rates/1000 person-years	5.5	7.6	5.9	8.6	
Age- and BMI-adjusted	1.00	1.48 (0.96–2.29)	1.27 (0.79–2.05)	2.09 (1.31–3.34)	0.004
Model 1	1.00	1.54 (0.99–2.39)	1.20 (0.74–1.96)	2.03 (1.27–3.27)	0.007
Model 2	1.00	1.49 (0.96–2.32)	1.12 (0.69–1.84)	1.91 (1.18–3.08)	0.02
Model 3	1.00	1.48 (0.95–2.31)	1.08 (0.66–1.79)	1.79 (1.10–2.91)	0.03
Model 4	1.00	1.48 (0.95–2.31)	1.09 (0.66–1.79)	1.73 (1.06–2.83)	0.04
	Quartiles (µg/mL), Adiponectin				P for trend
	1 (<4.346)	2 (4.346–6.965)	3 (6.966–10.838)	4 (>10.839)	
No. (cases)	843 (50)	843 (39)	844 (56)	842 (46)	
Rates/1000 person-years	6.5	5.9	8.3	6.8	
Age- and BMI-adjusted	1.00	0.74 (0.49–1.14)	0.98 (0.67–1.45)	0.74 (0.49–1.12)	0.60
Model 1	1.00	0.71 (0.47–1.09)	0.92 (0.62–1.36)	0.73 (0.48–1.10)	0.48

BMI indicates body mass index; CRP, C-reactive protein; GGT, γ -glutamyl transferase; vWF, von Willebrand factor. Model 1=adjusted for age, BMI, diabetes mellitus, angina, atrial fibrillation, smoking, social class, alcohol intake, physical activity, lung function, systolic blood pressure, and use of antihypertensive drugs. Model 2=model 1+CRP. Model 3=model 1+CRP+GGT+vWF. Model 4=model 1+CRP+GGT+vWF+D-dimer.

with incident stroke.^{15,17} Leptin levels vary by gender in keeping with greater fat mass in women, and it is possible that there are possible interactions between gender, leptin, and incident stroke that we were not able to explore in this study of men only. Leptin and adiponectin levels in this older population were comparable with other studies.^{16,17} The findings were based on a single measurement at the baseline re-examination. However, both leptin and adiponectin are reasonably stable over time in individuals, as reflected by the within-individual consistency over a 4-year period for leptin ($r=0.79$) and adiponectin ($r=0.58$).^{6,7} This may have led to some underestimation of the true strength of the association between leptin and stroke but is unlikely to effect the null association between adiponectin and stroke. The study population is socially representative of the United Kingdom, and follow-up rates in the British Regional Heart Study are exceptionally high. Although ascertainment of strokes in this study is based on general practice medical records of the men, our incidence rates of 6.9/1000 person-years correspond closely with those of the Oxfordshire Vascular Study (6.8/1000 per year) and the Scottish Borders Stroke Study (6.6/1000 per year).³³ Information on type of stroke was not routinely available in all stroke cases, although most stroke cases (85%) in the United Kingdom are because of ischemia.³⁴ In a sensitivity analysis based on confirmed ischemic stroke cases, findings were similar to those for the whole study population, confirming an association with ischemic stroke. The number of confirmed hemorrhagic stroke in this study was too small to examine separately, but previous reports have observed an association between leptin and both ischemic and hemorrhagic stroke.^{14,35}

In conclusion, we have shown that BMI and WC are not associated with increased risk of stroke in older men. However, the adipose tissue-derived hormone leptin, but not adiponectin, predicted stroke in older men, independent of

established risk factors for stroke and markers of inflammation (CRP IL-6), endothelial dysfunction (vWF), and fibrinolytic factors (D-dimer). Whether our observation represents a direct or indirect link between leptin and stroke risk requires future study.

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Disclosures

None.

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