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Comments, Opinions, and Reviews

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Meta-Analysis of Prospective Studies With 2 Million Participants

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Background and Purpose—A systematic review of the prospective studies addressing the relationship of overweight and obesity to major stroke subtypes is lacking. We evaluated the occurrence of a graded association between overweight, obesity, and incidence of ischemic and hemorrhagic stroke by a meta-analysis of cohort studies.

Methods—A search of online databases and relevant reviews was performed. Inclusion criteria were original article in English, prospective study design, follow-up ≥4 years, indication of number of subjects exposed, and number of events across body mass index categories. Crude unadjusted relative risk (RR) and 95% CI were calculated for each study for overweight or obese compared with normal-weight categories. Log-transformed values and SE were used to calculate the pooled RR with random effects models; publication bias was checked. Additional analyses were performed using the multivariate estimates of risk reported in the individual studies.

Results—Twenty-five studies were included, with 2 274 961 participants and 30 757 events. RR for ischemic stroke was 1.22 (95% CI, 1.05–1.41) for overweight and 1.64 (95% CI, 1.36–1.99) for obesity, whereas RR for hemorrhagic stroke was 1.01 (95% CI, 0.88–1.17) and 1.24 (95% CI, 0.99–1.54), respectively. Subgroup and meta-regression analyses ruled out gender, population average age, body mass index and blood pressure, year of recruitment, year of study publication, and length of follow-up as significant sources of heterogeneity. The additional analyses relying on the published multivariate estimates of risk provided qualitatively similar results.

Conclusions—Overweight and obesity are associated with progressively increasing risk of ischemic stroke, at least in part, independently from age, lifestyle, and other cardiovascular risk factors. **(*Stroke*. 2010;41:e418-e426.)**

Key Words: body mass index ■ cerebrovascular disease ■ excess body weight ■ meta-analysis ■ stroke

Stroke is a major cause of death in developed countries. Its prevalence and disability burden are expected to increase in the future because of population aging.[1] Besides age, risk factors include hypertension, smoking, diabetes mellitus, left ventricular hypertrophy, and atrial fibrillation.[2] Obesity is a precursor of hypertension, diabetes, and their complications, which play an important indirect role in the epidemiology of stroke; moreover, it is associated with the action of powerful cytokines impacting on the sympathetic nervous system activity, the renin-angiotensin axis, the endothelial function, and the microcirculation.[3]

Randomized, controlled trials of the effects of treating obesity on the risk of stroke are lacking. Recently, a large collaborative study provided prospective results about the relationship between obesity and mortality from stroke on a total population of nearly 900 000 individuals, mainly from Western countries, but it did not provide incidence rates, which are actually a more informative index of the burden imposed by stroke on the community.[4] Another recent study was a meta-analysis that did provide information on the rate of stroke (and other comorbidities) but included only 7 studies, for a total population of 150 000 participants, all from Western countries.[5] Three other less recent meta-analyses included only populations from Eastern countries and were mostly focused on the relation with subarachnoid hemorrhage.[6–8]

We report here on a systematic review and meta-analysis of the prospective studies published up to May 2009 that addressed the relationship between excess body weight and stroke in a total population of ≈2 million subjects from both Western and Eastern countries. We aimed to establish whether a graded association occurs between excess body weight and stroke, whether the features of this association are different for ischemic and hemorrhagic stroke, given the differences in the epidemiology and pathogenesis of the 2 main stroke subtypes, and whether multivariate adjustment for various potential confounders modifies the strength of the association.

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Materials and Methods

Data Sources and Study Selection Criteria

A literature search of the online databases (PUBMED, EMBASE, HTA) from January 1966 through May 2009 was performed using the following key words: "BMI," "body mass index," "overweight AND stroke," "cerebrovascular disease," or combinations thereof either in medical subject headings or in the title/abstract. Further information was retrieved through a manual search of references from recent reviews and relevant published original studies.

To be included in the meta-analysis, a published study had to meet the following criteria: (1) original article in English; (2) prospective (cohort) study design; (3) follow-up of at least 4 years (mean or median); (4) adult population; and (5) indication of the number of subjects exposed and the number of events occurred in different body mass index (BMI) categories.

Data Extraction

The following characteristics of the identified studies and respective populations were recorded: publication reference, total number of participants, country, gender, age range/mean age, recruitment time, length of follow-up (years), stroke type investigated (total/ischemic/hemorrhagic), number of events, and stroke incidence. For each study, the data were independently extracted by 2 investigators (L.D., F.G.) and, in case of divergent evaluation, the discrepancy was resolved in conference with arbitration by a third investigator (P.S.). In the case of missing data, the authors were contacted and asked to provide the necessary information.

Categorization of excess body weight differed among studies, and in some cases it was necessary to combine ≥2 BMI subgroups to comply with the conventional normal weight (BMI $<$25 kg/m^2), overweight (BMI between 25 and 29.9 kg/m^2), and obesity (BMI ≥30 kg/m^2) categories for Western populations.[9] For Eastern populations, the categories' cut-offs were BMI $<$23 kg/m^2 for normal weight, 23 to 27.5 kg/m^2 for overweight, and $>$27.5 kg/m^2 for the obese subjects.[10]

Statistical Analysis

The quality of the studies included in the meta-analysis was evaluated by the Downs and Black score system.[11] We calculated an unadjusted relative risk (RR) and its 95% CI for each study as a measure of stroke incidence among overweight and obese individuals in comparison with normal-weight participants, respectively, using the formula: RR=(Eo/Eo+NEo)/(Enw/Enw+NEnw), where E=events, NE=not events, o=overweight and/or obesity, and nw=normal weight. The respective SE were calculated from the RR CI. The value from each study and the corresponding SE were transformed into their natural logarithms to stabilize the variances and to normalize their distribution. Pooled RR and their 95% CI were estimated using both fixed effects (weighting method: inverse variance) and random effects (weighting method: DerSimonian-Laird) models.[12] Eventually, the pooled estimates from random effects models were used because the tests for heterogeneity were statistically significant in all analyses. The heterogeneity among studies was tested by Q statistic and quantified by I^2 statistic.[13] Possible publication bias was investigated by funnel plot asymmetry, Egger regression test, and the trim-and-fill method.[14,15]

Sensitivity analysis was used to see the extent to which inferences might depend on a particular study or group of studies. Meta-regression and subgroup analyses were performed to check for specific sources of heterogeneity.

Finally, further meta-analyses of the relationship between excess body weight and incidence of ischemic and hemorrhagic stroke were performed including all the suitable studies available in the literature (supplemental Figure I, available online at http://stroke.ahajournals.org), provided that the adjusted RR or hazard ratios (HR) were reported by the authors as result of multivariate analyses. Statistical analyses were performed using the MIX software version 1.7[16] and the Stata software (version 9.1) for meta-regression analysis.

Results

Characteristics of the Study Cohorts

According to the stepwise procedure depicted in supplemental Figure I, 25 studies[17–41] were included in the meta-analysis; their relevant features are reported in Table 1. All the studies had a quality score of at least 15 out of 19. Overall, the meta-analysis involved 2 274 961 participants from 10 countries. Nine studies were from Asia, 10 were from Europe, and 6 were from the United States, whereas no studies were found from Africa and Latin America. The total number of cerebrovascular events reported was 30 757. There were separate reports of 11 722 ischemic and 8380 hemorrhagic strokes. Fourteen studies registered fatal and nonfatal strokes, 9 registered only fatal strokes, and 2 registered only nonfatal strokes. For the 7 studies that reported outcomes separately for male and female participants[23,26,28,29,31,34,37] and the 1 reporting separate results for individuals with or without preexisting coronary heart disease,[27] the different subgroups were counted as separate cohorts in the meta-analysis; thus, the total number of cohorts identified was 33. It must be noted, however, that for each different comparison made in this study, only a limited number of cohorts was available depending on the type of data provided in the individual studies. The weighted average follow-up time for all the studies included in the meta-analysis was 17.5 years.

Overweight, Obesity, and Incidence of Total Stroke

The pooled RR of total stroke for overweight and obese subjects combined vs normal-weight individuals was 1.05 (95% CI, 0.89–1.24; z=0.59; P=0.56; 28 cohorts with 2 274 941 participants and 30 767 events). The heterogeneity between studies was significant ($P<0.0001$; $I^2=97\%$) and there was no evidence of publication bias (Egger test, P=0.98).

The comparison of total stroke rates in obese vs normal-weight individuals was based on 28[18–27,30–41] cohorts (1 800 924 participants and 22 279 events). The pooled RR of obese vs normal-weight subjects was 1.26 (95% CI, 1.07–1.48; z=2.79; P=0.005), with a significant heterogeneity ($P<0.0001$; $I^2=91\%$). There was evidence of publication bias (Egger test, P=0.01), but no missing study was identified by the trim-and-fill method.

From 28 cohorts[18–27,30–41] available for the comparison of total stroke rates in overweight vs normal-weight individuals (2 159 827 participants and 27 357 events), the pooled RR (overweight vs normal-weight) was 1.05 (95% CI, 0.93–1.17; z=0.80; P=0.42). Significant heterogeneity ($P<0.0001$; $I^2=93\%$) was detected, with no conclusive evidence for publication bias and no missing study being identified by the trim-and-fill method. In the sensitivity analysis, for both analyses, the stroke risk did not vary substantially with the exclusion of individual studies.

Excess Body Weight and Incidence of Ischemic Stroke

The pooled RR of ischemic stroke for overweight and obese subjects combined vs normal-weight individuals was 1.30 (95% CI, 1.06–1.60; z=2.55; P=0.01; 19 cohorts with 1 792 418 participants and 11 170 events). The heterogeneity

Table 1. Main Characteristics of the Studies Included in the Meta-Analysis

Author	Country	Recruitment Time	Follow-Up, yr	Age		End Point	Gender	Population	N of Events for Stroke Subtype			Study Quality Score
				Mean	Range				Total	Ischemic	Hemorrhagic	
Abbott, 1994[17]	US	1965–1968	22	59.8	55–68	Fatal/nonfatal	M	1163	…	48	…	16
Walker, 1996[18]	US	1987	5	…	40–75	Fatal/nonfatal	M	28 643	118	…	…	16
Shaper, 1997[19]	GB	1978–1980	14.8	…	40–59	Fatal/nonfatal	M	7735	290	…	…	17
Wassertheil-Smoller, 2000[20]	US	1985–1988	5	71	…	Nonfatal	Total	3975	183	…	…	17
Kurth, 2002[21]	US	1982	12.5		40–84	Fatal/nonfatal	M	21 414	747	631	104	16
Jood, 2004[22]	Sweden	1970–1973	28	51.6	…	Fatal/nonfatal	M	7402	873	495	144	16
Cui, 2005[23]	Japan	1988–1990	9.9	…	40–79	Fatal	M	43 889	765	300	271	16
							F	61 039	685	240	288	
Kurth, 2005[24]	US	1993	10	≥45		Fatal/nonfatal	F	39 053	432	347	81	18
Tanne, 2005[25]	Israel	1963–1968	23	≥40		Fatal	M	9151	316	…	…	15
Murphy, 2006[26]	Scotland	1972–1976	20	54	45–64	Fatal/nonfatal	M	7048	601	…	…	17
							F	8354	687	…	…	
Batty, 2006[27]	GB	1967–1970	35	…	40–64	Fatal (no CHD)	M	14 400	755	…	…	16
						Fatal (with CHD)	M	2526	154	…	…	
Chen, 2006[28]	Taiwan	1991–1993	10.4	≥20		Fatal/nonfatal	M	1499	…	72	…	16
							F	1954	…	60	…	
Li, 2006[29]	Sweden	1991–1996	7	…	45–73	Fatal/nonfatal	M	10 369	…	315	…	17
							F	16 638	…	237	…	
Lu, 2006[30]	Sweden	1991–1992	11.4	…	30–50	Fatal/nonfatal	F	45 449	170	111	47	17
Oki, 2006[31]	Japan	1980	19	>30		Fatal	M	4171	165	101	39	18
							F	5355	154	81	31	
Park, 2006[32]	Korea	1992	9	…	20–69	Fatal	M	246 146	493	…	…	15
Hong, 2007[33]	Korea	1985	15.8	66.3	…	Fatal	M	2608	196	…	…	17
Hu, 2007[34]	Finland	1972–1977	19.5	…	25–74	Fatal/nonfatal	M	23 967	1673	1331	342	17
							F	26 029	1555	1223	332	
Song, 2007[35]	US	1992–1995	10.2	…	39–89	Nonfatal	Total	25 626	256	…	…	16
Funada, 2008[36]	Japan	1994	7	…	40–79	Fatal	Total	43 916	467	218	140	17
Sauvaget, 2008[37]	India	1996–1998	8	49	…	Fatal	M	49 284	579	…	…	15
							F	78 575	653	…	…	
Zhou, 2008[38]	China	1990–1991	10	54	40–79	Fatal	M	211 946	5766	1231	3609	16
Eeg-Olofsson, 2009[39]	Sweden	1997–1998	5.6	60.3	30–74	Fatal/nonfatal	Total	13 087	756	…	…	15
Silventoinen, 2009[40]	Sweden	1969–1994	24.4	18.2	16–25	Fatal/nonfatal	M	1 145 467	8865	2944	2747	16
Zhang, 2009[41]	China	1996–2000	7.3	51.3	40–70	Fatal/nonfatal	F	67 083	2403	1737	205	16
Total								2 274 961	30 757	11 722	8380	

CHD indicates coronary heart disease; F, female; M, male.

between studies was significant ($P<0.0001$; $I^2=96\%$) and there was no evidence of publication bias (Egger test, $P=0.80$).

The comparison of ischemic stroke rate in obese vs normal-weight subjects (pooled RR, 1.64; $P<0.0001$; data from 18 cohorts with 1 477 909 participants and 7800 events) is shown in Figure 1A. There was significant heterogeneity between studies ($P<0.0001$; $I^2=88\%$) and evidence of publication bias by the Eggers test ($P=0.002$), but no missing study was identified by the trim-and-fill method.

In overweight compared with normal weight individuals, the pooled RR was 1.22 ($P=0.01$; data from 19 cohorts with 1 715 939 participants and 9444 events; Figure 1B). There was significant heterogeneity between studies ($P<0.0001$; $I^2=89\%$) and no evidence of publication bias (Egger test, $P=0.32$).

Sensitivity analysis showed that the pooled estimate did not vary substantially with the exclusion of any one study. In particular, after exclusion of the study by Silventoinen et al,[40] which accounted for ≈50% of all participants in the meta-analysis and nearly 30% of all strokes, the pooled RR was, respectively, 1.62 (95% CI, 1.32–1.98; $P<0.0001$) and 1.21 (95% CI, 1.03–1.43; $P=0.02$) in obese and overweight subjects compared with normal-weight individuals.

Sources of Heterogeneity

Further analyses were performed to check for potential sources of heterogeneity with respect to the relationship between excess body weight and ischemic stroke. Meta-regression was used for continuous variables and subgroup analyses for categorical variables. With both methods, to include the largest possible number of studies, the outcomes for overweight and obese individuals were combined.

The relationship between excess body weight and risk of ischemic stroke was not significantly different in men (pooled RR, 1.21) and women (RR, 1.55; heterogeneity between

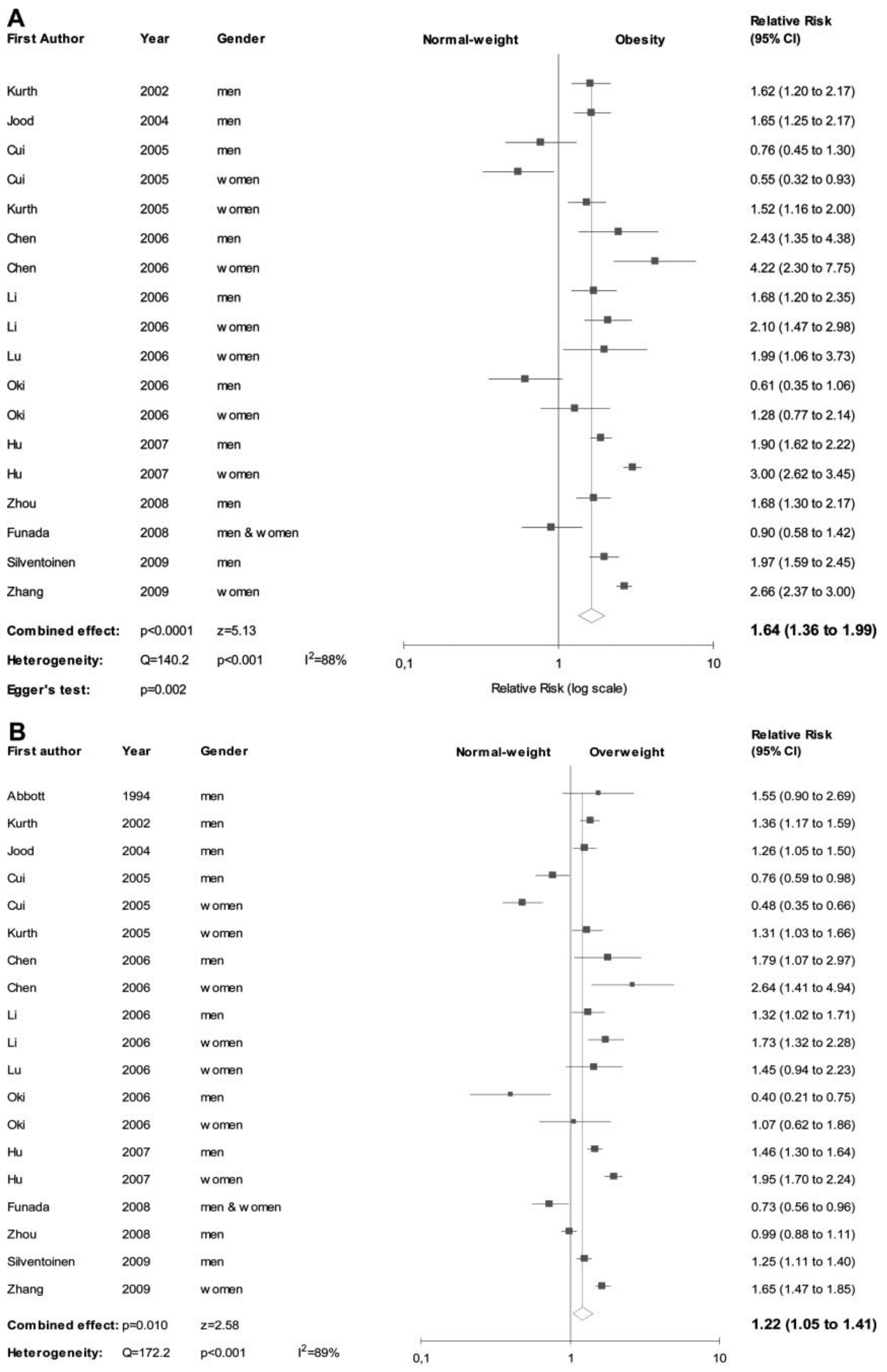

Figure 1. A, Risk of ischemic stroke in obese vs normal-weight subjects. B, Risk of ischemic stroke in overweight vs normal-weight subjects.

groups, $P=0.20$). With regard to the populations' geographical origin, excess body weight seemed to be a better predictor of the risk of ischemic stroke in European and North American populations (pooled RR, 1.55) than in Asian populations (RR, 1.08), with the heterogeneity level between groups approaching, albeit not quite reaching, statistical significance ($P=0.10$). The results of meta-regression analyses (supplemental Table I, available online at http://stroke.ahajournals.org) indicated that population average age, baseline BMI and blood pressure, year of recruitment or of study publication, and length of follow-up were not significant sources of heterogeneity in the relationship between excess body weight and ischemic stroke.

Excess Body Weight and Incidence of Hemorrhagic Stroke

Fourteen cohorts were available for the comparison of hemorrhagic stroke rates in subjects in the obese and overweight category combined vs normal-weight individuals (1 762 795 participants and 8380 events). The pooled RR was 1.06 (95% CI, 0.83–1.36; $z=0.47$; $P=0.64$). The heterogeneity between studies was significant ($P<0.0001$; $I^2=95\%$), with borderline evidence of publication bias (Egger test, $P=0.09$), but no missing study identified by the trim-and-fill method.

Figure 2 shows the results of separate analyses of the incidence of hemorrhagic stroke in obese (14 cohorts available with 1 461 057 individuals and 6382 events) and overweight (14 cohorts, 1 688 375 participants, and 7855 events) subjects, respectively, vs normal-weight individuals. There was a trend for obesity being associated with a greater risk of hemorrhagic stroke compared to the normal-weight condition (pooled RR, 1.24; $P=0.059$). However, there was no evidence for different risk of hemorrhagic stroke between overweight and normal-weight subjects (pooled RR, 1.01; $P=0.84$). Sensitivity analysis showed that the pooled estimates of risk did not vary with the exclusion of individual studies. In both cases, there was significant heterogeneity and no evidence of publication bias.

Systematic Review of the Studies That Explored the Association Between Excess Body Weight and Stroke: Evidence From Multivariate Analysis

Table 2 illustrates the relevant features and the main results of the studies that provided RR or HR derived from multivariate analyses. The number and the type of confounders accounted for were different for different studies. Some, but not all, studies reported RR or HR obtained by adjustment for age only. Given the importance of the adjustment for age, we first conducted a meta-analysis of these studies. Thereafter, we performed another set of analyses including all the studies included in our basic meta-analysis and using the RR or HR adjusted for all the confounders accounted for in each study.

Ischemic Stroke

The meta-analysis of the studies providing RR or HR adjusted for age only showed evidence of a direct association with both obesity (13 cohorts, pooled RR, 1.60; 95% CI, 1.48–1.72; $P<0.0001$; heterogeneity, $P=0.8$; $I^2=0\%$) and overweight (14 cohorts, pooled RR, 1.20; 95% CI, 1.14–1.26; $P<0.0001$; heterogeneity, $P=0.4$; $I^2=2\%$).

The meta-analysis performed using the RR or HR adjusted for all the confounders accounted for in each study also indicated a direct association with overweight and obesity (Table 2, combined effect I). The results were similar on inclusion of 5 additional studies[42–46] that did not provide crude unadjusted data and thus were not included in the basic meta-analysis (Table 2, combined effect II).

Hemorrhagic Stroke

For hemorrhagic stroke, the pooled estimates of risk obtained using the reported RR or HR derived from multivariate analyses indicate a statistically significant association with obesity but no evidence of association with overweight (Table 2). After inclusion of the aforementioned 5 additional studies,[42–46] the association between hemorrhagic stroke and obesity was missed (Table 2, combined effect II). Also, the meta-analysis of the studies that provided RR or HR adjusted for age only did not provide evidence of association either with obesity (11 cohorts, pooled RR, 1.19; 95% CI, 0.91–1.56; $P=0.20$; heterogeneity, $P<0.001$; $I^2=67\%$) or with overweight (11 cohorts, pooled RR, 1.03; 95% CI, 0.88–1.21; $P=0.7$; heterogeneity, $P=0.06$, $I^2=43\%$).

Discussion

The present work is the most comprehensive systematic review and meta-analysis of the prospective relationship of overweight and obesity with the risk of ischemic and hemorrhagic stroke. Its strengths are selection of precise criteria for study inclusion/exclusion, consideration of fatal and nonfatal events, inclusion of studies of Western and Eastern populations, use of crude unadjusted data providing an unbiased estimate of risk, large number of participants and events entered in the calculation of the pooled estimates of risk, separate analyses of stroke subtypes whenever possible, and further analysis using multivariate estimates of risk.

The most important finding was the demonstration of a graded positive relationship of overweight and obesity with the incidence of ischemic stroke. Based on the pooled estimates of risk, overweight and obese individuals had, respectively, 22% and 64% greater probability of an ischemic stroke compared with normal-weight subjects. The relationship was not significantly different in men and women, nor did it differ in relation to the average blood pressure level of the populations examined or to the length of follow-up. By contrast, the geographical origin of the study population appeared to be an important source of heterogeneity, with the impact of excess body weight being highly significant in European and North American cohorts but not in Asian populations, which had a low prevalence of obesity. The association between excess body weight and rate of hemorrhagic stroke was much weaker and approached statistical significance only for the obese condition.

We conducted our basic analysis using crude unadjusted rates of ischemic and hemorrhagic stroke derived from single studies. By doing so, we obtained unbiased estimates of the association and avoided the risk of overadjustment occurring very often when accounting for possible confounding by a

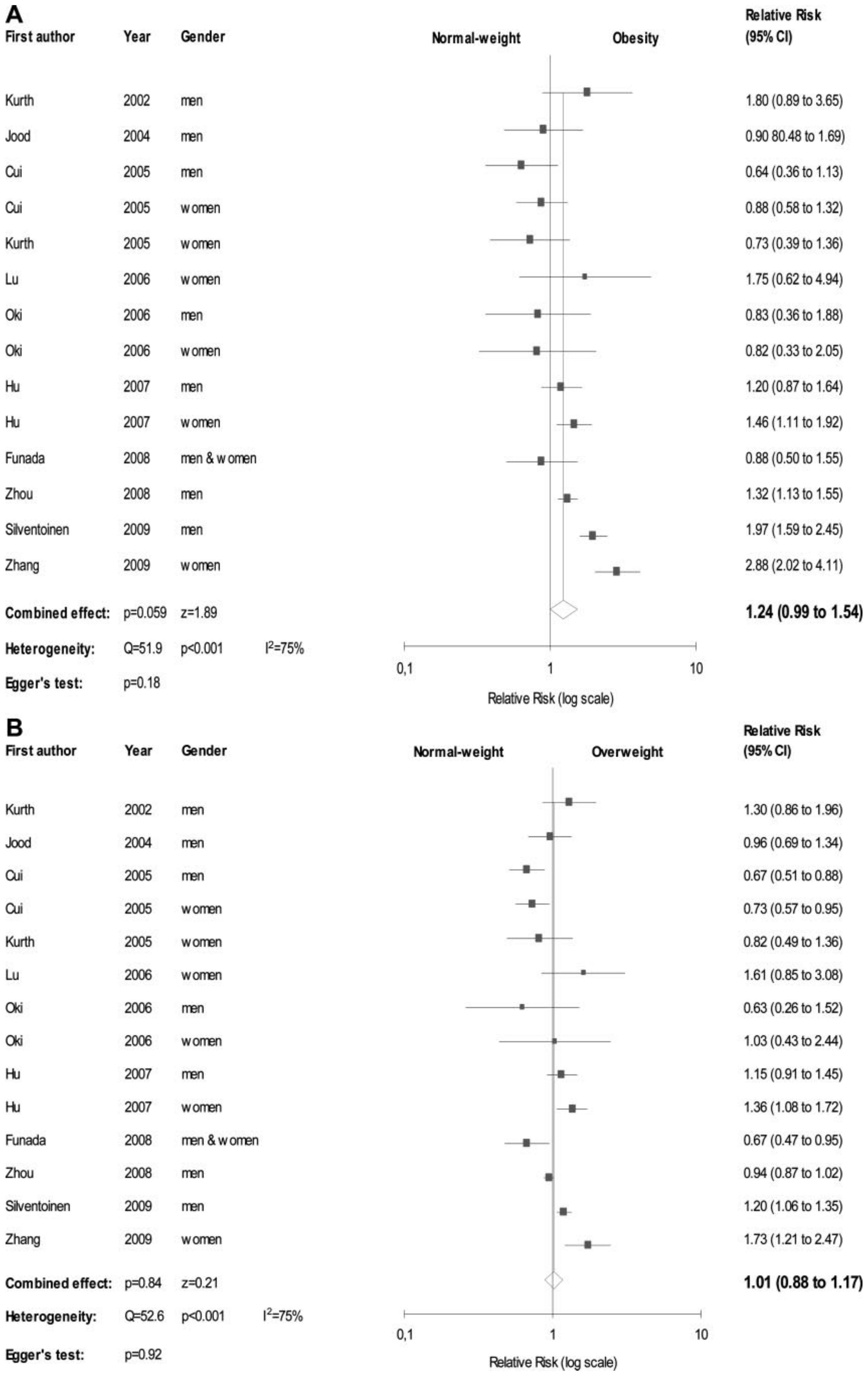

Figure 2. A, Risk of hemorrhagic stroke in obese vs normal-weight subjects. B, Risk of hemorrhagic stroke in overweight vs normal-weight subjects.

Table 2. Systematic Review: Multivariate Association Between Excess Body Weight and Ischemic/Hemorrhagic Stroke

Author	Stroke Subtype	Gender	Association Measures, RR or HR (95% CI): Overweight	Obesity	Factors Controlled for in Multivariate Analysis
Abbott, 1994[17]	Ischemic	M	2.10 (1.10–4.10)	…	Age, systolic blood pressure, physical activity, glucose, uric acid,hematocrit, total cholesterol
Kurth, 2002[21]	Ischemic	M	1.33 (1.06–1.67)	1.95 (1.39–2.72)	Age, smoking, alcohol, physical activity, history of angina, parental history of myocardial infarction <60 years, randomized treatment assignment
	Hemorrhagic		1.45 (0.81–2.60)	2.25 (1.01–5.01)	
Jood, 2004[22]	Ischemic	M	1.10 (0.81–1.51)	1.45 (0.98–2.14)	Age, smoking, physical activity, parental history of stroke, occupational class, psychological stress, systolic blood pressure, hypertension treatment, diabetes, cholesterol
	Hemorrhagic		0.88 (0.50–1.54)	0.87 (0.40–1.89)	
Cui, 2005[23]	Ischemic	M	0.99 (0.63–1.56)	1.05 (0.60–1.86)	Age, hypertension, diabetes, smoking, alcohol, physical activity, sleep, perceived mental stress, education, fish intake
		F	1.19 (0.68–2.08)	1.05 (0.56–1.97)	
	Hemorrhagic	M	1.62 (0.92–2.85)	1.25 (0.59–2.66)	
		F	0.95 (0.48–1.89)	1.02 (0.49–2.10)	
Kurth, 2005[24]	Ischemic	F	1.12 (0.61–2.10)	1.29 (0.69–2.41)	Age, smoking, physical activity, alcohol, hormone therapy, hypertension, diabetes, high cholesterol
	Hemorrhagic		0.58 (0.24–1.41)	0.38 (0.13–1.09)	
Li, 2006[29]	Ischemic	M	1.23 (1.05–1.43)	1.57 (1.28–1.93)	Age, smoking, alcohol, physical activity, education, diabetes, hypertension, lipid-lowering drugs, menopausal status
		F	1.30 (1.07–1.59)	1.32 (1.03–1.68)	
Lu, 2006[30]	Ischemic	F	1.00 (0.60–1.50)	1.00 (0.50–1.90)	Age, smoking, alcohol, age at first birth, education, oral contraceptives, hypertension, diabetes
	Hemorrhagic		1.20 (0.60–2.30)	1.10 (0.40–3.10)	
Oki, 2006[31]	Ischemic	M	1.91 (0.86–4.22)	4.73 (0.61–36.9)	Age, smoking, alcohol, systolic blood pressure, cholesterol, glucose
		F	1.05 (0.53–2.09)	1.85 (0.68–5.09)	
	Hemorrhagic	M	1.36 (0.44–4.23)	6.61 (0.79–55.6)	
		F	0.50 (0.15–1.72)	1.47 (0.30–7.25)	
Hu, 2007[34]	Ischemic	M	1.17 (1.03–1.33)	1.42 (1.21–1.67)	Age, study year, smoking, physical activity, education, alcohol, family history of stroke, systolic blood pressure, total cholesterol, diabetes
		F	1.06 (0.92–1.23)	1.23 (1.05–1.44)	
	Hemorrhagic	M	1.02 (0.80–1.30)	1.01 (0.72–1.41)	
		F	0.92 (0.71–1.20)	0.77 (0.56–1.06)	
Funada, 2008[36]	Ischemic	M F	1.07 (0.69–1.64)	1.15 (0.62–2.13)	Age, gender, smoking, alcohol, physical activity, education, weight change since age 20 years
	Hemorrhagic		0.90 (0.51–1.57)	1.45 (0.77–2.72)	
Zhou, 2008[38]	Ischemic	M	0.94 (0.83–1.06)	1.67 (1.28–2.19)	Age, area, smoking, alcohol
	Hemorrhagic		1.06 (0.99–1.14)	1.67 (1.40–1.98)	
Silventoinen, 2009[40]	Ischemic	M	1.46 (1.28–1.67)	2.37 (1.83–3.05)	Age, conscription office, systolic and diastolic blood pressure, elbow flexion strength, grip strength, knee extension strength, own and parental educational, occupational socioeconomic position
	Hemorrhagic		1.80 (1.51–2.15)	2.83 (2.03–3.93)	
Zhang, 2009[41]	Ischemic	F	1.17 (0.98–1.41)	1.59 (1.36–1.88)	Age, education, occupation, family income, menopausal status, oral contraceptives, hormone therapy, aspirin, physical activity, smoking, alcohol, intake of saturated fat, vegetables, fruits, and sodium
	Hemorrhagic		1.68 (0.98–2.88)	2.11 (1.27–3.50)	

		Association Measures (95% CI): Overweight	Obesity		Test for Overall Effect	Test for Heterogeneity
Combined effect I	Ischemic	1.18 (1.08–1.28)	1.50 (1.34–1.67)	Overweight	$z=3.8$; $P<0.001$	$Q=33.7$; $P=0.006$; $I^2=52\%$
				Obesity	$z=7.2$; $P<0.001$	$Q=30.0$; $P=0.012$; $I^2=50\%$
	Hemorrhagic	1.14 (0.96–1.37)	1.34 (1.01–1.79)	Overweight	$z=1.5$; $P=0.14$	$Q=43.8$; $P<0.001$; $I^2=70\%$
				Obesity	$z=2.0$; $P=0.04$	$Q=52.3$; $P<0.001$; $I^2=75\%$

Other studies not included in the basic meta-analysis

Author	Stroke Subtype	Gender	Overweight	Obesity	Factors Controlled for in Multivariate Analysis
Rexrode, 1997[42]	Ischemic	F	0.88 (0.57–1.36)	1.17 (0.74–1.83)	Age, smoking, contraceptive use, menopausal status, hormone therapy, time period, aspirin, physical activity, antioxidant score, alcohol, hypertension, diabetes, high cholesterol
	Hemorrhagic		0.54 (0.31–0.94)	0.56 (0.29–1.06)	
Song, 2004[43]	Ischemic	M	1.10 (1.00–1.30)	1.20 (1.00–1.50)	Age, alcohol, smoking, physical activity, monthly salary level, blood pressure, glucose, cholesterol
	Hemorrhagic		1.00 (0.90–1.20)	1.10 (0.80–1.60)	
Pharm, 2007[44]	Ischemic	M F		1.00 (0.61–1.76)	Age, gender, diabetes, hypertension, smoking, alcohol, vegetable and fruit intake, history of transfusion
	Hemorrhagic			0.60 (0.23–1.66)	
Sturgeon, 2007[45]	Hemorrhagic	M F	0.87 (0.59–1.27)	0.94 (0.60–1.47)	Age
Park, 2008[46]	Ischemic	F	1.15 (1.04–1.27)	1.30 (1.15–1.46)	Age, alcohol, physical activity, fasting blood glucose, systolic blood pressure, cholesterol
	Hemorrhagic		0.98 (0.85–1.12)	1.00 (0.84–1.19)	

		Overweight	Obesity		Test for Overall Effect	Test for Heterogeneity
Combined effect II	Ischemic	1.16 (1.08–1.24)	1.44 (1.31–1.58)	Overweight	$z=4.3$; $P<0.001$	$Q=36.2$; $P=0.01$; $I^2=45\%$
				Obesity	$z=7.5$; $P<0.001$	$Q=37.7$; $P=0.004$; $I^2=52\%$
	Hemorrhagic	1.06 (0.93–1.20)	1.20 (0.96–1.51)	Overweight	$z=0.8$; $P=0.39$	$Q=56.5$; $P<0.001$; $I^2=68\%$
				Obesity	$z=1.6$; $P=0.11$	$Q=72.9$; $P<0.001$; $I^2=77\%$

For a few cohorts the BMI interval defining the overweight or the obese category differed to some extent from the values indicated in the Table.

number of related factors, such as age, hypertension, diabetes, dyslipidemia, sedentary lifestyle, and abuse of alcohol. Some of these factors are causally related to weight gain whereas others may be in the pathogenetic pathway between overweight and stroke. Most published studies included these factors as covariate. When we performed supplementary tests using these multivariate risk estimates, the results were qualitatively similar to those obtained with the use of crude unadjusted data: however, the strength of the association with risk of ischemic stroke was attenuated for both overweight and obesity, whereas the association with hemorrhagic stroke was no longer statistically significant.

Study Limitations

We regret that a few studies potentially relevant to our review could not be included in the meta-analysis because crude data were not available[42,43,45–52] or because publication occurred after the deadline of our literature review.[53] In 3 such studies featuring large study populations,[42,43,46] statistically significant direct associations were reported between excess body weight and risk of total or ischemic stroke on adjustment for most conventional cardiovascular risk factors. In another large study collecting data from 18 populations from 8 European countries, however, BMI conferred only a modest increase in risk in men but not in women.[53]

By choosing to compare the incidence of stroke in the overweight and obese categories against normal-weight individuals, we lack information about the relationship between BMI and stroke rate in the BMI category <25. Noteworthy, according to the Prospective Study Collaboration results, the relationship between BMI and stroke mortality was J-shaped, with evidence of a clear-cut direct association for BMI 25 to 50, but some evidence of an inverse trend in the BMI range 15 to 25.[4]

Finally, a further limitation of our study was the lack of separate analysis of the effects of visceral and peripheral adiposity, attributable to the small number of suitable studies and to their methodological heterogeneity. Moreover, the possibility of some degree of publication bias cannot be ruled out.

Conclusion

In summary, this meta-analysis shows a statistically significant direct and graded association between excess body weight and incidence of ischemic stroke. The association is at least partly independent from age and from other cardiovascular risk factors and lifestyle habits. Regarding the current obesity epidemic, these results reinforce the claim in favor of strong educational campaigns focusing on prevention of this condition.

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Disclosure

P.S. conceived the study aims and design, contributed to the systematic review, performed the analysis, interpreted the results, and drafted the manuscript. L.D., G.C., F.G., F.P.C., and L.S. contributed to the data extraction, interpretation of results, and the revision of the manuscript. This work was partly presented at the AHA 2008 Scientific sessions in New Orleans and at the 19th Scientific Meeting of the European Society of Hypertension in Milan.

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