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Measures of Abdominal Adiposity and the Risk of Stroke
The MOnica Risk, Genetics, Archiving and Monograph (MORGAM) Study

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Background and Purpose—Excess fat accumulates in the subcutaneous and visceral adipose tissue compartments. We tested the hypothesis that indicators of visceral adiposity, namely, waist circumference (WC), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR), are better predictors of stroke risk than body mass index (BMI).

Methods–The association of BMI, WC, WHR, and WHtR with stroke was assessed in 31 201 men and 23 516 women, free of vascular disease at baseline, from the MOnica Risk, Genetics, Archiving and Monograph (MORGAM) study. During a mean follow-up of 11 years, 1130 strokes were recorded. Relative risks (95% CI) were calculated by Cox regression after stratification for center and adjustment for age, smoking, educational level, alcohol consumption, hypertension, diabetes, total cholesterol, high-density lipoprotein cholesterol, and BMI and model fit was assessed using log-likelihoods.

Results—BMI, WC, WHR, and WHtR were associated with the risk of stroke in men. After full adjustment including BMI, the relative risks for stroke remained significant for WC (1.19 [1.02 to 1.34] per 1 SD increase in WC), WHR (1.14 [1.03 to 1.26]), and WHtR (1.50 [1.28 to 1.77]). Among women, the extent of the associations with stroke risk was similar for WHtR (1.31 [1.04 to 1.65]), WC (1.19 [0.96 to 1.47]), and WHR (1.08 [0.97 to 1.22]). Further analyses by World Health Organization obesity categories showed that WC, WHR, and WHtR were associated with the risk of stroke also in lean men and women (BMI <25 kg/m^2), independently of confounders, cardiovascular risk factors, and BMI.

Conclusions—Indicators of abdominal adiposity, especially WHtR, are more strongly associated with stroke risk than BMI. These results emphasize the importance of measuring abdominal adiposity, especially in lean subjects. **(*Stroke*. 2011;42:2872-2877.)**

Key Words: abdominal adiposity ■ body mass index ■ cardiovascular risk factors ■ obesity ■ stroke ■ waist circumference ■ waist-to-height ratio ■ waist-to-hip ratio

Body mass index (BMI) is the most common anthropometric marker for assessing body fat and diagnosing overweight and obesity. The sensitivity of the most common cutoff value for obesity (30 kg/m^2) for identifying excessive adiposity is low, missing approximately half of the people with excess body fat, who have BMI values <30 kg/m^2.[1] Despite these limitations, BMI has consistently been associated with an elevated risk of vascular mortality.[2]

Excess adiposity accumulates in the subcutaneous and visceral compartments. Studies have shown that visceral fat has stronger endocrine activity and inflammatory characteristics and is more closely associated with insulin resistance than is subcutaneous adipose tissue.[3] Waist circumference (WC), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR) are common proxy measures of visceral adipose tissue.[4] Several studies have shown that WHtR correlates better than BMI with cardiovascular risk factors (hypertension, diabetes mellitus, and dyslipidemia),[5] and coronary heart disease risk.[6,7]

Abdominal adiposity is a risk marker for coronary heart disease and stroke in men and women.[8,9] Insulin resistance, dyslipidemia, and hypertension play major roles in this process. The extent to which different anthropometric markers of general (BMI) and abdominal adiposity (WC, WHR, and WHtR) are useful for assessing the risk of stroke has been studied less often. The goal of this study was to compare the association of anthropometric markers with the risk of stroke.

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*See Supplemental Appendix.

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Methods

Study Population

The detailed methods are presented in the Supplemental Materials (http://stroke.ahajournals.org). The MOnica Risk, Genetics, Archiving and Monograph (MORGAM) Project is a multinational collaborative study exploring the relationships between the development of cardiovascular diseases and their classic and genetic risk factors and biomarkers.[10] The cohorts had either been a part of the World Health Organization Multinational MONItoring of Trends and Determinants in CArdiovascular Disease (MONICA) Project or applied MONICA survey procedures.[11] The Prospective Epidemiological Study of Myocardial Infarction (PRIME) cohort included only men. We analyzed the cohorts with data available for anthropometric indicators of abdominal adiposity (Supplemental Table I).

Baseline Measurements

Data collection about risk factors and vascular end points followed a standardized protocol or were harmonized retrospectively as described in MORGAM web publications.[12] At inclusion, each MORGAM member (1) completed a questionnaire about demographic information, socioeconomic factors (educational level), lifestyle habits (tobacco and alcohol consumption), vascular risk factors (self-reported diabetes, serum total and high-density lipoprotein cholesterol), and medication use; (2) had anthropometric (weight, height, BMI, WC, WHR, WHtR) and blood pressure measurements taken; and (3) provided a blood sample for analysis.

Follow-Up and Outcome Ascertainment

Each member of the MORGAM cohort was followed up for stroke diagnosis or censoring. The primary end point included all first fatal or nonfatal strokes, except for Newcastle and Augsburg, where death from stroke was the end point. An upper age limit of follow-up was applied in Poland and Lithuania (<65 years). The follow-up for the PRIME cohort was 10 years. Fatal cases were identified by national or regional health information systems or case ascertainment. In nearly all cohorts, nonfatal stroke cases were identified by hospital discharge registers. Most MORGAM cohorts used the World Health Organization diagnostic criteria, as applied by the MONICA Project, to validate stroke events during follow-up. The MONICA criteria for stroke (yes/no) are based on clinical presentation.[13] Details, including quality assessments, are available at the MORGAM web site.[14]

Statistical Analysis

Cohorts were considered for analyses if abdominal adiposity indicators were measured at baseline (n=71 116). We excluded subjects with a documented or self-reported myocardial infarction or stroke at baseline (n=3280) and those with missing data for anthropometric measures (n=1501), for cardiovascular risk factors (n=11,611), or with incorrect follow-up data (n=7). In all, 31 201 men and 23 516 women remained for analysis. Five hundred ninety subjects (1%) were lost to follow-up. During 601 762 person-years of follow-up, 1130 strokes were documented, including 280 fatal strokes (that is, death in the first 28 days after stroke). Entry time was defined as age at enrollment, and exit time was defined as age at stroke diagnosis, death, or censoring.

Analyses were performed separately for each gender. Baseline characteristics were compared with generalized linear models and were stratified by center. Pearson correlation coefficient was calculated to assess the relationship between anthropometric variables. The likelihood ratio test statistics thus obtained were compared with χ^2 distribution with 3 degrees of freedom.

Cox proportional hazard models were used to calculate the relative risks (RRs [95% CI]) of stroke for a 1-SD increase of anthropometric indicator as well as their 95% CIs and to adjust for various confounding risk factors. The first model was stratified for center and adjusted for age (Model I). We further adjusted for confounding factors (upstream: such as tobacco consumption, educational level, alcohol consumption), including possible intermediary factors (hypertension, diabetes, total cholesterol, and high-density lipoprotein cholesterol; Model II). The fits of the models were compared with nested models with and without BMI using the likelihood ratio test. In these models, the RRs for the abdominal adiposity indicators reflect associations with cerebrovascular disease beyond those conveyed by BMI. Statistical analysis were performed with SAS statistical software (Version 9.1; SAS Institute Inc), and statistical significance was defined as $P<0.05$.

Table 1. Baseline Characteristics by Gender

	Men	Women
No. of subjects	31 201	23 516
Age, y	52.2 [41.8–57.6]	47.8 [37.7–58.0]
Tobacco, %		
Current smoker	9834 (31.5)	5478 (23.3)
Past smoker	10 439 (33.5)	3639 (15.5)
Never smoker	10 928 (35.0)	14 399 (61.2)
Educational level, %		
University	3663 (11.7)	2058 (8.7)
Intermediary	4149 (13.3)	3272 (13.9)
Secondary school	12 244 (39.2)	7037 (29.9)
Primary	11 145 (35.7)	11 149 (47.4)
Alcohol intake, g/d	16 [3–36]	2 [0–9]
High blood pressure, %	13 785 (44.2)	8461 (36.0)
Diabetes, %	1052 (3.4)	623 (2.6)
Total cholesterol, g/L	2.2 [1.95–2.50]	2.17 [1.90–2.50]
High-density lipoprotein cholesterol, g/L	0.48 [0.40–0.56]	0.58 [0.49–0.68]
Body mass index, kg/m^2	26.3 [24.2–28.7]	25.3 [22.6–28.9]
Waist circumference, cm	93.0 [86.5–100.0]	80.0 [72.5–89.0]
Hip circumference, cm	100.0 [95.0–104.5]	100.0 [94.5–107.0]
Waist-to-hip ratio	0.94 [0.89–0.98]	0.80 [0.76–0.84]
Waist-to-height ratio	0.54 [0.50–0.58]	0.50 [0.45–0.56]
Stroke incidence, (no./1000 patient-years	2.2	1.5

Values are median [interquartile] and no. of subjects (%).

Results

This study followed 31 201 men and 23 516 women who were free of vascular disease at baseline for an average of 11 years. During this period, 720 strokes occurred in men and 410 in women; in all, 280 were fatal.

Table 1 presents the population's baseline characteristics separately for men and women. Median age was 52.2 years for men and 47.8 years for women. Distribution of smoking categories was relatively even for men, whereas nonsmokers predominated among women. The median alcohol intake and the proportion of high educational levels were both higher for men than women.

BMI was strongly and positively correlated with WC and WHtR in men and women; the correlation with WHR was slightly lower for both. WHR was weakly correlated with hip circumference and WHtR inversely correlated with height (Table 2).

Supplemental Figure I and Table II present the associations between anthropometric indicators and selected characteristics of the study population in men and women. Age, total

Table 2. Pearson Correlation Coefficient for Anthropometric Indicators

	Men (n=31 201)					Women (n=23 516)				
	WC	WHR	WHtR	HC	Ht	WC	WHR	WHtR	HC	Ht
BMI	0.86	0.54	0.86	0.75	−0.11	0.88	0.48	0.89	0.88	−0.24
WC	. . .	0.73	0.94	0.78	0.05	. . .	0.74	0.96	0.84	−0.10
WHR	. . .	. . .	0.76	0.14	−0.17	. . .	. . .	0.74	0.27	−0.19
WHtR	. . .	. . .	. . .	0.66	−0.30	. . .	. . .	. . .	0.79	−0.37

All correlations $P<0.0001$.

WC indicates waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; HC, hip circumference; Ht, height; BMI, body mass index.

cholesterol, hypertension, and diabetes mellitus were positively associated with all the anthropometric markers. In contrast, high educational level, being a current smoker. and having low high-density lipoprotein cholesterol were inversely related to adiposity markers. These associations were similar in men and women, with the exception of alcohol consumption, which varied in opposite directions among men (positively) and women (negatively). In general, similar associations were found with WC, WHR, and WHtR, except that WHR was more weakly associated with smoking than the other markers in women.

The Figure (and Supplemental Tables IIIa and IIIb) present the RRs and 95% CIs for stroke by fifths of each anthropometric indicator. In men, BMI, WC, WHR, and WHtR were all positively and significantly associated (Model I) with stroke risk in a dose–response fashion (all probability values for trend <0.0001). After further adjustment for confounders, hypertension, diabetes, and dyslipidemia (Model II), the associations remained significant only for WC, WHR, and WHtR. BMI was not associated with risk of stroke in women in any of the 2 models. In contrast, WC, WHR, and WHtR were positively and significantly associated with women's

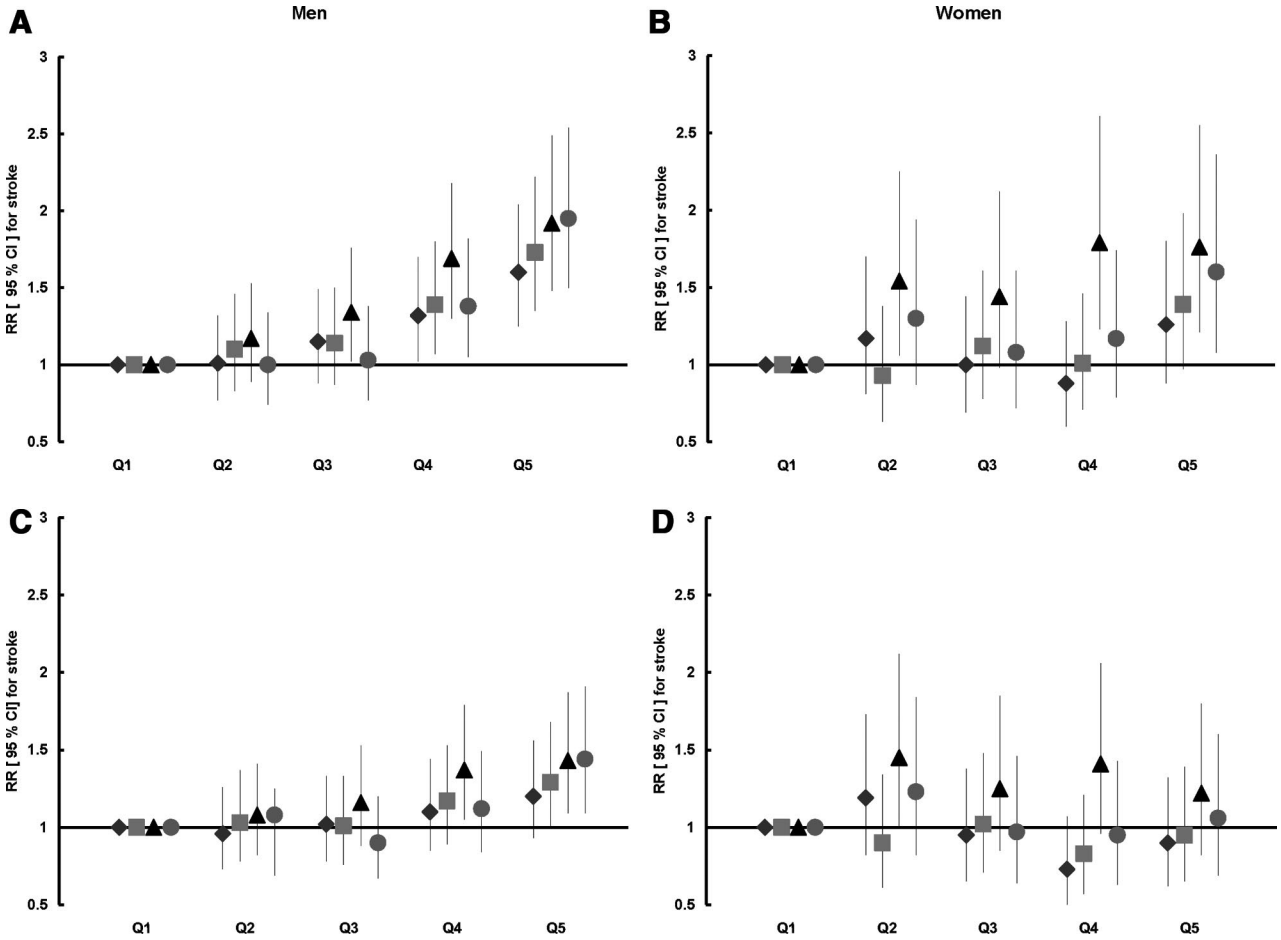

Figure. Relative risks (RRs; 95% CI) for stroke by fifths of body mass index (diamonds), waist circumference (squares), waist-to-hip ratio (triangles), and waist-to-height ratio (circles). **A–B**, RRs stratified for center and adjusted for age (Model I) in men and women, respectively. **C–D**, Model I+adjustment for tobacco consumption, educational level, alcohol consumption, hypertension, diabetes, total cholesterol, high-density lipoprotein cholesterol adjusted (Model II) in men and women, respectively. Cutoffs for fifths are presented in Supplemental Tables IIIa and IIIb.

Table 3. Relative Risk (95% CI) of Stroke for a 1-SD Increase in Anthropometric Indicator

	Model I RR (95% CI)	−2 Log-Likelihood	Difference*	*P*	Model II RR (95% CI)	−2 Log-Likelihood	Difference*	*P*
Men								
BMI	1.18 (1.10–1.27)	11 086			1.07 (0.99–1.15)	10 970		
WC	1.23 (1.14–1.32)	11 077			1.11 (1.08–1.10)	10 966		
WHR	1.27 (1.17–1.38)	11 073			1.14 (1.05–1.24)	10 963		
WHtR	1.30 (1.21–1.40)	11 060			1.17 (1.08–1.27)	10 958		
Combined model with BMI								
WC	1.26 (1.09–1.47)	11 076	9	0.002	1.19 (1.02–1.34)	10 965	5	0.03
BMI	0.97 (0.84–1.12)		0	0.7	0.93 (0.80–1.07)		1	0.3
WHR	1.22 (1.10–1.34)	11 071	15	0.0001	1.14 (1.03–1.26)	10 963	6	0.01
BMI	1.07 (0.98–1.17)		2	0.13	1.0 (0.92–1.10)		0	0.9
WHtR	1.64 (1.40–1.93)	11 050	35	<0.0001	1.50 (1.28–1.77)	10 946	23	<0.0001
BMI	0.78 (0.67–0.91)		10	0.0015	0.77 (0.66–0.89)		11	0.0007
Women								
BMI	1.09 (0.98–1.20)	6417			0.96 (0.86–1.07)	6319		
WC	1.16 (1.05–1.28)	6411			1.01 (0.90–1.13)	6319		
WHR	1.19 (1.08–1.31)	6407			1.05 (0.95–1.17)	6318		
WHtR	1.18 (1.07–1.31)	6410			1.03 (0.92–1.15)	6319		
Combined model with BMI								
WC	1.37 (1.11–1.67)	6408	9	0.003	1.19 (0.96–1.47)	6316	3	0.08
BMI	0.83 (0.68–1.02)		3	0.08	0.83 (0.67–1.02)		3	0.1
WHR	1.19 (1.07–1.32)	6407	10	0.002	1.08 (0.97–1.22)	6317	2	0.17
BMI	1.00 (0.89–1.12)		0	0.96	0.93 (0.82–1.05)		2	0.22
WHtR	1.51 (1.21–1.88)	6404	13	0.0003	1.31 (1.04–1.65)	6313	6	0.02
BMI	0.77 (0.62–0.95)		6	0.02	0.77 (0.62–0.95)		6	0.02

Model I: stratified for center, adjusted for age; Model II: Model I+adjustment for tobacco consumption, educational level, alcohol consumption, hypertension, diabetes, total cholesterol, and high-density lipoprotein cholesterol. The SD for BMI, WC, WHR, and WHtR equals 3.7 kg/m^2, 10.4 cm, 0.07, and 0.06 in men, respectively, and 5.0 kg/m^2, 11.9 cm, 0.06, and 0.08 in women, respectively.

BMI indicates body mass index; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; RR, relative risk; CI, confidence interval; SD, standard deviation.

*Difference for the likelihood of the models and *P* value for the likelihood ratio test with 1 degree of freedom.

risk of stroke in a dose–response fashion (all *P* trend <0.005) in Model I. These associations were no longer significant after the adjustments (Model II).

Table 3 presents the RRs of stroke for each 1-SD increase in the measures of adiposity and the −2 log-likelihood for the 2 models by gender. The SD for BMI was 3.7 kg/m^2 for men and 5.0 kg/m^2 for women; 10.4 cm and 11.9 cm, respectively, for WC; 0.07 and 0.06 for WHR; and 0.06 and 0.08 for WHtR. In men, the RRs (Model I) were higher for WHtR followed by WHR, WC, and BMI. Similar trends were observed in the fully adjusted model. Further adjustment on height did not affect the results. In women, the RRs were less pronounced than for men and larger for WHR followed by WHtR, WC, and BMI. The associations were no longer significant after adjustment on confounders and cardiovascular risk factors. The results were not modified after exclusion of stroke that occurred before 1 year of follow-up or after adding height to the models.

In unadjusted models, adding BMI to models with WC and WHR did not significantly improve model fit (for men: $P=0.7$ and $P=0.13$, respectively; for women: $P=0.08$ and $P=0.96$). In contrast, adding WC and WHR to BMI significantly improved the model fit (for men: $P=0.002$ and $P=0.0001$, respectively; for women: $P=0.003$ and$=0.002$). Similar results were obtained after adjustments for confounders and cardiovascular risk factors (Model II). The RRs were smaller than in unadjusted models but still statistically significant in men for WC and WHR but not for BMI. In unadjusted model, adding BMI to the model with WHtR improved model fit (for men: $P=0.0015$; for women: $P=0.02$). Similarly, adding WHtR to the model with BMI strongly improved model fit (for men: $P<0.0001$; for women: $P=0.0003$). In both men and women, WHtR was strongly associated with stroke risk, whereas BMI was inversely associated with stroke risk in models with WHtR (further adjustment on height did change the results). Analyses, adjusting for confounders and cardiovascular risk factors (Model II) and/or height, yield similar results.

Table 4 shows the RRs of stroke for a 1-SD increase of WC, WHR, and WHtR according to body weight categories. In normal-weight men and women, the RR of stroke increased with WC, WHR, and WHtR. The association remained significant for WHtR among lean men and for WHtR and WHR among lean women after full adjustment. The

Table 4. Relative Risk of Stroke for a 1-SD Increase in Waist Circumference, Waist-to-Hip Ratio, and Waist-to-Height Ratio, by Categories of Body Mass Index, in Men and Women

Body Mass Index, kg/m^2	Men		Women	
	Model I RR (95% CI)	Model II RR (95% CI)	Model I RR (95% CI)	Model II RR (95% CI)
<25				
WC	1.42 (1.07–1.88)	1.26 (0.95–1.68)	1.45 (0.97–2.16)	1.38 (0.92–2.09)
WHR	1.39 (1.12–1.71)	1.26 (1.01–1.57)	1.29 (1.09–1.54)	1.26 (1.04–1.53)
WHtR	1.63 (1.23–2.15)	1.37 (1.01–1.85)	1.75 (1.14–2.69)	1.62 (1.04–2.54)
25–30				
WC	1.16 (0.93–1.45)	1.08 (0.86–1.45)	1.45 (1.02–2.07)	1.22 (0.84–1.76)
WHR	1.17 (0.86–1.35)	1.08 (0.93–1.26)	1.18 (0.97–1.43)	1.03 (0.84–1.26)
WHtR	1.73 (1.36–2.21)	1.54 (1.20–1.96)	1.59 (1.08–2.36)	1.32 (0.88–1.97)
>30				
WC	1.27 (0.96–1.69)	1.26 (0.94–1.69)	1.28 (0.93–1.76)	1.11 (0.80–1.54)
WHR	1.22 (1.00–1.47)	1.19 (0.98–1.45)	1.13 (0.95–1.35)	1.02 (0.84–1.24)
WHtR	1.42 (1.04–1.95)	1.44 (1.04–1.99)	1.35 (0.96–1.90)	1.19 (0.83–1.70)

Model I: stratified for center, adjusted for age and body mass index; Model II: Model I+adjustment for tobacco consumption, educational level, alcohol consumption, hypertension, diabetes, total cholesterol, and high-density lipoprotein cholesterol.

RR indicates relative risk; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; SD, standard deviation; CI, confidence interval.

results were not modified after exclusion of stroke occurred before 1 year of follow-up.

Discussion

WC and WHtR are clinical proxy measures of abdominal adipose tissue. WHtR is less common and its association with stroke risk less often investigated. The results of this cohort study of 31 201 men and 23 516 women show that abdominal fat indicators, and especially WHtR, are strongly associated with stroke risk in men and women. This association persisted after adjustment for cardiovascular risk factors and BMI. These data suggest that measurement of abdominal adiposity improves the assessment of stroke risk beyond that of BMI only.

The positive associations between measures of abdominal adiposity and stroke risk are consistent with those of earlier reports in men and women.[9,15–18] Although WC, WHR, and WHtR were strongly associated with confounders and intermediate risk factors, the association between abdominal fat indicators and the risk of stroke remained statistically significant after adjustment the later confounders and cardiovascular risk factors in men. Furthermore, adjustment on height yielded similar results. These results are supported by clinical and biological studies, which have shown that visceral fat has stronger endocrine activity and inflammatory characteristics than subcutaneous adipose tissue.

In women, the associations between abdominal fat measures and stroke risk were less pronounced than in men. Similarly, Zhang et al found that the estimators of general (BMI) and abdominal (WC, WHR, and WHtR) adiposity did not differ in their predictive value for stroke in Chinese women.[15] Together with the current study, this suggests that the association between abdominal adiposity indicators and stroke risk may differ according to gender. In support of this hypothesis, some studies have shown that anthropometric measures of abdominal adiposity are less accurate markers of body and visceral fat in women than men because of their different distributions of muscle and fat mass.[19,20]

An important limitation of BMI is that it does not distinguish between subjects with excess adipose tissue and those with high muscle mass, so it may incorrectly estimate the risk associated with adiposity for subjects with heavy muscle mass. Interestingly, adding WC, WHR, and especially WHtR improved the global fit for Cox regression models with BMI, suggesting that measuring abdominal adiposity improves stroke risk assessment. In contrast, adding BMI to models with abdominal fat indicators improves the fit of the model with WHtR, but not WC and WHR models. For a given WHtR, BMI was inversely correlated to stroke risk, an observation that may reflect the beneficial contribution of fat-free mass to vascular risk once adiposity is accounted for by WHtR. In a recent review, Okorodudu et al concluded that the BMI cutoff value for obesity (30 kg/m^2) is relatively insensitive for identifying excessive adiposity, missing approximately half of the people with excess body fat, who have BMI values <30 kg/m^2.[1] Interestingly, WHtR was associated with an increased risk of stroke in lean men and women, suggesting that WHtR improves the assessment of vascular risk in subjects whose risk may be underestimated by current BMI standard cutoffs.

The main strength of this study is the large number of subjects and the >1000 events. Baseline data collection was undertaken using the standardized MONICA criteria or by procedures similar to those used by MONICA or retrospectively harmonized. Anthropometric indicators were measured according to standard protocols by trained examiners and with standardized instruments, thereby limiting measurement errors. The study has, on the other hand, several limitations. First, a general limitation to observational cohorts is that residual confounding due to unmeasured factors or to measurement errors affecting cardiovascular risk factors cannot

be completely ruled out. However, additional sensitivity analyses performed after exclusion of current and past smokers or after adjustment for mean systolic blood pressure and use of blood pressure-lowering drugs did not change the RRs for stroke. Thus, these issues are unlikely to have strongly influenced the results. Second, stroke is a heterogeneous clinical syndrome with different pathophysiological mechanisms and etiologic background. The main risk factors differ according to the etiology of stroke event. Because the precise etiologic diagnosis was not available, we could not analyze the data according to stroke subtypes. This limitation, by diluting the precision of the end point, tends to flatten the associations and thus underestimates the risk of stroke associated with the anthropometric indicators. Third, anthropometric markers were measured once, at study entry, so assessment of changes in body fat was not possible. Finally, the number of events in women might still be insufficient to detect small associations.

In conclusion, our study reveals that in men, measures of abdominal adiposity, especially WHtR, are associated more strongly with stroke risk than is BMI. Furthermore, a substantial additional risk of stroke may be mediated by abdominal adiposity, especially in subjects thought to be lean on BMI criteria. These findings emphasize the importance of measuring WC in addition to body weight and height, especially in lean subjects. New studies are needed to confirm this result in women.

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Disclosures

None.

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Supplemental Material to :

Measures of abdominal adiposity and risk of stroke : the MORGAM study

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Supplemental Appendix

Sites and Key Personnel of Contributing Centres

MORGAM Centers

Australia—Faculty of Health, University of Newcastle, New South Wales: P. McElduff (principal investigator), University of Queensland, Brisbane: A. Dobson (former principal investigator); Denmark—Research Centre for Prevention and Health, Capital Region, Denmark: T. Jørgensen (principal investigator), C. Agger, and A. Borglykke; Finland—FINRISK, National Institute for Health and Welfare, Helsinki: V. Salomaa (principal investigator), A. Juolevi, E. Vartiainen, and P. Jousilahti; MORGAM Data Centre, National Public Health Institute, Helsinki: K. Kuulasmaa (head), Z. Cepaitis, A. Haukijärvi, B. Joseph, J. Karvanen, S. Kulathinal, M. Niemelä, and O. Saarela; France—National Coordinating Centre, National Institute of Health and Medical Research (U258), Paris: P. Ducimetière (national coordinator) and A. Bingham; PRIME/Strasbourg, Department of Epidemiology and Public Health, Louis Pasteur University, Faculty of Medicine, Strasbourg: D. Arveiler (principal investigator), B. Haas, and A. Wagner; PRIME/Toulouse, Department of Epidemiology, Faculty of Medicine, Toulouse–Purpan, Toulouse: J. Ferrières (principal investigator), J.-B. Ruidavets and V. Bongard; PRIME/Lille, Department of Epidemiology and Public Health, Pasteur Institute of Lille: P. Amouyel (principal investigator), M. Montaye, and J. Dallongeville; Germany—Helmholtz Zentrum München - German Research Center for Environmental Health, Institute of Epidemiology, Neuherberg: A. Peters (principal investigator), A. Döring (former principal investigator), A. Hörmann, C. Meisinger, J. Baumert, B. Thorand, A. Schneider, H.-E. Wichmann; Italy—National Coordinating Centre MORGAM, Dipartimento di Medicina Sperimentale, Universita` degli Studi dell'Insubria, Varese: M. Ferrario (national coordinator), G Veronesi; Brianza: Dipartimento di Medicina Sperimentale, Universita` degli Studi dell'Insubria, Varese: M. Ferrario (principal investigator); Dipartimento di Medicina, Prevenzione e Biotecnologie Sanitarie, Universita` degli Studi Milano-Bicocca, Monza: G. Cesana (principal investigator) and C. Fornari; Rome: Unit of Epidemiology of Cerebro and Cardiovascular Diseases, National Centre for Epidemiology, Surveillance and Health Promotion, Istituto Superiore di Sanita`: S. Giampaoli, L. Palmieri, and C. Donfrancesco; Lithuania—Kaunas University of Medicine, Institute of Cardiology, Kaunas: A. Tamosiunas (principal investigator), S. Domarkiene (former principal investigator), D. Rastenyte, G. Bernotiene, and R. Reklaitiene; Poland—Warsaw, Department of Cardiovascular Epidemiology and Prevention, National Institute of Cardiology, Warsaw: G. Broda (principal investigator), P. Kurjata, S.L. Rywik, M. Polakowska, and A. Pytlak; United Kingdom—PRIME/Belfast, Queen's University Belfast, Belfast, Northern Ireland: F. Kee (principal investigator), A. Evans (former principal investigator), J. Yarnell, and E. Gardner; MORGAM Coordinating Centre, Queen's University Belfast, Belfast, Northern Ireland: A. Evans (MORGAM coordinator) and S. Cashman.

MORGAM Management Group

A. Evans (chair), S. Blankenberg (Mainz, Germany), F. Cambien (Paris, France), M. Ferrario (Varese, Italy), K. Kuulasmaa, A. Palotie (Hinxton, England), M. Perola (Helsinki, Finland), A. Peters, V. Salomaa, H. Tunstall-Pedoe (Dundee, Scotland) and P.-G. Wiklund (publications coordinator, Umeå Sweden). Previous members: K. Asplund (Stockholm, Sweden), L. Peltonen (Helsinki, Finland), D. Shields (Dublin, Ireland) and B. Stegmayr (Umeå, Sweden).

Detailed methods

Study population
The MORGAM Project is a multinational collaborative study exploring the relationships between the development of cardiovascular diseases and their classic and genetic risk factors and biomarkers (1;2). The cohorts had either been a part of the WHO MONICA Project or applied MONICA survey procedures (3). The Prospective Epidemiological Study of Myocardial Infarction (PRIME) cohort included only men. Here we analyzed the cohorts with data available for anthropometric indicators of abdominal adiposity (**supplemental Table 1**).

Baseline measurements
Data collection about risk factors and vascular end points followed a standardized protocol or were harmonized retrospectively as described in MORGAM web publications (4;5). At inclusion, each MORGAM member (1) completed a questionnaire about demographic information, socioeconomic factors, lifestyle habits, vascular risk factors, and medication use; (2) had anthropometric and blood pressure measurements taken and (3) provided a blood sample for analysis.
Educational level was classified according to the highest level completed: primary, secondary school, intermediate between secondary and university (e.g., technical training), or college or university. Tobacco consumption was categorized according to the individual's smoking history as a never-smoker, ex-smoker, or current smoker. Alcohol consumption was expressed in three categories: abstinent, moderate consumption (≤ 30 grams per day for women and ≤ 40 grams per day for men), excessive consumption (> 30 grams per day for women and > 40 grams per day for men).
Weight was measured in light clothing to the nearest 0.2 kg on a digital or balance scale. Height was measured to the nearest centimeter (cm). BMI was calculated as weight (kg) divided by height, in meters, squared (m^2). WC was measured at a level midway between the lower rib margin and the iliac crest in cm to the nearest 0.0 or 0.5 cm. Hip circumference was measured as the maximum circumference over the buttocks in cm to the nearest 0.0 or 0.5 cm. WHR and WHtR ratios were calculated as waist circumference (cm) divided by hip circumference (cm) and height (cm), respectively. Blood pressure was measured twice in the right arm in a sitting position, with a standard or random zero sphygmomanometer after a 5-minute rest, except in the three French cohorts, which measured blood pressure only once, with an automated device. Hypertension was defined by mean systolic/diastolic blood pressure ≥ 140/90 mm Hg or use of medications to lower blood pressure. Diabetes mellitus was defined as self-reported diabetes or current dietary or blood glucose-lowering drugs. Total serum cholesterol and high-density lipoprotein (HDL) cholesterol were measured in serum samples by local laboratories, in grams per liter.

Follow-up and outcome ascertainment
Each member of the MORGAM cohort was followed up for stroke diagnosis or censoring. The primary end point included all first fatal or nonfatal strokes, except for Newcastle and Augsburg, where death from stroke was the end-point. An upper age limit of follow-up was applied in Poland and Lithuania (< 65 years). The follow-up for the PRIME cohort was 10 years. Fatal cases were identified by national or regional health information systems or case ascertainment. In nearly all cohorts, nonfatal stroke cases were identified by hospital discharge registers. Most MORGAM cohorts used the WHO diagnostic criteria, as applied by the MONICA Project, to validate stroke events during follow-up. The MONICA criteria for stroke (yes/no) are based on clinical presentation (6). Details, including quality assessments, are available at the MORGAM web site (7).

Statistical analysis
Cohorts were considered for analyses if abdominal adiposity indicators were measured at baseline (n= 71,116). We excluded subjects with a documented or self-reported MI or stroke at baseline (not including revascularizations without MI or angina pectoris, except for Warsaw and Brianza, where this cannot be separated from MI) (n= 3280), and those with missing data for anthropometric measures (n=1501), for cardiovascular risk factors (n=11,611) or with incorrect follow-up data (n=7). In all, 31,201 men and 23,516 women remained for analysis. 590 subjects (1%) were lost to follow-up. During 601,762 person-years of follow-up, 1130 strokes were documented, including 280 fatal strokes (that is, death in the first 28 days after stroke). Entry time was defined as age at enrollment, and exit time was defined as age at stroke diagnosis, death, or censoring.
Analyses were performed separately for each gender owing to a statistically significant gender * BMI interaction for the occurrence of stroke events. For the sake of presentation, subjects were

categorized by gender-specific fifths of anthropometric measures. Baseline characteristics were compared with generalized linear models and were stratified by center (with each center usually including several cohorts and the 3 French PRIME cohorts forming one center). Pearson's correlation coefficient was calculated to assess the relationship between anthropometric variables. To test for linear trends across the fifths of anthropometric measurements, the fifths (four dummy variables) of BMI, WC, WHR, and WHtR were replaced in the model by a linear term (median of the fifths). The likelihood ratio test statistics thus obtained were compared to chi² distribution with three degrees of freedom.

Cox proportional hazard models were used to calculate the relative risks (RRs) of stroke for a 1-standard deviation increase in BMI, WC, WHR, and WHtR, as well as their 95% confidence intervals (95% CIs) and to adjust for various confounding risk factors. The first model was stratified for center and adjusted for age (Model I). We further adjusted for confounding factors (upstream: such as tobacco consumption, educational level, alcohol consumption), including possible intermediary factors (hypertension, diabetes, total cholesterol, and HDL cholesterol) (Model II). The assumption of hazard proportionality was tested graphically and by regressing the scaled Scheonfeld residuals on time. . The fits of the models were compared with nested models with and without BMI using the likelihood ratio test (LRT). In these models, the RRs for the abdominal adiposity indicators reflect associations with CVD beyond those conveyed by BMI. Finally, we calculated the RR of stroke for a 1-standard deviation increase of WC, WHR, and WHtR by BMI categories (<25/25-30/>30 kg/m²).

Sensitivity analyses were also performed after exclusion of past and current smokers and after adjustment for hypertension indicators (mean systolic blood pressure +/- blood pressure lowering drugs). Statistical analysis were performed with SAS statistical software (version 9.1; SAS Institute Inc), and statistical significance was defined as $p < 0.05$.

Reference List

(1) The MORGAM Project. *MORGAM Home Page*. 2010.
Ref Type: Internet Communication

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Ref Type: Internet Communication

(5) Niemelä M KSaKKeftMP. Description and quality assessment of MORGAM data. 2007.
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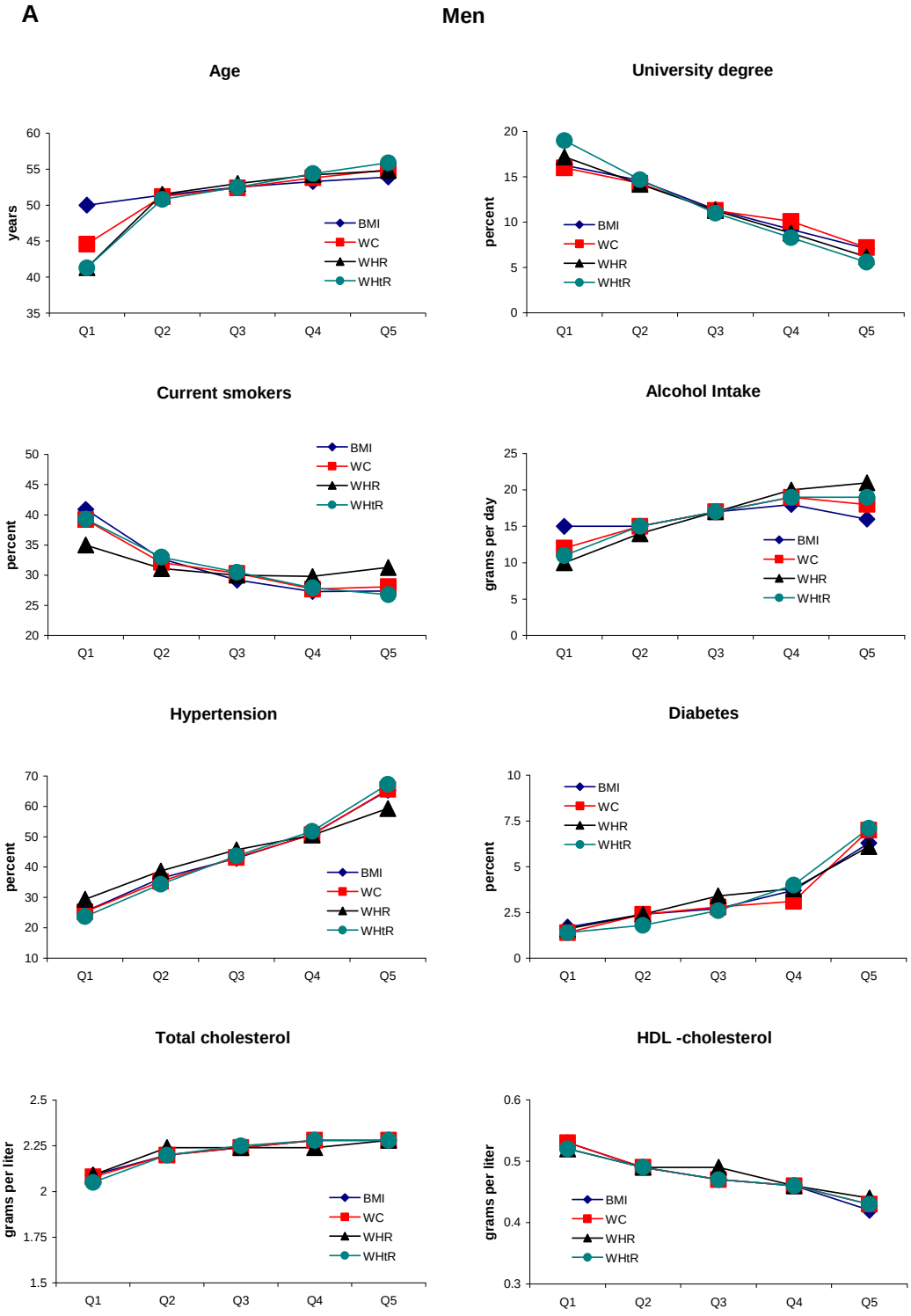
(7) Niemelä M, Kulathinal S, Kulathinal S, Kuulasmaa K. Description and Quality Assessment of MORGAM Data. eds for the MORGAM Project. 9-7-2010.
Ref Type: Electronic Citation

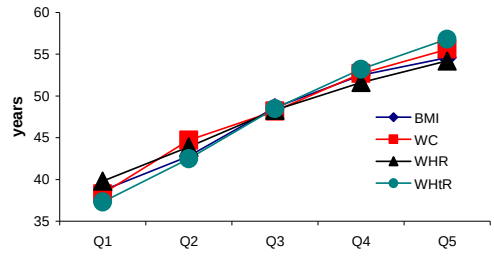
Supplemental Figure 1. Association between characteristics of the study population and fifths of body mass index (diamonds), waist circumference (squares), waist-to-hip ratio (triangles) and waist-to-height ratio (circles) in men (panel A) and women (panel B).



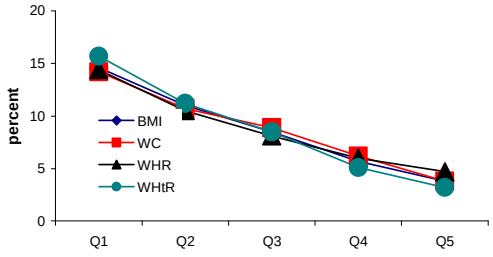
B

Women

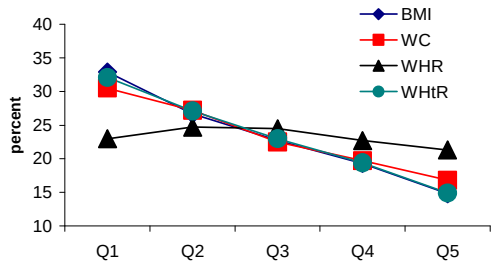
Age



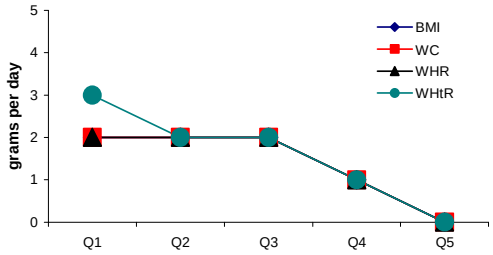
University degree



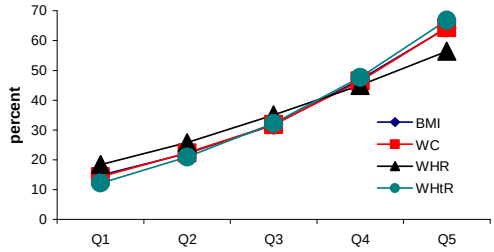
Current smokers



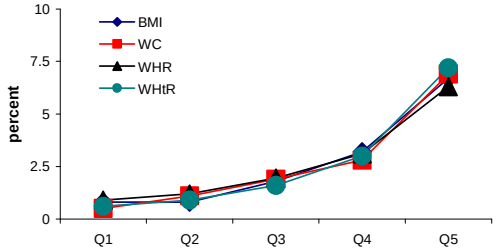
Alcohol Intake



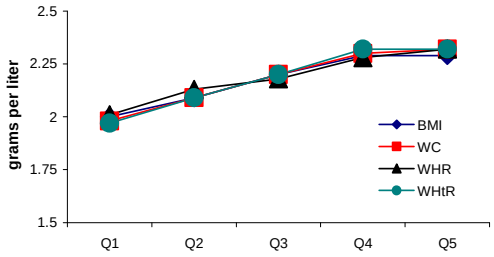
Hypertension



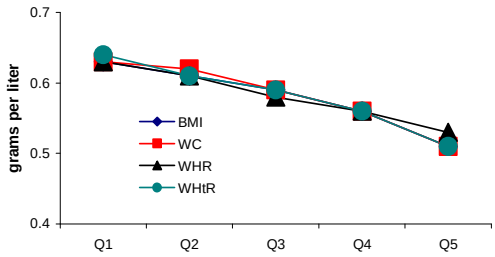
Diabetes



Total cholesterol



HDL -cholesterol



Supplement Table 1. Characteristics of cohorts included in the analyses

Center	Cohorts	*Men*									*Women*								
		Follow-up (years)	No. of subjects	No. of stroke	Incidence /1000 PY	Age (years)	BMI (kg/m²)	WC (cm)	WHR	WHtR	Follow-up (years)	No. of subjects	No. of stroke	Incidence /1000 PY	Age (years)	BMI (kg/m²)	WC (cm)	WHR	WHtR
Finland	Finrisk	15.8	8346	378	3.17	45.1	26.3	92.5	0.91	0.53	15.8	9330	265	1.91	44.8	25.2	78.0	0.78	0.48
Lithuania	Kaunas	6.1	539	5	1.57	48.9	26.4	90.0	0.90	0.52	6.1	567	3	0.86	49.7	27.5	83.0	0.80	0.51
Poland	Warsaw	5.7	445	1	0.41	47.2	26.8	93.0	0.95	0.54	5.7	312	0	NA	48.0	26.2	80.0	0.80	0.50
Denmark	Glostrup	9.8	2632	92	3.50	50.3	25.4	92.0	0.95	0.52	10.2	2659	68	2.51	50.2	23.9	78.0	0.81	0.47
United Kindom	Belfast-PRIME	10.0	2513	51	2.13	54.6	25.9	90.5	0.94	0.52									
Germany	Augsburg	8.1	4321	31	0.74	50.2	26.9	95.0	0.92	0.54	8.2	4335	23	0.53	49.9	25.5	81.0	0.80	0.50
France	Lille-PRIME	10.0	2321	38	1.70	55.2	26.3	96.0	0.95	0.56									
France	Strasbourg·PRIME	10.0	2320	24	1.08	54.5	26.9	96.5	0.99	0.56									
France	Toulouse-PRIME	10.0	2370	22	0.97	55.1	26.1	93.0	0.96	0.54									
Italy	Brianza	11.2	2269	45	1.87	48.3	25.6	90.0	0.90	0.53	11.3	2372	18	0.70	46.9	24.2	77.5	0.80	0.49
Italy	Rome MATISS	8.5	1634	30	2.26	47.5	26.8	93.5	0.98	0.56	8.2	2365	30	1.60	50.6	27.9	86.0	0.84	0.56
Australia	Newcastle	6.0	1491	3	0.29	53.9	27.0	97.0	0.93	0.56	5.9	1576	3	0.27	52.9	25.8	82.0	0.79	0.51

Values are number of subjects or median values

No. number, BMI: body mass index, WC: waist circumference, WHR: waist-to-hip ratio, WHtR: waist-to-height ratio, NA: not applicable, PY: person-year

* See reference 25 for a description of each cohort

Supplement Table 2a. Baseline characteristics of the subjects according to quintiles of Body Mass Index

	Men					
BMI	Q1	Q2	Q3	Q4	Q5	p *
quintile cut-offs (Kg/m²)	<23.7	23.7-25.5	25.6-27.2	27.3-29.4	>29.4	
No. of subjects	6264	6231	6231	6239	6236	
Age (years)	50.0 [35.6-55.6]	51.4 [40.1-56.8]	52.5 [42.7-57.6]	53.3 [46.0-58.4]	53.9 [47.1-59.0]	*<0.0001*
Tobacco (%)						*<0.0001*
Current smokers	2564 (40.9)	2035 (32.7)	1819 (29.2)	1705 (27.3)	1711 (27.4)	
Past smokers	1454 (23.2)	1919 (30.8)	2153 (34.5)	2405 (38.5)	2508 (40.2)	
Never smokers	2246 (35.9)	2277 (36.5)	2259 (36.2)	2129 (34.1)	2017 (32.3)	
Educational level (%)						*<0.0001*
University	1022 (16.3)	911 (14.6)	710 (11.4)	576 (9.2)	444 (7.1)	
Intermediary	963 (15.4)	904 (14.5)	860 (13.8)	765 (12.3)	657 (10.5)	
High school	2539 (40.5)	2538 (40.7)	2509 (40.3)	2424 (38.8)	2234 (35.8)	
Primary	1740 (27.8)	1878 (30.1)	2152 (34.5)	2474 (39.6)	2901 (46.5)	
Alcohol intake (g/d)	15 [2-30]	15 [3-32]	17 [3-38]	18 [3-39]	16 [2-40]	*<0.0001*
High blood pressure (%)	1592 (25.4)	2268 (36.4)	2672 (42.9)	3179 (50.9)	4074 (65.3)	*<0.0001*
Diabetes (%)	108 (1.7)	150 (2.4)	167 (2.7)	231 (3.7)	396 (6.3)	*<0.0001*
Total cholesterol (g/l)	2.09 [1.82-2.36]	2.20 [1.93-2.47]	2.24 [1.97-2.51]	2.28 [2.01-2.55]	2.25 [2.01-2.56]	*<0.0001*
HDL-cholesterol (g/l)	0.53 [0.45-0.62]	0.49 [0.42-0.58]	0.47 [0.40-0.56]	0.46 (0.39-0.53]	0.42 [0.36-0.51]	*<0.0001*
BMI (kg/m²)	22.4 [21.3-23.1]	24.6 [24.2-25.1]	26.3 [25.9-26.7]	28.1 [27.6-28.7]	31.3 [30.2-33.1]	
WC (cm)	82.0 [78.0-86.0]	89.0 [85.0-92.0]	93.0 [90.0-97.0]	97.5 [94.0-101.0]	106.0 [101.5-11.5]	*<0.0001*
WHR	0.88 [0.84-0.92]	0.91 [0.88-0.95]	0.94 [0.90-0.97]	0.96 [0.92-0.99]	0.99 [0.95-1.02]	*<0.0001*
WHtR	0.47 [0.45-0.49]	0.51 [0.49-0.53]	0.54 [0.52-0.56]	0.56 [0.54-0.59]	0.62 [0.59-0.65]	*<0.0001*

values are medians for continuous variables and percentage of subjects for categorical variables

* p value by generalised linear model or logistic regression, stratified on centre

HDL High Density Lipoprotein, BMI Body Mass Index, WC Waist Circumference, WHR Waist to Hip Ratio, WHtR Waist to Height Ratio

Supplement Table 2a. Baseline characteristics of the subjects according to quintiles of Body Mass Index

	Women					
BMI	Q1	Q2	Q3	Q4	Q5	p *
quintile cut-offs (Kg/m²)	<22.0	22-24.2	24.3-26.6	26.7-30	>30	
No. of subjects	4713	4688	4728	4684	4703	
Age (years)	38.7 [30.5-47.7]	42.8 [34.9-52.5]	48.6 [39.4-57.8]	52.48 [43.4-60.7]	54.6 [45.9-61.8]	*<0.0001*
Tobacco (%)						*<0.0001*
Current smokers	1550 (32.9)	1254 (26.7)	1073 (22.7)	905 (19.3)	696 (14.8)	
Past smokers	768 (16.3)	821 (17.5)	774 (16.4)	648 (13.8)	628 (13.3)	
Never smokers	2395 (50.8)	2613 (55.7)	2881 (60.9)	3131 (66.8)	3379 (71.8)	
Educational level (%)						*<0.0001*
University	690 (14.6)	518 (11.0)	404 (8.5)	269 (5.7)	177 (3.8)	
Intermediary	982 (20..8)	885 (18.9)	631 (13.3)	449 (9.6)	325 (6.9)	
High school	1673 (35.5)	1529 (32.6)	1485 (31.4)	1245 (26.6)	1105 (23.5)	
Primary	1368 (29.0)	1756 (37.5)	2208 (46.7)	2721 (58.1)	3096 (65.8)	
Alcohol intake (g/d)	2 [0-11]	2 [0-10]	2 [0-10]	1 [0-9]	0 [0-5]	*<0.0001*
High blood pressure (%)	700 (14.8)	1038 (22.1)	1497 (31.7)	2204 (47.0)	3022 (64.3)	*<0.0001*
Diabetes (%)	38 (0.8)	38 (0.8)	86 (1.8)	148 (3.2)	313 (6.7)	*<0.0001*
Total cholesterol (g/l)	2.00 [1.76-2.28]	2.09 [1.86-2.40]	2.20 [1.93-2.55]	2.29 [2.01-2.60]	2.29 [2.01-2.59]	*<0.0001*
HDL-cholesterol (g/l)	0.63 [0.55-0.73]	0.61 [0.53-0.71]	0.59 [0.51-0.70]	0.56 [0.48-0.65]	0.51 [0.44-0.60]	*<0.0001*
BMI (kg/m²)	20.7 [19.7-21.4]	23.1 [22.6-23.6]	25.3 [24.7-25.9]	28.1 [27.3-29.0]	32.9 [31.2-35.6]	
WC (cm)	69.0 [66.0-72.0]	74.0 [71.0-78.0]	79.0 [76.0-83.0]	86.0 [82.0-90.0]	97.0 [92.0-104.0]	*<0.0001*
WHR	0.76 [0.73-0.79]	0.78 [0.74-0.81]	0.80 [0.76-0.83]	0.82 [0.78-0.86]	0.85 [0.81-0.89]	*<0.0001*
WHtR	0.42 [0.40-0.44]	0.46 [0.44-0.48]	0.49 [0.47-0.52]	0.54 [0.51-0.57]	0.61 [0.58-0.66]	*<0.0001*

values are medians for continuous variables and percentage of subjects for categorical variables

* p value by generalised linear model or logistic regression, stratified on centre

HDL High Density Lipoprotein, BMI Body Mass Index, WC Waist Circumference, WHR Waist to Hip Ratio, WHtR Waist to Height Ratio

Supplemental Table 3a. Relative Risk (RRs) of stroke according to quintiles of body mass index, waist circumference, waist-to-hip ratio, waist-to-height ratio in men

Men	Quintile	Quintile of anthropometrics measures					p^*
		Q1	Q2	Q3	Q4	Q5	
Body mass index	Quintile cut-offs (kg/m²)	<23.7	23.7-25.5	25.6-27.2	27.3-29.4	>29.4	
	No of stroke / total no of subjects	96/6264	111/6231	135/6231	165/6239	213/6236	
	incidence	1.41	1.64	2.04	2.53	3.30	
	Model I	1	1.01 [0.77-1.32]	1.15 [0.88-1.49]	1.32 [1.02-1.70]	1.60 [1.25-2.04]	*<0.0001*
	Model II	1	0.96 [0.73-1.26]	1.02 [0.78-1.33]	1.10 [0.85-1.44]	1.20 [0.93-1.56]	*0.0892*
Waist circumference	Quintile cutoffs (cm)	<85.0	85.0-90.8	90.9-95.5	95.6-101.5	>101.5	
	No of stroke / total no of subjects	91/6492	107/5820	127/6182	164/6234	231/6473	
	incidence	1.24	1.70	1.94	2.54	3.51	
	Model I	1	1.10 [0.83-1.46]	1.14 [0.87-1.50]	1.39 [1.07-1.80]	1.73 [1.35-2.22]	*<0.0001*
	Model II	1	1.03 [0.78-1.37]	1.01 [0.76-1.33]	1.17 [0.89-1.53]	1.29 [0.99-1.68]	*0.0087*
Waist-to-hip ratio	Quintile cutoffs	<0.88	0.88-0.92	0.93-0.95	0.96-0.99	>0.99	
	No of stroke / total no of subjects	93/6784	124/6467	128/5694	184/6611	191/5645	
	incidence	1.15	1.77	2.18	2.79	3.40	
	Model I	1	1.17 [0.89-1.53]	1.34 [1.02-1.76]	1.69 [1.30-2.18]	1.92 [1.48-2.49]	*<0.0001*
	Model II	1	1.08 [0.82-1.41]	1.16 [0.88-1.53]	1.37 [1.05-1.79]	1.43 [1.09-1.87]	*0.0022*
Waist-to-height ratio	Quintile cutoffs	<0.49	0.49-0.52	0.53-0.55	0.55-0.59	>0.59	
	No of stroke / total no of subjects	81/6241	102/6222	118/6260	169/6241	250/6237	
	incidence	1.13	1.51	1.78	2.63	4.05	
	Model I	1	1.00 [0.74-1.34]	1.03 [0.77-1.38]	1.38 [1.05-1.82]	1.95 [1.50-2.54]	*<0.0001*
	Model II	1	0.93 [0.69-1.25]	0.90 [0.67-1.20]	1.12 [0.84-1.49]	1.44 [1.09-1.91]	*<0.0001*

* p for trend
Model I : stratified for center, adjusted for age
Model II : model I and adjusted for tobacco consumption, educational level, alcohol consumption, hypertension, diabetes, total cholesterol and high density lipoprotein cholesterol

Supplemental Table 3b. Relative Risk (RRs) of stroke according to quintiles of body mass index, waist circumference, waist-to-hip ratio, waist-to-height ratio in women

Women	Quintile	Quintile of anthropometrics measures					p^*
		Q1	Q2	Q3	Q4	Q5	
Body mass index	Quintile cut-offs (kg/m²)	<22.0	22.0-24.2	24.3-26.6	26.7-30.0	>30.0	
	No of stroke / total no of subjects	45/4713	74/4688	80/4728	85/4684	126/4703	
	incidence	0.80	1.33	1.46	1.62	2.50	
	Model I	1	1.17 [0.81-1.70]	1.00 [0.69-1.44]	0.88 [0.60-1.28]	1.26 [0.88-1.80]	*0.1054*
	Model II	1	1.19 [0.82-1.73]	0.95 [0.65-1.38]	0.73 [0.50-1.07]	0.90 [0.62-1.32]	*0.4429*
Waist circumference	Quintile cutoffs (cm)	<71.0	71.0-76.5	76.6-82.5	82.6-91.0	>91.0	
	No of stroke / total no of subjects	46/4772	56/4487	89/4669	95/4889	124/4699	
	incidence	0.78	1.03	1.65	1.76	2.53	
	Model I	1	0.93 [0.63-1.38]	1.12 [0.78-1.61]	1.01 [0.71-1.46]	1.39 [0.97-1.98]	*0.0035*
	Model II	1	0.90 [0.61-1.34]	1.02 [0.71-1.48]	0.83 [0.57-1.21]	0.95 [0.65-1.39]	*0.8480*
Waist-to-hip ratio	Quintile cutoffs	<0.74	0.74-0.78	0.79-0.81	0.82-0.85	>0.85	
	No of stroke / total no of subjects	40/4399	84/5440	76/4463	101/4516	109/4698	
	incidence	0.71	1.30	1.50	2.04	2.23	
	Model I	1	1.54 [1.06-2.25]	1.44 [0.98-2.12]	1.79 [1.23-2.61]	1.76 [1.21-2.55]	*0.0003*
	Model II	1	1.45 [0.99-2.12]	1.25 [0.85-1.85]	1.41 [0.96-2.06]	1.22 [0.82-1.80]	*0.3343*
Waist-to-height ratio	Quintile cutoffs	<0.44	0.45-0.47	0.48-0.52	0.53-0.57	>0.57	
	No of stroke / total no of subjects	37/4697	70/4726	76/4688	97/4706	130/4699	
	incidence	0.63	1.22	1.39	1.84	2.68	
	Model I	1	1.30 [0.87-1.94]	1.08 [0.72-1.61]	1.17 [0.79-1.74]	1.60 [1.08-2.36]	*0.0015*
	Model II	1	1.23 [0.82-1.84]	0.97 [0.64-1.46]	0.95 [0.63-1.43]	1.06 [0.69-1.60]	*0.6378*

* p for trend
Model I : stratified for center, adjusted for age
Model II : model I and adjusted for tobacco consumption, educational level, alcohol consumption, hypertension, diabetes, total cholesterol and high density lipoprotein cholesterol