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Background and Purpose—Within the framework of the MOnica Risk, Genetics, Archiving and Monograph (MORGAM) Project, the variations in impact of classical risk factors of stroke by population, sex, and age were analyzed.

Methods—Follow-up data were collected in 43 cohorts in 18 populations in 8 European countries surveyed for cardiovascular risk factors. In 93 695 persons aged 19 to 77 years and free of major cardiovascular disease at baseline, total observation years were 1 234 252 and the number of stroke events analyzed was 3142. Hazard ratios were calculated by Cox regression analyses.

Results—Each year of age increased the risk of stroke (fatal and nonfatal together) by 9% (95% CI, 9% to 10%) in men and by 10% (9% to 10%) in women. A 10-mm Hg increase in systolic blood pressure involved a similar increase in risk in men (28%; 24% to 32%) and women (25%; 20% to 29%). Smoking conferred a similar excess risk in women (104%; 78% to 133%) and in men (82%; 66% to 100%). The effect of increasing body mass index was very modest. Higher high-density lipoprotein cholesterol levels decreased the risk of stroke more in women (hazard ratio per mmol/L 0.58; 0.49 to 0.68) than in men (0.80; 0.69 to 0.92). The impact of the individual risk factors differed somewhat between countries/regions with high blood pressure being particularly important in central Europe (Poland and Lithuania).

Conclusions—Age, sex, and region-specific estimates of relative risks for stroke conferred by classical risk factors in various regions of Europe are provided. From a public health perspective, an important lesson is that smoking confers a high risk for stroke across Europe. (***Stroke***. 2009;40:2319-2326.)

Key Words: blood pressure ■ cholesterol ■ cohort studies ■ smoking ■ stroke risk factors

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The appraisal of stroke risk in populations or individuals is based on the recognition that all cardiovascular disorders are multifactorial in nature. The most widely used risk score for stroke was developed within the framework of The Framingham Heart Study, the original version being published in 1971 with later refinements based on longer follow-up, addition of more predictors, and using more sophisticated statistical techniques.[1] The Framingham stroke risk score has been used extensively when international and national guidelines for cardiovascular prevention have been developed. Other stroke prediction scores have been developed later, for instance based on data from a large population-based US cohort of elderly men and women (the Cardiovascular Health Study),[2] a large number of cohorts within the Systematic COronary Risk

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Table 1.   Characteristics of Cohorts Included in the Analyses

Region, Country	Population	No. of Cohorts	Type of Cohort (Reference)*	Age Range at Baseline (Survey Period)	Years of Follow-Up	Total Years of Observation†	No. of Fatal Strokes†‡			No. of All Strokes, Fatal and Nonfatal†‡		
							Men	Women	Total	Men	Women	Total
Central Europe												
Lithuania	LTU-KAU (Kaunas)	3	MONICA center	33–65 (1986–1993)	5–13	35 520/40 351	13/17	15/17	28/34	44/54	32/40	76/94
Poland	POL-WAR (Warsaw)	3	MONICA center	34–65 (1988–1993)	2–8	27 485/31 903	29/39	7/16	36/55	25/32	11/15	36/47
France												
France	FRA-LIL (Lille)	1	PRIME (MONICA procedures), men only	49–64 (1991–1993)	10	24 249/25 139	5/6	0/0	5/6	42/57	0/0	42/57
France	FRA-STR (Strasbourg)	1	PRIME (MONICA procedures), men only	49–60 (1991–1993)	10	23 672/24 892	4/5	0/0	4/5	26/27	0/0	26/27
France	FRA-TOU (Toulouse)	1	PRIME (MONICA procedures), men only	49–60 (1991–1993)	10	24 438/24 933	2/2	0/0	2/2	22/24	0/0	22/24
Italy												
Italy	ITA-BRI (Brianza)	3	MONICA center	25–66 (1986–1994)	9–16	55 430/59 476	12/15	8/10	20/25	39/45	21/26	60/71
Italy	ITA-PAM (Pamela)	1	MONICA procedures	25–75 (1990–1993)	9–12	20 207/21 712	8/11	2/2	10/13	24/29	14/15	38/44
Italy	ITA-FRI (Friuli)	4	MONICA center (3 cohorts) and MONICA procedures (1 cohort)	24–65 (1986–1994)	3–12	45 829/47 865	4/7	7/7	11/14	21/26	17/20	38/46
Italy	ITA-ROM (Rome and Area Latina)	4	MONICA center and MONICA procedures	19–77 (1982–1996)	4–14	115 783/152 458	63/79	60/78	123/157	108/144	101/130	209/274
Nordic countries												
Finland	FIN-EAS (Eastern Finland and Oulu)	4	MONICA center and MONICA procedures	25–64, 25–74 (1987–1997)	11–26	282 561/295 182	120/148	106/123	226/271	503/613	421/480	924/1093
Finland	FIN-WES (Turku-Loimaa and Helsinki)	4	MONICA center and MONICA procedures	25–64, 25–74 (1982–1997)	11–26	166 755/171 299	67/81	54/57	121/138	256/309	198/221	454/530
Sweden	SWE-NSW (Northern Sweden)	3	MONICA center	24–65, 24–74 (1986–1994)	5–13	44 216/46 142	9/15	7/7	16/22	52/68	42/44	94/112
Denmark	DEN-GLO (Glostrup)	3	MONICA center	30, 40, 50, 60 (1982–1994)	9–19	99 924/102 123	44/52	32/37	76/89	167/185	128/136	295/321
United Kingdom												
Scotland	UNK-EDI (Edinburgh)	1	MONICA procedures	25–64 (1986)	19	22 483/23 414	15/20	8/9	23/29	35/42	23/25	58/67
Scotland	UNK-GLA (Glasgow)	4	MONICA center	25–64, 25–75 (1989–1995)	10–19	62 472/72 142	42/61	44/52	86/113	128/195	113/145	241/340
Scotland	UNK-SHH (nationwide)	1	MONICA-based procedures	39–59 (1984–1987)	18–21	150 272/163 971	81/106	68/80	149/186	249/310	170/202	419/512
Northern Ireland	UNK-BEL (Belfast)	1	PRIME (MONICA procedures), men only	50–60 (1991–1994)	5	12 515/13 500	4/5	0/0	4/5	14/16	0/0	14/16
Wales	UNK-CAE (Caerphilly)	1	Non-MONICA, men only	47–67 (1984–1988)	12–16	20 441/29 567	23/45	0/0	23/45	96/181	0/0	96/181
All MORGAM cohorts		43				1 234 252/1 346 069	545/714	418/495	963/1209	1851/2357	1291/1499	3142/3856

*Reference(s) to detailed information on the cohort and methods used for obtaining baseline information.

†Analysis data set/subjects on whom data were transferred to the MORGAM data center (including subjects with missing data).

‡In some populations, follow-up for stroke deaths covered a wider age group than follow-up for nonfatal strokes as described in ″Methods.″ The ″No. of All Strokes″ covers the follow-up period of nonfatal strokes only. Therefore, the no. of fatal strokes is occasionally as high as no. of fatal and nonfatal events together.

Evaluation (SCORE) Project,[3] the Prospective Cardiovascular Münster (PROCAM) cohort in Germany,[4] a Chinese cohort of male steelworkers,[5] and the Italian Progetto Epidemiologia e prevenzione delle malattie cerebro e cardiovascolari (CUORE) study.[6]

It seems that these stroke risk scores capture a substantial amount of variation of stroke risk.[2] However, the risk equations available have been based on fatal strokes only,[3]

limited to one population,[2,4,5] or not large enough to permit detailed analyses by age and sex. It has become obvious that stroke or cardiovascular risk equations developed in one population may not be very accurate to predict stroke risk in other populations.[7–10]

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Table 2. Comparisons of HRs and their 95% Confidence Limits Between Calculations Based on All Strokes (Fatal+Nonfatal) and Fatal Strokes Only*

	HR (95% Confidence Limits)	
	Fatal and Nonfatal Strokes	Fatal Strokes Only
Men (N=51 703)		
No. of events	1851	545
Age per year	1.09 (1.09–1.10)	1.12 (1.10–1.13)
Blood pressure† per 10 mm Hg	1.28 (1.24–1.32)	1.38 (1.31–1.45)
BMI per unit	1.02 (1.01–1.03)	1.03 (1.00–1.05)
Smoking, yes/no	1.82 (1.66–2.00)	2.00 (1.68–2.38)
HDL cholesterol per mmol/L	0.80 (0.69–0.92)	1.01 (0.78–1.31)
Women (N=41 992)		
No. of events	1291	418
Age per year	1.10 (1.09–1.10)	1.13 (1.11–1.14)
Blood pressure† per 10 mm Hg	1.25 (1.20–1.29)	1.26 (1.19–1.34)
BMI per unit	1.00 (0.99–1.01)	0.99 (0.97–1.01)
Smoking (yes/no)	2.04 (1.78–2.33)	2.56 (2.01–3.24)
HDL cholesterol per mmol/L	0.58 (0.49–0.68)	0.48 (0.36–0.65)

*Risk factor data missing in <2.4% of each population except HDL cholesterol in LTU-KAU (9.2% missing), UNK-CAE (24.0%), and UNK-GLA (7.8%).

†Mean of systolic and diastolic blood pressure.

(MONICA) Project, cardiovascular risk factor surveys were conducted during the 1980s and 1990s in a large number of populations, most of them in Europe.[11] The ensuing MOnica Risk, Genetics, Archiving and Monograph (MORGAM) Project[12] has used baseline and follow-up data from many of the MONICA centers, but also from other studies that used similar data collection procedures. The MORGAM data set with follow-up data on stroke covers 18 populations in 8 European countries. Risk factor measurements at baseline and assessment of both fatal and nonfatal stroke events during follow-up are largely standardized. This permits analyses of differences in the impact of classic risk factors between populations and between population subgroups. In this article, we have investigated similarities (or differences) in the relative risks conferred by blood pressure, cholesterol, body mass index (BMI), and smoking on incident (first-ever) stroke events. Variations in the impact of risk factors in men and women and in different age groups have been analyzed.

Methods

The MORGAM Project has a risk factor and a genetic component. As stated in the study protocol,[12] the main objective of the risk factor component is to assess the similarity of risk coefficients for the classic cardiovascular disease risk factors in different parts of Europe, between men and women, and between age groups using large cohorts with standardized baseline measurements and carefully validated fatal and nonfatal coronary heart disease and stroke end points. In these analyses, data from several cohorts are pooled to reach a sufficient number of outcome events.

In the present MORGAM study[12] and the MORGAM web site (www.ktl.fi/publications/morgam/cohorts/index.html), baseline and follow-up data on fatal and nonfatal stroke from 43 cohorts in 18 populations in 8 European countries have been used. The cohorts, references to description of survey methods, cohort sizes, and the number of stroke events occurring during follow-up are described in Table 1. The populations had either been a part of the World Health Organization's MONICA Project or MONICA survey procedures had been used. The Prospective Epidemiological Study of Myocardial Infarction (PRIME) cohorts (one from Northern Ireland and 3 from France) included men only.

Data collection on risk factors and cardiovascular end points followed a standardized protocol described in the MORGAM Manual.[13] Blood pressure was measured twice in the right arm in the sitting position using a standard or random zero sphygmomanometer after a 5-minute rest,[11] except in the 3 French cohorts in which blood pressure was measured only once using an automated device. For the present calculations, the mean of the first and second systolic and diastolic blood pressures was used. Total serum cholesterol was measured in serum samples by local laboratories. BMI was calculated as weight (kg) divided by the square meters of height (m^2). People who were smoking cigarettes daily were classified as smokers. The results of extensive quality assessments of baseline data are summarized at the MORGAM web site.[14]

Each member of a MORGAM cohort was followed up for death and nonfatal stroke. The primary end point included all fatal and nonfatal strokes, and the secondary end point was fatal strokes only. The follow-up continued until death or the end of a fixed follow-up period or, in occasional cases, loss to follow-up for another reason. An upper age limit at the end of follow-up was applied in the 3 French cohorts (66 years), Warsaw (nonfatal stroke 65 years; no upper age limit for recording of fatal stroke), Kaunas (nonfatal stroke 65 years; no upper age limit for fatal stroke), and northern Sweden (75 years). Fatal cases were identified by national or regional health information systems. In the great majority of populations, nonfatal stroke cases were identified by hospital discharge registers. Most MORGAM centers used the World Health Organization diagnostic criteria, as applied by the MONICA Project,[15] to validate the stroke events occurring during follow-up. The MONICA criteria for stroke (yes/no) are based on clinical presentation and not on imaging techniques.[15] Details, including quality assessments, are available at the MORGAM web site.[14]

Statistics

Members of the cohorts were used for analyses if (1) baseline data on blood pressure, total and high-density lipoprotein (HDL) serum cholesterol, weight, height, and smoking status were available; and (1) the person did not have a documented (by medicals records) or self-reported history of myocardial infarction or stroke at baseline (including angina pectoris when the data did not permit its separation from myocardial infarction). If information on history of cardiovascular disease was missing, the individual was not classified and, hence, was excluded from the analyses.[16] Restriction (1) was made for statistical convenience but its impact was small because full information on risk factors was available in the great majority of participants.

Testing several model specifications showed the most reasonable model to use was the proportional hazards model and assuming linear effects of age at baseline, mean of systolic and diastolic blood pressure, HDL cholesterol, and BMI without interactions between these risk factors. In the initial analyses, non-HDL cholesterol (including low-density lipoprotein cholesterol) was not a statistical predictor of stroke in any of the subgroups and it was therefore not included in the final models. Population and sex were considered as stratifying variables in the analyses, ie, the baseline hazard was allowed to vary between populations and between men and women. The same was applied to age groups when differences between age groups were analyzed. Populations within one country were merged and, to reduce statistical variation, some countries were also aggregated. Thus, Lithuania and Poland were analyzed together as "central Europe" and data from Finland, Sweden, and Denmark were pooled as "Nordic countries." The 5 regions compared in the analysis were Nordic countries, central Europe, the United Kingdom, France, and Italy.
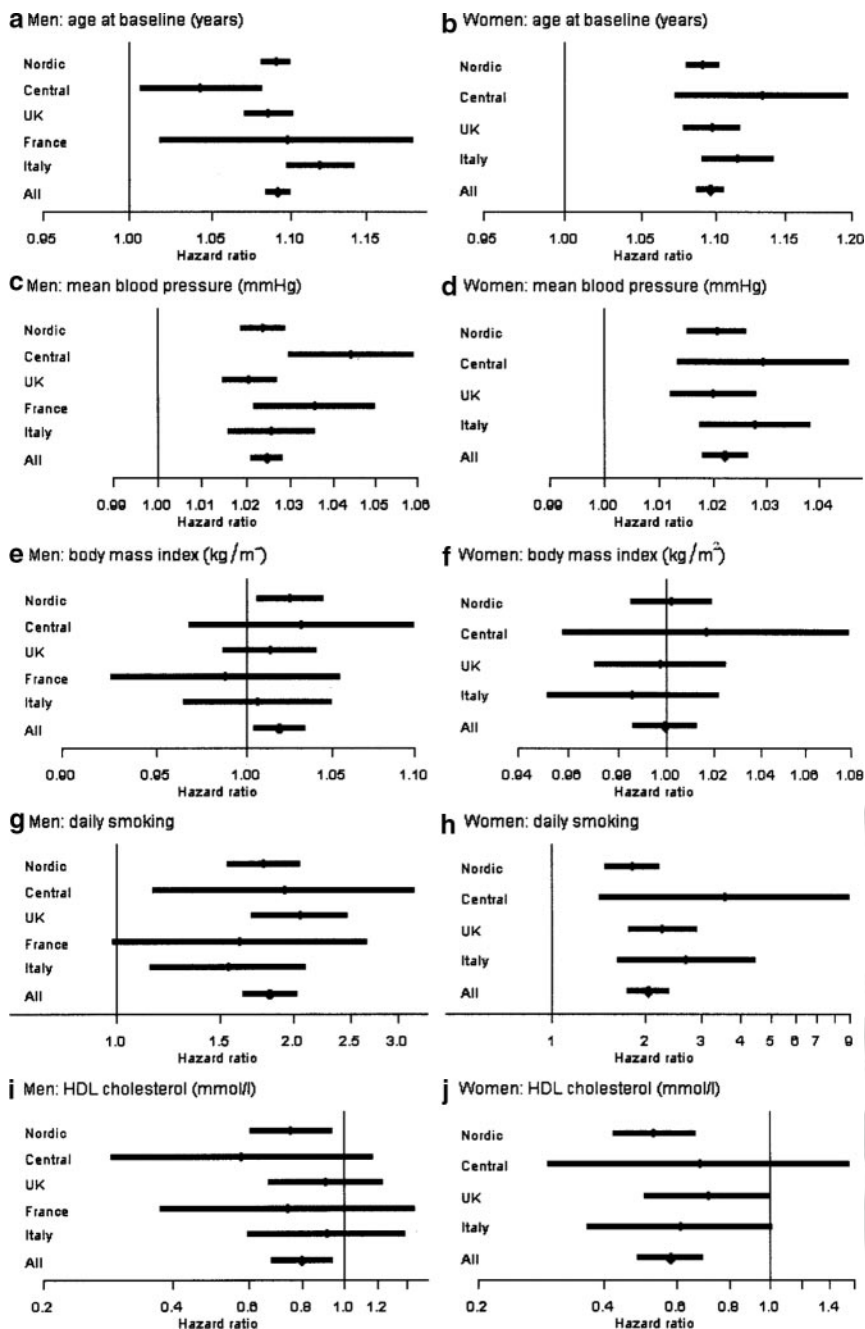
Figure 1. HRs for stroke during follow-up of men and women free of cardiovascular disease at baseline shown for 5 European regions and all MORGAM populations together. The horizontal lines represent 95% CIs of the estimates. The data are adjusted for other factors in a multivariate model with no other explanatory variables than those shown in the figure included in the model.

The following 3 hypotheses were tested using likelihood ratio tests: (1) the risk factors have similar effects in all 5 regions; (2) the risk factors have similar effects for men and women; and (3) the risk factors have similar effects for age groups <45 years, 45 to 54 years, 55 to 65 years, and >65 years at baseline. Details of the statistical models are given on the MORGAM web site (www.ktl.fi/publications/morgam/stroke). The analyses were performed using R.[17]

Results

Characteristics of the MORGAM Populations
In the stroke component of the MORGAM Project, 51 703 men and 41 992 women who were free of cardiovascular disease at baseline were followed for an average of 13.2 years (total of 1 234 252 observation years), during which 1851 strokes occurred in men and 1291 in women. As shown in

Table 1, the study covered 43 cohorts in 18 populations in 8 European countries. After aggregation, 5 European regions were used in the analyses: central Europe (Lithuania and Poland), France, Italy, Nordic countries (Finland, Sweden, and Denmark), and the United Kingdom (Scotland, Northern Ireland, and Wales). In the populations from Northern Ireland, Wales, and France, only men were studied.

Hazard Ratios for All Populations Together
Table 2 shows the hazards ratios for age, blood pressure, smoking, BMI, and HDL cholesterol as predictors of stroke during follow-up of people free of serious cardiovascular disease (as defined in "Methods") at baseline. Total serum

cholesterol was not a significant independent predictor of stroke and is therefore not reported.

For each 10-mm Hg increase in blood pressure, the risk of stroke increased by 23% to 29%. Smoking conferred almost a doubling of the risk of stroke (hazard ratio [HR], 1.8 in men and 2.0 in women). One BMI unit increased the risk by 2% in men but not in women. Higher HDL serum cholesterol levels decreased the risk of stroke during follow-up (HR per mmol/L, 0.80; 95% CI, 0.69 to 0.92 in men and 0.58; 95% CI, 0.49 to 0.68 in women).

HRs by Region, Sex, and Age

As indicated by Figure 1, the coefficients showed some heterogeneity across the regions. The heterogeneity was statistically significant in men but not in women. For men, age was less important as a risk factor in central Europe and more important in Italy than in the other regions. On the other hand, blood pressure levels at baseline predicted future stroke more strongly in central Europe than in other regions; the difference was statistically significant in men. There were no significant differences between regions in the impact of smoking on stroke risk. Increasing BMI or decreasing HDL conferred a similar excess risk of stroke in all regions. It was also checked whether the exclusion of Wales and Northern Ireland changes the results for the United Kingdom, but no major changes in the point estimates were observed.

When all populations were analyzed together, there were significant differences between men and women in hazard ratios for HDL cholesterol. The other 4 variables all had similar HRs in men and women (Figure 2).

On average, one additional year at baseline increased the risk of stroke by 9% to 10% (Table 2). However, there was a general pattern of greater impact of risk factors at younger ages (Figure 3). For high blood pressure, the differences by age group were statistically significant.

Discussion

There are many reasons why stroke risk factors would have varying impact in different populations, whether they are defined by sex, age, or geography. In addition to genetic variations, the burden of socioeconomic risk factors in whole populations or subsets may well interact with classical cardiovascular risk factors to modify the risk of stroke.

Several scores based on data collected during clinical trials for predicting risk of death from stroke have been developed. This includes scores based on follow-up of participants in randomized trials of antihypertensive treatment[18] and stroke risk estimates of participants in the Multiple Risk Factor Intervention Trial (MRFIT).[19] The risk coefficients differ markedly among the scores presented, illustrating the problems involved in analyzing highly selected cohorts such as people fulfilling all entry criteria of a clinical trial. Therefore, risk equations or risk charts based on follow-up of whole populations and with a sufficiently large number of stroke events are preferred. Such strictly population-derived risk estimates based on at least 300 stroke events have been presented within the frameworks of the Framingham study,[1,20] the US Cardiovascular Health Study,[2] the Honolulu
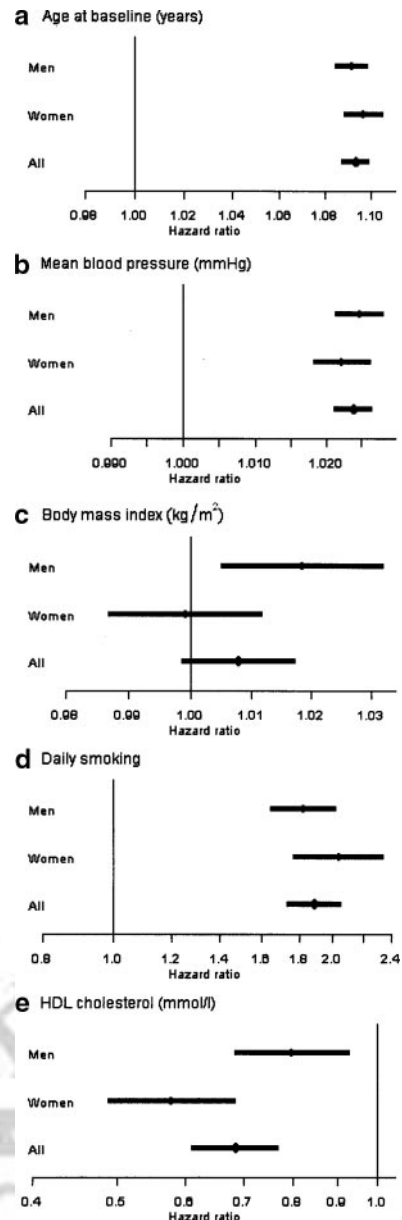

Figure 2. HRs for stroke during follow-up of men versus women free of cardiovascular disease, all MORGAM populations together. The horizontal lines represent 95% CIs of the estimates. The data are adjusted for other factors in a multivariate model with no other explanatory variables than those shown in the figure included in the model.

Heart Programme,[21] the Copenhagen City Heart Study,[22] the Seven Countries Study,[23] the Scottish Renfrew/Paisley study,[24] and the Dijon stroke study.[25] The widely used SCORE risk equations are based on follow-up of a large number of European populations, but only fatal stroke events as diagnosed in routine cause-of-death registers have been recorded.[3]

The strengths of this study are that it includes a very large number of population-based cohorts of both men and women across Europe and that it includes both fatal and nonfatal strokes with individual validation of the diagnosis in the majority of stroke events. With more than 3100 stroke events, MORGAM is, by far, the largest prospective stroke study performed. In 15 of the 16 populations, baseline data collec-
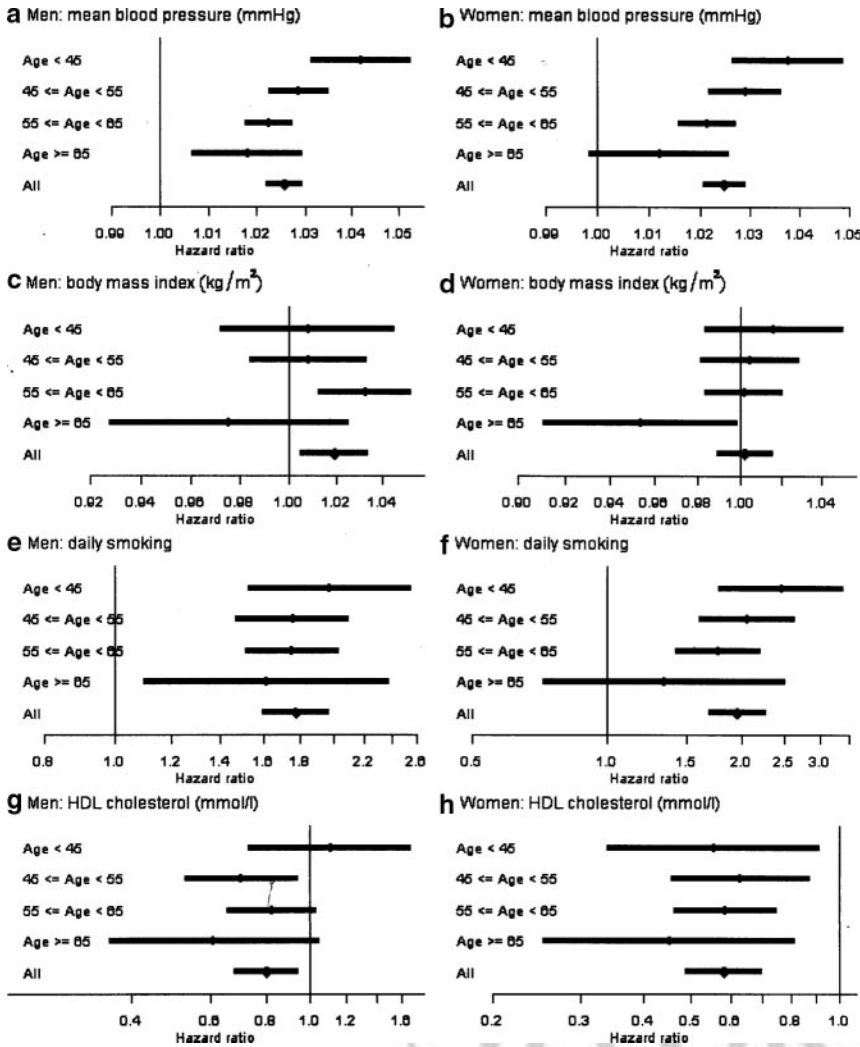
Figure 3. HRs for stroke during follow-up of men and women free of cardiovascular disease at baseline by age at baseline, all MORGAM populations together. The horizontal lines represent 95% CIs of the estimates. The data are adjusted for other factors in a multivariate model with no other explanatory variables than those shown in the figure included in the model.

tion was performed by the standardized MONICA criteria or by procedures similar to those used by MONICA (the 3 French cohorts used only one blood pressure measurement by an automatic device). An obvious limitation of a very large study like this is that only a very limited set of risk factors were available for analysis. For instance, data on diabetes, atrial fibrillation, physical inactivity, excess alcohol consumption, or left ventricular hypertrophy, all well established risks for stroke, were not available from all cohorts.

Because relative risks conferred by amenable stroke risk factors usually decline with increasing age, a relatively low upper age limit at baseline (60 years) and short follow-up (5 to 10 years) could possibly have led to slightly inflated hazard ratios in the PRIME cohorts in France and Northern Ireland when compared with the other MORGAM populations.

For several reasons, HRs for ischemic and hemorrhagic strokes together were calculated. First, in some of the populations, CT scanners were not widely available for patients with stroke (particularly so in Lithuania but during the initial years of the MONICA Project; also in several other populations) or autopsy rates were low in patients dying out of the hospital (several west European populations) so that accurate stroke subtyping was not always possible. Second,

the statistical power to determine risk for hemorrhagic stroke was low. Third, previous risk appraisals have identified the same risk factors for ischemic and hemorrhagic stroke. The risk estimates have been reported to differ between the stroke subtypes, but the CIs have been very wide for intracerebral hemorrhages and overlapping with those of ischemic stroke.[26]

The extent to which elevated blood pressure increased the risk of stroke varied between populations and regions. For each 10-mm Hg increase in blood pressure, the stroke risk increased, on average, by >50% in men and >40% in central European women, whereas the excess risk was as low as 25% in Nordic men and women. A weakness of cohort studies is that exposure may change during the observation time. It is conceivable that, in some MORGAM populations, better blood pressure control during follow-up in those identified as being hypertensive could contribute to an apparent lower stroke risk. The geographic variation in risk was less for cigarette smoking than for blood pressure levels. An important message from MORGAM is that smoking confers a high risk for stroke across Europe.

When the present risk estimates for all 18 European populations together are compared with those based on other cohorts, some similarities and some differences are noted.

Although relative risks differ, high blood pressure has generally been the strongest predictor of stroke. Total cholesterol levels were not a predictor of stroke either in the Framingham study or in the present study. Higher HDL cholesterol levels were associated with a lower risk of stroke. The same was observed in the male, but not in the female, cohorts followed in EUROSTROKE (Prediction of Stroke in the General Population in Europe).[27] The excess risk increase conveyed by increasing BMI was much greater in previous studies than in the MORGAM cohorts. Thus, the excess risk was approximately 30% per BMI unit in Framingham men,[26] 10% in Japanese–American men in Honolulu,[26] and only 3% per BMI unit in the present study. On the other hand, daily smoking involved about the same excess risk (doubling) in the present European male populations as in Honolulu and China,[5,21,26] but it was much higher than reported from Framingham ($+$30% at 20 cigarettes per day),[1] in Danes aged of $>$55 years ($+$18%),[22] and in Americans $>$65 years (no apparent excess risk).[2] Among smoking women, the relative risk reported in previous studies ranged from no excess risk (elderly Americans[2]) to 1.54 (Framingham[1]) to be compared with a HR of 2.04 in the MORGAM cohorts. There are many reasons why the slopes of relation between risk factors and stroke events may differ between populations. An important reason would be that other risk factors, for instance, socioeconomic conditions, physical activity, and dietary factors not captured by the studies, may modify the impact of the conventional risk factors on stroke. Different factors included in the multivariate models may also contribute to the discrepancies. For instance, when we in the MORGAM study adjusted for HDL cholesterol levels, nonlow-density lipoprotein cholesterol no longer remained a significant predictor of stroke.

It should be emphasized that the present results refer only to relative risks for stroke. These relative risks do not necessarily translate into risks of stroke in absolute terms. In the stroke component of the World Health Organization MONICA Project, which included a large number of populations from high-income, middle-income, and low-income countries, differences in population levels of conventional risk factors have explained only a modest part of the variation in stroke incidence rates in cross-sectional comparisons.[28] Furthermore, secular risk factor trends in the populations were poor predictors of stroke trends.[29] These results from ecological analyses indicate that there are population-specific factors that explain much of the absolute levels of stroke incidence and/or mortality in a population. Forthcoming analyses within the MORGAM Project will attempt to address determinants of variations in absolute risks for stroke between populations.

Acknowledgments

Disclosures

None.

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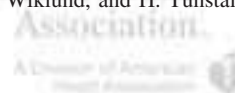
Supplemental Appendix

Sites and Key Personnel of Contributing MORGAM Centers

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