



Original Contribution

Favorable Cardiovascular Risk Profile (Low Risk) and 10-Year Stroke Incidence in Women and Men: Findings from 12 Italian Population Samples

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Recently, the focus of research on cardiovascular risk factors has broadened because of new data demonstrating benefits of low risk (i.e., favorable) levels of all major modifiable risk factors. Most data on low risk relate to coronary heart disease, not stroke. This population-based, 12-sample, Italian study (Progetto CUORE, 1983–2002), with 10-year follow-up, assessed the relation of low risk to stroke and implications for prevention. At baseline, women and men were 35–69 years of age. Only 3% were low risk; 80% were high risk. Overall, stroke incidence rates were 20.7 for men and 9.6 for women per 10,000 person-years. No strokes occurred in low risk participants, and stroke incidence was low with borderline elevation of only one risk factor. Four modifiable risk factors—elevated blood pressure, smoking, diabetes, and high total cholesterol/high density lipoprotein cholesterol ratio—related independently to stroke risk. For those at low risk or who had only one unfavorable (but not high) risk factor, the stroke rate was 76% lower than for high risk participants; for all persons not at high risk, the stroke rate was 57% lower than for those at high risk. Results show that favorable risk factor levels assure minimal stroke risk. Population-wide prevention is needed, especially improved lifestyles, to increase the prevalence of low risk.

cerebrovascular accident; incidence; longitudinal studies; primary prevention; risk; risk factors; risk reduction behavior

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; MONICA, Monitoring of Trends and Determinants in Cardiovascular Disease; MRFIT, Multiple Risk Factor Intervention Trial; SBP, systolic blood pressure; U-NHRI, unfavorable but not high risk.

Recent years have witnessed an important conceptual advance with regard to the major cardiovascular disease risk factors: the focus is no longer exclusively on their long-term adverse effects. It now encompasses the long-term protective effects of favorable levels of all major modifiable risk factors, that is, low risk. This paradigm shift resulted from

new data on large cohorts followed long-term—cohorts large enough to include meaningful subsamples of low risk men and women despite the rarity of low risk given prevailing lifestyles (1–4). Data on these cohorts demonstrate that for their low-risk substrata, cardiovascular disease—coronary heart disease in particular—occurs rarely and is

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endemic, not epidemic, throughout adulthood. However, little information is available on low risk and stroke; to our knowledge, only three cohorts (one female, two male) have been studied (1–3).

The possibility that low risk protects against stroke is important, since stroke remains a major cause of morbidity, disability, and death worldwide. This situation is particularly true for Italy, where stroke mortality rates have, for decades, been higher than those for most Western countries (5). This paper reports data on low risk and 10-year stroke incidence in large cohorts of women and men from 12 Italian population samples (Progetto CUORE) who, at baseline, were aged 35–69 years (6, 7).

MATERIALS AND METHODS

Population samples

Twelve random samples of persons aged 35–69 years were studied (baseline surveys from 1983 through 1997) (6, 7)—1) seven from general populations in northern Italy: the Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) Study; Brianza: 1986, 1990, and 1993; Friuli: 1986, 1989, and 1994 (8); and Friuli Emostatico; 2) one factory-based sample in northern Italy: Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA), which monitored blood pressures and their relations; 3) three samples from general populations in central Italy: Rome Malattie Aterosclerotiche Istituto Superiore di Sanità–Atherosclerotic diseases Istituto Superiore di Sanità (MATISS) 1984, 1987, and 1993; and 4) one sample from a general population of southern Italian women: Naples Atherosclerosi Napoli–Atherosclerosis Naples (ATENA). Random sampling was based on population lists obtained from municipal electoral registers or the factory employee roll, stratified by age and gender. The samples were recruited by letter; the process was repeated once as needed. Participation rates were 64–78 percent except for the MATISS 1987 sample (40 percent). Across the samples, follow-up—through 2002—ranged from 5 to 19 years; the average was 10.

Baseline measurements

Risk factors were assessed by using standardized procedures (6–8). Blood pressure (right arm) was measured twice (using a mercury sphygmomanometer), with the participant sitting after resting for 5 minutes. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded (first and fifth Korotkoff sounds); the first and second measurements were averaged for analyses. Serum total cholesterol and high density lipoprotein cholesterol were assayed by enzymatic colorimetry in three laboratories in the MONICA external quality control and standardization program. Fasting plasma glucose was measured in 63 percent of the participants. Height and weight were measured with participants wearing light clothing without shoes. Body mass index (BMI) was computed as weight in kilograms divided by height in meters squared (kg/m^2).

Information was collected by questionnaire on cigarette smoking; personal history of myocardial infarction, stroke,

diabetes mellitus, and hospitalization for major cardiovascular events; medication use; and family history of premature coronary or cerebrovascular event (before age 55 years in men and age 65 years in women).

Stroke registration/validation

During follow-up (median: 10.5 years), deaths were identified from vital statistics. Death certificates were coded by using *International Classification of Diseases and Causes of Death*, Ninth Revision (9). Suspected strokes were investigated for validation.

Nonfatal strokes—ascertained through linkage with hospital discharge records (including tomography data if available), MONICA registers, sample reexamination, and contacts with physicians, patients, and families—were validated per MONICA diagnostic criteria (10) as follows: rapid development of focal signs (or global) or disturbance of cerebrovascular function lasting more than 24 hours (unless interrupted by surgery or death) with no apparent cause other than vascular origin. This category includes patients presenting clinical signs and symptoms suggestive of subarachnoid hemorrhage, intracerebral hemorrhage, or cerebral ischemic infarct. The term “global” applies to a patient experiencing subarachnoid hemorrhage or deep coma but excluding coma of systemic vascular origin such as shock, Stokes-Adams syndrome, or hypertensive encephalopathy (10).

Data analyses

Three cohorts were identified for separate analyses. Cohort 1 comprised all participants except those with a personal history of stroke ($n = 20,796$: 13,136 women, 7,660 men). Cohort 2 included all participants except those with a personal history of major cardiovascular disease, that is, stroke or myocardial infarction ($n = 20,647$: 13,127 women, 7,520 men). Cohort 3 was composed of all participants except those with a personal history of major cardiovascular disease and a family history of premature cardiovascular disease (as defined above) ($n = 14,247$: 9,132 women, 5,115 men). Cohort 3 is the focus for data tabulation here since it considered risk defined solely by preventable or modifiable established risk factors (with control for age and gender). Analyses were also conducted for cohorts 1 and 2 to assess sensitivity (robustness) of results for cohort 3, for those participants aged 50–69 years from all three cohorts, and for women and men separately.

Ten-year stroke incidence rates were calculated and were adjusted for age and gender (direct method) for men and women separately; the European 1995 population was used for adjustment (11). Risk factors included serum total cholesterol, high density lipoprotein cholesterol, and total cholesterol/high density lipoprotein cholesterol; fasting plasma glucose; SBP, DBP, and BMI; and SBP/DBP to identify normal, prehypertensive, hypertensive stage I, or hypertensive stage II strata (12). Diabetes was defined as a fasting plasma glucose level of ≥ 6.99 mmol/liter (≥ 126 mg/dl) (13) or self-reported drug-treated diabetes. Cigarette use was classified as never, past only, and current and number of cigarettes/day.

Stroke incidence adjusted for age and gender was calculated for participants stratified as low risk, unfavorable but not high risk (U-NHRi), or high risk. Persons were defined as low risk when all of the following applied at baseline: SBP, ≤ 120 mmHg; DBP, ≤ 80 mmHg; no hypertensive drug treatment; serum total cholesterol, < 5.17 mmol/liter (< 200 mg/dl); BMI, < 25.0 kg/m²; nonsmoking; and no diabetes. The U-NHRi definition applied when any one or more of the following were evident: SBP, 121–139 mmHg; DBP, 81–89 mmHg; serum total cholesterol, 5.17–6.18 mmol/liter (200–239 mg/dl); BMI, 25.0–29.9 kg/m²; and no high levels of other risk factors. All other participants were designated high risk. Those classified as U-NHRi or high risk were further stratified on the basis of the presence of only one or of two or more unfavorable/adverse findings.

Age-gender-specific analyses controlled for sample were also conducted to assess the relation to 10-year stroke incidence of each risk factor considered singly. Both categorical and continuous analyses were performed, as appropriate. Computations included age-adjusted incidence rate, Cox proportional hazards regression coefficient (standard error), and hazard ratio (95 percent confidence interval) (14). Multivariate proportional hazards models were computed for combinations of risk factors related to stroke in univariate analyses; they were computed for men and women combined from all three cohorts aged 35–69 and aged 50–69 years, and for women and men separately.

RESULTS

Baseline descriptive statistics

Of the 9,132 women and 5,115 men constituting cohort 3, the average ages were 50.0 years and 50.4 years, only 3.5 percent and 1.6 percent were low risk, and most (78.4 percent and 83.7 percent) were high risk, respectively (table 1). Two or more risk factors were high in 48.4 percent of the women and 55.2 percent of the men; three or more were high in 27.0 percent and 29.9 percent, respectively. Correspondingly, for all men and women, average SBP/DBP was in the prehypertensive range, and only a small minority had normal blood pressure; total cholesterol mean values were borderline high, total cholesterol/high density lipoprotein cholesterol ratio was elevated; average BMI was in the overweight range; and the prevalence of current cigarette smoking was 40 percent for men and 27 percent for women. As expected, findings were even more adverse for cohorts 1 and 2 and for persons aged 50–69 years. This population-wide adverse risk factor status prevailed for all 12 samples. Thus, for cohort 3 across samples, the range for the prevalence of high-risk status was 74–85 percent; low-risk status was only 1–5 percent; normal blood pressure was only 6–29 percent; average BMI was 25.5–28.7 kg/m²; and average serum total cholesterol was 5.5–6.2 mmol/liter.

Partial correlation analysis (cohort 3 data controlled for age and gender) showed positive relations of BMI to SBP, DBP, total cholesterol/high density lipoprotein cholesterol, and glycemia ($r = 0.16$ – 0.31) and an inverse relation to high density lipoprotein cholesterol ($r = -0.29$). Diabetes prevalence

was higher across BMI strata; for cohort 3 participants aged 35–69 years, it was 2.5, 3.1, 5.9, 10.2, and 15.7 percent for men and 1.7, 1.9, 3.0, 6.4, 9.0 percent for women whose BMI was 18.5–22.9, 23.0–24.9, 25.0–29.9, 30.0–34.9, and ≥ 35.0 kg/m², respectively. That is, for those participants who were markedly obese (BMI ≥ 35.0 kg/m²) compared with those who were lean, diabetes prevalence was 6.3 times higher among men and 5.3 times higher among women. Findings were similar in this regard for all three cohorts and also for those aged 50–69 years at baseline. For example, for lean men and women aged 50–69 years, diabetes prevalence was only 3.0 percent and 3.2 percent, whereas, for those markedly obese, it was 18.6 percent and 11.5 percent, 6.2- and 3.6-fold higher, respectively.

Stroke incidence

First strokes among cohort 3 participants numbered 200 (117 in men, 83 in women); 124 were nonfatal and 76 were fatal. Of the 200 incident strokes, 167 (83.5 percent) occurred in the approximately 50 percent of cohort 3 participants aged 50–69 years. Age- and gender-standardized incidence was 1.9 times higher in men (23.5/10,000) than in women (12.7/10,000) because of sex differentials in ischemic and unclassified strokes, accounting for most strokes (80.5 percent: 40.5 percent ischemic and 40.0 percent unclassified). Risk of death associated with first stroke was 38 percent overall, 19.8 percent for ischemic stroke, 51.9 percent for intracranial hemorrhage, and 58.3 percent for subarachnoid hemorrhage. For both genders, stroke incidence per 1,000 persons increased markedly across 5-year age groups, from 1.6 for ages 35–39 years at baseline to 60.7 for ages 65–69 years at baseline. For cohorts 1 and 2, first strokes numbered 369 and 355, respectively; the respective age- and gender-adjusted rates were 19.7/10,000 person-years (men: 26.0, women: 15.3) and 19.3/10,000 person-years (men: 25.5, women: 15.0). For these two cohorts, and for persons aged 50–69 years from the three cohorts, patterns of mortality by type of stroke and incidence by age paralleled those for cohort 3, as described above.

Relation of baseline low-risk, U-NHRi, and high-risk status to stroke incidence

On average, low risk and U-NHRi were younger than high risk participants (table 2). Findings were similar for women and men aged 35–69 and 50–69 years in all three cohorts. In this table, data for persons in cohort 3 aged 35–69 years are tabulated for the two genders combined. When the multiple criteria defining these three mutually exclusive strata were used, baseline risk factor levels differed markedly, especially for low risk compared with high risk—for example, SBP/DBP: 111.1/71.7 mmHg and 139.8/85.9 mmHg; serum total cholesterol: 4.5 mmol/liter and 6.1 mmol/liter (175.3 mg/dl and 234.3 mg/dl); and BMI: 22.2 kg/m² and 27.6 kg/m², respectively.

No low risk participant experienced stroke (table 2). Of 2,407 persons classified as U-NHRi, 10 (five men, five women) developed stroke. The age- and gender-adjusted rate was 8.5/10,000 person-years. For seven of the 10, two or

TABLE 1. Baseline descriptive statistics for Italian population samples (Progetto CUORE, 1983–2002) of men and women aged 35–69 years at baseline and free of previous cardiovascular disease and family history of cardiovascular disease (cohort 3)

Variable	Men (n = 5,115)			Women (n = 9,132)			Men and women combined (n = 14,247)		
	No.	Mean (SD)*	%	No.	Mean (SD)	%	No.	Mean (SD)	%
Age (years)	5,115	50.4 (9.2)		9,132	50.0 (8.4)		14,247	50.1 (8.7)	
Systolic blood pressure (mm Hg)	5,086	138.0 (20.5)		9,114	134.9 (21.6)		14,200	136.0 (21.2)	
Diastolic blood pressure (mm Hg)	5,085	86.5 (11.0)		9,113	82.8 (11.1)		14,198	84.1 (11.2)	
Serum total cholesterol (mmol/liter)	5,082	5.8 (1.2)		9,088	5.9 (1.1)		14,170	5.9 (1.1)	
Serum HDL* cholesterol (mmol/liter)	5,075	1.3 (0.4)		9,068	1.6 (0.4)		14,143	1.5 (0.4)	
Total/HDL cholesterol	5,072	4.8 (1.6)		9,063	4.0 (1.3)		14,135	4.3 (1.4)	
Body mass index†	5,065	26.7 (3.6)		9,066	27.2 (4.8)		14,131	27.0 (4.4)	
Body mass index (current smokers)	2,048	26.2 (3.7)		2,495	26.1 (4.3)		4,543	26.2 (4.0)	
Body mass index (never/past smokers)	3,009	27.0 (3.6)		6,560	27.6 (4.9)		9,569	27.4 (4.6)	
Plasma fasting glucose (mmol/liter)	4,247	5.4 (1.4)		4,249	5.1 (1.3)		8,496	5.3 (1.4)	
No. of cigarettes/day (current smokers only)	2,065	17.3 (10.5)		2,502	12.4 (8.4)		4,567	14.6 (9.8)	
Diabetes	293		5.8	327		3.6	620		4.4
Hypertension treatment	416		8.2	1,198		13.2	1,614		11.4
Cigarette smoking									
Never	1,330		26.0	5,407		59.3	6,737		47.4
Past	1,712		33.5	1,212		13.3	2,924		20.6
Current	2,065		40.4	2,502		27.4	4,567		32.1
Blood pressure: SBP*/DBP*									
Normal‡	775		15.2	2,224		24.4	2,999		21.1
Prehypertension§	1,625		32.0	3,060		33.6	4,685		33.0
Hypertension: stage I¶	1,666		32.8	2,373		26.0	4,039		28.4
Hypertension: stage II or treated#	1,020		20.1	1,457		16.0	2,477		17.4
Body mass index									
<18.5	30		0.6	67		0.7	97		0.7
18.5–22.9	699		13.8	1,628		18.0	2,327		16.5
23.0–24.9	934		18.4	1,548		17.1	2,482		17.6
25.0–29.9	2,558		50.5	3,531		39.0	6,089		43.1
30.0–34.9	736		14.5	1,677		18.5	2,413		17.1
≥35.0	108		2.1	615		6.8	723		5.1
Body mass index									
≤24.9	1,663		32.8	3,243		35.8	4,906		34.7
25.0–29.9	2,558		50.5	3,531		39.0	6,089		43.1
≥30.0	844		16.7	2,292		25.3	3,136		22.2
Low risk**	81		1.6	314		3.5	395		2.8
Unfavorable but not high risk††	750		14.7	1,657		18.2	2,407		16.9
High risk‡‡	4,269		83.7	7,141		78.4	11,410		80.3

* SD, standard deviation; HDL, high density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure.

† Weight (kg)/height (m)².

‡ SBP ≤120 mmHg and DBP ≤80 mmHg, no antihypertensive drug treatment.

§ SBP 121–139 mmHg or DBP 81–89 mmHg, no antihypertensive drug treatment.

¶ SBP 140–159 mmHg or DBP 90–99 mmHg, no antihypertensive drug treatment.

SBP ≥160 mmHg or DBP ≥100 mmHg or antihypertensive drug treatment.

** Serum total cholesterol <200 mg/dl and SBP ≤120 mmHg and DBP ≤80 mmHg and body mass index <25.0 and no antihypertensive medication and no smoking and no diabetes.

†† Serum total cholesterol 200–239 mg/dl and/or SBP 121–139 mmHg and/or DBP 81–89 mmHg and/or body mass index 25.0–29.9 and no antihypertensive medication and no smoking and no diabetes.

‡‡ Serum total cholesterol ≥240 mg/dl and/or SBP ≥140 mmHg and/or DBP ≥90 mmHg and/or body mass index ≥30 and/or antihypertensive medication and/or smoking and/or diabetes.

TABLE 2. Number of persons, baseline average age, person-years, number of strokes, and age- and gender-adjusted rate of stroke, by risk group, for Italian population samples (Progetto CUORE, 1983–2002) of men and women aged 35–69 years at baseline and free of previous cardiovascular disease and family history of cardiovascular disease (cohort 3)

Risk group	Men and women combined				
	No. of persons	Baseline average age (years)	No. of person-years	No. of stroke events	Age- and gender-adjusted rate/10,000 person-years
Low risk*	395	43.0	3,841	0	0.0
Unfavorable but not high risk†					
All	2,407	46.4	24,151	10	8.5
Any 1 risk factor only	769	44.2	7,885	3	6.2
≥2 risk factors	1,638	47.4	16,266	7	8.5
Low and unfavorable					
All	2,802	45.9	27,992	10	8.0
Low and unfavorable any 1 risk factor only	1,164	43.8	11,725	3	4.5
High risk‡					
All	11,410	51.1	114,378	190	18.5
Any 1 risk factor only	4,188	48.3	40,905	36	16.2
≥2 risk factors	7,222	52.8	73,473	154	20.3
≥3 risk factors	3,987	53.9	41,042	112	24.3

* Serum total cholesterol <200 mg/dl and systolic blood pressure (SBP) ≤120 mmHg and diastolic blood pressure (DBP) ≤80 mmHg and body mass index <25.0 and no antihypertensive medication and no smoking and no diabetes.

† Serum total cholesterol 200–239 mg/dl and/or SBP 121–139 mmHg and/or DBP 81–89 mmHg and/or body mass index 25.0–29.9 and no antihypertensive medication and no smoking and no diabetes.

‡ Serum total cholesterol ≥240 mg/dl and/or SBP ≥140 mmHg and/or DBP ≥90 mmHg and/or body mass index ≥30.0 and/or antihypertensive medication and/or smoking and/or diabetes.

more (of four) risk factors were unfavorable (but not high). Of the 769 participants for whom only one of these four traits was unfavorable, three experienced stroke. For 1,164 low risk plus UNHRi participants with only one risk factor unfavorable (table 2), the age- and gender-adjusted rate of stroke was 4.5/10,000 person-years.

Of 11,410 high risk participants, 190 experienced stroke. The age- and gender-adjusted stroke rate was 18.5/10,000 person-years, 4.1 times higher than for those considered low risk or U-NHRi with only one risk factor unfavorable. Compared with that for those at high risk, the relative risk was 0.24–76 percent lower. For high-risk substrata in which only one risk factor was high, two or more were high (50.7 percent of cohort 3), and three or more were high (28.0 percent of cohort 3), the respective age- and gender-adjusted stroke rates were 16.2, 20.3, and 24.3/10,000 person-years; respective relative risks were 3.6, 4.5, and 5.4 compared with those for the combined strata of low risk plus UNHRi only one factor unfavorable (but not high).

Results were similar for cohorts 1 and 2, with sample sizes considerably larger than those for cohort 3. Thus, with the low-risk strata numbering 547 for cohort 1 and 543 for cohort 2, no strokes were recorded for either cohort. For the combined strata of low risk plus U-NHRi only one risk factor unfavorable (but not high), the respective age- and gender-adjusted stroke incidence rates were 5.5 and 5.6/

10,000 person-years. In contrast, for the great majority of these two cohorts classified as baseline high risk, age- and gender-adjusted incidence rates were 21.2 and 20.8/10,000 person-years, with a gradient related to the number of risk factors considered high that was concordant with the findings for cohort 3. For these high risk persons overall, stroke incidence rates were, respectively, 3.9 and 3.7 times higher than for the combined strata of low risk plus UNHRi only one factor unfavorable. Correspondingly, for these combined low-risk strata, the relative risks of stroke were 0.26 and 0.27, that is, lower by 74 percent for cohort 1 and by 73 percent for cohort 2. Data were similar for the three cohorts aged 50–69 years; for example, compared with high risk, for low risk plus UNHRi only one factor unfavorable (but not high), respective hazard ratios for stroke were 0.25, 0.26, and 0.24—lower by 75 percent, 74 percent, and 76 percent (for cohort 3, age- and gender-adjusted stroke rates were 7.6 and 31.5/10,000 person-years).

Correspondingly, for all persons aged 35–69 years and not at high risk (low risk + all UNHRi) compared with those at high risk in cohorts 1, 2, and 3, the hazard ratios of stroke were 0.35, 0.36, and 0.43; that is, stroke risks were lower by 65 percent, 64 percent, and 57 percent, respectively. For those aged 50–69 years, the corresponding hazard ratios were 0.37, 0.39, and 0.49; that is, stroke risks were 63 percent, 61 percent, and 51 percent lower.

TABLE 3. Relation of risk factors considered singly to 10-year stroke risk for Italian population samples (Progetto CUORE, 1983–2002) of men and women combined, aged 35–69 years at baseline and free of previous cardiovascular disease and family history of cardiovascular disease (cohort 3)

Variable	Age, gender, and sample adjusted			Hazard ratio			
	Coefficient	Significance	SE†	More adverse level‡	95% CI†	More favorable level§	95% CI
Age (years)	0.1143	***	0.0096	2.71	2.30, 3.20	0.37	0.31, 0.43
Gender (men/women)	0.4896	***	0.1455	1.63	1.23, 2.17	0.61	0.46, 0.81
Systolic blood pressure (mmHg)	0.0221	***	0.0029	1.60	1.41, 1.81	0.63	0.55, 0.71
Diastolic blood pressure (mmHg)	0.0212	***	0.0060	1.27	1.11, 1.45	0.79	0.69, 0.90
Serum total cholesterol (mmol/liter)	0.0175	NS†	0.0645	1.02	0.88, 1.18	0.98	0.85, 1.13
Serum HDL‡ cholesterol (mmol/liter)	–0.0232	NS	0.1946	1.01	0.86, 1.18	0.99	0.85, 1.16
Serum total/HDL cholesterol	0.0479	NS	0.0472	1.07	0.94, 1.23	0.93	0.82, 1.07
Body mass index¶	–0.0090	NS	0.0170	0.96	0.83, 1.11	1.04	0.90, 1.21
Body mass index (current smokers)	–0.0362	NS	0.0327	0.86	0.67, 1.12	1.16	0.89, 1.49
Body mass index (nonsmokers)	0.0063	NS	0.0201	1.03	0.86, 1.23	0.97	0.81, 1.16
Fasting plasma glucose (mmol/liter)	0.1735	***	0.0322	1.26	1.16, 1.38	0.79	0.73, 0.86
Current cigarette smoking (yes, no)	0.4100	*	0.1595	1.51	1.10, 2.06	0.66	0.49, 0.91
No. of cigarettes/day	0.0327	***	0.0074	1.33	1.17, 1.51	0.75	0.66, 0.85
Diabetes (yes, no)	0.7490	***	0.2138	2.12	1.39, 3.22	0.47	0.31, 0.72
Hypertensive treatment (yes, no)	0.7308	***	0.1687	2.08	1.49, 2.89	0.48	0.35, 0.67

* $p < 0.05$; *** $p < 0.001$.

† SE, standard error; CI, confidence interval; NS, not significant; HDL, high density lipoprotein.

‡ For continuous variables, hazard ratio with level 1 standard deviation higher except for HDL cholesterol with level 1 standard deviation lower (refer to table 1); for dichotomized variables, yes vs. no; for no. of cigarettes/day, 15 vs. 0.

§ For continuous variables, hazard ratio with level 1 standard deviation lower except for HDL cholesterol with level 1 standard deviation higher (refer to table 1); for dichotomized variables, no vs. yes; for no. of cigarettes/day, 0 vs. 15.

¶ Weight (kg)/height (m)².

Relation of risk factors considered singly to stroke risk

For cohort 3, there was a significant, continuous graded relation of SBP and DBP to stroke incidence ($p < 0.001$) (table 3), stronger for SBP than for DBP (respective hazard ratios = 1.60 and 1.27 with 1 standard deviation higher SBP, DBP). For persons at hypertension stage II, the hazard ratio was 2.32 compared with that for participants whose SBP/DBP was normal. Correspondingly, need for hypertensive drug treatment was associated with a hazard ratio of 2.08. Stroke risk was much higher for current smokers compared with baseline nonsmokers (never + past smokers) ($p < 0.05$, hazard ratio = 1.51). Fasting plasma glucose level was positively related to stroke risk ($p < 0.001$, hazard ratio = 1.26, 1 standard deviation higher). For diabetic participants, the hazard ratio was 2.12 ($p < 0.001$). For this cohort, baseline serum lipids and BMI were not significantly related to stroke risk.

In corresponding univariate analyses for cohorts 1 and 2, findings were similar qualitatively and quantitatively to those for cohort 3 regarding all variables significantly related to stroke risk. However, results for serum lipids and stroke were different for cohorts 1 and 2 compared with cohort 3; that is, significant relations were recorded for both high density lipoprotein cholesterol and total cholesterol/

high density lipoprotein cholesterol ratio—inverse for the former (respective hazard ratios = 1.16 and 1.15 with high density lipoprotein cholesterol 1 standard deviation lower vs. 1.01 for cohort 3) and direct for the latter (respective hazard ratios = 1.14 and 1.13 with total cholesterol/high density lipoprotein cholesterol 1 standard deviation higher vs. 1.07 for cohort 3). For cohorts 1 and 2, family history of premature cardiovascular disease was significantly related to stroke risk (respective hazard ratios = 1.39 and 1.35). For all three cohorts, BMI was not significantly related to stroke risk (respective hazard ratios with BMI 1 standard deviation higher = 1.05, 1.06, and 0.96). For persons aged 50–69 years in all three cohorts, relations of high density lipoprotein cholesterol, total cholesterol/high density lipoprotein cholesterol, and BMI to stroke risk were not significant.

Relation of multiple risk factors considered together to stroke

For cohort 3, modifiable baseline risk factors significantly, independently, and directly related to stroke were SBP, need for antihypertensive treatment, cigarette smoking, and diabetes (table 4). Hazard ratios for these variables were all sizable, in the range of 1.52–1.74. Findings on these variables were similar qualitatively and quantitatively for all

TABLE 4. Independent relation of risk factors to 10-year stroke risk from multivariate proportional hazards regression models† for Italian population samples (Progetto CUORE, 1983–2002) of men and women aged 35–69 years at baseline and free of previous cardiovascular disease and family history of cardiovascular disease (cohort 3)

Variable	Multivariate-adjusted coefficient				Hazard ratio (model 2)			
	Model 1		Model 2		More adverse level‡	95% CI§	More favorable level‡	95% CI
Age (years)	0.094	***	0.092	***	2.24	1.87, 2.68	0.45	0.37, 0.54
Male gender (yes/no)	0.382	*	0.390	*	1.48	1.07, 2.03	0.68	0.49, 0.93
Systolic blood pressure (mmHg)	0.023	***	0.020	***	1.52	1.33, 1.74	0.66	0.58, 0.75
Hypertension treatment (yes, no)			0.423	*	1.53	1.06, 2.19	0.66	0.46, 0.94
Current cigarette smoking (yes, no)	0.489	**	0.473	**	1.60	1.16, 2.21	0.62	0.45, 0.86
Diabetes (yes, no)			0.553	*	1.74	1.12, 2.70	0.47	0.26, 0.86
Serum total/HDL cholesterol			0.045	NS§	1.07	0.93, 1.23	0.94	0.82, 1.08
Body mass index (kg/m ²)			-0.037	NS	1.18	1.00, 1.38	0.85	0.72, 1.00
No. of people	14,184		13,916					
No. of strokes	199		194					

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

† Models were adjusted for samples.

‡ For continuous variables, hazard ratio with level 1 standard deviation higher except for high density lipoprotein (HDL) cholesterol with level 1 standard deviation lower; for dichotomized variables, yes vs. no.

§ CI, confidence interval; NS, not significant.

three cohorts. For the total cholesterol/high density lipoprotein cholesterol ratio in multivariate model 2, for a 1 standard deviation higher level, hazard ratios for cohorts 1, 2, and 3 were 1.11 ($p < 0.05$), 1.09, and 1.07 ($p > 0.05$ for the latter two cohorts), respectively. In these multivariate analyses for all three cohorts, BMI was not significantly related to stroke risk; inclusion of BMI and BMI² in model 2 yielded no evidence for a quadratic (U-shaped) relation of BMI to stroke risk. Again, findings were similar for persons aged 50–69 years.

Particularly since tests for model 2 interactions yielded putatively significant findings for gender \times smoking (cohort 1) and gender \times diabetes (cohorts 2 and 3), as part of extensive sensitivity analyses, all table 4 data were also generated by gender for all three cohorts aged 35–69 and 50–69 years. Consistently for both women and men, key modifiable risk factors related significantly and independently to stroke risk were SBP (hazard ratios = 1.42–1.48 for 1 standard deviation higher SBP), need for antihypertensive drug treatment (yes vs. no, hazard ratios = 1.45–1.68), and cigarette smoking at baseline (yes vs. no, hazard ratios = 1.61–1.78). Hazard ratios were similar for women and men. The total cholesterol/high density lipoprotein cholesterol ratio also related positively to stroke risk, with low-order hazard ratios (1.04–1.19) in multivariate models, statistically significant for only cohort 1 women. Unlike the foregoing variables, findings for diabetes varied for men and women according to interaction tests: for men, high-order significant ($p < 0.001$) hazard ratios in the range of 2.22–2.59 were found (diabetes, yes vs. no); for women, results showed much smaller, non-significant, low-order positive hazard ratios for cohorts 1 and 2, inverse for cohort 3. For both genders in all three cohorts, BMI was not significantly related to stroke risk in

these model 2 multivariate analyses. All hazard ratios were of low order and inverse.

DISCUSSION

Main findings of this 12-sample, population-based study on low risk and 10-year stroke incidence among Italian men and women aged 35–69 years at baseline are as follows: 1) At baseline, only 3 percent of participants were low risk, 80 percent were high risk, and 51 percent had two or more high risk factors; 2) for all three cohorts, no strokes occurred in women or men with favorable levels of all major modifiable risk factors, and low stroke rates were found for those with borderline high blood pressure or total cholesterol or BMI (any one only) and all other risk factors favorable; 3) for low risk persons or those with only one risk factor unfavorable (but not high), the stroke rate was about 75 percent lower than that for high risk persons; and 4) for all high risk persons, stroke risk was about four times higher than that for the stipulated combined strata (low risk + UNHRi only one risk factor unfavorable) not high risk. Adverse stroke outcomes for high risk women and men were similar.

These findings on the protective effects of low risk against stroke for both genders are concordant with data on the large cohort of men aged 35–57 years screened in 18 US cities for the Multiple Risk Factor Intervention Trial (MRFIT) and on two Chicago, Illinois, cohorts (7,490 men and 6,229 women aged 40–59 years) (1, 2). Thus, for 11,098 low-risk MRFIT men (favorable findings for six risk factors: total cholesterol, SBP, DBP, no smoking, diabetes, and myocardial infarction), only three fatal strokes occurred in 11.6 years; the age-adjusted rate was 0.4/10,000 person-years. For the other

342,242 men, the rate was 1.9; that is, for low risk men compared with all others, the relative risk was 0.21–79 percent lower. These results persisted with 16-year follow-up (2). For the Chicago cohorts (22-year follow-up), the relative risk of stroke for low risk persons compared with all others was lower by 64 percent (women) and 52 percent (men) (2).

Limitations of the present study include the following six: 1) Small size of low-risk subcohorts (male, female); however, the similar results on stroke in this study and for the three other low-risk cohorts (MRFIT, Chicago) (1, 2) support the inference that low risk generally protects against stroke. 2) Low-risk status based on only one measurement of the several risk factors; however, this limitation—the regression dilution bias problem (15–17)—leads to some participants being improperly designated as low risk, with resultant underestimation of the favorable effects of low risk. 3) No data on eating, drinking, or exercise—lifestyle traits also implicated as major modifiable risk factors for cardiovascular disease; however, lack of data on these traits makes more impressive the benefit against stroke with favorable baseline levels of the readily measured, modifiable risk factors. 4) Only 10-year follow-up data available; however, favorable findings for low risk and stroke prevailed for the MRFIT and Chicago cohorts with 16- and 22-year follow-up (2). 5) Varied participation rate—from 40 percent to 78 percent; however, for all 12 samples, average levels and distributions of baseline risk factors were similar and resembled those for other Western population samples of corresponding ages. 6) Diagnostic criteria applied to validate stroke events from the MONICA project; however, more precise criteria based on computerized tomography and magnetic resonance imaging are available today.

Concerning the stroke incidence and mortality rates reported here for Italian population samples aged 35–69 years at baseline, they are concordant with Italian mortality data and with results from the Italian Longitudinal Study on Aging (5, 18). That investigation recorded a first stroke incidence rate of 95.1/10,000 person-years for persons aged 63–84 years. For each group 5 years older, the stroke rate was higher by 37 percent.

With regard to the present findings on the individual major modifiable cardiovascular risk factors and stroke, significant independent relations—recorded for SBP; cigarette smoking; diabetes (in men particularly); and the low-order, nonsignificant relation of serum total cholesterol/high density lipoprotein cholesterol—are all concordant with results from other population-based prospective studies, including MRFIT (19).

The Progetto Cuore finding that BMI did not relate to stroke risk in either univariate or multivariate analyses is consistent with some (but not all) other reports. In this regard, it is important to emphasize the significant strong relation of BMI to major preventable and controllable risk factors for stroke, particularly blood pressure and diabetes but also dyslipidemia. Clearly, prevention and control of overweight/obesity is key to combating these major modifiable risk factors. (The finding here that diabetes related significantly to stroke risk for men only, not for women, was unexpected, exceptional, and anomalous; further assessment is needed.)

As to the low prevalence of low risk and the high prevalence of high risk in the Italian population samples, most of the variables defining risk are diet related: SBP/DBP, lipidemia, diabetes, and BMI. Hence, this question arises: What has happened to the “Mediterranean dietary advantage” in Italy? Multiple data sets show serial transformation of Italian eating patterns from generally favorable ones in the late 1950s and early 1960s to adverse ones thereafter (20–26). Per capita consumption of total energy, total and saturated fats, cholesterol, and sugars has risen considerably. Correspondingly, average total cholesterol levels for middle-aged Italian cohorts in the 1980s and 1990s were in the range of 5.70–5.96 mmol/liter (220–230 mg/dl), considerably higher than for Italian cohorts surveyed in the late 1950s and early 1960s (22). Along with declines in work- and leisure-related physical activity, the serially more unfavorable eating patterns also account for increasing overweight and obesity.

Therefore, it is also relevant to note recent research advances on relations of multiple dietary factors to blood pressure: data from several epidemiologic studies and from the well-controlled DASH and the Optimal Macronutrient Intake Trial to Prevent Heart Disease (OMNIHEART) feeding trials indicate that multiple dietary factors—macro- and micro-nutrients, and electrolytes (sodium chloride, potassium)—influence blood pressure as well as caloric imbalance (overweight/obesity) (16, 27–33). Habitual dietary patterns that favorably influence blood pressure are lower in salt and alcohol; higher in multiple minerals and vitamins, vegetable protein, and fiber; and lower in total fats, saturated fats, cholesterol, and sugars (27, 29). In all these instances, the DASH and OMNIHEART combination diets, highly efficacious in reducing SBP/DBP for both prehypertensive and hypertensive adults, generally resemble Italian dietary patterns of the late 1950s and 1960s: high in fruits, vegetables, and whole grains; emphasis on seafood, lean poultry, fat-free and low-fat dairy products, legumes, nuts, and olive and seed oils in modest amounts; and low in red meats, fat-containing dairy products, eggs, and sugars and sweets. However, these eating patterns differ from traditional Italian fare in two respects. For Italians, salt and alcohol intakes have been on average high, not low. It is a reasonable inference that these two aspects, along with caloric imbalance (overweight/obesity), account importantly for unfavorable average SBP/DBP levels among Italian adults.

Low risk—favorable levels of all readily measured, major modifiable risk factors for cardiovascular disease—is associated with low stroke rates. Low prevalence rates of low risk in contemporary populations are a result of adverse lifestyles, including smoking, adverse eating and drinking patterns, and sedentary habits, which cause common problems such as elevated blood pressure, hyperglycemia/diabetes, dyslipidemia, and obesity, all amenable to prevention and control. Intervention in the general population needs to be implemented. Emphasis should be placed on improved lifestyles: nonsmoking; prevention and control of overweight/obesity; and eating patterns of original Mediterranean composition, including lower salt and alcohol intakes and greater habitual physical activity. The priority strategic aim is to increase progressively the proportion of the

population at low risk, at all ages, key to ending the epidemic of cerebrovascular/cardiovascular disease.

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