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.

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) for 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 Estomastico; 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 Ateriosclerotiche 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 Aterioscleroti 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/m²).

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)

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

* 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.
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 UNHRi 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 risk 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 UNHRi 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 7.4/10,000 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)**

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

* 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)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Multivariate-adjusted coefficient</th>
<th>Hazard ratio (model 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1</td>
<td>Model 2</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.094</td>
<td>0.092</td>
</tr>
<tr>
<td>Male gender (yes/no)</td>
<td>0.382</td>
<td>0.390</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>0.023</td>
<td>0.020</td>
</tr>
<tr>
<td>Hypertension treatment (yes, no)</td>
<td>0.423</td>
<td>0.467</td>
</tr>
<tr>
<td>Current cigarette smoking (yes, no)</td>
<td>0.489</td>
<td>0.473</td>
</tr>
<tr>
<td>Diabetes (yes, no)</td>
<td>0.553</td>
<td>0.473</td>
</tr>
<tr>
<td>Serum total/HDL cholesterol</td>
<td>0.045</td>
<td>NS§</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>−0.037</td>
<td>NS§</td>
</tr>
<tr>
<td>No. of people</td>
<td>14,184</td>
<td>13,916</td>
</tr>
<tr>
<td>No. of strokes</td>
<td>199</td>
<td>194</td>
</tr>
</tbody>
</table>

* 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.

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 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
was unexpected, exceptional, and anomalous; further as-
significantly to stroke risk for men only, not for women,
able risk factors. (The finding here that diabetes related
overweight/obesity is key to combating these major modifi-
but also dyslipidemia. Clearly, prevention and control of
the several risk factors; however, this limitation—the re-
sultant 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 favor-
able 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 per-
cent; however, for all 12 samples, average levels and distri-
butions of baseline risk factors were similar and resembled
those for other Western population samples of correspond-
ing 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 in-
cidence 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 ma-
jor modifiable cardiovascular risk factors and stroke, signif-
icant independent relations—recorded for SBP; cigarette
smoking; diabetes (in men particularly); and the low-order,
nonsignificant relation of serum total cholesterol/high den-
sity 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 re-
gard, it is important to emphasize the significant strong re-
lation 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 modifi-
able risk factors. (The finding here that diabetes related
significantly to stroke risk for men only, not for women,
was unexpected, exceptional, and anomalous; further as-
essment is needed.)

As to the low prevalence of low risk and the high preva-
ence of high risk in the Italian population samples, most of
the variables defining risk are diet related: SBP/DBP, lipi-
demia, diabetes, and BMI. Hence, this question arises: What
has happened to the “Mediterranean dietary advantage” in
Italy? Multiple data sets show serial transformation of Ita-
lian 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. Corre-
spondingly, 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 unfavor-
able eating patterns also account for increasing overweight
and obesity.

Therefore, it is also relevant to note recent research ad-
vances on relations of multiple dietary factors to blood pres-
sure: data from several epidemiologic studies and from the
well-controlled DASH and the Optimal Macronutrient Intake
Trial to Prevent Heart Disease (OMNIHEART) feeding tri-
als indicate that multiple dietary factors—macro- and micro-
nutrients, and electrolytes (sodium chloride, potassium)—
influence blood pressure as well as caloric imbalance (over-
weight/obesity) (16, 27–33). Habitual dietary patterns that
favorably influence blood pressure are lower in salt and al-
cohol; higher in multiple minerals and vitamins, vegetable
protein, and fiber; and lower in total fats, saturated fats, cho-
lesterol, and sugars (27, 29). In all these instances, the DASH
and OMNIHEART combination diets, highly efficacious in
reducing SBP/DBP for both prehypertensive and hyperten-
sive 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 lev-
els among Italian adults.

Low risk—favorable levels of all readily measured, major
modifiable risk factors for cardiovascular disease—is asso-
ciated 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 prob-
lems such as elevated blood pressure, hyperglycemia/diabe-
tes, 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 over-
weight/obesity; and eating patterns of original Mediterrane-
nan composition, including lower salt and alcohol intakes
and greater habitual physical activity. The priority strate-
gic aim is to increase progressively the proportion of the

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

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Conflict of interest: none declared.

REFERENCES


