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Favorable cardiovascular risk profile and 10-year coronary heart disease incidence in women and men: results from the Progetto CUORE

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Background **Cardiovascular risk factor research has recently broadened its focus based on new data indicating the benefits of low risk, i.e. favorable levels of all major risk factors. The aims of this study were to assess further the relation of low risk to coronary heart disease risk, and implications for prevention.**

Design **We conducted a prospective population-based Italian study, of 7438 men and 13 009 women aged 35–69 years, with a mean follow-up of 10.4 years and validated first coronary events.**

Methods **Baseline coronary heart disease risk was classified into three categories: low risk; unfavorable but not high risk; and high risk. To analyze the relation of these risk profiles to coronary heart disease incidence, age-adjusted, sex-averaged coronary heart disease incidence was calculated for persons free of coronary heart disease and stroke, stratified as baseline low risk, unfavorable but not high risk or high risk. To assess the independent relationship of individual risk factors to coronary heart disease incidence, multivariate proportional hazards models were computed for combinations of risk factors.**

Results **Only 2.7% of participants met low risk criteria; 81.4% were high risk. Age-adjusted coronary heart disease incidence for the whole cohort was 37.1 out of 10 000 person–years (men 59.0; women 15.3). No coronary heart disease events occurred in low-risk men, only two in low-risk women. For women and men who were not high risk, the age–sex standardized coronary heart disease rate was 62% lower than for high-risk participants. Blood pressure, need for antihypertensive medication, smoking, hyperglycemia, diabetes, total and high-density lipoprotein cholesterol were independently related to coronary heart disease risk.**

Conclusions **Favorable levels of all modifiable readily measured risk factors – rare among Italian adults – assure minimal coronary heart disease risk. Population-wide prevention is needed, especially improved lifestyles, to increase the proportion of the population at low risk. *Eur J Cardiovasc Prev Rehabil* 13:562–570 © 2006 The European Society of Cardiology**

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Introduction

In recent years, an important conceptual advance has been introduced concerning the major cardiovascular

disease (CVD) risk factors: the focus is no longer exclusively on their adverse effects, but also on protective effects of favorable levels of all readily measured modifiable major coronary heart disease (CHD) risk factors, namely low risk. Low-risk persons are rare in the general population and therefore research on the impact of low risk requires large cohorts followed long-term. Available data indicate that for low risk substrata, CVD, particularly CHD, is rare and endemic, not epidemic, throughout adulthood. These findings come from only three studies, however, all of US cohorts [1–5].

The possibility that low-risk protects against CHD is important, since CHD remains a major cause of morbidity, disability, and death (European Health for All Database, website: http://www.WHO.dk/hfadb). In this study we assessed the impact of low risk on 10-year CHD incidence in 20 447 women and men at baseline ages of 35–69 years, from the Italian longitudinal study, the Progetto CUORE [6].

Methods

Population samples

Twelve random samples of general populations aged 35–69 years were studied: seven from general populations in north Italy (the MONICA study, Brianza 1986, 1990, 1993; Friuli 1986, 1989, 1994; the PAMELA study); five in central or southern Italy (MONICA Latina, 1984–86; MATISS 1984, 1987, 1993; ATENA).

Baseline measurements

Risk factors were assessed by standardized procedures [6,7]. Blood pressure (right arm) was measured twice with a mercury sphygmomanometer, participant sitting, rested 5 min; systolic blood pressure (SBP)/diastolic blood pressure (DBP) were recorded (first and fifth Korotkoff sounds); these first and second measurements were averaged for analyses. Serum total and high-density lipoprotein (HDL) cholesterol were assayed by enzymatic colorimetry. Fasting plasma glucose was measured in 63% of participants. Height and weight were measured with the participant wearing light clothing without shoes. Body mass index (BMI) was computed as weight/height^2 (kg/m^2). Information was collected by questionnaire on cigarette smoking, personal history of myocardial infarction (MI), stroke, diabetes mellitus, hospitalization for cardiovascular events and medication use. Sources for checking data included MONICA registers and hospital discharge records (i.e., information from medical doctors). As to medication use, this was checked (verified) by having the participant bring in his or her medications to the baseline examination, for review and recording by trained staff.

Coronary events registration/validation

During follow-up (mean time 10.4 years), deaths were identified from vital statistics. Death certificates were coded using the International Classification of Diseases and Causes of Death, Ninth Revision (ICD-9) [8]. Vital status and death certificates were available for 99% of participants. Underlying causes of death ICD-9 codes 410–414 (ischemic heart disease), 798 (sudden death), 799 (other ill-defined and unknown causes of morbidity and mortality) as well as codes 250 (diabetes mellitus), 428 (heart failure), 440 (atherosclerosis) in association with 410–414 codes, were considered as suspected coronary deaths and further investigated for validation. Non-fatal coronary events were ascertained through record linkage using hospital discharge diagnosis records with ICD-9 410–411 (acute myocardial infarction, other acute and sub-acute forms of ischemic heart disease) codes for suspected acute infarction and ICD-9-CM 36.0–36.9 codes for coronary surgery revascularization; MONICA registers, sample re-examinations, contacts with general practitioners, patients, and relatives were used. Fatal and non-fatal coronary events were validated using MONICA diagnostic criteria [9], based on symptom combinations, electrocardiograms, cardiac enzymes, history of CHD, and available autopsy findings.

Data analyses

Ten-year coronary incidence rates were calculated and age-adjusted (direct method) using the European population 1995 (World Population Prospects: The 2002 Revision United Nations, Population database; website http://esa.un.org/unpp/). For both low-risk and unfavorable-but-not-high-risk men and women, CHD events were few (or none) in 5-year age groups, especially at younger ages. Accordingly, to reduce possible distortion in age adjusted rates, adjustment was based on the strata ages 35–49, 50–59, and 60–69 years, for men and women separately. Given the considerably greater number of women than men, to avoid sex weighting of overall incidence rates, non-weighted averages of male and female rates were calculated. CHD incidence rates were so calculated for the strata classified by baseline risk factor findings as low risk, unfavorable but not high risk, low risk plus unfavorable but not high risk, and high risk (see below for strata definitions). For low risk, paucity of CHD events precluded calculation of age–sex standardized rates. Based on age–sex standardized rates for the low risk plus unfavorable but not high risk stratum, expected numbers of CHD events were calculated for the high-risk stratum.

Risk factors included total cholesterol, HDL cholesterol, fasting glucose, SBP, DBP, BMI; SBP/DBP identified normal (SBP $\leq$ 120 mmHg and DBP $\leq$ 80 mmHg), prehypertensive (SBP 121–139 mmHg or DBP 81–89 mmHg), hypertensive stage I (SBP 140–159 mmHg or DBP 90–99 mmHg), or hypertensive stage II (SBP $\geq$ 160 mmHg or DBP $\geq$ 100 mmHg or antihypertensive drug treatment irrespective of SBP/DBP) [10].

Diabetes definition was a fasting plasma glucose ≥ 6.99 mmol/l (≥ 126 mg/dl) [11], or self-reported drug-treated diabetes. Cigarette use was classified as never, past only, current and by the number of cigarettes per day.

Low risk included persons with all the following characteristics: total cholesterol < 5.17 mmol/l (< 200 mg/dl), SBP ≤ 120 mmHg, DBP ≤ 80 mmHg, no antihypertensive medication, BMI < 25.0 kg/m^2, no diabetes, no smoking, i.e., favorable levels of all readily measured modifiable major CHD/CVD risk factors.

Unfavorable but not high risk included persons with one or more of the following: total cholesterol 5.17–6.18 mmol/l (200–239 mg/dl), SBP 121–139 mmHg, DBP 81–89 mmHg (no antihypertensive medication), BMI 25.0–29.9 kg/m^2; also, no diabetes, no smoking.

High risk included persons with one or more of the following: total cholesterol ≥ 6.19 mmol/l (≥ 240 mg/dl), SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, need for antihypertensive medication, BMI ≥ 30.0 kg/m^2, diabetes, smoking.

To assess the relationship of each risk factor to CHD incidence, univariate analyses–categorical and continuous as appropriate–adjusted for age, sex and sample were also done, yielding for each risk factor a proportional hazards regression coefficient (standard error, SE), hazard ratio (HR) and 95% confidence interval (CI) [12]. Age, sex, and sample-adjusted multivariate proportional hazards models were then computed for combinations of risk factors significant in the univariate analyses.

Multicolinearity was first checked by partial correlation analysis (controlled for age, sex, sample); no highly correlated variables were included in a multivariate model. Interactions were assessed of sex with each modifiable risk factor; also of smoking with each other risk factor.

Results

Since baseline and follow-up findings were similar for men and women, detailed data tabulated here are for the two sexes combined. Participation rates were between 64 and 78% except for MATISS 1987 (40%) [13]. Less than 1% were lost to 10-year follow-up (150 out of 20 447); they contributed to the follow-up period until the date of the last available information.

Baseline descriptive statistics

Of the 20 447 participants, average age 50.4 years, only 543 (2.7%) were low risk (1.4% of men and 3.4% of women); most (81.4%) (84.9% of men and 79.3% of women) were high risk (Table 1). Among both men and women, the high risk proportion was progressively greater with age, for example, for men 76.4% at age 35–39 years, 90.9% at ages 65–69 years; for women, 57.5% and 94.3%. By definition, risk factor levels differed markedly across risk factor strata, especially for low risk compared with high risk, for example, SBP/DBP 111/72 mmHg for low risk, 141/86 for high risk; serum total cholesterol 4.53 and 5.96 mmol/l (175.0 and 234.6 mg/dl); BMI 22.2 and 27.6 kg/m^2. Of 16 638 high risk persons, 39% were smokers, 61% were hypertensive (31% stage II elevation or receiving antihypertensive drug treatment).

For all 20 447 participants, the whole cohort, baseline average SBP and DBP were in prehypertensive ranges, only 20% had normal blood pressure; the total cholesterol mean was borderline high; average BMI was in the overweight range; the prevalence of current cigarette smoking was 31% (40% of men and 26% of women) (Table 1).

Coronary heart disease incidence

First coronary events numbered 656 (men 469; women 187), 464 non-fatal, 192 fatal; age-adjusted incidence was 3.9 times higher in men (59.0/10 000 person–years) than women (15.3/10 000 person–years). CHD incidence increased markedly across the 5-year age groups: for men ages 35–39, 22.9/10 000 person–years, at ages 65–69, 115.8; women ages 35–39, 3.1/10 000 person–years, at ages 65–69, 50.6 (detailed data not tabulated).

Relation of baseline risk status to coronary heart disease

Of 439 low-risk women, two developed CHD, at ages 57 and 60 years; of 104 low-risk men, none experienced CHD in 10 years; the averaged crude rate for the two sexes combined was 2.3/10 000 person–years (Table 2). In contrast, the averaged crude rate for high-risk men and women combined was 40.6/10 000 person–years; the corresponding adjusted rate being 39.8 (62.6 for men, 17.0 for women). For persons not high risk (i.e., low risk plus unfavorable but not high risk), the sex-averaged age-adjusted rate was 15.2/10 000 person–years (22.0 for men, 8.4 for women); that is, the risk ratio of low risk plus unfavorable but not high risk compared with the high-risk stratum was 0.38 or 62% lower CHD risk. As these data indicate, CHD risk was also much lower for the unfavorable-but-not-high-risk stratum, compared with the high-risk stratum (Table 2).

Expected numbers of CHD events for high-risk men and women, having the age-adjusted, sex-specific rates of those not high risk, were 240.4 (155.7 for men and 84.7 for women), compared with 614.2 (442.0 and 172.2) estimated from their adjusted rates: 373.8 fewer events total (61% fewer events) (Table 2).

Table 1 Baseline descriptive statistics by risk status, men and women combined

Variable	Low risk[a] ($n=543$)			Unfavorable but not high risk[b] ($n=3266$)			Low + unfavorable but not high risk ($n=3809$)			High risk[c] ($n=16\,638$)			All ($n=20\,447$)		
	n	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD
Age (years)	543	42.9	6.5	3266	46.6	7.9	3809	46.1	7.9	16 638	51.4	8.6	20 447	50.4	8.7
Systolic pressure (mmHg)	543	111.0	6.8	3248	122.4	9.7	3791	120.8	10.2	16 592	140.8	21.7	20 383	137.1	21.6
Diastolic pressure (mmHg)	543	71.9	5.3	3247	78.1	6.5	3790	77.2	6.7	16 591	86.5	11.4	20 381	84.7	11.3
Serum total cholesterol (mg/dl)	543	175.0	18.7	3255	202.6	24.7	3798	198.7	25.8	16 545	234.6	45.3	20 343	227.9	44.6
Serum HDL-C (mg/dl)	543	58.1	13.2	3252	58.7	15.4	3795	58.6	15.1	16 509	56.0	15.7	20 304	56.5	15.6
(Total/HDL) cholesterol (mg/dl)	543	3.2	0.8	3249	3.7	1.0	3792	3.6	1.0	16 498	4.5	1.5	20 290	4.3	1.5
Plasma fasting glucose (mg/dl)	373	84.7	10.5	2160	88.8	11.0	2533	88.2	11.0	10 154	97.0	26.0	12 687	95.2	24.0
Serum triglycerides (mg/dl)	478	75.1	37.7	2859	95.9	55.2	3337	92.9	53.5	14 301	136.5	89.2	17 638	128.3	85.4
Body mass index (kg/m^2)	543	22.2	1.8	3239	25.0	2.7	3782	24.6	2.8	16 509	27.6	4.6	20 291	27.1	4.5
Cigarettes/day (All)	543	0.0	0.0	3266	0.0	0.0	3809	0.0	0.0	16 638	5.6	9.4	20 447	4.6	8.8
Cigarettes/day (current smokers only)	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	6370	14.7	9.9	6370	14.7	9.9
	n	Percentage		*n*	Percentage		*n*	Percentage		*n*	Percentage		*n*	Percentage	
Women	439	80.9		2250	68.9		2689	70.6		10 320	62.0		13 009	63.6	
Diabetes	0	0.0		0	0.0		0	0.0		918	5.7		918	4.6	
Hypertension treatment	0	0.0		0	0.0		0	0.0		2595	15.7		2595	12.8	
Cigarette smoking															
Never	374	68.9		2303	70.5		2677	70.3		7133	43.1		9810	48.2	
Past	169	31.1		963	29.5		1132	29.7		3035	18.4		4167	20.5	
Current	0	0.0		0	0.0		0	0.0		6370	38.5		6370	31.3	
Blood pressure SBP/DBP[d]															
Normal	543	100.0		1023	31.5		1566	41.3		2415	14.6		3981	19.5	
Prehypertension	0	0.0		2225	68.5		2225	58.7		3979	24.0		6203	30.4	
Hypertension-stage I	0	0.0		0	0.0		0	0.0		5082	30.6		5082	24.9	
Hypertension-stage II or treated	0	0.0		0	0.0		0	0.0		5125	30.9		5125	25.1	
Total cholesterol (mg/dl)															
<200	543	100.0		1245	38.3		1788	47.1		3692	22.3		5480	26.9	
200–239	0	0.0		2010	61.8		2010	52.9		5363	32.4		7373	36.2	
≥ 240	0	0.0		0	0.0		0	0.0		7490	45.3		7490	36.8	
HDL-C (mg/dl)															
<40	42	7.7		291	9.0		333	8.8		2160	13.1		2493	12.3	
40–59	253	46.6		1498	46.1		1751	46.1		8347	50.6		10 098	49.7	
≥ 60	248	45.7		1463	45.0		1711	45.1		6002	36.4		7713	38.0	
Glycemia (mg/dl)															
<110	365	97.9		2074	96.0		2439	96.3		8627	85.0		11 066	87.2	
110–125	8	2.1		86	4.0		94	3.7		882	8.7		976	7.7	
≥ 126	0	0.0		0	0.0		0	0.0		645	6.4		645	5.1	
Triglycerides (mg/dl)															
<86	352	73.6		1507	52.7		1859	55.7		3838	26.8		5697	32.3	
86–133	100	20.9		916	32.0		1016	30.5		5004	35.0		6020	34.1	
≥ 134	26	5.4		436	15.3		462	13.8		5459	38.2		5921	33.6	
Body mass index (kg/m^2)															
<25.0	543	100.0		1492	46.1		2035	53.8		4953	30.0		6988	34.4	
25.0–29.9	0	0.0		1747	53.9		1747	46.2		6949	42.1		8696	42.9	
≥ 30.0	0	0.0		0	0.0		0	0.0		4607	27.9		4607	22.7	

[a]Low risk: Serum total cholesterol <200 mg/dl and systolic blood pressure (SBP) ≤ 120 mmHg and diastolic blood pressure (DBP) ≤ 80 mmHg and no antihypertensive medication and body mass index <25.0 kg/m^2 and no smoking and no diabetes. [b]Unfavorable but not high risk: Serum total cholesterol 200–239 mg/dl and/or SBP 121–139 mmHg and/or DBP 81–89 mmHg and no antihypertensive medication and/or body mass index 25.0–29.9 kg/m^2 and no smoking and no diabetes. [c]High risk: Serum total cholesterol ≥ 240 mg/dl and/or SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg and/or antihypertensive medication and/or body mass index ≥ 30 kg/m^2 and/or current smoking and/or diabetes. [d]Normal: SBP ≤ 120 and DBP ≤ 80 mmHg, no antihypertensive drug treatment; Prehypertension: SBP 121–139 or DBP 81–89 mmHg, no antihypertensive drug treatment; Hypertension stage I: SBP 140–159 or DBP 90–99 mmHg, no antihypertensive drug treatment; Hypertension stage II: SBP ≥ 160 or DBP ≥ 100 or antihypertensive drug treatment. HDL-C, high-density lipoprotein cholesterol.

For high-risk substrata, sex-averaged, age-adjusted CHD incidence increased with number of high-risk factors, such as, with one risk factor only high 26.4/10 000 person–years; for two or more high (52.7% of all 20 447 participants) 48.5/10 000 person–years; four or more high, 66.7 (Table 2).

Relation of risk factors considered singly to coronary heart disease risk

Findings were similar for both sexes with no significant sex risk factor interactions. There were significant continuous graded relations of SBP and DBP to CHD incidence ($P<0.001$), stronger for SBP than DBP (HR

Table 2 Ten-year coronary heart disease incidence by baseline risk status, men and women combined

Baseline status	Number of people	Person–years	Observed number of CHD events	Crude 10-year rate per 1000 persons	Sex-averaged age-adjusted rate per 1000 persons	Crude rate per 10 000 person–years	Sex-averaged age-adjusted rate per 10 000 person–years	Expected number of events based on $L+U$ adjusted rate per 10 000 person–years
All	20 447	211 076	656	32.1	39.3	31.1	37.1	–
Low-risk (L)[a]	543	5351	2	3.7	–	3.7	–	–
Unfavorable but not high (U)[b]	3266	33 635	28	8.6	15.4	8.3	14.8	–
$L+U$	3809	38 986	30	7.9	15.4	7.7	15.2	–
High risk[c]	16 638	172 090	626	37.6	43.0	36.4	39.8	240.4
any 1 risk factor only high	5855	59 322	106	18.1	27.5	17.9	26.4	81.2
any 2 risk factor only high	4730	48 882	151	31.9	35.7	30.9	33.2	70.4
any 3 risk factor only high	3393	36 395	182	53.6	57.4	50.0	51.7	51.2
2 or more risk factors high	10 783	112 768	520	48.2	52.1	46.1	48.5	159.2
3 or more risk factors high	6053	63 886	369	61.0	63.0	57.8	58.3	88.8
4 or more risk factors high	2660	27 491	187	70.3	69.8	68.0	66.7	37.6

CHD, coronary heart disease. [a]Low risk (L): Serum total cholesterol <200 mg/dl and systolic blood pressure ≤ 120 mmHg and diastolic blood pressure ≤ 80 mmHg and no antihypertensive medication and body mass index <25.0 kg/m^2 and no smoking and no diabetes. [b]Unfavorable but not high risk (U): Serum total cholesterol 200–239 mg/dl and/or systolic blood pressure 121–139 mmHg and/or diastolic blood pressure 81–89 mmHg and no antihypertensive medication and/or body mass index 25.0–29.9 kg/m^2 and no smoking and no diabetes. [c]High risk: Serum total cholesterol ≥ 240 mg/dl and/or systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or antihypertensive medication and/or body mass index ≥ 30 kg/m^2 and/or current smoking and/or diabetes.

1.45 and 1.25 with 1 SD higher SBP, DBP) (Table 3). For the large stratum with hypertension stage I, HR was 1.61 compared with those with normal SBP/DBP ($P<0.01$); for those with stage II high blood pressure, 2.72 ($P<0.001$). Total cholesterol was significantly related to CHD risk ($P<0.001$, HR 1.40, 1 SD higher); HDL cholesterol was related inversely ($P<0.001$, HR 1.35, 1 SD lower); cigarette smoking was strongly related to CHD risk, HR 2.00 for current versus never smokers ($P<0.001$); past smoking was also significantly related to CHD, HR 1.41 ($P<0.01$). As a continuous variable, BMI was significantly related to CHD risk (HR 1.12, 1 SD higher; $P<0.05$); considered as a categoric variable, BMI in both the overweight and in the obese range was associated with increased CHD risk, HR 1.37 ($P<0.001$) and 1.25 (not statistically significant). Fasting plasma glucose was positively related to CHD risk ($P<0.001$, HR 1.12, 1 SD higher); for persons with glucose concentration ≥ 126 mg/dl, HR was 1.69 ($P<0.001$) compared with those with fasting glucose under 110 mg/dl. For diabetic participants, HR was 1.71 ($P<0.001$).

For each risk factor except total cholesterol and BMI, HRs were higher for women than men: for total cholesterol, the HR for women was less than for men (1.31 and 1.44); for BMI, HRs for the two sexes were virtually identical. There was no significant interaction of smoking and any of the other risk factors.

Relation of multiple risk factors considered together to coronary heart disease risk

In Cox multivariate models, risk factors significantly, independently, directly related to CHD were SBP, total cholesterol, lower HDL cholesterol, need for antihypertensive treatment, current cigarette smoking, diabetes; hazard ratios ranged from 1.33 (SBP) to 1.80 (current cigarette smoking) (Table 4). Given no significant risk factor interactions, these independent risks are multiplicative, such as for persons who smoke (compared with non-smokers) with SBP 137 mmHg (versus 115) and total cholesterol 228 mg/dl (versus 183), from model 1, HR = 1.80 (smoking) × 1.33 (SBP) × 1.38 (total cholesterol) = 3.30 times; or, the inverse, with favorable levels, lower risk HR = 0.30, i.e., CHD risk 70% lower.

As in univariate Cox analyses, sex-specific coefficients were higher for women than men for each risk factor except total cholesterol, conspicuously so for cigarette smoking (2.49 and 1.68) (detailed data not tabulated).

Discussion

The main findings of this Italian longitudinal study of more than 20 000 men and women aged 35–69 years, in relation to 10-year CHD incidence of low-risk status (favorable levels of all readily measured modifiable major CVD risk factors) are as follows: at baseline, only 2.7% low risk, 81.4% high risk (one or more risk factor levels high); only two CHD events in 543 low-risk individuals; and for all persons not high risk (low risk plus unfavorable but not high risk), the age–sex standardized coronary event rate was 62% lower than for those high risk. The findings are consistent for men and women.

These results on the protective effects against CHD in both sexes with favorable levels of all (or most) readily measured modifiable major risk factors are concordant with data on the large cohort of men aged 35–57 screened in 18 US cities for the Multiple Risk Factor Intervention Trial (MRFIT) followed for 25 years and on the large cohorts of Chicago men and women ages 18–59 followed for 30 years [1,4]. Across six cohorts of low-risk young adult and middle-aged men and women, 25–30-year CHD

Table 3 Relation of risk factors considered singly to 10-year coronary heart disease risk, men and women combined: hazard ratios (HR) and 95% confidence intervals (CI), Cox proportional hazards regression analyses

Variable	Hazard ratio[a]			Coefficient	SE	Significance
	More adverse level[b]	95% CI				
Age (years)	2.07	1.90	2.25	0.0830	0.0049	***
Sex (men/women)	3.67	3.06	4.40	1.3009	0.0927	***
Systolic blood pressure (mmHg)	1.45	1.35	1.56	0.0172	0.0017	***
Diastolic blood pressure (mmHg)	1.25	1.16	1.35	0.0200	0.0034	***
Serum total cholesterol (mg/dl)	1.40	1.31	1.50	0.0076	0.0008	***
Serum HDL-cholesterol (mg/dl)	1.35	1.23	1.48	−0.0192	0.0031	***
Serum triglycerides (mg/dl)	1.11	1.05	1.18	0.0013	0.0004	***
Body mass index (BMI) (kg/m^2)	1.12	1.03	1.21	0.0245	0.0095	*
Fasting plasma glucose (mg/dl)[d]	1.12	1.05	1.20	0.0048	0.0014	***
Current cigarette smoking (yes, no)	1.65	1.41	1.94	0.5022	0.0827	***
Diabetes (yes, no)	1.71	1.31	2.22	0.5359	0.1341	***
Hypertension Treatment (yes, no)	2.28	1.90	2.73	0.8224	0.0933	***
	Standard adversity level					
Blood pressure (mmHg)[c]						
Normal	1.00					
Prehypertension	1.25	0.88	1.77	0.2241	0.1782	NS
Hypertension – Stage I	1.61	1.14	2.25	0.4732	0.1731	**
Hypertension – Stage II or treated	2.72	1.96	3.78	1.0008	0.1680	***
Total cholesterol (mg/dl)						
<200	1.00					
200–239	1.38	1.09	1.75	0.3213	0.1202	**
≥ 240	2.20	1.76	2.75	0.7880	0.1138	***
HDL-cholesterol (mg/dl)						
<40	1.00					
40–59	0.74	0.61	0.90	−0.2992	0.0973	**
≥ 60	0.47	0.37	0.60	−0.7466	0.1235	***
Glycemia (mg/dl)						
<110[e]	1.00					
110–125[f]	1.04	0.78	1.39	0.0379	0.1484	NS
≥ 126[g]	1.69	1.25	2.27	0.5233	0.1518	***
Triglycerides (mg/dl)						
<86	1.00					
86–133	1.64	1.25	2.15	0.4938	0.1395	***
≥ 134	2.05	1.58	2.66	0.7182	0.1330	***
BMI (kg/m^2)						
<25.0	1.00					
25.0–29.9	1.37	1.13	1.66	0.3149	0.0966	***
≥ 30.0	1.25	1.00	1.57	0.2246	0.1162	NS
Cigarette smoking						
Never	1.00					
Past	1.41	1.12	1.78	0.3435	0.1189	**
Current	2.00	1.62	2.47	0.6920	0.1074	***

SE, standard error; NS, not statistically significant; HDL, high-density lipoprotein. [a]Age-sex-sample adjusted HR, except for age (sex-sample adjusted HR) and sex (age-sample adjusted HR). [b]For continuous variables, HR with level 1 standard deviation higher (see Table 1); for dichotomized variables, yes versus no. [c]Normal: SBP ≤ 120 and DBP ≤ 80 mmHg, no antihypertensive drug treatment; Prehypertension: SBP 121–139 or DBP 81–89 mmHg, no antihypertensive drug treatment; Hypertension stage I: SBP 140–159 or DBP 90–99 mmHg, no antihypertensive drug treatment; Hypertension stage II: SBP ≥ 160 or DBP ≥ 100 or antihypertensive drug treatment. [d]n=12 746. [e]n=11 124. [f]n=977. [g]n=645. ***$P<0.001$; **$P<0.01$; *$P<0.05$.

risk was lower by 69–92% compared with all others (not low-risk), and lower by 79–96% compared to those with two or more risk factors high [4]. The Progetto CUORE data are also concordant with 14-year findings from the large Nurses Health Study of US women with baseline ages 30–55, using, absent directly measured major risk factor data, lifestyle data collected by questionnaire [5]. Low-risk was defined as all of no smoking, BMI $< 25.0\,kg/m^2$, moderate-to-vigorous physical activity at least one-half hour per day; score in the highest 40% of the cohort for diet high in cereal fiber, marine omega-3 fatty acids, folate, polyunsaturated/saturated fatty acids ratio, low in trans fatty acids and glycemic load, and average alcohol intake of at last half a drink per day. For low-risk women so defined, the risk of a major CHD event was 83% less than for all other women (with control for age, diagnosed high blood pressure or serum total cholesterol, menopausal status, and family history of CVD). Across all seven of these US cohorts, only a small minority were low risk, such as in the Nurses Health Study only 3% were low risk based on the stipulated lifestyle criteria [5], as was the case for the Progetto CUORE cohort based on all readily measured modifiable major risk factors. Among all seven US cohorts and the Progetto CUORE cohort, the great majority were high risk at baseline.

For the several population samples from northern, central, and southern Italy making up the Progetto CUORE, the adverse risk factor levels recorded in the 1980–1990s

Table 4 Relation of risk factors considered together to 10-year coronary heart disease risk, men and women combined: multivariate proportional hazards regression models

Variable	Multivariate coefficient						Hazard ratio (model 1)		
	Model 1 (n=19 622; 607 coronary events)			Model 2[a] (n=12 473; 475 coronary events)			More adverse level[b]	95% CI	
	Coefficient	SE	Significance	Coefficient	SE	Significance			
Age (years)	0.0673	0.0056	***	0.0688	0.0063	***	1.80	1.64	1.98
Sex (men/women)	1.1679	0.1044	***	1.1990	0.1189	***	3.22	2.62	3.95
Systolic blood pressure (mmHg)	0.0131	0.0019	***	0.0113	0.0023	***	1.33	1.22	1.44
Serum total cholesterol (mg/dl)	0.0073	0.0009	***	0.0071	0.0010	***	1.38	1.28	1.49
Serum HDL-cholesterol (mg/dl)	−0.0192	0.0032	***	−0.0169	0.0037	***	1.35	1.22	1.49
Fasting plasma glucose (mg/dl)	–	–	–	0.0025	0.0016	NS	–	–	–
Current cigarette smoking (yes, no)	0.5875	0.0873	***	0.6105	0.0999	***	1.80	1.52	2.14
Diabetes (yes, no)	0.3578	0.1369	**	–	–	–	1.43	1.09	1.87
Hypertension treatment (yes, no)	0.5544	0.1043	***	0.4936	0.1207	***	1.74	1.42	2.14

SE, standard error; CI, confidence interval; HDL, high-density lipoprotein; NS, not significant. [a]Model 2 differs from Model 1 only in the exclusion as a variable of diabetes and the inclusion instead of fasting plasma glucose. Both models are also controlled for sample. [b]For continuous variables, hazard ratio with level 1 standard deviation higher (see Table 1); for dichotomized variables, yes versus no. ***$P<0.001$; **$P<0.01$; *$P<0.05$.

contrast markedly with 1950–1960s population-based data on Italian middle-aged cohorts, such as from the Seven Countries Study, especially in regard to average levels and distributions of serum cholesterol and BMI [14–20]. In Italy during these decades, per capita intakes of total energy, total and saturated fats, cholesterol, sugars have all gone up considerably. Correspondingly, average total cholesterol levels for middle-aged Italian cohorts in the 1980 and 1990s were in the range 5.70–5.96 mmol/l (220–230 mg/dl), which was considerably higher than for Italian cohorts surveyed in the late 1950 and early 1960s [16]. Along with declines in physical activity of work and leisure, the serially more unfavorable eating patterns account also for increasing overweight/obesity.

In these regards it is relevant also 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 OMNIHEART feeding trials indicate that multiple dietary factors–macronutrients and micronutrients, electrolytes (NaCl, K)–influence blood pressure, as well as caloric imbalance (overweight/obesity) and excess alcohol intake [21–28]. Habitual dietary patterns that favorably influence blood pressure are diets lower in salt and alcohol; higher in multiple minerals and vitamins, vegetable and total protein, monounsaturated fats, fiber; lower in total fats, saturated fats, cholesterol, sugars [22,23]. In all these regards the DASH combination diet, which was highly efficacious in reducing SBP/DBP for both prehypertensive and hypertensive adults, resembles Italian dietary patterns of the late 1950s and 1960s: high in fruits, vegetables, whole grains; emphasizing seafood, lean poultry, fat-free and low fat dairy products, legumes, nuts, olive and seed oils in modest amounts; low in red meats, fat-containing dairy products, eggs, sugars and sweets. The recommended DASH eating pattern, however, differs 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.

In this context a reasonable deduction is that the apparent attrition/loss by the Italian population in the latter decades of the 20th century of the earlier prevailing 'Mediterranean advantage' relates to extensive lifestyle changes during these years, particularly altered dietary and physical activity patterns [29].

The limitations of the present study include the small size of low-risk sub-cohorts (male, female); the concordant results on CHD here and for the six low-risk cohorts similarly defined (MRFIT, Chicago), however, support the inference that low risk as defined protects generally against CHD, an inference given further broad support by the concordant results from the Nurses Health Study with low risk defined by favorable lifestyle traits [5]. A further limitation is that low-risk status is based on only one measurement of the risk factors; this limitation, the regression dilution bias problem [30], however, leads to some people being improperly designated low risk, with resultant underestimation of the favorable effects of low risk. Furthermore, there are no data on eating, drinking or exercise, lifestyle traits implicated as important CVD risk factors; the lack of data on these traits, however, makes more impressive the benefit against CHD with favorable levels of readily measured modifiable major risk factors, and again it is relevant to note the concordant findings from the Nurses Health Study with low risk defined based on multiple lifestyle criteria. That only 10-year follow-up data were obtained is another limitation; favorable findings for low risk and CHD prevailed for the Nurses, MRFIT, and Chicago cohorts, however, with 14, 25, and 30-year follow-up [1–5]. Finally, the participation rate was from 40–78%;

risk factor average levels and distributions were similar, however, across all 12 samples and like those for samples in other European countries in the 1980s–1990s.

In conclusion, low risk, favorable levels of all readily measured modifiable major CVD risk factors, is associated with low CHD rates. Low prevalence rates of low risk in contemporary populations are products of adverse lifestyles, all amenable to prevention and control, including smoking, adverse eating and drinking patterns, sedentary habit, causing commonality of elevated blood pressure, hyperglycemia/diabetes, dyslipidemia, obesity. Intervention in the general population needs to be implemented, emphasizing improved lifestyles: non-smoking, prevention and control of overweight/obesity with eating patterns of original Mediterranean composition, enhanced to include 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, and this is key to ending the CHD/CVD epidemic.

References

1 Stamler J. Established major coronary risk factors. In: Marmot M, Elliott P, editors. *Coronary heart disease epidemiology: from aetiology to public health*. New York: Oxford University Press; 1992. pp. 35–66.

2 Stamler J, Stamler R, Neaton JD, Wentworth D, Daviglus M, Garside D, *et al.* Low risk factor profile and long-term cardiovascular and non-cardiovascular mortality and life expectancy. *JAMA* 1999; **282**:2012–2018.

3 Daviglus ML, Stamler J, Pirzada A, Yan LL, Garside DB, Liu K, *et al.* Favorable cardiovascular risk profile in young women and long-term risk of cardiovascular and all-cause mortality. *JAMA* 2004; **292**:1588–1592.

4 Stamler J, Neaton JD, Garside DB, Daviglus M. Current status: six established major risk factors–and low risk. In: Marmot M, Elliott P, editors. *Coronary heart disease epidemiology: from aetiology to public health*. 2nd ed. New York: Oxford University Press; 2005. pp. 32–69.

5 Stampfer MJ, Hu FB, Manson JE, Rimm EB, Willett WC. Primary prevention of coronary heart disease in women through diet and lifestyle. *N Engl J Med* 2000; **343**:16–22.

6 Ferrario M, Chiodini P, Chambless LE, Cesana GC, Vanuzzo D, Panico S, *et al.* For the CUORE Project Research Group. Prediction of coronary events in a low incidence population. Assessing accuracy of the CUORE Cohort Study prediction equation. *Int J Epidemiol* 2005; **34**:413–421.

7 WHO MONICA Project. MONICA Manual [online resource]. Office of Cardiovascular Diseases, World Health Organization; 31 March 1999. Available at http://www.ktl.fi/publications/monica/manual/index.htm; URN:NBN:fi-fe19981146.

8 *Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death, IX Revision*. Geneva: WHO; 1977.

9 Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project: registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. *Circulation* 1994; **90**:583–612.

10 Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, *et al.* The National High Blood Pressure Education Program Coordinating Committee. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003; **42**:1206–1252.

11 American Diabetes Association. Standards of medical care for patients with diabetes mellitus. *Diabetes Care* 2002; **25(Suppl 1)**:S33–S49.

12 Cox DR. Regression models and life tables. *J R Stat Soc B* 1972; **34**: 187–220.

13 Palmieri L, Panico S, Vanuzzo D, Ferrario M, Pilotto L, Sega R, *et al.* Gruppo di Ricerca del progetto CUORE. Evaluation of the global cardiovascular absolute risk: the Progetto CUORE individual score [in Italian]. *Ann Ist Super Sanita* 2004; **40**:393–399.

14 Stamler J. Population studies. In: Levy RI, Rifkind BM, Dennis BH, Ernst ND (editors). *Nutrition, lipids, and coronary heart disease: a global view*. New York: Raven Press; 1979. pp. 25–88.

15 Sasaki S, Kesteloot H. Value of Food and Agriculture Organization data on food balance sheets as a data source for dietary fat intake in epidemiologic studies. *Am J Clin Nutr* 1992; **56**:716–723.

16 Keys A, editor, Aravanis C, Blackburn H, Buzina R, Djordjevic BS, Dontas AS, *et al. Seven countries study: a multivariate analysis of death and coronary heart disease*. Cambridge: Harvard University Press; 1980. pp. 1–381.

17 Kromhout D, Menotti A, Bloemberg B, Aravanis C, Blackburn H, Buzina R, *et al.* Dietary saturated and trans fatty acids and cholesterol and 25-year mortality from coronary heart disease: the Seven Countries Study. *Prev Med* 1995; **24**:308–315.

18 Alberti-Fidanza A, Fidanza F, Chiuchiù MP, Verducci G, Fruttini D. Dietary studies on two Italian population groups of the Seven Countries Study. 3. Trends in food and nutrient intake from 1960 and 1991. *Eur J Clin Nutr* 1999; **53**:854–860.

19 Fidanza F. Who remembers the true Italian Mediterranean diet? *Diab Nutr Metab* 2001; **14**:119–120.

20 Fidanza F, Alberti A, Lanti M, Menotti A. Mediterranean Adequacy Index: correlation with 25-year mortality from coronary heart disease in the Seven Countries Study. *Nutr Metab Cardiovasc Dis* 2004; **14**:254–258.

21 Stamler J, Caggiula AW, Cutler JA, Dolccek TA, Grandits GA, Kjelsberg MO, Tillotson JL, (editors). Dietary and nutritional methods and findings: the Multiple Risk Factor Intervention Trial (MRFIT). *Am J Clin Nutr* 1997; **65(Suppl 1)**:183S–*Am J Clin Nutr* 1997; **65(Suppl 1)**:402S.

22 Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, *et al.* for the DASH Collaborative Research Group. A clinical trial of the effects of dietary patterns on blood pressure. *N Engl J Med* 1997; **336**:1117–1124.

23 Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, *et al.* DASH-Sodium Collaborative Research Group. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. *N Engl J Med* 2001; **344**:3–10.

24 Stamler J. The INTERSALT study: background, methods, findings and implications. *Am J Clin Nutr* 1997; **65(Suppl 2)**:626S–642S.

25 Stamler J, Elliot P, Kesteloot H, Nichols R, Claeys G, Dyer AR, Stamler R. The INTERSALT Cooperative research Group. Inverse relation of dietary protein markers with blood pressure: findings for 10,020 men and women in the INTERSALT Study. *Circulation* 1996; **94**:1629–1634.

26 Stamler J, Caggiula AW, Grandits GA, Kjelsberg MO, Cutler JA. The MRFIT Research Group. Relationship to blood pressure of combinations of dietary macronutrients: findings of the Multiple Risk Factor Intervention Trial. *Circulation* 1996; **94**:2417–2423.

27 Stamler J (guest editor). INTERMAP: International study of macro- and micro-nutrients and blood pressure. *J Hum Hypertens* 2003; **17**:585–775.

28 Appel LJ, Sacks FM, Carey VJ, Obarzanek E, Swain JF, Miller ER 3rd, *et al.* OmniHeart Collaborative Research Group. Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: results of the OmniHeart randomized trial. *JAMA* 2005; **294**:2455–2464.

29 Laurenzi M, Stamler R, Trevisan M, Dyer A, Stamler J. Is Italy losing the "Mediterranean advantage?" Report on the Gubbio population study: Cardiovascular risk factors at baseline. Gubbio Collaborative Study Group. *Prev Med* 1989; **18**:35–44.

30 Liu K, Stamler J, Dyer A, McKeever J, McKeever P. Statistical methods to assess and minimize the role of intra-individual variability in obscuring the relationship between dietary lipids and serum cholesterol. *J Chronic Dis* 1978; **31**:399–418.

Appendix

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