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Syndrome X and Mortality: A Population-based Study

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The present report analyzes the prevalence of the cluster of metabolic abnormalities defined as syndrome X (high blood glucose, high blood pressure, low high density lipoprotein (HDL) cholesterol, and high triglycerides) and its impact on cardiovascular disease mortality in a large cohort of men and women (22,561 men and 18,495 women). These individuals were participants in a series of epidemiologic investigations of cardiovascular disease conducted in Italy between 1978 and 1987. They were followed for an average of 7 years, during which time a total of 1,218 deaths occurred (1,003 in men and 215 in women). Deaths were coded according to the *International Classification of Diseases*, 9th Revision (ICD-9). The prevalence of the full cluster of metabolic abnormalities (syndrome X) was low in the population as a whole, with only 3.0 percent of men and 3.4 percent of women exhibiting the full cluster of abnormalities that comprise syndrome X. The risk of death from all causes and cardiovascular disease increased with increased numbers of metabolic abnormalities in both men and women. Mortality from cancer was significantly increased in women (but not in men) with syndrome X, compared with women with no metabolic abnormalities. Population attributable risks for all cause mortality and cardiovascular disease mortality were 0.06 and 0.09 in men and 0.04 and 0.48 in women when assessed by population cutpoints. These data from a large population-based epidemiologic investigation indicate that the presence of a full cluster of metabolic abnormalities from syndrome X is an important risk factor for cardiovascular disease and all-cause mortality in both men and women, but that the low prevalence of such a cluster in the population reduces the public health impact of syndrome X. The majority of individuals who die from cardiovascular disease present elevations in any one, two, or three of the metabolic abnormalities. The notion of the cluster of metabolic abnormalities (syndrome X) should not distract our attention from established individual risk factors that have been proven to be major causes of cardiovascular disease death and disability in our society. *Am J Epidemiol* 1998;148:958–66.

cause of death; insulin resistance; mortality; prospective studies; risk factors; syndrome X

The term syndrome X has been used to describe a cluster of metabolic abnormalities that have been associated with insulin resistance and are considered to be an important cause of mortality and morbidity for cardiovascular disease (1, 2).

Since the first description of the syndrome, this cluster of metabolic abnormalities (3–5) has been the focus of intensive investigation. Recently, other metabolic abnormalities have been added to the four originally described as part of syndrome X (i.e., hypertriglyceridemia, hypertension, low high density lipoprotein (HDL) cholesterol, and disturbances in glucose metabolism).

The majority of the studies presented to date focus on selected clinical samples. So far, it appears that either limited or no data have been presented with regard to the prevalence of syndrome X in the general population and its relation to mortality.

The present report analyzes the prevalence of the cluster of metabolic abnormalities comprising syndrome X and its relation to mortality in a large group of adult men and women who were participants in a series of epidemiologic investigations of cardiovascular disease epidemiology in Italy.

MATERIALS AND METHODS

The Risk Factors and Life Expectancy Project represents the pooling of nine different large-scale epidemiologic studies focused on cardiovascular diseases, conducted in Italy between 1978 and 1987. Fifty-two

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Abbreviations: HDL, high density lipoprotein; ICD-9, *International Classification of Diseases*, 9th Revision.

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population samples of men and women were included. Fifty of the 52 samples were drawn from local electoral rolls in defined geographic or administrative areas, while two samples were drawn from occupational settings. A total of 62,285 men and women, aged 20–69 years, were included in the original project. Over 150 entry characteristics were measured at baseline, although not all of them in all the studies. Details on the study are given elsewhere (6).

In 37 of the samples, information was gathered on the metabolic factors comprising syndrome X (i.e., serum triglycerides, HDL cholesterol, blood glucose, and blood pressure), and age, body mass index, and serum cholesterol.

Serum total and HDL cholesterol, triglycerides, and blood glucose were measured in blood samples drawn from the antecubital vein after 12 hours of fasting. Serum total cholesterol and triglycerides were measured by several automated enzymatic methods. However, all of the laboratories were under the quality control procedures of the World Health Organization Lipid Reference Center in Prague, Czechoslovakia. Serum HDL cholesterol was measured after precipitation with phosphotungstic acid or with heparin or dextran sulphane in different studies. However, comparability among centers was guaranteed by centralized quality control as for total cholesterol. Blood glucose, was measured by several automated enzymatic methods, but all laboratories were under quality control and standardization of a central laboratory.

Blood pressure was measured on the right arm with the participant in a sitting position, and after a 4-minute rest, using a recently calibrated mercury sphygmomanometer. Observers were trained and tested following the rules described in the World Health Organization's *Cardiovascular Survey Methods Manual* (7) and the cassettes developed by the London School of Hygiene and later by the Laboratory of Physiological Hygiene, University of Minnesota. Systolic and diastolic (fifth phase) levels were recorded. The average of two consecutive measurements (one minute apart) are reported.

Weight and height were measured with participants wearing light clothing, without shoes, according to the procedures described by the World Health Organization manual (7).

The mortality data were collected during an average follow-up period of 7 years (range 4–12), during which 2.1 percent of subjects were lost to follow-up. Information on vital status, and time and cause of death in the deceased was collected by the responsible investigators of the individual cohorts. Coding of causes of death was performed centrally by a single nosologist using the *International Classification of Diseases*, 9th Revision (ICD-9). In cases of multiple causes of death, a hierarchical preference was adopted, with priority given to accidents, cancer, coronary heart disease, and stroke in rank order with other causes reported in the same order as on the death certificate. No validation of death certificates was performed. Causes of death were grouped as follows: cardiovascular disease, ICD-9 codes 390 to 459; coronary disease, ICD-9 codes 410–414; cerebrovascular disease, ICD-9 codes 430–437; non-cardiovascular disease, all deaths except ICD-9 codes 390–459; and cancer, ICD-9 codes 140–239.

Population for analysis

In 35 of the 52 samples, information was collected on the variables of interest for the present study for a total of 24,254 men and 19,931 women aged 20–69 years. After exclusion of participants with missing information for any of the variables considered in the analyses, there remained a total of 41,056 persons (22,561 men and 18,495 women) with complete information, who are the focus of this report.

Statistical analyses

For the mortality analyses, hazard ratios as an indication of relative risks were computed using individuals with no metabolic abnormalities as a reference category. Survival analysis using the Cox proportional hazards model (8) was our primary mode of analysis and allowed adjustment for age using participants with no abnormalities as a reference category. The assumption of proportionality of the hazards was tested and found not to be violated. Population and clinical attributable risks were computed according to Levin (9), i.e.,

$$\text{population attributable risk} = \frac{p(\text{RR} - 1)}{1 + p\,(\text{RR} - 1)},$$

and

$$\text{clinical attributable risk} = \frac{\text{RR} - 1}{\text{RR}},$$

where p is the prevalence of syndrome X and RR is the hazard ratio from the Cox regression analysis. Excess risk for all causes and specific causes of mortality attributable to the number of metabolic abnormalities was computed according to standard statistical methods (10), and was calculated based on the estimated number of deaths that would have occurred if all participants had experienced the mortality rate of participants with no abnormalities.

Definition of syndrome X

For the purpose of this analysis, syndrome X is defined as having "abnormal" levels of serum total cholesterol, triglycerides, HDL cholesterol, and blood pressure. The presence of abnormal values was defined, except for high blood pressure, based on distribution cutpoints (i.e., values in the highest 25 percent of the sex-specific distribution for glucose and triglycerides and the lowest 25 percent of the sex-specific distribution for HDL cholesterol on medication for diabetes mellitus and hyperlipidemia). For hypertension, a cutpoint of systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg or being on antihypertensive treatment was used. The following cutpoints were used for each sex: *Men*: blood pressure, SBP ≥140 mmHg or DBP ≥90 mmHg, or on antihypertensive therapy; serum triglycerides, ≥175 mg/dl, or on lipid lowering drugs; blood glucose, ≥100 mg/dl, or on antidiabetic therapy; HDL cholesterol ≤40 mg/dl. *Women*: blood pressure, SBP ≥140 or DBP ≥90 mmHg, or on antihypertensive therapy; serum triglycerides, ≥133 mg/dl, or on lipid lowering drugs; blood glucose, ≥95 mg/dl, or on antidiabetic therapy; HDL cholesterol, ≤46 mg/dl.

For blood lipids and blood glucose, these distribution-based cutpoints were used instead of those based on recommendations from expert panels (i.e., triglycerides, ≤200 mg/dl, blood glucose 140 mg/dl, and HDL cholesterol, 35 mg/dl in men and 45 mg/dl in women) because when these latter were used only a very limited number of participants exhibited the full cluster of metabolic abnormalities (n = 126 or 0.6 percent in men and n = 160 or 0.9 percent in women).

RESULTS

In table 1, the baseline characteristics of the participants are summarized together with the number of deaths, person-years of follow-up, and the rates of death that occurred during the average 7 years of follow-up. It should be noted that the number of deaths in women only total 215, and, as a consequence, the statistical power and the stability of our estimates of risk are low.

Table 2 displays the prevalence of the metabolic abnormalities in the two sexes separately by age group and in the population as a whole. Participants are divided according to the presence of any one, any two, any three, and the full cluster of the metabolic abnormalities that comprise syndrome X. As expected, the number of participants with no metabolic abnormalities goes sharply down with increasing age with only 8.4 percent of men and 7.0 percent of women aged 65 years and older showing no elevation in any of the metabolic factors. Presence of a single abnormality is a common occurrence, in both sexes, while only a limited number of participants display the full cluster of metabolic abnormalities. In the population as a whole, a total of 687 men (3.0 percent) and 624 women (3.4 percent) fall into this category. Despite the low figures, the observed prevalences of the full cluster of metabolic abnormalities in the two sexes are higher than those expected based on the product of prevalences of elevation of individual metabolic factors (expected = 0.008 [0.25 × 0.25 × 0.25 × 0.52] in men and 0.007 [0.25 × 0.25 × 0.25 × 0.45] in women vs. observed = 0.030 in men and 0.034 in women).

TABLE 1. Baseline characteristics of participants by sex: Risk Factors and Life Expectancy Project, Italy, 1978–1987

Characteristic	Men (n = 22,561)	Women (n = 18,495)
Age (years), mean (SD*)	48.1 (10.9)	46.3 (10.6)
Systolic blood pressure (mmHg), mean (SD)	135.3 (17.3)	132.7 (18.6)
Diastolic blood pressure (mmHg), mean (SD)	85.1 (10.0)	83.1 (10.3)
Serum total cholesterol (mg/dl), mean (SD)	217.6 (45.2)	214.1 (45.1)
HDL* cholesterol (mg/dl), mean (SD)	48.9 (12.5)	55.6 (12.5)
Serum triglyceride (mg/dl), mean (SD)	145.3 (91.7)	109.7 (54.2)
Fasting glucose (mg/dl), mean (SD)	95.0 (21.8)	90.3 (18.4)
Body mass index (kg/m²), mean (SD)	26.4 (3.3)	26.4 (4.5)
Follow-up years, mean (SD)	7.1 (1.8)	6.9 (1.3)
Total mortality (/1,000 person-years)	6.3 (1,003/160,086)	1.7 (215/128,608)
CVD*,† mortality (/1,000 person-years)	2.3 (374/160,086)	0.4 (48/128,608)
CHD*,† mortality (/1,000 person-years)	1.8 (290/160,086)	0.2 (26/128,608)
Cancer† mortality (/1,000 person-years)	2.7 (428/160,086)	0.9 (116/128,608)
Other† mortality (/1,000 person-years)	1.2 (201/160,086)	0.4 (51/128,608)

* SD, standard deviation; HDL, high density lipoprotein; CVD, cardiovascular disease; CHD, coronary heart disease.

† CVD, *International Classification of Diseases*, 9th Revision (ICD-9) codes 390.0–459.9; CHD, ICD-9 codes 410.0–414.9; cancer, ICD-9 codes 140.0–239.9; other, death by causes other than CVD and cancer.

TABLE 2. Distribution (%) of metabolic abnormalities comprising syndrome X at baseline by age and sex: Risk Factors and Life Expectancy Project, Italy, 1978–1987

Age (years)	No.	Abnormalities of syndrome X									
		None		1		2		3		4	
		No.	%	No.	%	No.	%	No.	%	No.	%
Males											
<30	1,203	529	43.9	413	34.3	159	13.2	83	6.8	19	1.5
30–34	1,956	727	37.1	720	36.8	342	17.4	152	7.7	15	0.7
35–39	2,531	848	33.5	861	34.0	552	21.8	230	9.1	40	1.6
40–44	2,527	648	25.6	969	38.3	588	23.2	266	10.5	64	2.5
45–49	3,260	741	22.7	1,192	36.5	841	25.8	385	11.8	101	3.1
50–54	3,538	679	19.2	1,276	36.0	963	27.2	486	13.7	134	3.8
55–59	3,675	581	15.8	1,302	35.4	1,131	30.8	514	13.9	147	4.0
60–64	2,512	313	12.4	903	35.9	806	32.1	394	15.6	96	3.8
≥65	1,359	115	8.4	507	37.3	442	32.5	224	16.5	71	5.2
Total	22,561	5,173	22.9	8,143	36.1	5,824	25.8	2,734	12.1	687	3.0
Females											
<30	1,436	784	54.6	449	31.2	116	8.1	80	5.6	7	0.5
30–34	1,846	913	49.4	617	33.4	230	12.4	75	4.0	11	0.6
35–39	2,423	1,130	46.6	827	34.1	322	13.3	122	5.0	22	0.9
40–44	2,424	894	36.9	838	34.5	444	18.3	199	8.2	49	2.0
45–49	2,563	713	27.8	939	36.6	553	21.6	283	11.0	75	2.9
50–54	2,634	513	19.5	912	34.6	709	26.9	380	14.4	120	4.5
55–59	2,442	329	13.5	763	31.2	722	29.5	486	19.9	142	5.8
60–64	1,700	162	9.5	502	29.5	563	33.1	349	20.5	124	7.3
≥65	1,024	72	7.0	274	26.7	387	37.8	220	21.5	74	7.2
Total	18,495	5,510	29.8	6,121	33.1	4,046	21.9	2,194	11.9	624	3.4

Tables 3 and 4 summarize the results of the Cox proportional hazards model using all cause, cardiovascular disease, coronary heart disease, and cancer mortality as outcomes in males (table 3) and females (table 4) separately. The age-adjusted models using individuals with no metabolic abnormality as a reference category indicate a steady increase in risk for all cause, cardiovascular disease, and coronary disease mortality with increasing abnormalities in both sexes. Cancer mortality increases with increasing numbers of abnormalities in women but not in men. The hazard ratios for all cause mortality, for individuals with three abnormalities, and those with the full cluster of abnormalities, are similar in both sexes. The point estimate for cardiovascular disease mortality risk in women with the full cluster category is lower compared with women with three metabolic abnormalities. Coronary disease mortality in both sexes is highest in participants with the full syndrome. For cancer mortality, men with the full cluster of metabolic abnormalities show a point estimate lower, while individuals with two or three abnormalities exhibit, as a group, significantly higher mortality than individuals with no abnormalities. In women, the risk of death from cancer increases with increasing number of abnormalities, and for participants with three abnormalities and the full cluster of abnormalities combined, the risk of death from cancer reaches borderline statistical significance compared with no abnormalities (data not shown).

In order to further test whether the combination of all four risk factors provides any added risk to the presence of the individual risk factors, we tested a model with the individual metabolic abnormalities included as continuous variables by a variable (yes/no) for the presence or absence of the full cluster of metabolic abnormalities. The results indicate that the presence of syndrome X does not provide any significant additional risk to those provided by the individual risk factors (data not shown).

Table 5 summarizes the findings of the attributable risk analysis, which was conducted using the unadjusted mortality data, in order to have a more realistic estimate of the impact of the factors on the population. Both population and clinical attributable risk are reported. The results indicate that syndrome X may be responsible for a large proportion of the deaths from all causes, cardiovascular disease, and coronary disease in individuals who exhibit the full cluster of metabolic abnormalities. However, the public health impact of syndrome X on mortality in the population as a whole is limited because of the limited prevalence of this condition in the population. The impact appears to be more significant in women than in men. How-

TABLE 3. Risk of death by hazard ratios (HR) in males, according to presence of metabolic abnormalities, with participants with no metabolic abnormalities* as the reference category: Risk Factors and Life Expectancy Project, Italy, 1978–1987

Abnormalities of syndrome X	All causes			CVD†			CHD†			Cancer		
	No.	HR	95% CI†	No.	HR	95% CI	No.	HR	95% CI	No.	HR	95% CI
No abnormalities	133	1.00		39	1.00		29	1.00		65	1.00	
One abnormality	336	1.23	1.00–1.51	121	1.44	0.99–2.07	90	1.44	0.94–2.19	144	1.10	0.82–1.49
Any two abnormalities	307	1.43	1.16–1.77	112	1.62	1.11–2.35	87	1.69	1.10–2.59	137	1.38	1.02–1.87
Any three abnormalities	175	1.76	1.39–2.22	79	2.42	1.63–3.59	63	2.58	1.64–4.06	65	1.44	1.01–2.05
Syndrome X (full cluster)	52	1.95	1.40–2.71	23	2.49	1.46–4.23	21	3.01	1.68–5.37	17	1.45	0.84–2.51

* Metabolic abnormalities are defined on the population cutpoint of each variable, except for blood pressure.
† CVD, cardiovascular disease; CHD, coronary heart disease; CI, confidence interval.

TABLE 4. Risk of death by hazard ratios (HR) in females, according to presence of metabolic abnormalities, with participants with no metabolic abnormalities* as the reference category: Risk Factors and Life Expectancy Project, Italy, 1978–1987

Abnormalities of syndrome X	All causes			CVD†			CHD†			Cancer		
	No.	HR	95% CI†	No.	HR	95% CI	No.	HR	95% CI	No.	HR	95% CI
No abnormalities	28	1.00		2	1.00		1	1.00		16	1.00	
One abnormality	57	1.23	0.77–1.95	9	2.68	0.57–12.58	4	2.47	0.27–22.53	37	1.39	0.76–2.53
Any two abnormalities	63	1.58	0.98–2.53	15	5.55	1.22–25.18	11	8.72	1.07–71.05	33	1.41	0.75–2.68
Any three abnormalities	49	2.09	1.26–3.43	16	11.19	2.45–51.01	7	10.63	1.23–91.93	22	1.58	0.79–3.15
Syndrome X (full cluster)	18	2.54	1.35–4.78	6	15.91	3.01–83.80	3	17.75	1.70–185.2	8	1.86	0.75–4.58

* Metabolic abnormalities are defined on the population cutpoint of each variable, except for blood pressure.
† CVD, cardiovascular disease; CHD, coronary heart disease; CI, confidence interval.

TABLE 5. Clinical and population attributable risk (AR)* of syndrome X by sex: Risk Factors and Life Expectancy Project, Italy, 1978–1987

Cause of death	Men				Women			
	Clinical AR	95% CI†	Population AR	95% CI	Clinical AR	95% CI	Population AR	95% CI
Total deaths	0.757	0.744 to 0.769	0.056	0.043 to 0.068	0.829	0.762 to 0.894	0.141	0.078 to 0.203
CVD†	0.866	0.843 to 0.889	0.094	0.072 to 0.115	0.964	0.889 to 1.044	0.476	0.396 to 0.558
CHD†	0.895	0.867 to 0.921	0.118	0.091 to 0.146	0.944	0.827 to 1.069	0.367	0.246 to 0.482
Cancer	0.503	0.476 to 0.329	0.029	−0.001 to 0.056	0.778	0.732 to 0.820	0.106	0.063 to 0.149

* Attributable risk among the exposed.
† CI, confidence interval; CVD, cardiovascular disease; CHD, coronary heart disease.

ever, these results should be interpreted with caution because of the small number of deaths in women and the resulting wide confidence interval of the risk estimates.

Finally, in table 6, the percent excess risk was calculated using participants with no metabolic abnormalities as a reference category. In men, 7.9, 8.6, 10.2, and 5.6 percent of the excess risk for mortality from all causes, cardiovascular disease, coronary disease, and cancer, respectively, is contributed by participants with the full cluster of metabolic abnormalities. In women, the corresponding figures are 10.8, 14.1, 12.6, and 9.8 percent, respectively. For most of the endpoints analyzed, participants with any two of the metabolic abnormalities comprising syndrome X were responsible for the largest portion of the excess risk in this population, except for cardiovascular disease mortality in women, in which the largest portion of the excess risk was contributed by participants with three metabolic abnormalities.

DISCUSSION

The findings from this large population-based study indicates that the presence of the full cluster of metabolic abnormalities characterizing syndrome X confers a significant risk of death from cardiovascular disease, coronary disease, and all causes in these middle-aged men and women, and particularly so in the women. However, the prevalence of this syndrome is limited; therefore, the public health impact of this cluster of metabolic abnormalities is limited.

As previously indicated, since the report by Reaven (1), numerous reports have focused on the cluster of metabolic abnormalities defined as syndrome X. This cluster of metabolic abnormalities is considered to be linked to insulin resistance, a condition that has been intensively investigated as a possible major cause of cardiovascular disease (2). Various estimates of the prevalence of insulin resistance in the population from industrialized countries have been provided, with some authors estimating that this condition is present in the majority of individuals with non-insulin-dependent diabetes mellitus and glucose intolerance in 25 percent of the population with normal glucose tolerance (5). According to these estimates, insulin resistance would represent a common condition in the population, and therefore represents a major cause of cardiovascular morbidity and mortality.

Estimates for the prevalence of syndrome X in the population have not yet been presented; however, the majority of these studies published to date stress the "common occurrence" of this cluster of metabolic abnormalities. Unfortunately, the majority of the studies that report on syndrome X to date have focused on clinical and/or selected samples, and limited information has been presented describing the prevalence of this condition in the general population. The San Antonio Heart Study (3) focused on a population sample

TABLE 6. Syndrome X, metabolic abnormalities, and percent excess risk* from all causes and specific causes of death: Risk Factors and Life Expectancy Project, Italy, 1978–1987

Abnormalities of syndrome X	Men, by % excess risk				Women, by % excess risk			
	All causes	CVD†	CHD†	Cancer	All causes	CVD	CHD	Cancer
One abnormality	29.9	29.2	27.5	28.9	30.0	16.5	12.9	30.6
Any two abnormalities	37.7	33.8	33.5	44.5	32.0	33.3	46.2	35.2
Any three abnormalities	24.0	28.5	28.8	21.0	27.2	36.1	28.4	24.4
Syndrome X (full cluster)	7.9	8.6	10.2	5.6	10.8	14.1	12.6	9.8

* Based on population-based cutpoints.
† CVD, cardiovascular disease; CHD, coronary heart disease.

of approximately 1,125 Mexican Americans and non-Hispanic whites of both sexes, aged 25–64 years, and reported a prevalence of syndrome X of 0.7 percent using cutpoints similar to those of the expert panels. Comparison of these studies are difficult because of different definitions used to determine elevated values for the metabolic factors comprising syndrome X. For the San Antonio Heart Study, the observed prevalence of syndrome X is higher than the expected based on the prevalence of the single metabolic abnormalities. However, both the present report and that from the San Antonio Heart Study indicate that the prevalence of syndrome X in the population is low. This prevalence will further diminish as new abnormalities are added to those originally identified.

To our knowledge, this is the first report to analyze the relation between the metabolic abnormalities comprising syndrome X and mortality. Our findings indicate that syndrome X represents a significant risk factor for mortality from all causes, cardiovascular disease, and coronary disease. In most of the analyses, risk appeared to increase linearly with increased number of metabolic abnormalities, and in men, the point estimates of hazard ratios were similar for participants with three abnormalities and the full cluster of abnormalities. The presence of the full cluster of abnormalities defined as syndrome X did not appear to confer a disproportionate increase in risk compared with the elevation in risk expected with the increased number of risk factors present.

In these data, cancer mortality risk appeared to increase with increasing number of metabolic abnormalities in women but not in men. The reason for this sex-specific relation between metabolic abnormalities and cancer is not clear, but it could be due to a specific relation between the metabolic abnormalities or the underlying insulin resistance and specific cancer sites. For instance, it has been hypothesized (11, 12) that insulin and insulin metabolism could play a role in etiology of breast and uterine cancer. The number of breast and uterine cancer deaths, however, is low and does not allow the test of this hypothesis.

The results of the clinical attributable risk analysis indicate that focusing on reducing the full cluster of metabolic abnormalities in individuals who exhibit syndrome X would benefit a large proportion of these individuals, but that focusing on just the full cluster in the population as a whole, particularly in men, would have limited impact in reducing the population burden of cardiovascular and coronary disease mortality. In women, estimates are larger, but they should be interpreted with caution because of the limited number of deaths on which these estimates are based. The uncertainty of our risk estimates is underlined by the very wide confidence intervals of the hazard ratios.

Our population-based sample is derived from a country that is characterized by lower cardiovascular disease mortality than many other European and North American countries. However, the available data from US population-based studies confirm the low prevalence of syndrome X in the population.

Our study presents a number of limitations, among them, the short period of follow-up, the limited number of deaths, particularly in women, the lack of information on morbidity, and the lack of validation of death certificates. The first two limitations, however, should not influence the main findings of the study, and the lack of validation of death certificates should have little impact on broad categories of death such as those from cardiovascular disease and cancer.

In summary, our findings indicate that the full cluster of metabolic abnormalities defined as syndrome X increases significantly the risk of cardiovascular disease mortality. However, syndrome X is not a very prevalent condition in the population; this low prevalence results in a limited population impact of such a cluster of metabolic abnormalities on mortality. The use of the full cluster of metabolic abnormalities as an indicator of the importance of insulin resistance as a cause of cardiovascular mortality would result in a clear underestimation of the role of insulin resistance as a cause of cardiovascular disease in the population. The notion of the cluster of metabolic abnormalities should not distract our attention from established individual risk factors that have been proven to be major causes of cardiovascular disease death and disability in our society.

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