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Combined effects of systolic blood pressure and serum cholesterol on cardiovascular mortality in young (<55 years) men and women

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Aims To evaluate the combined effects of the two most frequent modifiable risk factors, systolic blood pressure and serum cholesterol, on cardiovascular and coronary mortality, in a large French population aged 18 to 55 years.

Methods and Results We studied 108 879 men (mean age 39·1 ± 9·4 years) and 84 931 women (mean age 37·3 ± 10·0 years) who had a health check-up at the IPC Center between 1978 and 1988. Mortality data for a mean period of 13 years were analysed. Systolic blood pressure and cholesterol levels were classified according to the cut-points proposed by international guidelines. In men, the prevalence of high cholesterol was more than twice as high in hypertensives as in normotensives; in women, it was more than three times higher. The combination of these two risk factors has additive effects on cardiovascular disease and coronary heart disease risk. In men, a borderline elevation of both systolic blood pressure (130–139 mmHg) and cholesterol (200–239 mg . dl^{-1}) leads to a three- to four-fold increase in cardiovascular disease risk. Men with systolic blood pressure ≥160 mmHg represent a small percentage (about 5%) who have a 10-fold increase in cardiovascular disease and coronary heart disease risk, especially when high cholesterol is present. In women of the same age, similar trends were observed, but the results were less significant, probably due to the low cardiovascular disease mortality rates.

Conclusions In conclusion, in French subjects under 55 years of age, a combination of high systolic blood pressure and high serum cholesterol dramatically increased cardiovascular disease and coronary heart disease risk, especially in men. A more aggressive public health policy is needed to prevent the development of risk factors in younger subjects.
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Key Words: Cholesterol, systolic blood pressure, cardiovascular disease, coronary heart disease, age, gender.

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Introduction

Hypertension and dyslipidaemia are the most common major cardiovascular disease risk factors. It has been shown that the presence of dyslipidaemia is more frequent in hypertensive than in normotensive subjects[1]. This association may reflect the presence of a common cause or aggravating factors for both high blood pressure and high cholesterol[2,3].

Several international guidelines for high blood pressure management[4,5] and cholesterol management[6] recommend that the presence of multiple cardiovascular disease risk factors should be considered in the evaluation and care of patients. The basic approach of such guidelines is that therapeutic strategies and treatment intensity should match the number and severity of cardiovascular disease risk. However, studies have shown that the combination of some risk factors may have less dramatic effects than those expected by the addition of the effects of each risk factor separately[7]. In contrast, the presence of high blood pressure in diabetics dramatically increases their cardiovascular disease risk[8,9]. The combined effects of cholesterol and high blood pressure on cardiovascular disease mortality have been evaluated in a number of epidemiological studies, mainly realized in North American populations[10,11]. These studies have shown additive effects of cholesterol and blood pressure on cardiovascular disease mortality. The role of risk factors on cardiovascular morbidity and mortality may be influenced by age[12], gender[13] and by ethnic or geographic factors[14]. Therefore, the aim

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of this report was to evaluate the combined effects of systolic blood pressure and serum cholesterol on cardiovascular disease mortality in a large French population of 108 879 men and 84 931 women aged 18 to 55 years.

Methods

Subjects

Subjects were examined at the IPC Center, a medical centre which is subsidized by the French national health care system (Sécurité Sociale-CNAM) and provides free medical examinations for all working and retired persons and their families. It is one of the largest medical centres of this kind in France, having carried out approximately 20 000–25 000 examinations per year since 1970 for people living in the Paris area. Between January 1978 and December 1988, 194 269 individuals under 55 years of age (109 211 men and 85 058 women, respectively 39·1 and 37·3 years old) had a free health check-up at the IPC Center. Subjects who indicated that they had a personal history of ischaemic heart disease or angina pectoris were excluded from the study (332 men and 127 women). All other subjects aged <55 years (108 879 men and 84 931 women) were included in the present analysis.

The IPC Center received authorization from the 'Comité National d'Informatique et des Libertés' to conduct these analyses. All subjects gave their informed consent at the time of the examination. Based on the national statistics of mortality, our cohort presented a 20% lower mortality rate than the general French population. This finding may be explained by the assumption that people who came for the health check-up were apparently healthy and motivated to be followed-up. Interestingly, compared to the national data, the distribution of the different causes of mortality in our cohort was identical to that of the general population.

Investigations

Supine blood pressure was measured three times in the right arm, after a 10-min rest period, using a manual sphygmomanometer. The mean of the last two measurements was calculated. The first and the fifth Korotkoff phases were used to define systolic and diastolic pressures. Tobacco use (current consumption of more than 10 cigarettes/day) and personal history of diabetes and hypertension were assessed with a self-administered questionnaire. Serum cholesterol was measured at the IPC Center under fasting conditions on the same day of the examination. ECG measurements were also recorded.

End-points

For all subjects, mortality data were obtained for an 8- to 18-year period (mean ± SD: 13·2 ± 3·5 years) which extended from the time of inclusion through December 1996. These data were obtained from the mortality records at the 'Institut National de Statistiques et d'Etudes Economiques' (INSEE), following a previously established procedure[9,10]. Causes of mortality, taken from death certificates, were provided by INSERM's Department of Mortality Studies (Unit SC 8). Causes of death were codified according to the International Classification of Disease (8th revision until 1978, and 9th revision thereafter). Cardiovascular-related deaths were coded 390–459, and 798 (for sudden death). Coronary deaths were coded 410–414 and 798. During this period, 597 men and 105 women died from cardiovascular disease, and 323 men and 33 women died from coronary heart disease.

Data analysis

Men and women were studied separately. They were divided into four groups of systolic blood pressure according to clinical cut-points proposed by the international guideline committees[4,5] for high blood pressure management: systolic blood pressure <130 mmHg (optimal and normal values); 130≤ systolic blood pressure <140 mmHg (high normal); 140≤ systolic blood pressure <160 mmHg (mild hypertension); and systolic blood pressure ≥160 (moderate to severe hypertension). Inside each systolic blood pressure group, subjects were divided into three cholesterol groups according to clinical cut-points proposed by the international guidelines committee for high cholesterol management[6]. These groups were: serum cholesterol <200 mg . dl^{-1} (normal values); 200≤ cholesterol <240 mg . dl^{-1} (moderate hypercholesterolaemia); and cholesterol ≥240 mg . dl^{-1} (hypercholesterolaemia).

For the different causes of mortality, risk ratios (RR) and 95% confidence intervals related to the increase of 10 mmHg of systolic blood pressure and 1 mmol . l^{-1} of cholesterol were calculated using a Cox proportional hazard regression analysis. In order to calculate relative risk, survival probabilities in each subgroup of systolic blood pressure and cholesterol were evaluated after adjustment for age, body mass index, tobacco use and triglycerides. The level of statistical significance was 5%. All statistical analyses were carried out using the SAS statistical software package.

Results

Prevalence of hypertension and hypercholesterolaemia in men and women

The distribution of the different categories of cholesterol and systolic blood pressure in men is shown in Table 1. Among the men, 26% presented normal levels of both systolic blood pressure (<140 mmHg) and cholesterol (<200 mg . dl^{-1}). Among them, one half had systolic

Table 1 Distribution of men according to cholesterol and systolic blood pressure

	<130 mmHg	130–139 mmHg	140–159 mmHg	≥160 mmHg	All systolic blood pressure
Total cholesterol <200 mg . dl^{-1}					
Number (%)	14 165 (13·0)	14 140 (13·0)	9866 (9·1)	1184 (1·1)	39 355 (36·2)
% column	43·7%	37·2%	30·4%	19·8%	—
% line	36·0%	35·9%	25·1%	3·0%	100%
Total cholesterol 200–239 mg . dl^{-1}					
Number	11 193 (10·3)	13 561 (12·5)	11 493 (10·6)	2021 (1·9)	38 268 (35·2)
% column	34·5%	35·7%	35·4%	33·8%	—
% line	29·2%	35·4%	30·0%	5·3%	100%
Total cholesterol ≥240 mg . dl^{-1}					
Number	7048 (6·5)	10 333 (9·5)	11 088 (10·2)	2767 (2·5)	31 236 (28·7)
% column	21·7%	27·1%	34·2%	46·3%	—
% line	22·6%	33·1%	35·5%	8·9%	100%
All total cholesterol					
Number	32 406 (29·8)	38 034 (34·9)	32 447 (29·8)	5972 (5·5)	108 859 (100·0)
% column	100%	100%	100%	100%	—
% line	—	—	—	—	—

Table 2 Distribution of women according to cholesterol and systolic blood pressure

	<130 mmHg	130–139 mmHg	140–159 mmHg	≥160 mmHg	Total
Total cholesterol <200 mg . dl^{-1}					
Number (%)	27 222 (32·1)	11 352 (13·4)	5001 (5·9)	615 (0·7)	44 190 (52·0)
% column	58·1%	50·0%	38·4%	26·4%	—
% line	61·6%	25·7%	11·3%	1·4%	100%
Total cholesterol 200–239 mg . dl^{-1}					
Number (%)	14 197 (16·7)	7571 (8·9)	4754 (5·6)	840 (1·0)	27 362 (32·2)
% column	30·3%	33·3%	36·5%	36·0%	—
% line	51·9%	27·7%	17·4%	3·1%	100%
Total cholesterol ≥240 mg . dl^{-1}					
Number (%)	5449 (6·4)	3790 (4·5)	3256 (3·8)	878 (1·0)	13 373 (15·8)
% column	11·1%	16·7%	25·0%	37·6%	—
% line	40·8%	28·3%	24·4%	6·6%	100%
All total cholesterol					
Number (%)	46 868 (55·2)	22 713 (26·7)	13 011 (15·3)	2333 (2·7)	84 925
% column	100%	100%	100%	100%	
% line	—	—	—	—	

blood pressure levels defined as optimal–normal (<130 mmHg) and the other half had systolic blood pressure levels defined as high–normal (130–139 mmHg). Approximately 35% of the men presented high blood pressure (≥140 mmHg) and about 30% had cholesterol values considered as high (≥240 mg . dl^{-1}), whereas 13% presented both of these abnormalities. The prevalence of high cholesterol increased in men with high blood pressure (chi-square test $P<0·0001$).

For the women (Table 2), more than 45% presented normal values for both systolic blood pressure and serum cholesterol (32% presented optimal–normal systolic blood pressure levels and 13% presented high–normal levels). The prevalence of high systolic blood pressure and hypercholesterolaemia was lower in women than in men ($P<0·0001$); about 16% had high blood pressure and 18% presented high cholesterol, whereas 5% presented both abnormalities. As in men, the prevalence of high cholesterol was greater in women with high blood pressure (chi-square test $P<0·0001$).

Presence of associated risk factors and mortality rates in the systolic blood pressure–cholesterol groups

Tables 3 and 4 show the presence of other risk factors and cardiovascular disease mortality rates in the different systolic blood pressure–cholesterol subgroups in men and women, respectively. In men, the prevalence of diabetes, the triglyceride levels and the percentage of cigarette smokers increased proportionally in the subgroups with higher cholesterol and/or systolic blood

Table 3 Main characteristics and mortality data according to cholesterol and systolic blood pressure in men

	<130 mmHg	130–139 mmHg	140–159 mmHg	≥160 mmHg	RR systolic blood pressure†
Total cholesterol <200 mg . dl^{-1}					
Age (years)	34·2 (8·9)	34·3 (9·1)	35·6 (10·0)	40·6 (10·5)	
Diastolic blood pressure (mmHg)	73 (7)	79 (6)	87 (7)	100 (11)	
% Diabetics	3·1	3·3	4·6	7·7	
Triglycerides (g . l^{-1})	0·87 (0·01)	0·89 (0·01)	0·93 (0·01)	1·04 (0·02)	
% Smokers	27·7	27·8	28·8	30·8	
Number of cardiovascular disease deaths	12 (6·5)*	30 (16·2)	26 (20·1)	15 (96·7)	1·4 [1·2–1·6]
Number of coronary heart disease deaths	5 (2·7)*	15 (8·1)	10 (7·7)	9 (58·1)	1·4 [1·1–1·6]
Total cholesterol 200–239 mg . dl^{-1}					
Age (years)	39·2 (8·4)	39·7 (9·0)	41·3 (8·9)	44·4 (8·6)	
Diastolic blood pressure (mmHg)	75 (7)	80 (6)	88 (7)	102 (11)	
% Diabetics	4·5	5·2	6·6	9·8	
Triglycerides (g . l^{-1})	1·07 (0·01)	1·11 (0·01)	1·19 (0·01)	1·29 (0·02)	
% Smokers	30·8	33·3	35·0	38·1	
Number of cardiovascular disease deaths	37 (19·9)	51 (28·7)	81 (53·8)	47 (177·5)	1·3 [1·2–1·4]
Number of coronary heart disease deaths	29 (19·8)	27 (15·2)	39 (25·9)	21 (79·3)	1·2 [1·1–1·4]
Total cholesterol ≥240 mg . dl^{-1}					
Age (years)	41·8 (7·7)	42·3 (7·8)	43·6 (7·9)	45·8 (7·4)	
Diastolic blood pressure (mmHg)	76 (7)	81 (6)	89 (7)	103 (10)	
% Diabetics	6·0	6·1	7·9	11·3	
Triglycerides (mmol . l^{-1})	1·37 (0·01)	1·45 (0·01)	1·63 (0·01)	1·81 (0·01)	
% Smokers (g . l^{-1})	33·0	35·2	36·2	39·0	
Number of cardiovascular disease deaths	37 (40·1)	68 (50·2)	128 (88·1)	65 (179·3)	1·3 [1·2–1·4]
Number of coronary heart disease deaths	26 (28·2)	45 (33·2)	68 (46·8)	29 (80·0)	1·2 [1·1–1·3]
RR cholest‡					
(cardiovascular disease)	1·6 [1·3–1·9]	1·2 [1·0–1·4]	1·3 [1·2–1·5]	1·3 [1·2–1·5]	
(coronary heart disease)	1·5 [1·2–1·9]	1·3 [1·1–1·6]	1·5 [1·3–1·8]	1·2 [0·9–1·5]	

Age-adjusted means (SEM) with the exception of age where mean (SD) is represented.
*In parenthesis mortality rate per 100 000 person/years.
†Adjusted risk ratios related to the increment of 10 mmHg of systolic blood pressure in each cholesterol group.
‡Adjusted risk ratios related to the increment of 1 mmol . l^{-1} of cholesterol in each systolic blood pressure group.

pressure levels. In women, the same associations were observed for diabetes and triglycerides, but not for the percentage of smokers. As expected, unadjusted cardiovascular disease and coronary heart disease mortality rates increased with increasing systolic blood pressure and/or serum cholesterol levels in both men and women.

Combined effects of systolic blood pressure and serum cholesterol on the risk of cardiovascular disease and coronary heart disease mortality

In men, as compared to the reference group, all other systolic blood pressure–cholesterol groups presented a significantly higher adjusted relative risk for cardiovascular disease (Fig. 1, upper panel) and coronary heart disease (Fig. 1, lower panel). The highest risks for cardiovascular disease mortality and coronary heart disease mortality were observed in the group of patients with both the highest levels of systolic blood pressure (≥160 mmHg) and serum cholesterol (≥240 mg . dl^{-1}). In this group, the multivariate-adjusted cardiovascular disease and coronary heart disease risks were multiplied by more than 17 times compared to the reference group. Multivariate relative risks for cardiovascular disease and coronary heart disease were also evaluated when serum cholesterol and systolic blood pressure were considered as continuous quantitative variables (Table 3). This analysis showed that the effect of cholesterol was significant in all systolic blood pressure groups, and inversely, the effect of systolic blood pressure was significant in all cholesterol groups. An elevation of 10 mmHg of systolic blood pressure induced a 40–60% increase in cardiovascular disease and coronary heart disease risk, which was similar to the increase in cardiovascular disease and coronary heart disease risk related to an elevation of 1 mmol . l^{-1} of serum cholesterol. The additive effects of serum cholesterol and systolic blood pressure on cardiovascular disease and coronary heart disease mortality were also confirmed by the absence of a significant interaction term in the Cox regression analysis.

In women (Fig. 2), the combined effects of systolic blood pressure and serum cholesterol on cardiovascular disease mortality were less important, and were statistically significant and clinically relevant only in the groups with cholesterol ≥240 mg . dl^{-1} and systolic blood pressure ≥140 mmHg. The absence of significance in the intermediate groups may be partially related to the

Table 4 Characteristics according to cholesterol and systolic blood pressure in women

	<130 mmHg	130–139 mmHg	140–159 mmHg	≥160 mmHg	RR systolic blood pressure†
Cholesterol <200 mg . dl^{-1}					
Age (years)	32·9 (8·2)	34·5 (9·1)	37·4 (9·8)	43·3 (8·5)	
Diastolic blood pressure (mmHg)	71 (0·007)	79 (0·006)	87 (0·007)	100 (0·010)	
% Diabetics	3·6	4·0	5·0	7·2	
Triglycerides (g . l^{-1})	0·65 (0·003)	0·65 (0·004)	0·69 (0·010)	0·76 (0·020)	
% Smokers	19·0	18·3	16·5	12·4	
Number of cardiovascular disease deaths	14 (3·9)*	11 (7·4)	7 (10·7)	2 (24·8)	1·2 [0·9–1·5]
Cholesterol 200–239 mg . dl^{-1}					
Age (years)	37·1 (9·2)	39·7 (9·6)	43·0 (9·2)	47·2 (7·1)	
Diastolic blood pressure (mmHg)	72 (0·007)	80 (0·006)	88 (0·007)	101 (0·009)	
% Diabetics	4·4	4·6	7·0	7·0	
Triglycerides (mmol . l^{-1})	0·75 (0·004)	0·76 (0·005)	0·82 (0·010)	0·90 (0·020)	
% Smokers	17·9	16·4	14·7	14·3	
Number of cardiovascular disease deaths	7 (3·8)	9 (9·1)	15 (24·1)	4 (36·4)	1·5 [1·2–1·7]
Cholesterol ≥240 mg . dl^{-1}					
Age (years)	41·7 (9·7)	44·9 (9·0)	47·5 (7·6)	49·5 (5·7)	
Diastolic blood pressure (mmHg)	73 (0·007)	81 (0·006)	88 (0·007)	101 (0·009)	
% Diabetics	4·9	7·2	8·1	10·6	
Triglycerides (mmol . l^{-1})	0·88 (0·01)	0·96 (0·01)	1·06 (0·01)	1·23 (0·02)	
% Smokers (g . l^{-1})	16·7	15·5	13·8	12·9	
Number of cardiovascular disease deaths	7 (9·8)	3 (7·92)	16 (37·5)	10 (86·8)	1·4 [1·2–1·7]
RR cholest‡ (cardiovascular disease)	1·2 [0·8–1·7]	0·9 [0·6–1·4]	1·2 [0·9–1·6]	1·3 [0·9–1·9]	

Age-adjusted means (SEM) with the exception of age where mean (SD) is represented.
*In parenthesis mortality rate per 100 000 person/years.
†Adjusted risk ratios related to the increment of 10 mmHg of systolic blood pressure in each cholesterol group.
‡Adjusted risk ratios related to the increment of 1 mmol . l^{-1} of cholesterol in each systolic blood pressure group.

relatively low number of cardiovascular deaths. Due to this factor, we did not conduct a more in-depth analysis for coronary heart disease mortality in women (33 deaths from coronary heart disease).

Discussion

The main results of this study realized in a large French population of subjects aged 18–55 years are: (a) hypertension and hypercholesterolaemia often occur in combination, (b) the combination of these two risk factors has additive effects on cardiovascular disease and coronary heart disease risk, (c) in men, a borderline elevation of both systolic blood pressure (130–139 mmHg) and serum cholesterol (200–239 mg . dl^{-1}) leads to a three- to four-fold increase in cardiovascular disease and coronary heart disease risk, and (d) men with a systolic blood pressure ≥160 mmHg represent a small percentage (about 5%) in which cardiovascular disease risk is dramatically increased especially when high cholesterol is present (cardiovascular disease risk × 10).

In this population study, we used the clinical cut-points proposed by the international guideline committees for cholesterol and high blood pressure management to describe the impact of combinations of cholesterol and blood pressure on cardiovascular disease mortality in young men and women[4–6]. Our results show that hypercholesterolaemia and hypertension tend to occur in combination, not in isolation. For example, among men with high blood pressure, the prevalence of high cholesterol was 46·3%, whereas it was only 21·7% among those with normal blood pressure. In women, the prevalence of high cholesterol was more than three times higher in hypertensives than in normotensives (37·6% vs 11·1%).

Therefore, risk assessment based on both these two cardiovascular disease risk factors seems appropriate and even necessary for decision-making pertaining to preventive interventions. This conclusion is in concordance with current recommendations[4–6] which emphasize that measurement of multiple major cardiovascular disease risk factors should be used to guide the type and intensity of cholesterol-lowering and antihypertensive drug treatments.

The results of the present analysis show that based on the systolic blood pressure and/or cholesterol levels, more than 15% of this young male population present a high or very high relative risk for cardiovascular disease mortality, and this percentage increases up to 30% when we evaluate the relative risk for coronary heart disease. These results are very similar to those described by Neaton *et al.*[10] for a large American population presenting very similar characteristics to the population we studied (white men, aged 35–57 years old). In that study the authors reported that for men who were non-smokers and who had systolic blood pressure and serum cholesterol levels in the highest quintile (systolic blood

CVD mortality

Choles/SBP	< 130	130–139	140–159	≥ 160
< 200	1·0 (RG)	2·5 [1·3–5·0]	3·1 [1·5–6·2]	8·9 [3·8–20·7]
200–239	2·6 [1·4–5·2]	2·9 [1·5–5·6]	4·6 [2·4–8·7]	13·3 [6·3–28·3]
≥ 240	3·8 [1·9–7·7]	4·7 [2·4–9·2]	7·3 [3·8–13·7]	17·6 [8·4–36·7]

CHD mortality

Choles/SBP	< 130	130–139	140–159	≥ 160
< 200	1·0 (RG)	2·9 [1·0–7·9]	2·9 [1·0–8·8]	11·5 [3·4–39·0]
200–239	5·0 [1·9–13·8]	3·8 [1·4–10·2]	4·6 [1·7–12·3]	14·5 [4·7–44·8]
≥ 240	5·9 [2·1–16·4]	7·4 [2·8–19·8]	10·4 [4·0–27·4]	17·7 [5·7–54·8]

Figure 1 **In men, we identified the following four cardiovascular disease risk groups (RR attributed to systolic blood pressure and cholesterol) (upper panel): 1 — low risk (reference group): systolic blood pressure <130 mmHg and cholesterol <200 mg . dl^{-1}; they represent 13% of the male population (white area in the figure); 2 — intermediate risk (RR × 2–5): systolic blood pressure=130–159 mmHg and/or cholesterol=200–239 mg . dl^{-1}, or cholesterol ≥240 mg . dl^{-1} but systolic blood pressure <140 mmHg (light gray area in the figure). They represent about 39% of our male population; 3 — high risk (RR × 5–10): systolic blood pressure ≥160 mmHg and cholesterol <200 mg . dl^{-1}, or cholesterol ≥240 mg . dl^{-1} and systolic blood pressure 140–159 mmHg (dark gray area in the figure). They represent about 11% of our male population; 4 — very high risk (RR >10 times compared to the reference group): systolic blood pressure ≥160 mmHg and cholesterol ≥200 mg . dl^{-1}. They represent 4·5% of our male population (black area in the figure). The results observed for coronary heart disease risk were similar, but the increase in RR with systolic blood pressure and cholesterol was more pronounced than for cardiovascular disease risk in men with systolic blood pressure ≥160 mmHg or cholesterol ≥240 mg . dl^{-1} (lower panel). RG=reference group; *age, triglycerides, body mass index, tobacco consumption.**

pressure >142 mmHg and cholesterol >245 mg . dl^{-1}, respectively), the age-adjusted coronary mortality was approximately 10 times greater than for non-smokers with serum cholesterol and systolic blood pressure in the lowest quintiles (systolic blood pressure <118 mmHg and cholesterol <182 mg . dl^{-1}). In that study, a similar increase in coronary heart disease risk according to systolic blood pressure and serum cholesterol was also observed in smokers. The results from our study show similar effects for these two risk factors in a large European population. Our results also show that the classification based on the limits defined in the international guidelines can clearly evaluate cardiovascular risk in men.

The results observed in young women are much less impressive. Lowe *et al.*[11] previously showed that high cholesterol and high blood pressure had similar effects in men and women in a large American population. The authors of that study demonstrated that the presence of multiple cardiovascular disease risk factors places women at considerably higher relative and absolute excess risk of cardiovascular disease and coronary heart disease compared with women without any risk factors and that women with multiple risk factors had a cardiovascular disease risk that equals that of men of the same age. In our study, we did not observe such an 'equalization' of the risk between men and women in the presence of high cholesterol and high systolic blood pressure. Our results show that for similar systolic blood pressure and cholesterol, women always had two to three times lower cardiovascular mortality rates than men (see Tables 3 and 4). The differences between our

CVD mortality

Choles/SBP	< 130	130–139	140–159	≥ 160
< 200	1·0 (RG)	1·8 [0·8–4·0]	1·3 [0·5–3·5]	2·1 [0·4–10·3]
200–239	0·6 [0·2–1·4]	1·3 [0·5–3·3]	2·6 [1·1–6·2]	1·8 [0·5–6·9]
≥ 240	0·9 [0·3–2·6]	0·4 [0·1–1·6]	3·8 [1·4–10·0]	4·3 [1·4–13·1]

Figure 2 **In women, we identified the following two cardiovascular disease risk groups (RR attributed to systolic blood pressure and cholesterol). 1 — low risk (reference group): systolic blood pressure <130 mmHg and cholesterol <200 mg . dl^{-1}. They represent 32% of the female population (white area in the figure); 2 — intermediate risk (RR × 2–5): systolic blood pressure ≥140 mmHg and cholesterol ≥200 mg . dl^{-1}. They represent 11·5% of our female population (light gray area in the figure). RG=reference group; *age, triglycerides, body mass index, tobacco consumption.**

data and those observed in the American population mentioned above may be explained by the fact that cardiovascular disease mortality, especially coronary heart disease mortality in women <55 years, is extremely low in France. The lack of statistical power may be the reason for a less significant increase in relative cardiovascular disease risk in women with high systolic blood pressure or high cholesterol (Fig. 2), despite an important increase in crude cardiovascular disease death rates, especially when both of these risk factors were present (Table 4). Therefore, the results presented here for women cannot be considered as conclusive and should be considered with great caution.

There are several other limitations to the present study. First, the participants in this study were self-selected and therefore were more interested in their health. The result of this is that as we mentioned in the Methods section, mortality rates in our cohort were 20% lower than mortality rates in the general French population. However, the distribution of the causes of death was identical to that of the general population. Also, the socioeconomic status of the IPC cohort is very similar to that observed in the general population in the Paris area. We believe that the results derived from our population can be extrapolated to the general population. Second, blood pressure values were based on a single visit, therefore they did not enable us to clearly identify people with permanently elevated blood pressure. However, it has previously been reported that multiple blood pressure measurements added little to determining the risk already predicted by a single measurement[15]. Third, there was no information about possible antihypertensive treatment after the visit. One could assume that patients with high levels of both systolic blood pressure and cholesterol were more likely to receive treatment after the visit. This would tend to minimize the effects of these two risk factors and of their combination on cardiovascular disease mortality. Finally, only total serum cholesterol concentration was measured. Information on other lipid risk factors, such as high-density lipoprotein cholesterol level, was not available. Despite these limitations, the data from the present study clearly demonstrate the adverse effects of unfavourable levels of major cardiovascular disease risk factors on coronary heart disease, cardiovascular disease, and all-cause mortality risks in both middle-aged men and women, especially when these factors are present in combination.

In conclusion, in French subjects under 55 years of age, systolic blood pressure and serum cholesterol, the two most frequent cardiovascular disease risk factors, have additive effects on cardiovascular disease risk. Our results point out the need for a more aggressive public health policy to prevent the development of these risk factors which increase the risk of cardiovascular disease mortality, especially coronary heart disease mortality, in a very significant way, in individuals under 55 years of age.

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