Cardiovascular Mortality in Overweight Subjects
The Key Role of Associated Risk Factors

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Abstract—The role of obesity and overweight as independent risk factors for cardiovascular disease is still debated. The aim of this study was to evaluate the impact of overweight on cardiovascular mortality according to the presence or absence of associated risk factors. This study included 139,562 men and 104,236 women, aged 18 to 95 years, who had a standard health checkup at the IPC Center between 1972 and 1988. The follow-up period for mortality ended in December 1997. In both genders, the prevalence of hypertension, diabetes, and hypercholesterolemia increased with body mass index ($P<0.001$). When compared with subjects with a body mass index $<25$ kg/m$^2$ without associated risk factors, overweight subjects without associated risk factors did not have an increased risk of cardiovascular mortality. Risk of cardiovascular death increased significantly when overweight was associated with hypertension alone [hazard ratio: 2.05 (1.71 to 2.46) in men; 2.15 (1.48 to 3.11) in women]. In both genders, the association of overweight with diabetes alone or hypercholesterolemia alone did not increase the risk. By contrast, in the presence of hypertension, cardiovascular mortality dramatically increased in overweight subjects with hypercholesterolemia [hazard ratio: 2.65 (2.20 to 3.19) in men, 2.57 (1.80 to 3.68) in women] or diabetes [hazard ratio: 3.01 (2.29 to 3.95) in men; 4.50 (2.67 to 7.58) in women]. The data suggest that the presence of high blood pressure in overweight subjects is the key factor leading to a significant increase in cardiovascular mortality. Because overweight significantly increases the prevalence of associated risk factors, especially hypertension, it should be considered as a major cardiovascular risk determinant. (Hypertension. 2005;46:654-659.)

Key Words: blood pressure ■ hypertension ■ obesity ■ risk factors

Excess weight is associated with an increased incidence of disease such as left ventricular hypertrophy, type II diabetes mellitus, hypertension and dyslipidemia. In both genders, overweight and obesity are associated with an increased risk of coronary heart disease and heart failure. However, the role of obesity as an independent risk factor is still debated. In several epidemiological studies, the positive relationship between weight and cardiovascular mortality disappeared after adjustment for associated risk factors such as hypertension and metabolic disorders. By contrast, in the Framingham study, which had a 26-year follow-up, it was found that obesity, after adjustment for other cardiovascular disease (CVD) risk factors, was an independent risk factor for cardiovascular mortality.

Because few data were available for southern Europe, the aim of the present study was to evaluate the relationship between overweight and cardiovascular mortality in the presence of hypertension, diabetes, and dyslipidemia in a large cohort of 240,000 unselected French men and women, aged 16 to 95 years, with a 25-year follow-up.

Subjects and Methods

Subjects
Subjects were recruited at the Centre d’Investigations Prévolutives et Cliniques (IPC Center; Paris, France), a medical center subsidized by the French national health care system (Sécurité Sociale-CNAM), which provides free medical examinations for all affiliated working and retired persons and their families. The IPC Center has performed $\approx 20,000$ to $25,000$ examinations per year since 1970 for people living in Paris area. Between January 1972 and December 1988, 243,798 subjects (139,562 men and 104,236 women), aged 16 to 95 years (42.7 ± 11.5 years and 40.9 ± 12.3 years for men and women, respectively), had an health check-up at the IPC Center. Mortality data for a 25-year follow-up period (mean: 14.1 ± 0.2 years) were available for this population. End point for follow-up was December 1997.

The IPC Center received authorization from the “Comité National d’Informatique et des Libertés” to conduct analyses on all data collected during the health check-up. All subjects gave their informed consent at the time of the examination. Based on national mortality statistics, our cohort presented a 20% lower mortality rate than the general French population. This finding may be explained by the assumption that the people who came for a health check-up were apparently healthy and motivated to be followed up. Interestingly, compared with 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 (BP) was measured in the right arm using a manual mercury sphygmomanometer, after a 10-minute rest period. The first and the fifth Korotkoff phases were used to define systolic blood pressure (SBP) and diastolic blood pressure (DBP). The mean of 3 measurements was considered as the BP value. Height (using a wall-mounted stadiometer) and weight (using calibrated scales) were recorded by a nurse. Standard biological parameters, including total plasma cholesterol and triglycerides, were measured under fasting conditions, and a resting ECG was recorded. Heart rate was also measured with ECG. Left ventricular hypertrophy was defined according to the Sokolow-Lydia criteria for ECG. Tobacco consumption, physical activity, personal and family medical history, current medications, and alcohol consumption were assessed using a self-administered standardized questionnaire. Subjects were classified into 2 groups for regular physical activity (yes or no) and into 3 groups for tobacco consumption (never smokers, ex-smokers, and current smokers). All clinical and biological parameters were evaluated on the same day of the examination.

End Points
For each screened subject, vital status was obtained from the “Institut National de Statistiques et d’Études Economiques” (INSEE, Paris, France). Causes of mortality, taken from death certificates, were provided by INSERM’s Department of Mortality Studies (“Institut National de la Santé et de la Recherche Médicale,” Unit SC8). 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 to 459, in accordance with the World Health Organization classification:

Heart disease:
- MI (310–315)
- Heart failure (410–429)
- Congenital heart diseases (741–749)
- Endocardial disease (390–398)
- Other diseases of the heart (390–398)

CVD mortality. To perform these investigations, supine blood pressure (SBP) and diastolic blood pressure (DBP). The mean of 3 measurements was considered as the BP value. Height (using a wall-mounted stadiometer) and weight (using calibrated scales) were recorded by a nurse. Standard biological parameters, including total plasma cholesterol and triglycerides, were measured under fasting conditions, and a resting ECG was recorded. Heart rate was also measured with ECG. Left ventricular hypertrophy was defined according to the Sokolow-Lydia criteria for ECG. Tobacco consumption, physical activity, personal and family medical history, current medications, and alcohol consumption were assessed using a self-administered standardized questionnaire. Subjects were classified into 2 groups for regular physical activity (yes or no) and into 3 groups for tobacco consumption (never smokers, ex-smokers, and current smokers). All clinical and biological parameters were evaluated on the same day of the examination.

The following definitions were used for diseases and risk factors associated with overweight:

- Hypertension: SBP ≥140 mm Hg and/or DBP ≥90 mm Hg or antihypertensive treatment.
- Hypercholesterolemia: total plasma cholesterol ≥240 mg/dL (≥6.2 mmol/L).
- Diabetes: personal history of diabetes as recorded in the self-administered questionnaire.

The first step of the analysis consisted of examining the relationship between body mass index (BMI), calculated as the ratio of weight/height$^2$ (kg/m$^2$), and CVD mortality. To perform these analyses, the following 6 BMI classes were established using the WHO classification:

BMI <18.5, 18.5 to 24.9, 25.0 to 29.9, 30.0 to 34.9, 35.0 to 39.9, and ≥40 kg/m$^2$; the last 2 classes were merged for adjusted analyses. Overweight was defined as a BMI ≥25 kg/m$^2$. Differences in CVD mortality among BMI groups were calculated using a Cox proportional hazards regression analysis, after adjustment for age alone, and after adjustment for age, physical activity, systolic/diastolic blood pressure, tobacco consumption, diabetes, cholesterol level, and heart rate. Complementary analyses were performed excluding current smokers and subjects who had died within the first 2 years of follow-up.

The second step of the analysis examined the impact of each associated risk factor in combination with overweight, using a Cox proportional hazard regression analysis. The reference group was defined as the group with a BMI 18.5 to 24.9 kg/m$^2$ and without associated risk factors (ARF), and was compared with the following 7 groups: (1) BMI ≥25 kg/m$^2$ with no ARF; (2) BMI ≥25 kg/m$^2$ with diabetes; (3) BMI ≥25 kg/m$^2$ with hypercholesterolemia; (4) BMI ≥25 kg/m$^2$ with hypertension; (5) BMI ≥25 kg/m$^2$ with hypertension and diabetes; (6) BMI ≥25 kg/m$^2$ with hypertension and hypercholesterolemia; (7) BMI ≥25 kg/m$^2$ with hypertension, hypercholesterolemia, and diabetes.

These comparisons were adjusted for age, physical activity, tobacco consumption, and heart rate. The level of statistical significance used was <5%. All statistical analyses were carried out using the SAS statistical software package (version 8.02 for Windows).

Results
Means for BMI were 24.6±3.1 kg/m$^2$ in men and 22.8±3.6 kg/m$^2$ in women. During the follow-up period, 11 688 deaths (2,949 from CVD) were recorded among men and 4188 deaths (929 from CVD) were recorded among women.

Table 1 shows the baseline characteristics and mortality rates among men and women in the 6 BMI groups. Among men (Table 1, upper panel), 42% were classified as “overweight,” which included 5.5% who were classified as “obese” (BMI ≥30 kg/m$^2$), among whom 0.1% were “morbidly obese” (BMI ≥40 kg/m$^2$). Among women (Table 1, lower panel), 21% were classified as “overweight,” which included 4.3% who were classified as “obese,” among whom 0.2% were “morbidly obese.” In both genders, the prevalence of hypertension, diabetes, and hypercholesterolemia progressively increased with BMI ($P<0.001$). In men and women, the percentage of current smokers was lower among overweight and obese subjects. In men, the percentage of ex-smokers increased with BMI; this relationship was not observed in women. Regular physical activity was less frequent among obese subjects, in both genders. High heart rate (>80 bpm) was observed more frequently among obese subjects, in both genders.

In men, a J-shaped curve between BMI and all-cause mortality was observed. As shown in Table 1, the lowest rates for all-cause mortality were observed in the group with a BMI between 18.5 and 24.9 kg/m$^2$ (6.8%). As compared with that group, mortality rates observed in the group with a BMI <18.5 kg/m$^2$ were significantly higher (8.3%, $P<0.05$). Excluding current smokers and subjects who had died during the first 2 years of follow-up did not modify the relationship. This finding was consistent with that described by Allison et al.$^{15}$ Mortality rates were also significantly higher in groups with BMI ≥25 kg/m$^2$ (trend test $P<0.001$).

As shown in Figure 1, after adjustment for age only, CVD mortality risk increased linearly with BMI ($P<0.001$). After adjustment for age, physical activity, BP, tobacco consumption, diabetes, total cholesterol, and heart rate (Figure 1, in both genders), CVD mortality risk did not significantly change with BMI categories, indicating that in obese subjects, the association between BMI and CVD mortality was mainly mediated by the presence of associated risk factors.

Table 2 provides the number of subjects and means for BMI, including the minimum and maximum in each group. BMI means and standard deviations differed only for the reference group but were similar in every subgroup. BMI means and standard deviations differed only for the reference group but were similar in every subgroup. BMI means and standard deviations differed only for the reference group but were similar in every subgroup.
cular death increased significantly when overweight was associated with hypertension alone [hazard ratio (HR): 2.05 (1.71 to 2.46) in men; 2.15 (1.48 to 3.11) in women]. By contrast, in both genders, and in the absence of hypertension, the association of overweight with diabetes did not increase the risk of cardiovascular mortality [HR: 1.28 (0.76 to 2.15) in men, HR: 1.14 (0.28 to 4.67) in women]. Also, in the absence of hypertension, the association of overweight with hypercholesterolemia slightly increased the risk of cardiovascular mortality in men [HR: 1.45 (1.13 to 1.86)], whereas in women no increase was observed [HR: 1.21 (0.71 to 2.07)]. However, the risk of cardiovascular deaths dramatically increased in overweight subjects with both hypertension and hypercholesterolemia [HR: 2.65 (2.20 to 3.19) in men, 2.57 (1.80 to 3.68) in women] and in subjects with both hypertension and diabetes [HR: 3.01 (2.29 to 3.95) in men; 4.50 (2.67 to 7.58) in women]. Finally, when BMI ≥25 kg/m² was associated with all 3 associated risk factors (hypertension, diabetes, and hypercholesterolemia), the risk of CVD mortality increased significantly [HR: 3.67 (2.78 to 4.85) and 2.87 (1.60 to 5.13) in men and women, respectively]. In women, the decreased risk observed in the last 2 groups was most likely caused by the small number of subjects in these groups; according to the confidence interval, the 2 groups were not statistically different.

Similar results were found when obese subjects (BMI ≥30 kg/m²) were excluded. After this secondary analysis, risk of cardiovascular disease significantly increased when overweight was associated with hypertension in both genders [HR: 1.96 (1.62 to 2.37) in men and 1.85 (1.24 to 2.79) in women] and with cholesterol in men [HR: 1.45 (1.12 to 1.88)]. An additional analysis, performed in 2 age groups (<50 years, ≥50 years), did not show a different impact of BMI on cardiovascular mortality according to age (data not shown).

### Discussion

An important finding in this study is that among overweight and obese subjects, who represented 42% and 21%, respectively, of the men and women in our population, the risk of CVD mortality did not significantly increase in the absence of associated risk factors. Hypertension in overweight or obese subjects, however, emerged as the key factor leading to a significant increase in the risk of CVD mortality.

Our study population was characterized by a low prevalence of obesity compared with the French population from the Obepi study, a recent survey conducted in ~20,000 representative households. In our population, the prevalence of obesity (BMI ≥30 kg/m²) was 5.6% and 4.5%, respectively, in men and women, whereas in the same age range in the Obepi study, the figures were 11.8% in men and 11.3% in women. The prevalence of obesity in our population was also lower than that found in the PROCAM study from Munster (11% in men) but it was similar to the prevalence observed in Northern Europe in the MALMO study (6% in men), a study with a similar design to ours. Differences could be
explained, in part, by the fact that our population consisted of individuals who had a standard health check-up on a voluntary basis and who therefore may have been more concerned about their health. They may have had lifestyles that led to beneficial consequences on their corpulence (better nutritional habits and greater physical activity). It is important to note, however, that data collection methodology for weight and height varies from one study to the next and could also explain differences in prevalence. For example, in our study, weight and height were collected during the clinical examination whereas in the OBEPI study,16 weight and height were self-reported.

Relationship Between BMI and Risk Factors and Mortality

As expected, we found strong relationships between BMI and the cardiovascular risk factors examined. Such relationships are well-documented for diabetes and hypertension and were reported in many previous studies such as the Nurses’ Health study for data pertaining to women,17–20 the Health Professional Follow-up study,21,22 the Malmö study,11 and the PROCAM study12 for data pertaining to men.

One of the main results of this study is that the relationship between overweight and CVD mortality was no longer significant after taking into account major CVD risk factors (age, physical activity, blood pressure, tobacco consumption, diabetes, cholesterol level, and heart rate). These results suggest the lack of an independent effect of BMI on CVD mortality. A similar result was observed in the PROCAM study,12 indicating that the effect of overweight and obesity on coronary heart disease mortality was partly mediated by other risk factors. This is consistent with results from anatomic studies conducted by Montenegro et al, in which it was reported that among subjects who died from an accidental death, there was no association between the degree of coronary atherosclerosis and the indices of obesity in the population.22 This was also confirmed by a review of anatomic studies23 in which inconsistent relationships between the level of obesity and coronary atheromatous disease were found. Another study reported that the prevalence of coronary stenosis in obese subjects versus normal weight subjects was similar when hypertensives and diabetics were excluded.24

More recently, Kip et al, based on coronary angiography results in 780 women,25 reported that overweight and obesity in women were not independent risk factors for coronary disease unless the metabolic syndrome were present. Our results were consistent with their results because the metabolic syndrome represents the association of obesity, high blood pressure, and metabolic disturbances. Also, a study in Japanese men found that after adjustment for age and BMI, visceral fat area was significantly greater in subjects with metabolic disorders than in subjects without metabolic problems.26

Therefore, it is possible that the risk of cardiovascular disease is present primarily in the subgroup of overweight

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>Associated Risk Factors</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.5–24.9</td>
<td>No</td>
<td>37 991</td>
<td>48 536</td>
</tr>
<tr>
<td>≥25</td>
<td>No</td>
<td>14 541</td>
<td>7542</td>
</tr>
<tr>
<td>≥25</td>
<td>DM</td>
<td>980</td>
<td>593</td>
</tr>
<tr>
<td>≥25</td>
<td>Hch</td>
<td>7657</td>
<td>2652</td>
</tr>
<tr>
<td>≥25</td>
<td>Htn</td>
<td>17 585</td>
<td>5454</td>
</tr>
<tr>
<td>≥25</td>
<td>Htn + Hch</td>
<td>13 531</td>
<td>4211</td>
</tr>
<tr>
<td>≥25</td>
<td>Htn + DM</td>
<td>1996</td>
<td>643</td>
</tr>
<tr>
<td>≥25</td>
<td>Htn + DM + Hch</td>
<td>1591</td>
<td>520</td>
</tr>
</tbody>
</table>

DM indicates diabetes mellitus; Hch, hypercholesterolemia; Htn, hypertension.
subjects who are characterized by the presence of abdominal
obesity. It has been shown that abdominal obesity and
visceral fat area are associated with an insulin-resistant
state, which appears to be an important link between the risk
of CVD morbidity and mortality, and many components of
the metabolic syndrome such as metabolic disturbances and
high blood pressure. Our study suggests that among over-
weight subjects, high blood pressure is the most important
determinant of added CVD risk. This relationship could not
be explained by BMI distribution in the different subgroups.
In a previous study, we showed the predominant role played
by blood pressure levels in CVD risk in patients with glucose
intolerance. Also, high blood pressure is the major deter-
minant of the evolution of diabetes and of its complica-
tions. It is possible that the development of high blood
pressure in obese subjects or in subjects with metabolic
disturbances is a sign of arteriolar or arterial remodeling,
which can contribute to an increase in CVD risk.

Limitations of the Study
Diabetic status was defined as a self-reported diagnosis.
Fasting glucose was only available for the population from
1982 to 1988. Before this period, evaluation of glucose
metabolism was obtained after an oral glucose tolerance test.
Among the population with a fasting glucose measure, a
statistical analysis revealed a concordance level of 95%
between the self-reported diabetes diagnosis and diabetes
criteria during the study period (>1.4 g/L).

The lack of relationship between BMI and cardiovascular
mortality could be explained by the low prevalence of obese
subjects in our population (5%). The low number of obese
subjects may be insufficient to show a statistically significant
relationship between BMI and cardiovascular mortality.

In this analysis, because BMI was used to evaluate obesity
status, the distribution and quantification of body fat mass
was not taken into account. The relationship between BMI
and all-cause mortality and CVD mortality could depend on
fat distribution [evaluated by waist circumference or waist to
hip ratio] or on body composition (fat mass, fat-free mass). In

a prospective cohort study, waist to hip ratio was found to be
a better anthropometric predictor for total mortality than
BMI. There is some evidence that all-cause mortality is
positively associated with fat mass but negatively associated
with fat-free mass. In the present cohort, circumference
measurements for assessing body fat distribution were not
available, nor were assessments of body composition such as
those provided by new technologies (eg, bioimpedance
analysis).

In conclusion, this study shows that in a large French
population of men and women, in the absence of associated
risk factors such as hypertension, hypercholesterolemia and
diabetes, the risk of CVD mortality did not increase in
overweight or obese subjects. An important finding from this
study is that among all of the associated risk factors exam-
ined, hypertension played a central role in the increase of
cardiovascular risk among overweight and obese subjects.
Because increased body weight for a given height signifi-
cantly increases the prevalence of associated risk factors,
especially hypertension, it should be considered as a major
cardiovascular risk determinant.

Perspectives
The results of this study emphasize the importance of
preventing associated conditions such as hypertension to limit
cardiovascular risk. Further longitudinal studies are needed to
evaluate the role of fat mass (in terms of quantity and
distribution) in the onset of metabolic disorders and to
determine which subjects are at a high risk for the metabolic
syndrome and, as a result, increasing their CVD risk in terms
of morbidity and mortality.

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