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,[1,2] type II diabetes mellitus,[3,4] hypertension[5] and dyslipidemia.[5] In both genders, overweight and obesity are associated with an increased risk of coronary heart disease and heart failure.[6–10] However, the role of obesity as an independent risk factor is still debated.[7] 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.[4,11,12] 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.[9,13]

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 Préventives 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 ≈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

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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-Lyon 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'Etudes 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, and 798 (sudden death). To validate this procedure, we took a random sample of 250 subjects and compared our data with those found in city hall registries. A discordance was found in only 2 cases (<1%). Based on the results of this validation, we considered that we had a complete follow-up for the entire study population.

Data Analysis

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:[14] 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.[14] 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, 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 ≥25kg/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.

Figure 2 shows the impact of overweight on the risk of CVD mortality, with or without ARF. When compared with subjects with a BMI 18.5 to 25 kg/m^2 without ARF (reference group), overweight subjects without ARF did not have an increased risk of cardiovascular mortality. Risk of cardiovas-

TABLE 1. Baseline Characteristics and Mortality Rates Among Men and Women According to BMI

	BMI <18.5	18.5–24.9	25.0–29.9	30.0–34.9	35.0–39.9	≥40 kg/m²
Men						
No. (%)	1871 (1.3)	79 144 (56.7)	50 928 (36.5)	6913 (5.0)	620 (0.4)	86 (0.1)
Age in years (SD)	36.0 (11.9)	40.2 (11.5)	46.0 (10.4)	48.0 (10.0)	47.5 (10.2)	47.9 (9.8)
% Current smokers	45.2	32.5	25.9	25.0	31.5	25.6
% Ex-smokers	17.3	26.3	32.8	34.8	32.6	32.6
% Physical activity (yes)	21.2	38.3	28.8	15.3	10.8	3.5
% HR >80 bpm	24.1	16.5	16.9	22.8	29.7	41.7
% With hypertension	26.2	37.5	56.7	76.1	84.8	95.4
% With diabetes	3.1	4.6	8.0	13.7	21.5	26.7
% With hypercholesterolemia	9.8	23.8	39.3	44.8	44.7	30.6
% Total mortality (n)	8.3 (156)	6.8 (5370)	9.9 (5042)	14.5 (999)	16.6 (103)	20.9 (18)
% CVD mortality (n)	1.0 (19)	1.5 (1155)	2.8 (1429)	4.4 (307)	5.5 (34)	5.8 (5)
Women						
No. (%)	6093 (5.9)	76 235 (73.1)	17 424 (16.7)	3564 (3.4)	736 (0.7)	184 (0.2)
Age in years (SD)	33.7 (10.9)	39.7 (11.9)	47.1 (11.6)	48.3 (11.0)	47.5 (10.2)	45.4 (10.1)
% Current smokers	31.6	21.5	13.2	11.3	11.0	12.0
% Ex-smokers	15.2	16.1	13.0	14.2	17.2	12.5
% Physical activity (yes)	24.0	26.8	13.6	6.2	4.4	3.3
% HR >80 bpm	25.4	22.0	23.3	27.6	31.5	37.9
% With hypertension	13.0	23.2	45.5	62.3	74.5	80.9
% With diabetes	3.1	4.1	7.7	14.1	18.3	19.6
% With hypercholesterolemia	10.5	18.0	34.0	39.5	34.9	32.6
% Total mortality	2.6 (160)	3.3 (2550)	6.5 (1129)	7.8 (278)	7.6 (56)	8.2 (15)
% CVD mortality	0.4 (27)	0.7 (523)	1.7 (287)	2.1 (75)	1.8 (13)	2.2 (4)

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.[16] 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)[12] but it was similar to the prevalence observed in Northern Europe in the MALMO study (6% in men),[11] a study with a similar design to ours. Differences could be

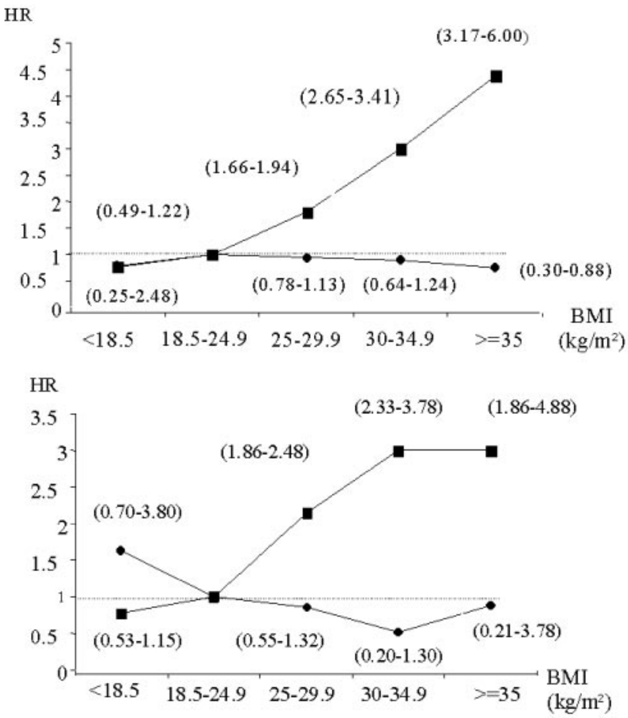

Figure 1. Hazard ratio for CVD mortality in each group of BMI compared with the reference group (BMI: 18.5 to 24.9 kg/m^2) in men (upper panel) and women (lower panel), adjusted for age (■) and adjusted for age, physical activity, blood pressure, tobacco consumption, diabetes, cholesterol, and heart rate (●).

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,[21,4] the Malmö study,[11] and the PROCAM study[12] 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 studies[23] 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 2. Number of Subjects and Mean Values of BMI (kg/m^2) in the Different Groups According to the Presence of Associated Risk Factors

		Men		Women	
BMI (kg/m^2)	Associated Risk Factors	No.	Mean (Min-Max)	No.	Mean (Min-Max)
18.5–24.9	No	37 991	22.4 (18.5–25.0)	48 536	21.4 (18.5–25.0)
≥25	No	14 541	26.9 (25.0–42.1)	7542	27.4 (25.0–64.1)
≥25	DM	980	27.4 (25.0–40.1)	593	28.2 (25.0–44.5)
≥25	Hch	7657	27.1 (25.0–43.2)	2652	27.6 (25.0–46.8)
≥25	Htn	17 585	27.7 (25.0–50.5)	5454	28.6 (25.0–57.9)
≥25	Htn+Hch	13 531	27.9 (25.0–48.1)	4211	28.6 (25.0–49.6)
≥25	Htn+DM	1996	28.5 (25.0–47.1)	643	30.0 (25.0–46.1)
≥25	Htn+DM+Hch	1591	28.7 (25.0–51.3)	520	29.7 (25.0–46.3)

DM indicates diabetes mellitus; Hch, hypercholesterolemia; Htn, hypertension.

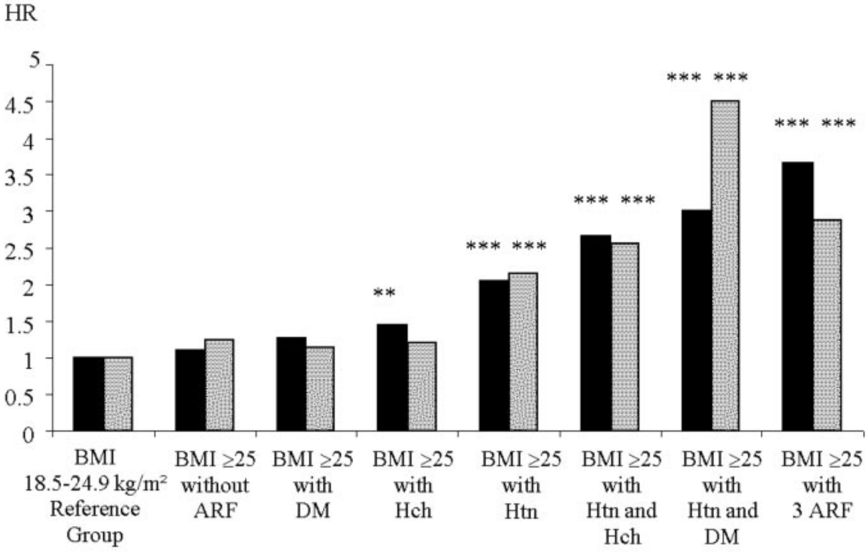

Figure 2. Hazard ratio for CVD mortality according to BMI and other associated risk factors (ARF) [diabetes (DM), hypercholesterolemia (Hch), hypertension (Htn)]. (Men: black bars; women: gray bars). ** $P<0.001$; *** $P<0.0001$.

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,[27] 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 overweight 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.[28] Also, high blood pressure is the major determinant of the evolution of diabetes and of its complications.[29,30] 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.[31] There is some evidence that all-cause mortality is positively associated with fat mass but negatively associated with fat-free mass.[32] 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 examined, hypertension played a central role in the increase of cardiovascular risk among overweight and obese subjects. Because increased body weight for a given height significantly 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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References

1. De Simone G, Devereux RB, Roman MJ, Alderman MH, Laragh JH. Relation of obesity and gender to left ventricular hypertrophy in normotensive and hypertensive adults. *Hypertension*. 1994;23:600–606.
2. Thomas F, Benetos A, Ducimetiere P, Bean K, Guize L. Determinants of left ventricular mass in a French male population. *Blood Press*. 1999;8: 79–84.
3. Goran MI, Ball GD, Cruz ML. Obesity and risk of type 2 diabetes and cardiovascular disease in children and adolescents. *J Clin Endocrinol Metab*. 2003;88:1417–1427.
4. Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. *Diabetes Care*. 1994;17:961–969.
5. Mokdad AH, Ford ES, Bowman BA, Dietz WH, Vinicor F, Bales VS, Marks JS. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *JAMA*. 2003;289:76–79.
6. Ashton WD, Nanchahal K, Wood DA. Body mass index and metabolic risk factors for coronary heart disease in women. *Eur Heart J*. 2001;22: 46–55.
7. Manson JE, Colditz GA, Stampfer MJ, Willett WC, Rosner B, Monson RR, Speizer FE, Hennekens CH. A prospective study of obesity and risk of coronary heart disease in women. *N Engl J Med*. 1990;322:882–889.
8. Field AE, Coakley EH, Must A, Spadano JL, Laird N, Dietz WH, Rimm E, Colditz GA. Impact of overweight on the risk of developing common chronic diseases during a 10-year period. *Arch Intern Med*. 2001;161: 1581–1586.
9. Pi-Sunyer FX. Medical hazards of obesity. *Ann Intern Med*. 1993;119: 655–660.
10. Kannel WB, Wilson PW, Nam BH, D'Agostino RB. Risk stratification of obesity as a coronary risk factor. *Am J Cardiol*. 2002;90:697–701.
11. Jonsson S, Hedblad B, Engstrom G, Nilsson P, Berglund G, Janzon L. Influence of obesity on cardiovascular risk. Twenty-three-year follow-up of 22,025 men from an urban Swedish population. *Int J Obes Relat Metab Disord*. 2002;8:1046–1053.
12. Schulte H, Cullen P, Assmann G. Obesity, mortality and cardiovascular disease in the Munster Heart Study (PROCAM). *Atherosclerosis*. 1999; 144:199–209.
13. Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation*. 1983;67: 968–977.
14. WHO. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser. 2000;894 i-xii:1–253.
15. Allison DB, Faith MS, Heo M, Townsend-Butterworth D, Williamson DF. Meta-analysis of the effect of excluding early deaths on the estimated relationship between body mass index and mortality. *Obes Res*. 1999;7: 342–354.
16. Charles MA, Basdevant A, Eschwege E. Prevalence of obesity in adults in France: the situation in 2000 established from the OBEPI Study. *Ann Endocrinol*. 2002;63:154–158.
17. Colditz GA, Willett WC, Rotnitzky A, Manson JE. Weight gain as a risk factor for clinical diabetes mellitus in women. *Ann Intern Med*. 1995; 122:481–486.
18. Bramlage P, Pittrow D, Wittchen HU, Kirch W, Boehler S, Lehnert H, Hoefler M, Unger T, Sharma AM. Hypertension in overweight and obese primary care patients is highly prevalent and poorly controlled. *Am J Hypertens.* 2004;17:904–910.
19. Willett WC, Manson JE, Stampfer MJ, Colditz GA, Rosner B, Speizer FE, Hennekens CH. Weight, weight change, and coronary heart disease in women. Risk within the 'normal' weight range. *JAMA*. 1995;273: 461–465.
20. Huang Z, Willett WC, Manson JE, Rosner B, Stampfer MJ, Speizer FE, Colditz GA. Body weight, weight change, and risk for hypertension in women. *Ann Intern Med*. 1998;128:81–88.
21. Rimm EB, Stampfer MJ, Giovannucci E, Ascherio A, Spiegelman D, Colditz GA, Willett WC. Body size and fat distribution as predictors of coronary heart disease among middle-aged and older US men. *Am J Epidemiol*. 1995;141:1117–1127.
22. Montenegro MR, Solberg LA. Obesity, body weight, body length, and atherosclerosis. *Lab Invest*. 1968;18:594–603.
23. Solberg LA, Strong JP. Risk factors and atherosclerotic lesions. A review of autopsy studies. *Arteriosclerosis*. 1983;3:187–198.
24. Sternby NH. Atherosclerosis and body build. *Bull World Health Organ*. 1976;53:601–604.
25. Kip KE, Marroquin OC, Kelley DE, Johnson BD, Kelsey SF, Shaw LJ, Rogers WJ, Reis SE. Clinical importance of obesity versus the metabolic syndrome in cardiovascular risk in women: a report from the Women's Ischemia Syndrome Evaluation (WISE) study. *Circulation*. 2004;109: 706–713.
26. Nagaretani H, Nakamura T, Funahashi T, Kotani K, Miyanaga M, Tokunaga K, Takahashi M, Nishizawa H, Kishida K, Kuriyama H, Hotta K, Yamashita S, Matsuzawa Y. Visceral fat is a major contributor for multiple risk factor clustering in Japanese men with impaired glucose tolerance. *Diabetes Care*. 2001;24:2127–2133.
27. Bjorntorp P. Obesity and risk of cardiovascular disease. *Ann Clin Res*. 1985;17:3–9.
28. Henry P, Thomas F, Benetos A, Guize L. Impaired fasting glucose, blood pressure and cardiovascular disease mortality. *Hypertension*. 2002;40: 458–463.
29. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in Type 2 diabetes. UKPDS38. *BMJ*. 1998;317:703–713.
30. Schrier RW, Estacio RO, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and stroke. *Kidney Int*. 2002;61:1086–1097.
31. Folsom AR, Kushi LH, Anderson KE, Mink PJ, Olson JE, Hong CP, Sellers TA, Lazovich D, Prineas RJ. Associations of general and abdominal obesity with multiple health outcomes in older women: the Iowa Women's Health Study. *Arch Intern Med*. 2000;160:2117–2128.
32. Allison DB, Zhu SK, Plankey M, Faith MS, Heo M. Differential associations of body mass index and adiposity with all-cause mortality among men in the first and second National Health and Nutrition Examination Surveys (NHANES I and NHANES II) follow-up studies. *Int J Obes Relat Metab Disord*. 2002;26:410–416.