Does Obesity Modify the Effect of Blood Pressure on the Risk of Cardiovascular Disease? 
A Population-Based Cohort Study of More Than One Million Swedish Men

Karri Silventoinen, PhD; Patrik K.E. Magnusson, PhD; Martin Neovius, PhD; Johan Sundström, MD, PhD; G. David Batty, PhD; Per Tynelius, MSc; Finn Rasmussen, MD, MPH, PhD

Background—Some studies have suggested that increased blood pressure has a stronger effect on the risk of cardiovascular disease (CVD) in lean persons than in obese persons, although this is not a universal finding. Given the inconsistency of this result, we tested it using a large population-based cohort data set.

Methods and Results—Systolic and diastolic blood pressures (BPs) and body mass index were measured in 1,145,758 Swedish men born between 1951 and 1976 who were in young adulthood (median age 18.2 years). During the register-based follow-up, which lasted until the end of 2006, 65,611 new CVD events took place, including 6,799 myocardial infarctions and 8,827 strokes. Hazard ratios (HRs) per 1-SD increase in systolic and diastolic BP were computed within established body mass index categories (underweight, normal, overweight, or obese) with Cox proportional hazards models. The strongest associations of diastolic BP with CVD (HR 1.18), myocardial infarction (HR 1.22), and stroke (HR 1.13) were observed in the obese category. For systolic BP, the strongest associations were observed in the obese category with CVD (HR 1.16) and stroke (HR 1.29) but in the overweight category with myocardial infarction (HR 1.19). We observed statistically significant interactions (P<0.0001) with body mass index for diastolic BP in relation to CVD and for systolic BP in relation to CVD and stroke.

Conclusions—In contrast to the findings of previous studies, we observed a general increase in the magnitude of the association between blood pressure and subsequent CVD with increasing body mass index. Hypertension should not be regarded as a less serious risk factor in obese than in lean or normal-weight persons. (Circulation. 2008;118:1637-1642.)

Key Words: blood pressure ■ myocardial infarction ■ obesity ■ epidemiology ■ stroke

Hypertension and obesity are important risk factors for cardiovascular disease (CVD), but the role of obesity as an effect modifier in the association between blood pressure and CVD is highly debatable. Several studies have suggested that hypertension or elevated blood pressure has a stronger effect on CVD risk in lean than in obese persons, but negative or opposite results have also been reported. These findings have led to the suggestion that hypertension in lean and obese subjects represents 2 distinct forms of hypertension or that obesity may modify the physiological effects of hypertension. This suggestion has some support from a small-scale study of 55 obese and 66 lean hypertensive patients. The investigators in that study found that obese subjects had less pronounced increases in blood levels of renin and epinephrine during treadmill exercise than lean subjects, which indicates different neuroendocrine responses to physical exercise. Evidence is also increasing that suggests that muscle tissue is an important organ in the regulation of human metabolism, and thus, lean body mass may also modulate the physiological effects of hypertension. However, previous studies have exclusively used relative weight as an indicator of obesity, which is a combination of lean and fat body mass.

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A stronger effect of hypertension on CVD risk in lean than in obese persons, as suggested by some previous studies, would have important clinical implications because hypertension among obese individuals might be considered a less serious risk factor. We have access to a very large population-based cohort study of Swedish men, which has enabled us to analyze this research question with greater precision than has been possible previously.
Methods

Data Collection
Physiological measures were made at conscription examination, which predates active military service. Conscription was mandatory by law for all male Swedish citizens in the present study cohort born between 1951 and 1976; only those with a severe handicap or a chronic disease were exempted. Age at the time of the conscription examination (1969 to 1994) varied from 16 to 25 years (median age 18.2 years), and only 1.36% of the participants were younger than 17 or older than 20 years.

Diastolic and systolic blood pressure (DBP and SBP), height (without shoes), and weight (in underwear) were measured. Body mass index (BMI, kg/m²) was used as an indicator of relative weight and was stratified to conventional weight categories (underweight <18.5 kg/m², normal weight 18.5 to 24.9 kg/m², overweight 25 to 29.9 kg/m², and obese ≥30 kg/m²). Blood pressure was measured after 5 to 10 minutes of rest in the supine position. No further measurements were made if SBP was 145 mm Hg or less and DBP was between 50 and 85 mm Hg. If the measurements were outside these limits, a second measure was made, and the result of the second measure was entered in the register and used in the analyses. For DBP, we found some evidence for rounding to the nearest 10 mm Hg, but the distribution of DBP was otherwise normal. Elbow flexion, hand grip, and knee extension strength were measured according to standard protocols and used as a proxy indicator of lean body mass.16,17

In the entire data set, we had conscription data available for 1 171 424 men, but in 13 674 men, we had missing or invalid information on DBP or SBP (the limits for accepted values were 40 to 100 mm Hg for DBP and 100 to 180 mm Hg for SBP). Of these men, 803 were excluded because of an invalid SBP value and 555 because of an invalid SBP value; other men were dropped from analyses owing to missing blood pressure data. In addition, we had a small number of extreme values for height (≤150 or ≥210 cm; 70 men), weight (≤40 or ≥150 kg; 85 men), or BMI (≤15 or ≥60 kg/m²; 359 men). These values may have been true values or may represent measurement or data entry errors. To minimize errors of misclassification, we excluded these men from the data, which resulted in the final analytical sample of 1 145 758 men.

We also had self-reported information on smoking at baseline in a subset of 34 643 participants born between 1951 and 1953. Smoking was classified into 5 categories: not smoking or smoking 1 to 5 cigarettes per day, 6 to 10 cigarettes per day, 11 to 20 cigarettes per day, or >20 cigarettes per day. We repeated the BMI-stratified analyses in this subsample to analyze whether adjustment for smoking had an effect on the results, using smoking as a categorized variable. Owing to a small number of myocardial infarction (MI) and stroke cases, we were not able to analyze these end points separately.

The follow-up data (1969 to 2006) were based on the Swedish Cause of Death Register, Swedish Hospital Discharge Register, and Statistics Sweden’s emigration registers, which cover the entire Swedish population, and were linked to the baseline data with personal identity numbers. Fatal and nonfatal cases were identified according to the eighth, ninth, and tenth revisions of the International Classification of Diseases (ICD8, ICD9, and ICD10) for all CVD (390 through 459 for ICD8 and ICD9 and I for ICD10), MI (410 for ICD8 and ICD9 and I21 for ICD10), and stroke (430 through 438, 342, and 344 for ICD8; 430 through 438, 342, and 344 for ICD9; and I66 through I66 and G45 for ICD10). Swedish register-based data have shown a high level of validity for acute stroke and MI.19 The follow-up time was calculated in days from conscription to death or hospitalization from the disease (cases), deaths due to other causes or emigration (censored observations), or December 31, 2006 (whichever came first). Because of a lag time in data entry and the checking of information in the Cause of Death Register, we did not have cause of death information for years 2005 to 2006, and therefore, we censored those persons who died but were not hospitalized during 2005 to 2006 at the end of 2004.

Statistical Analysis
Data were analyzed with Cox proportional hazards models. We analyzed the modifying effect of BMI on the association between blood pressure and CVD (including subtypes) by computing the hazard ratios (HRs) for a 1-SD increase in DBP and SBP by fitting a separate model for each of the BMI categories (see above). We adjusted for year of birth, age at the time of baseline measure, and conscription office in all models by including these variables in the models as covariates. Interactions between blood pressure and BMI

### Table 1. Baseline Characteristics and CVD Incidence Rates at Follow-Up According to Baseline BMI

<table>
<thead>
<tr>
<th>Baseline BMI, kg/m²</th>
<th>&lt;18.5</th>
<th>18.5–24.9</th>
<th>25–29.9</th>
<th>≥30</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mm Hg</td>
<td>126 (10.7)</td>
<td>128 (10.7)</td>
<td>132 (10.8)</td>
<td>135 (11.1)</td>
<td>128 (10.9)</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>67 (9.6)</td>
<td>67 (9.9)</td>
<td>69 (10.5)</td>
<td>71 (11.1)</td>
<td>67 (10.0)</td>
</tr>
<tr>
<td>Elbow flexion strength, N</td>
<td>312 (60.1)</td>
<td>388 (79.0)</td>
<td>445 (91.0)</td>
<td>465 (100)</td>
<td>387 (84.4)</td>
</tr>
<tr>
<td>Hand grip strength, N</td>
<td>549 (85.6)</td>
<td>619 (94.6)</td>
<td>654 (104.0)</td>
<td>658 (110.5)</td>
<td>616 (97.8)</td>
</tr>
<tr>
<td>Knee extension strength, N</td>
<td>467 (90.3)</td>
<td>570 (110.9)</td>
<td>639 (124.5)</td>
<td>668 (136.6)</td>
<td>569 (117.6)</td>
</tr>
<tr>
<td>Incidence rates†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal and nonfatal CVD</td>
<td>22.46 (5792)</td>
<td>22.92 (50 934)</td>
<td>31.84 (6985)</td>
<td>48.80 (1900)</td>
<td>24.0 (65 611)</td>
</tr>
<tr>
<td>Fatal CVD</td>
<td>1.13 (277)</td>
<td>0.96 (2027)</td>
<td>1.67 (347)</td>
<td>3.64 (135)</td>
<td>1.08 (2786)</td>
</tr>
<tr>
<td>Fatal and nonfatal MI</td>
<td>2.24 (590)</td>
<td>2.24 (5089)</td>
<td>3.91 (882)</td>
<td>5.89 (238)</td>
<td>2.43 (6799)</td>
</tr>
<tr>
<td>Fatal MI</td>
<td>0.28 (69)</td>
<td>0.26 (544)</td>
<td>0.57 (118)</td>
<td>0.92 (34)</td>
<td>0.30 (765)</td>
</tr>
<tr>
<td>Fatal and nonfatal stroke</td>
<td>3.45 (907)</td>
<td>3.01 (6822)</td>
<td>3.78 (852)</td>
<td>6.10 (246)</td>
<td>3.15 (8827)</td>
</tr>
<tr>
<td>Fatal stroke</td>
<td>0.27 (67)</td>
<td>0.18 (368)</td>
<td>0.20 (42)</td>
<td>0.73 (27)</td>
<td>0.19 (504)</td>
</tr>
<tr>
<td>No. of person-years, millions</td>
<td>2.58</td>
<td>22.22</td>
<td>2.19</td>
<td>0.39</td>
<td>27.4</td>
</tr>
<tr>
<td>No. of participants</td>
<td>100 684</td>
<td>929 426</td>
<td>97 401</td>
<td>18 247</td>
<td>1 145 758</td>
</tr>
</tbody>
</table>

*Results are mean (SD).
†Results are events per 10 000 person-years (No. of cases).
were then modeled by incorporating an interaction term between DBP or SBP and BMI as a continuous variable. We also analyzed whether muscle strength confounded the interactions between blood pressure and BMI by adjusting the analyses for elbow flexion, hand grip, and knee extension strength. Finally, we adjusted the interactions for subject’s own, mother’s, and father’s education and occupation-based social position by using them as categorized variables.

The proportional hazards assumptions of the Cox models were tested by Schoenfeld residuals separately for DBP and SBP in the categories of BMI. We found statistically significant deviance from proportionality in the CVD models in the BMI category of 18.5 to 24.9 kg/m² for both DBP (P<0.001) and SBP (P=0.01) and in the stroke models in the BMI category of ≥30 kg/m² for SBP (P=0.03). Otherwise, the P values varied between 0.08 and 0.99. Given that multiple proportionality tests (24 tests altogether) were necessarily conducted and given that the present sample size was very large, it is likely that these 3 statistically significant results occurred as a result of type I error. We present our results as standardized HRs by transforming DBP and SBP to have a mean value of 0 and an SD of 1 across the entire population. All statistical models were performed with the Stata statistical package, version 9.2 (StataCorp, College Station, Tex).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Table 1 presents the basic characteristics of the study participants at baseline and during follow-up categorized by baseline BMI. SBP and DBP increased modestly with increasing BMI (Pearson r=0.05 and 0.17, respectively) and showed a modest mutual correlation (Pearson r=0.16). In the entire data set, 65 611 CVD cases were found, which included 6799 MI and 8827 stroke cases during the follow-up of 27.4 million person years (median follow-up time 24.3 years). The crude incidence and mortality rates were similar in the underweight and normal-weight categories but otherwise increased strongly with increasing BMI. We also inspected the log-linearity of the association of blood pressure with the disease outcomes by calculating HRs for each quartile of DBP (HR=1.00, 1.05, 1.12, and 1.32 for CVD; 1.00, 1.16, 1.27, and 1.56 for MI; and 1.00, 1.03, 1.09, and 1.28 for stroke) and SBP (HR=1.00, 1.03, 1.12, and 1.27 for CVD; 1.00, 1.12, 1.38, and 1.53 for MI; and 1.00, 0.97, 1.06, and 1.13 for stroke). These associations were accepted as linear despite possible slight nonlinearity in the association between SBP and stroke. Thereafter, all analyses were performed with DBP and SBP on a continuous scale.

Table 2 presents the results for the associations of blood pressure with incident CVD, MI, and stroke (fatal and nonfatal cases together) by separate baseline BMI categories and for all categories combined (without adjustment for BMI). As anticipated, both DBP and SBP were strongly associated with CVD, MI, and stroke, with statistical significance at conventional levels apparent in most analyses. Statistical evidence was also found for interactions between BMI and both SBP and DBP in the prediction of all CVD (P<0.0001), as well as between BMI and SBP in the prediction of stroke. In contrast to the hypothesis, the interactions were positive, ie, the effects of blood pressure on disease incidence were generally stronger in obese participants than in the lower BMI categories. Adjustment for interactions with elbow flexion, hand grip, and knee extension strength or for subject’s own and parental education and occupation-based social position did not change these results. We also adjusted the analyses for smoking in the subsample of men with this information. Controlling for smoking had only a slight effect on the results, and the HRs for SBP and DBP remained highest in the BMI category 25 to 29.9 kg/m² (for the BMI category >30 kg/m², we were not able to calculate HRs because of the small number of cases). Finally,

![Table 2. HRs (95% CIs) for the Relation of a 1-SD Increase in DBP and SBP According to Baseline BMI](http://circ.ahajournals.org/)

<table>
<thead>
<tr>
<th>BMI</th>
<th>DBP</th>
<th>SBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>All CVD</td>
<td>HR 95% CI</td>
<td>HR 95% CI</td>
</tr>
<tr>
<td>&lt;18.5 kg/m²</td>
<td>1.11 1.07–1.14 1.09 1.06–1.12</td>
<td></td>
</tr>
<tr>
<td>18.5–24.9 kg/m²</td>
<td>1.10 1.09–1.11 1.08 1.07–1.08</td>
<td></td>
</tr>
<tr>
<td>≥30 kg/m²</td>
<td>1.18 1.12–1.23 1.16 1.11–1.22</td>
<td></td>
</tr>
</tbody>
</table>

P for interaction*
Baseline model†  <0.0001 <0.0001
Adjusted for strength‡ <0.0001 <0.0001
Adjusted for social position§ <0.0001 <0.0001

MI

<table>
<thead>
<tr>
<th>BMI</th>
<th>DBP</th>
<th>SBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18.5 kg/m²</td>
<td>1.13 1.03–1.24 1.13 1.05–1.23</td>
<td></td>
</tr>
<tr>
<td>18.5–24.9 kg/m²</td>
<td>1.15 1.11–1.18 1.15 1.12–1.18</td>
<td></td>
</tr>
<tr>
<td>25–29.9 kg/m²</td>
<td>1.18 1.10–1.27 1.19 1.11–1.27</td>
<td></td>
</tr>
<tr>
<td>≥30 kg/m²</td>
<td>1.22 1.06–1.40 1.06 0.94–1.20</td>
<td></td>
</tr>
</tbody>
</table>

P for interaction*
Baseline model†  <0.8823 0.8964
Adjusted for strength‡ <0.6175 0.5541
Adjusted for social position§ <0.6409 0.5194

Stroke

<table>
<thead>
<tr>
<th>BMI</th>
<th>DBP</th>
<th>SBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18.5 kg/m²</td>
<td>1.10 1.02–1.18 1.06 1.00–1.13</td>
<td></td>
</tr>
<tr>
<td>18.5–24.9 kg/m²</td>
<td>1.11 1.08–1.14 1.02 1.00–1.05</td>
<td></td>
</tr>
<tr>
<td>25–29.9 kg/m²</td>
<td>1.06 0.98–1.14 1.05 0.98–1.12</td>
<td></td>
</tr>
<tr>
<td>≥30 kg/m²</td>
<td>1.13 0.99–1.28 1.29 1.14–1.45</td>
<td></td>
</tr>
</tbody>
</table>

P for interaction*
Baseline model†  0.4397 <0.0001
Adjusted for strength‡ 0.8045 <0.0001
Adjusted for social position§ 0.5759 0.0026

*BMI used as a continuous variable.
†Adjusted for year of birth, conscription age, and conscription office.
‡Additionally adjusted for elbow flexion, hand grip, and knee extension strength.
§Additionally adjusted for subject’s own, mother’s, and father’s education and occupation-based social position as categorized variables.
we examined whether the absence of mortality data for the period 2005 to 2006 would have affected the results by censoring all men at the end of the year 2004. No evidence was found of a change in our findings (data available from the corresponding author).

Finally, we analyzed the nature of the interaction by BMI on the blood pressure–CVD gradient by splitting DBP and SBP into quartiles (Figure). We conducted these analyses only for CVD because of a limited number of MI and stroke cases in the extreme categories. In both figures, the lowest risk of CVD was seen in the leanest men with the lowest blood pressure; conversely, the highest risk was evident in the heaviest men with the highest blood pressure.

Discussion
In the present very large cohort of young Swedish men, our findings did not support the suggestion that blood pressure was more strongly associated with CVD risk in lean rather than obese persons at baseline, as has suggested by several studies but not all previous studies. Indeed, we observed a stronger effect of blood pressure on CVD risk in obese as opposed to lean or normal-weight men. We adjusted these interactions for muscle strength and for each subject’s own and parental education and occupation-based social position to ascertain whether lean body mass or socioeconomic factors confounded these relations, but we found no evidence that they did.

Certain differences in the present study cohort can be observed compared with those of previous studies that may explain the discrepancy in the findings. The present study subjects were all in early adulthood at the time of baseline measurement of BMI and blood pressure. Previous studies have included mainly middle-aged or elderly subjects with a wider age range. In the present study, the oldest subjects were 56 years of age at the end of follow-up, and therefore, we analyzed especially early CVD morbidity and mortality. It is thus possible that the reverse interaction between blood pressure and BMI observed in other studies may emerge in middle age or that it is specifically associated with CVD morbidity at older age. In lean middle-aged persons, hypertension may be more influenced by an accumulation of environmental risk factors, such as salt consumption, leading to higher CVD risk, whereas in young persons, hypertension may be determined more genetically. High risk among lean hypertensive persons has also been reported for total mortality. Stamler and coauthors reported that lean hypertensive persons had a higher risk for death due to cirrhosis, nonmalignant respiratory disease, violence, and malignant...
neoplasms than obese hypertensive persons. This suggests differences in alcohol consumption and smoking. However in the present study, we found that the adjustment for socioeconomic factors had no effect on the interactions between blood pressure and BMI. It is also noteworthy that the prevalence of overweight or obesity (BMI ≥25 kg/m²) in the present study cohort was only 10%, but this was likely to increase dramatically during aging. To fit the observations from the present study to those from the previous contrasting studies in older age groups, it may be speculated that the blood pressure increases that occur after young adulthood due to reasons other than weight gain may be more strongly associated with an increased risk of CVD.

Another explanation for our contrasting findings may be publication bias. BMI and blood pressure are 2 very commonly measured risk factors in epidemiological studies, and thus, a large number of cohort studies allows for the study of this interaction. It is noteworthy that the first studies based on French® and US® cohorts included a modest number of CVD cases (203 and 241 cases, respectively) during short follow-up periods (9 and 11 years, respectively). It is possible that the first studies reporting this interaction may have facilitated publication of results that supported the initial findings, whereas in many cases, when this interaction was nonsignificant or showed the reverse outcome, the results failed to be published.

The present study has several advantages but also has limitations. Its main advantage is the very large sample size, which enabled analysis of the effect of blood pressure on CVD risk with adequate power stratified by baseline BMI. This is especially important because the main results of the present study contrast with those of previous studies. It is also noteworthy that a conscription examination was mandatory by law in the birth cohorts studied here; however, because handicap, chronic disease, and non-Swedish citizenship were legal reasons to be exempted, the present cohort represents mainly healthy Swedish men at baseline. Nonetheless, very unusually, the present cohort essentially covers a full nation of Swedish men born during a 25-year period. A further advantage is that the present study cohort was young, and the measures were performed in a narrow age range. Thus, this cohort was very homogeneous, and blood pressure was less affected by environmental exposures, which may also be independently associated with CVD risk. Furthermore, the risk of reverse causality because of underlying diseases that affect BMI, which may affect the results in middle-aged cohorts, is small in what is, by comparison, a largely disease-free cohort. Young age at baseline is naturally also a limitation of the present data, because we cannot analyze whether the associations between BMI, blood pressure, and CVD risk changed during aging. Follow-up data with multiple measures of blood pressure would thus be valuable.

A limitation of the present data is that for those persons having blood pressure within normal limits in the first measurement, no additional reading was taken. Thus, the blood pressure measurement in the present study probably has more random variation than in some other epidemiological cohorts with a greater number of assessments. However, we believe it is reasonable to assume that the random error did not vary between BMI categories and thus did not contribute to the interaction effect between BMI and blood pressure. Additionally, we had only limited information on other metabolic and behavioral risk factors of CVD and thus cannot fully test whether adjustment of the HRs for these risk factors would change the interactive effect between blood pressure and BMI. A further limitation is that because the present data were based solely on men, the extent to which our findings can be generalized to women is unclear.

In conclusion, in the present large, nationwide cohort study of Swedish men, we did not find any evidence that suggested that high blood pressure would be more harmful in lean than in obese persons, at least not in young adulthood and when predicting CVD morbidity before 56 years of age. However, because we do not have information on many other risk factors of CVD, we cannot exclude the possibility that this would be the case in certain subpopulations with a clustering of other risk factors. Nevertheless, the present results strongly suggest that high blood pressure should not be regarded as a less serious risk factor in obese than in lean persons in this age group and in the general Swedish male population.

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Disclosures
None.

References


**CLINICAL PERSPECTIVE**

Some studies have suggested that increased blood pressure has a stronger effect on the risk of cardiovascular disease in lean than in obese persons, although this is not a universal finding. In a very large population-based cohort study of >1 million Swedish men, which accumulated 65,611 new cardiovascular disease events during follow-up, we have been able to analyze this unresolved research question with greater precision than has been possible previously. Hazard ratios per 1-SD increase in blood pressure were computed within established categories of body mass index (underweight, normal weight, overweight, or obese) with Cox proportional hazards models. In contrast to the hypothesis, the strongest associations of diastolic blood pressure with cardiovascular disease (hazard ratio 1.18), myocardial infarction (hazard ratio 1.22), and stroke (hazard ratio 1.13) were in fact observed in the obese category. Similar results were apparent for systolic blood pressure. Our results suggest that raised blood pressure should be regarded as an equally important risk factor for cardiovascular disease in both obese individuals and normal-weight and underweight persons.
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