Interplay of overweight and insulin resistance on hypertension development

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Objectives: Obesity and hypertension are associated, possibly through causal pathways involving insulin resistance and metabolic derangements. We aimed to investigate in a whites sample if overweight or obese persons without insulin resistance are at risk of developing hypertension or blood pressure progression.

Methods: In a meta-analysis, using multivariable-adjusted mixed-effects logistic regression models, we investigated the risks of hypertension development and blood pressure progression by combinations of relative weight classes and presence or absence of insulin resistance (defined as highest vs. lower three quartiles using the homeostatic model assessment method) in the Uppsala Longitudinal Study of Adult Men (n = 2322) and the Prospective Investigation of the Vasculature in Uppsala Seniors studies (n = 1066). These two samples, consisting mainly of middle-aged and elderly men, provided 1846 observations for the development of hypertension in normotensive individuals and 4223 observations for progressing to a higher blood pressure stage.

Results: During a median of 10 years of follow-up, 884 (47.9%) developed hypertension and 1639 (38.8%) progressed to a higher blood pressure stage. Overweight or obese persons without insulin resistance had an increased risk of hypertension development [odds ratio (OR) 1.46, 95% confidence interval 1.14–1.88] and blood pressure progression (OR 1.32, 1.10–1.59) compared with normal-weight persons without insulin resistance.

Conclusion: According to this study, being overweight or obese without insulin resistance increases the risk of hypertension and blood pressure progression. This adds to the evidence that overweight and obesity may be harmful per se, and that overweight and obesity without glucometabolic derangements are not benign conditions.

Keywords: hypertension, insulin resistance, obesity, overweight

Abbreviations: AHA/NHLBI, American Heart Association/National Heart Lung and Blood Institute; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; IR, insulin resistance; LDL, low-density lipoprotein; MetS, metabolic syndrome

INTRODUCTION

Hypertension is the leading risk factor for global disease burden and premature death [1], and its global burden is increasing [2]. The occurrence of obesity varies geographically, but in many societies, has reached epidemic proportions, and its global burden has increased between 1980 and 2008 [3].

Because obesity, especially of truncal [4–6] or intra-abdominal [7] localization, precedes manifest hypertension, [4–11] it has been proposed as a cause of hypertension; a notion supported by the blood pressure-lowering effects of nonpharmacological [12] or orlistat-based [13] weight loss treatments. However, discordant obesity and blood pressure trends [14–16] have been reported, some of which may be attributed to changes in antihypertensive treatment, but not those in young, untreated persons [17]. Further, changes in the relations between obesity measures and blood pressures have been described over time, [18,19] indicating that perhaps obesity per se is not the sole explanation for obesity-related hypertension.

The increased risk associated with obesity [20] may be partly explained by metabolic risk factors, such as the ones included in the metabolic syndrome (MetS) [21]. About 10–25% of obese individuals do not fulfill the condition of the MetS [22] and have hence been referred to as having ‘metabolically healthy obesity’ [23,24]. Other definitions of metabolically healthy obesity have focused on insulin resistance, measured by invasive hyperinsulenic-euglycemic clamp technique [23] or the more practical homeostasis model assessment (HOMA) [25].

The prognosis of metabolically healthy obesity has been suggested as benign in some studies [25,26], but it has been associated with subclinical cardiovascular disease [27] and increased risk of cardiovascular events and mortality [28] in others. Associations of metabolically healthy obesity with
hypertension development have recently been reported in Asian samples [29,30]. Because of reports of differential obesity phenotypes and associations of obesity with cardiovascular risk factors between Asians and whites, [31–33] these associations should also be explored in whites.

We hypothesized that overweight and obesity are associated with the development of hypertension and blood pressure progression irrespectively of insulin resistance, and our aim was to investigate this hypothesis using individual participant meta-analysis of two community-based cohorts.

METHODS

Study sample

We used data from two cohort studies: the Uppsala Longitudinal Study of Adult Men (ULSAM; www.pubcare.uu.se/ulsam) and the Uppsala Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS; www.meds-ci.uu.se/pivus). Informed consent from all participants and an approval from Uppsala University Ethics Committee were obtained in both studies.

The ULSAM study

In 1970–73, the ULSAM study invited all men who at the time were 50-year-old to participate in repeated health surveys focused on identifying cardiovascular risk factors. Eighty-two % of the invited men participated (n = 2322). The cohort was re-examined at age 60 (n = 1860, 87% of invited), age 70 (n = 1221, 77% of invited) and age 77 (n = 839, 60% of invited). The cumulative mortality of the cohort has been previously reported [34]. The present study used data from the first three examinations as baseline values. Incidence of hypertension or blood pressure progression was determined at follow-up at the subsequent examination.

The PIVUS study

In 2001–04, a random sample of all 70-year-old men and women living in Uppsala were invited to participate in the PIVUS study, with the primary aim to investigate the predictive power of endothelial function on different cardiovascular outcomes. Fifty percent of the invited persons participated (n = 1016, 51% women). The cohort was re-examined at age 75 (n = 827, 81%) at which time 55 persons of the initial cohort had died.

Inclusion and exclusion criteria

We included participants who had complete data on SBP and DBP and antihypertensive medication. In order to be eligible for a particular time period, participants had to have attended both the baseline and the follow-up examinations. We excluded all participants with diabetes at baseline, defined as a fasting plasma glucose at least 7.0 mmol/l, or using antidiabetic medication; and those using antihypertensive medication at baseline.

The final sample constituted of 4223 observations from 2502 participants (377, 8.9% woman). We created two samples, one without hypertension at baseline (n = 1846) and one without blood pressure-lowering drugs at baseline (n = 4223). Hence, an individual could account for more than one study-case if they fulfilled the inclusion criteria at re-examination (ULSAM), which was the case for 1080 individuals at 60 years and 641 individuals at 70 years.

Baseline examinations

In both cohorts, participants were investigated in the morning after an overnight fast, and no medication was taken on the day of the investigation. Anthropometric measurements were collected, and blood samples were taken and analysed by standard laboratory techniques.

Serum insulin was measured by an enzymatic-immunological assay (Boehringer Mannheim, Germany). HOMA-IR was defined using fasting plasma glucose and insulin concentrations by the formula: fasting insulin x fasting glucose/22.5 [35].

At the examination age of 50 (ULSAM study), fasting cholesterol and triglyceride concentrations in serum and high-density lipoproteins (HDL) were assayed by enzymatic techniques. Coding of smoking was based on interview reports.

At the age of 50 and 60 years (ULSAM), a nurse or physician measured blood pressure in the right arm to the nearest 5 mmHg-mark using a mercury manometer after 10 min of rest in a supine position. At the age of 70 (ULSAM), blood pressure was measured twice to the nearest even number after a 10-min rest in supine position, and a mean value was calculated. In PIVUS, blood pressure was measured using a calibrated mercury sphygmomanometer to the nearest 1 mmHg after at least 30 min of rest in a supine position, and the average of three recordings was used. Appropriately sized blood pressure manometer cuffs were used in both studies.

Exposures and outcomes

The main exposures in the primary analyses were being overweight or obese (using WHO BMI definitions: normal-weight BMI < 25, overweight BMI ≥25 and < 30, obese BMI ≥ 30); and being insulin resistant (highest quartile of HOMA-IR, vs. lower three quartiles). In secondary analyses, a MetS categorization (using the American Heart Association/National Heart Lung and Blood Institute definition, Supplementary Table 1, http://links.lww.com/HJH/A311) replaced insulin resistance. Because of low numbers of individuals with obesity, overweight and obese groups were combined in our primary analyses, with subsequent analyses investigating the groups separated. The two samples consisted of mainly men, thus a sensitivity analysis was performed with women excluded.

We investigated two outcomes. In normotensive individuals, the outcome was development of hypertension at follow-up, defined as supine SBP at least 140 mmHg and/or DBP at least 90 mmHg, and/or current use of antihypertensive medication. In persons untreated with blood pressure-lowering drugs, the outcome was progression of blood pressure stage at follow-up, defined as an increase by one or more Joint National Committee 7 blood pressure categories. Progression of blood pressure stage has been
used as outcome previously in blood pressure tracking studies [36,37].

Statistical analysis
Missing data (0.2% of glucose, 0.2% of smokers, 0.4% of follow-up BMI, 18% of triglyceride, 28% of insulin, 51% of HDL cholesterol and 49% of waist values) were imputed for all analyses using multiple imputations with multivariate normal regression. A one-step approach for meta-analysis of individual participant data was performed. The one-step approach is preferable over the two-step approach when including several covariates, and when investigating interactions, as in the present study [38]. All analyses were conducted using three-level mixed-effects logistic regression models, using the Laplacian approximation, with random intercepts on the participants, and examinations and levels and fixed effects for all other variables, accommodating the facts that observations were clustered within participants, and participants within cohorts.

Interactions between overweight or obesity and HOMA-IR groups were investigated as departure from multiplicity [39]. Thereafter, statistical modelling with covariates as in previous studies of predictors of hypertension of blood pressure progression was performed [36,40]. The model for each outcome included sex, age, smoking and baseline SBP and DBP. All analyses were two-tailed and P-values < 0.05 were considered statistically significant. Analyses were performed using Stata 12.1 (Stata Corporation, College Station, Texas, USA).

RESULTS

Baseline characteristics of participants by categories of relative weight and insulin resistance are presented in Table 1.

In the normotensive sample of 1846 observations, 884 (47.9%) developed hypertension over a median follow-up of 9.9 (range 4.9–14.4) years. In the untreated sample of 4223 observations, 1639 (38.8%) progressed in their blood pressure stage over a median follow-up of 9.5 (range 4.5–14.6) years. The development of events by study and examination is illustrated in Table 2.

In the primary analysis, being overweight or obese without insulin resistance was associated with 46% higher odds of hypertension development and 32% higher odds of blood pressure progression, than being normal-weight without insulin resistance (Table 3). In the analyses based on separate BMI categorization groups and insulin resistance, being overweight without insulin resistance was associated with 41% higher odds of hypertension development and 31% higher odds of blood pressure progression, than being normal-weight (Supplementary Table 2, http://links.lww.com/HJH/A311). The sensitivity analysis, conducted on men only, confirmed all significant findings in the primary analysis (Supplementary Table 3, http://links.lww.com/HJH/A311). In the secondary analyses, using the MetS categorization instead of insulin resistance, being overweight or obese without the MetS was associated with 43% higher odds of hypertension development and 30% higher odds of blood pressure progression than being normal weight (Supplementary Table 4, http://links.lww.com/HJH/A311).

| TABLE 1. Baseline characteristics by relative weight and insulin-resistance categories |
|---------------------------------|---------------------------------|----------------|----------------|
|                                 | Normal-weight without insulin resistance | Normal-weight with insulin resistance | Overweight or obese without insulin resistance | Overweight or obese with insulin resistance |
| HTN, N = 1846 | BPP, N = 4223 | HTN | BPP | HTN | BPP | HTN | BPP | HTN | BPP |
| Number of observations | 939 | 1721 | 133 | 245 | 43 | 211 | 731 | 2046 |
| Sex (% women) | 4.5 | 7.6 | 1.5 | 3.3 | 7.8 | 12.4 | 1.5 | 6.2 |
| Age (years, mean, SD) | 55.6 (7.9) | 58.0 (8.5) | 52.7 (7.6) | 54.8 (9.2) | 58.0 (8.8) | 60.9 (8.6) | 56.1 (9.7) | 58.9 (10.2) |
| SBP (mmHg, SD) | 122 (9) | 135 (18) | 123 (9) | 135 (19) | 125 (8) | 142 (20) | 125 (8) | 145 (19) |
| DBP (mmHg, SD) | 76 (7) | 81 (10) | 77 (6) | 82 (10) | 78 (6) | 85 (10) | 78 (6) | 87 (11) |
| LDL (mmol/L, SD) | 4.7 (1.4) | 4.6 (1.4) | 4.9 (1.3) | 4.8 (1.3) | 4.5 (1.4) | 4.3 (1.3) | 4.8 (1.3) | 4.6 (1.4) |
| HDL (mmol/L, SD) | 1.5 (4) | 1.5 (4) | 1.4 (4) | 1.4 (4) | 1.3 (4) | 1.4 (4) | 1.2 (3) | 1.2 (3) |
| Plasma glucose (mmol/L, SD) | 5.3 (5) | 5.3 (5) | 5.6 (16) | 5.7 (15) | 5.4 (5) | 5.4 (5) | 5.6 (5) | 5.7 (5) |
| BMI (kg/m2, SD) | 22.6 (16) | 22.8 (16) | 22.9 (15.5) | 23.2 (14) | 27.0 (19) | 27.6 (23) | 27.9 (25) | 28.6 (29) |
| Waist circumference (cm, SD) | 82 (6) | 83 (6) | 85 (6) | 86 (6) | 93 (7) | 94 (8) | 98 (8) | 100 (9) |
| Smoker (%) | 43.1 | 37.0 | 58.3 | 45.7 | 34.1 | 25.6 | 35.5 | 29.3 |
| HOMA-IR (units, SD) | 1.8 (7) | 1.8 (7) | 4.4 (1.5) | 4.4 (1.5) | 2.6 (6) | 2.0 (6) | 4.8 (2) | 4.8 (2) |

BPP: sample for analysis of blood pressure progression; HDL, high-density lipoprotein. Data are means (SD) or percentage, by relative weight group and insulin resistance, defined as highest quartile of HOMA-IR; HTN, sample for analysis of development of hypertension; LDL, low-density lipoprotein.
Obese subgroups and normal-weight subgroups with MetS or insulin resistance were too small to provide precise estimates (Supplementary Tables 2, 3, 4 and 5, http://links.lww.com/HJH/A311). Unfortunately, normal-weight persons with metabolic derangements as well as obese person with and without metabolic derangements were too few to provide reliable estimates for their specific subgroups in this study.

There were no significant interactions between overweight or obesity and HOMA-IR groups.

**DISCUSSION**

In this study, we hypothesised that overweight or obese but metabolically healthy individuals would be at risk of development of hypertension and blood pressure progression. This hypothesis was supported by the data, which suggest that obesity without metabolic derangements is not a benign condition from a hypertension pathophysiology perspective.

Our results extend to whites recent findings in Asian samples [29,30] that absence of insulin resistance and other metabolic derangements in nonnormal weight individuals provides no protection against the development of hypertension or blood pressure progression.

Some previous studies have suggested that insulin resistance is associated with higher risk of development of hypertension [9,41,42]. This relation has mainly been observed in nonobese persons, [9,42] or in analyses not accounting for obesity measures [9], highlighting the close link between obesity and insulin resistance, but insulin resistance has also been related to subsequent blood pressure increase independently of BMI [11,41]. In the present study, no relative weight-independent association of insulin resistance with hypertension incidence was observed. Other study approaches, such as ones using Mendelian randomization methods, support that obesity per se is associated with hypertension development [43].

In the present study, we studied the interplay between relative weight and insulin resistance. An alternative approach is to study the interaction between relative weight and the MetS. We considered this, but the analytic strategy is problematic because hypertension, the outcome, is also included in the MetS criteria. We nevertheless performed secondary analyses using relative weight classes and the MetS, and the results were consistent with the main findings (Supplementary Tables 4 and 5, http://links.lww.com/HJH/A311). Unfortunately, normal-weight persons with metabolic derangements as well as obese person with and without metabolic derangements were too few to provide reliable estimates for their specific subgroups in this study.

Notably, although not within the aim of this study, persons with overweight or obesity with insulin resistance did not demonstrate much higher risks than corresponding weight groups without insulin resistance (Table 3). The meaning of this observation remains unclear, and it should be interpreted with caution as this group had fewer individuals and events, and thus lower precision.

Lipid levels, particularly HDL-cholesterol [40] and triglycerides [11,44] have also been associated with hypertension development. In addition to the variables included in the MetS, which by themselves may be causally related to hypertension development, the MetS signifies other changes such as higher levels of C-reactive protein and uric acid. These have also been associated with the risk of hypertension development [36,45]. Other suggested mechanisms linking obesity with hypertension include fibrinolysis, adipokines, oxidative stress and ventricular remodelling [46].

The strength of this study includes the use of two relatively large prospective cohorts with long follow-up using standardized techniques of blood pressure measures. We used two outcomes – development of hypertension and progression of blood pressure stage – and metabolic impairment defined in two ways, with coherent results. The consistency of the results across all of these methods supports the notion that the increased risk of hypertensive evolution over time with overweight or obesity occurs regardless of metabolically healthiness. Among the weaknesses of the study are the small subgroups, making the study underpowered to study several separate weight groups. Further, ambulatory blood pressure assessment would provide more robust measurements. The MetS categorization, used in the secondary analyses, called for imputations of missing data. This was considered appropriate, as the alternative, that is exclusion, requires stronger assumptions than imputation and would further decrease power.

In conclusion, this study of two cohorts including mainly middle-aged and elderly men, overweight or obese persons

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**TABLE 3. Hypertension development and blood pressure progression by relative weight and insulin-resistance categories adjusted for sex, age, smoking status, systolic and diastolic blood pressure, change in body mass index, study, examination and individual participant data (three-level mixed-effects logistic regression model)**

<table>
<thead>
<tr>
<th>Relative weight and insulin resistance categories</th>
<th>Events/n (%)</th>
<th>Mean BP change at follow-up (sys/dia, mmHg)</th>
<th>Development of hypertension or MetS (95% CI) P-value</th>
<th>Events/n (%)</th>
<th>Mean BP change at follow-up (sys/dia, mmHg)</th>
<th>Progression of blood pressure stage (95% CI) P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal weight without insulin resistance</td>
<td>397/939</td>
<td>11.6/4.5</td>
<td>1 n/a</td>
<td>713/1721</td>
<td>7.6/1.2</td>
<td>1 n/a</td>
</tr>
<tr>
<td>Normal weight with insulin resistance</td>
<td>65/133</td>
<td>12.1/7.0</td>
<td>1.19 (0.86–1.66)</td>
<td>29</td>
<td>113/245</td>
<td>8.0/0.4</td>
</tr>
<tr>
<td>Overweight + obese without insulin resistance</td>
<td>310/575</td>
<td>13.0/7.3</td>
<td>1.46 (1.14–1.88)</td>
<td>.003</td>
<td>574/1568</td>
<td>5.7/1.0</td>
</tr>
<tr>
<td>Overweight + obese with insulin resistance</td>
<td>112/199</td>
<td>12.4/4.4</td>
<td>1.52 (1.13–2.06)</td>
<td>.006</td>
<td>239/689</td>
<td>5.2/1.0</td>
</tr>
</tbody>
</table>

BP, blood pressure; CI, confidence interval; dia, diastolic; Insulin resistance defined as highest quartile of HOMA-IR; OR, odds ratio; sys, systolic.
without insulin resistance were at higher risk of hypertension development and blood pressure progression than normal-weight persons without insulin resistance. These findings add to the evidence that metabolically healthy overweight or obesity are not benign conditions.

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REFERENCES

Lytsy et al.


Reviewers’ Summary Evaluations

Reviewer 1

The authors showed that overweight and obesity predispose to arterial hypertension even in the absence of metabolic disease. The strength of the study is the large number of well characterized subjects and the carefully conducted long term follow up. Due to the low number, the findings cannot be simply extrapolated to women.

Reviewer 2

The link between obesity and hypertension is still foggy. It is hypothesized that peripheral insulin resistance leads to hyperinsulinemia which in turn is operative in raising blood pressure. This carefully conducted study documents that obesity has a strong positive association with development of hypertension even in absence of insulin resistance thus supporting the concept of obesity as an independent risk factor per se.