Insulin Resistance and Risk of Congestive Heart Failure

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Congestive Heart Failure (CHF) is a major cause of morbidity and mortality. The age-adjusted mortality for patients with CHF is 4 to 8 times that of the general population. The predominant causes of heart failure are hypertension and coronary heart disease. Other established risk factors for CHF include left ventricular hypertrophy (LVH), valvular heart disease, diabetes, cigarette smoking, obesity, and dyslipidemia.

Diabetes as a predictor of subsequent CHF was first described in the Framingham Heart Study 3 decades ago, and the disease is frequently cited as a risk factor for CHF. Yet, more detailed characterizations of the association between diabetes and subsequent CHF are still lacking. In recent years, associations between diabetes or impaired glucose regulation and altered left ventricular geometry and function have been reported. Furthermore, in patients with manifest CHF, insulin resistance is associated with more severe disease and a worse prognosis, but insulin resistance has not been investigated as a predictor of CHF. Obesity is a more recently described risk factor for CHF, and is also associated with changes in left ventricular geometry and function. Abdominal obesity is closely associated with insulin resistance and manifest diabetes.

We hence hypothesized that insulin resistance may predict CHF and may provide the link between obesity and CHF. Our primary aim was to analyze measures of insulin sensitivity (including euglycemic insulin clamp glucose disposal rate) and secretion as predictors of CHF incidence in a community-based sample of elderly men, adjusting for diabetes and other traditional risk factors for CHF. Our secondary aim was to analyze if the previously described association between obesity and CHF may be mediated by insulin resistance.

Context Diabetes and obesity are established risk factors for congestive heart failure (CHF) and are both associated with insulin resistance.

Objective To explore if insulin resistance may predict CHF and may provide the link between obesity and CHF.

Design, Setting, and Participants The Uppsala Longitudinal Study of Adult Men, a prospective, community-based, observational cohort in Uppsala, Sweden. We investigated 1187 elderly (≥70 years) men free from CHF and valvular disease at baseline between 1990 and 1995, with follow-up until the end of 2002. Variables reflecting insulin sensitivity (including euglycemic insulin clamp glucose disposal rate) and obesity were analyzed together with established risk factors (prior myocardial infarction, hypertension, diabetes, electrocardiographic left ventricular hypertrophy, smoking, and serum cholesterol level) as predictors of subsequent incidence of CHF, using Cox proportional hazards analyses.

Main Outcome Measure First hospitalization for heart failure.

Results One hundred four men developed CHF during a median follow-up of 8.9 (range, 0.01-11.4) years. In multivariable Cox proportional hazards models adjusted for established risk factors for CHF, increased risk of CHF was associated with a 1-SD increase in the 2-hour glucose value of an oral glucose tolerance test (hazard ratio [HR], 1.44; 95% confidence interval [CI], 1.08-1.93), fasting serum proinsulin level (HR, 1.29; 95% CI, 1.02-1.64), body mass index (HR, 1.35; 95% CI, 1.11-1.65), and waist circumference (HR, 1.36; 95% CI, 1.10-1.69), whereas a 1-SD increase in clamp glucose disposal rate decreased the risk (HR, 0.66; 95% CI, 0.51-0.86). When adding clamp glucose disposal rate to these models as a covariate, the obesity variables were no longer significant predictors of subsequent CHF.

Conclusions Insulin resistance predicted CHF incidence independently of established risk factors including diabetes in our large community-based sample of elderly men. The previously described association between obesity and subsequent CHF may be mediated largely by insulin resistance.

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Methods Study Sample

The study is based on the Uppsala Longitudinal Study of Adult Men cohort (http://www.pubcare.uu.se/ULSAM/), a health investigation focusing on identifi-
tifying metabolic risk factors for cardiovascular disease, to which all 50-
year-old men living in Uppsala, Sweden, in 1970-1974 were invited. Of these,
2322 (82%) participated in the investigation. The cohort was re-investi-
gated 20 years later (1990-1995, i.e., the baseline of the present study). Of the
1681 available 70-year-old men in-
vited to the follow-up investigation, 1221 (73%) attended. For the present
study, 20 participants were excluded due to a previous diagnosis of CHF and
14 due to a diagnosis of valvular dis-
ease in the hospital discharge register at baseline. Thus, 1187 men were elig-
able for the present investigation. We examined a subsample of 1061 non-
diabetic men after exclusion of all par-
ticipants with diabetes at baseline
(n=126). Furthermore, we examined a subsample of 1034 nonobese men af-
fter exclusion of all men with body mass
index (BMI) (calculated as weight in kilo-
grams divided by the square of height in meters) greater than 30 at baseline
(n=153) and another subsample of 433 normal-weight men after exclusion of all 
men with BMI greater than 25 at baseline (n=754). All participants gave
written informed consent, and the eth-
ics committee of Uppsala University ap-
proved the study.

Baseline Examinations
Examinations performed when the par-
ticipants were 70 years of age in-
cluded a medical examination, a ques-
tionnaire, blood sampling (after an
overnight fast), supine blood pressure
measurement, anthropometric mea-
surements, a euglycemic insulin clamp,
an oral glucose tolerance test (OGTT),
and measurement of insulin, proinsu-
lin, and lipid levels as previously de-
scribed.10,17 Insulin sensitivity was de-
termined using the euglycemic insulin
clamp technique, according to De-
Fronzo et al.,18 with a slight modifica-
tion: insulin was infused at a constant
rate of 56 instead of 40 mU/(min × m²)
to achieve nearly complete suppres-
sion of hepatic glucose output.19 Glu-
cose disposal rate, representing insu-
lin sensitivity, was calculated as the
amount of glucose taken up during the
last 60 minutes of the clamp proce-
dure and is presented in mg/kg of body
weight per minute. An OGTT was per-
formed by measuring the concentra-
tions of plasma glucose and immuno-
reactive insulin immediately before and
120 minutes after ingestion of 75 g of
anhydrous dextrose. The OGTT and the
clamp procedure were performed at
least 1 week apart. The concentra-
tions of intact and 32-33 split proinsu-
lin were analyzed using a 2-site immu-
nometric assay technique.20 Specific
insulin concentrations were deter-
mined using a chemiluminescent im-
munoenzymatic assay. Homeostasis
model assessment insulin resistance
index was calculated as fasting insulin
congestion × fasting glucose con-
centration/22.5.21

Blood pressure was measured in the
supine position after resting for 10 min-
utes. The values were recorded twice
to the nearest even value, and the means
of the 2 values were given. The pres-
ence of hypertension at baseline was de-
fined as systolic blood pressure at least
140 mm Hg and/or diastolic blood blood
pressure at least 90 mm Hg, and/or use
of antihypertensive medication. At base-
line, 46% of patients with hyperten-
sion were treated with antihyperten-
sive medication. The presence of
diabetes at baseline was defined as fast-
ing plasma glucose level of 126.1 mg/dL
(7.0 mmol/L) or more and/or the use
of oral hypoglycemic agents or insu-
lin.22 Electrocardiographic LVH was de-
efined as high-amplitude R waves ac-
cording to the revised Minnesota code23
together with left ventricular strain pat-
ttern.4 Coding of smoking was based on
interview reports, and coding of demo-
graphic data was based on the ques-
tionnaire. The Swedish hospital dis-
charge register was used to assess the
presence of valvular disease (Inter-
national Classification of Diseases, Ninth
Revision [ICD-9] codes 394-397 and 424
or ICD-10 codes I05-I08 and I34-I37)
and prior myocardial infarction (MI)
(ICD-9 code 410 or ICD-10 code I21).
The precision of the diagnosis of MI in
the discharge register is high.24,25

Follow-up and Outcome Parameter
The participants had a median fol-
low-up time of 8.9 years (range, 0.01-
11.4 years), contributing to 9899 per-
son-years at risk. One hundred thirty-
two men had a hospital discharge
register diagnosis of heart failure be-
 tween the age 70 baseline and the cen-
sor date at the end of 2002. As a pos-
sible diagnosis of heart failure, we
considered ICD heart failure codes 428
(ICD-9) and 150 (ICD-10) and hyper-
tensive heart disease with heart fail-
ure, 111.0 (ICD-10). The medical rec-
ords from the hospitalization were
reviewed by 2 physicians (E.I. and L.L.)
blinded to the baseline data, who clas-
sified the cases as definite, question-
able, or miscoded. The classification re-
lied on the definition proposed by the
European Society of Cardiology,26
and the review process has been described
extensively.27 After this validation, 104
definitive cases of heart failure were in-
cluded in the total cohort, 87 cases in
the subsample without diabetes, and 80
cases in the subsample without obe-
sity. None of the participants was lost
to follow-up.

Statistical Methods
All analyses were defined a priori. Data
are presented as mean (SD) or percent-
age. Logarithmic transformation was
performed to achieve normal distribu-
tion if necessary. The residuals of all re-
gression analyses were examined and
found to be normally distributed.
Proportional hazards was confirmed by
visually examining Nelson-Aalen cur-
ees. We examined incidence rates
in quartiles of all continuous indepen-
dent variables, and no obvious devia-
tions from linearity were observed. All
variables were treated as continuous, ex-
cept for prior acute MI, hypertension,
diabetes, electrocardiographic LVH,
smoking, and interim MI, which were
treated as dichotomous. The prognos-
tic values for CHF incidence of a 1-SD
increase in the continuous variables, or
a transfer from one level to another of
the dichotomous variables, were inves-
tigated with Cox proportional haz-
ards analyses.
Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Cohort (N = 1187)</th>
<th>Diabetes (n = 126)</th>
<th>Obesity (n = 1061)</th>
<th>Diabetes (n = 153)</th>
<th>Obesity (n = 1034)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established risk factors for CHF</td>
<td></td>
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</tr>
<tr>
<td>Prior MI, No. (%) (n = 1187)</td>
<td>87 (7.3)</td>
<td>14 (11.1)</td>
<td>73 (6.9)</td>
<td>18 (11.8)</td>
<td>69 (6.7)</td>
</tr>
<tr>
<td>Hypertension prevalence, No. (%) (n = 1187)*</td>
<td>883 (74.4)</td>
<td>108 (85.7)</td>
<td>775 (73.0)</td>
<td>138 (90.2)</td>
<td>745 (72.1)</td>
</tr>
<tr>
<td>Diabetes prevalence, No. (%) (n = 1187)†</td>
<td>126 (10.6)</td>
<td>126 (100)</td>
<td>0</td>
<td>36 (23.5)</td>
<td>90 (8.7)</td>
</tr>
<tr>
<td>Electrocardiographic LVH, No. (%) (n = 1079)</td>
<td>76 (7.0)</td>
<td>11 (10.7)</td>
<td>65 (6.7)</td>
<td>10 (7.5)</td>
<td>66 (7.0)</td>
</tr>
<tr>
<td>Current cigarette smoking, No. (%) (n = 1152)</td>
<td>241 (20.9)</td>
<td>26 (21.5)</td>
<td>215 (20.9)</td>
<td>33 (23.1)</td>
<td>208 (20.6)</td>
</tr>
<tr>
<td>Serum cholesterol, mean (SD), mg/dL (n = 1186)</td>
<td>224.7 (39.6)</td>
<td>222.9 (36.3)</td>
<td>224.7 (39.0)</td>
<td>223.6 (43.2)</td>
<td>224.7 (37.8)</td>
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<tr>
<td>Demographic data, No. (%)</td>
<td></td>
<td></td>
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<tr>
<td>Marital status (n = 1090)</td>
<td></td>
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</tr>
<tr>
<td>Single</td>
<td>893 (81.9)</td>
<td>86 (71.5)</td>
<td>807 (74.9)</td>
<td>96 (73.9)</td>
<td>797 (73.0)</td>
</tr>
<tr>
<td>Widowed/divorced</td>
<td>137 (12.6)</td>
<td>17 (15.3)</td>
<td>120 (11.2)</td>
<td>24 (18.5)</td>
<td>113 (11.8)</td>
</tr>
<tr>
<td>Living with other relatives</td>
<td>9 (0.8)</td>
<td>2 (1.8)</td>
<td>7 (0.7)</td>
<td>3 (2.3)</td>
<td>6 (0.6)</td>
</tr>
<tr>
<td>Educational level (n = 1104)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Elementary school</td>
<td>658 (59.6)</td>
<td>74 (66.1)</td>
<td>584 (54.9)</td>
<td>92 (70.2)</td>
<td>566 (58.2)</td>
</tr>
<tr>
<td>Upper secondary school</td>
<td>102 (9.2)</td>
<td>9 (8.0)</td>
<td>93 (9.4)</td>
<td>8 (6.1)</td>
<td>94 (9.7)</td>
</tr>
<tr>
<td>Community college</td>
<td>160 (14.5)</td>
<td>17 (15.2)</td>
<td>143 (13.4)</td>
<td>16 (12.2)</td>
<td>144 (14.8)</td>
</tr>
<tr>
<td>College/university</td>
<td>184 (16.7)</td>
<td>12 (10.7)</td>
<td>172 (17.3)</td>
<td>15 (11.5)</td>
<td>169 (17.4)</td>
</tr>
<tr>
<td>Glucometabolic variables, mean (SD)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Clamp glucose disposal rate, mg/kg per minute (n = 1134)</td>
<td>5.2 (2.1)</td>
<td>2.8 (1.3)</td>
<td>5.4 (2.0)</td>
<td>3.1 (1.3)</td>
<td>5.5 (2.0)</td>
</tr>
<tr>
<td>Fasting plasma glucose, mg/dL (n = 1185)</td>
<td>103.8 (26.1)</td>
<td>163.1 (41.8)</td>
<td>96.8 (10.1)</td>
<td>113.3 (30.3)</td>
<td>102.3 (25.2)</td>
</tr>
<tr>
<td>OGTT 2-h glucose, mg/dL (n = 1149)</td>
<td>149.2 (72.3)</td>
<td>307.7 (86.8)</td>
<td>130.6 (40.9)</td>
<td>177.5 (76.4)</td>
<td>145.0 (70.8)</td>
</tr>
<tr>
<td>Fasting insulin, pmol/L (n = 1142)</td>
<td>52.3 (45.2)</td>
<td>83.3 (97.2)</td>
<td>48.8 (32.9)</td>
<td>83.1 (51.9)</td>
<td>47.8 (42.4)</td>
</tr>
<tr>
<td>Fasting proinsulin, pmol/L (n = 1133)</td>
<td>8.4 (8.5)</td>
<td>19.9 (17.2)</td>
<td>7.1 (5.5)</td>
<td>14.3 (15.7)</td>
<td>7.6 (6.4)</td>
</tr>
<tr>
<td>Fasting 23-33 sp proinsulin, pmol/L (n = 1133)</td>
<td>11.0 (12.1)</td>
<td>24.9 (20.1)</td>
<td>9.4 (9.6)</td>
<td>20.5 (20.0)</td>
<td>9.8 (9.7)</td>
</tr>
<tr>
<td>HOMA insulin resistance index (n = 1174)</td>
<td>3.4 (2.7)</td>
<td>7.4 (5.0)</td>
<td>2.9 (1.7)</td>
<td>5.3 (3.3)</td>
<td>3.1 (2.4)</td>
</tr>
<tr>
<td>Anthropometric variables, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index (n = 1183)‡</td>
<td>26.3 (3.4)</td>
<td>28.5 (4.1)</td>
<td>26.0 (3.2)</td>
<td>32.4 (2.5)</td>
<td>25.4 (2.5)</td>
</tr>
<tr>
<td>Waist circumference, cm (n = 1162)</td>
<td>94.7 (9.6)</td>
<td>101.3 (11.1)</td>
<td>94.0 (9.2)</td>
<td>110.3 (7.3)</td>
<td>92.5 (7.6)</td>
</tr>
</tbody>
</table>

Abbreviations: CHF, congestive heart failure; HOMA, homeostasis model assessment; LVH, left ventricular hypertrophy; MI, myocardial infarction; OGTT, oral glucose tolerance test.

SI conversion factors: To convert mg/dL to mmol/L, multiply serum cholesterol values by 0.0259 and fasting plasma glucose and OGTT 2-hour glucose values by 0.0555. To convert insulin values to µIU/mL, divide pmol/L values by 6.945.

*Hypertension defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg, and/or use of antihypertensive medication.
†Diabetes defined as fasting plasma glucose level ≥126.1 mg/dL (7.0 mmol/L) and/or use of oral hypoglycemic agents or insulin.
‡Calculated as weight in kilograms divided by the square of height in meters.

RESULTS

One hundred four participants developed CHF during follow-up, and the incidence rate was 10.5 per 1000 person-years at risk. Table 1 shows the clinical characteristics at baseline.
In unadjusted Cox proportional hazards analyses, all examined variables reflecting impaired glucose regulation and obesity were significant predictors of heart failure incidence (Table 2, second column). Incidence rates by quartiles of clamp glucose disposal rate are shown in the Figure. When adjusting for the presence of diabetes at baseline, the following variables remained significant: clamp glucose disposal rate; OGTT 2-hour glucose level; fasting levels of insulin, proinsulin, and 32-33 split proinsulin; BMI; and waist circumference (Table 2, last column). These 5 variables each remained significant predictors of subsequent CHF, with essentially the same point estimates and CIs when adding interim MI during follow-up to the covariates (Table 3, second column).

In unadjusted Cox proportional hazards analyses in the subsample excluding participants with diabetes, the significant predictors of CHF incidence were clamp glucose disposal rate, OGTT 2-hour glucose level, fasting levels of proinsulin and 32-33 split proinsulin, BMI, and waist circumference (Table 4, second column). When adjusting for established risk factors for CHF (prior acute MI, hypertension, diabetes, electrocardiographic LVH, smoking, and serum cholesterol level), the significant independent predictors of subsequent CHF in separate models were clamp glucose disposal rate, OGTT 2-hour glucose level, fasting proinsulin level, BMI, and waist circumference (Table 2, last column). These 5 variables each remained significant predictors of subsequent CHF, with essentially the same point estimates and CIs, when adjusting interim MI during follow-up to the covariates (Table 3, second column).

When repeating the unadjusted Cox proportional hazards analyses in the subsample of nonobese men, the significant predictors of CHF incidence were clamp glucose disposal rate, fasting glucose level, OGTT 2-hour glucose level, fasting proinsulin level, BMI, and waist circumference (Table 2, second column). When adjusting for established risk factors for CHF (prior acute MI, hypertension, electrocardiographic LVH, smoking, and serum cholesterol level), the following variables remained significant: clamp glucose disposal rate; OGTT 2-hour glucose level, BMI, and waist circumference (Table 5, second column). When adjusting for the presence of diabetes, the following variables remained significant: clamp glucose disposal rate, OGTT 2-hour glucose level, BMI, and waist circumference (Table 5, third column). When adjusting also for other established risk factors for CHF (prior acute MI, hypertension, diabetes, electrocardiographic LVH, smoking, and serum cholesterol level), only clamp glucose disposal rate remained a significant predictor of CHF (Table 5, last column). Clamp glucose disposal rate remained a significant predictor of subsequent CHF in this subsample also when adjusting for interim MI as well as diabetes plus established risk factors (hazard ratio [HR], 0.73; 95% CI, 0.55-0.97). We also examined a subsample of normal-weight men (ex-
including all participants with BMI >25 \( n=754 \), but this left us with a sample too small (433 participants, 23 cases) to draw any firm conclusions. Nevertheless, the point estimates for clamp glucose disposal rate remained similar but with wider CIs due to low statistical power (HR, 0.78; 95% CI, 0.51-1.18, in the unadjusted model and HR, 0.75; 95% CI, 0.45-1.24, in the models adjusted for diabetes plus established risk factors).

### Table 3. Heart Failure Incidence in Relation to Established Risk Factors and Glucometabolic and Anthropometric Variables in the Total Cohort of Elderly Men and the Subsample Without Diabetes at Baseline, in the Models Adjusted for Established Risk Factors and Interim Myocardial Infarction

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Cohort (( n=1187 ))</th>
<th>Subsample Without Diabetes (( n=1061 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted HR (95% CI)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clamp glucose disposal rate</td>
<td>0.65 (0.50-0.84)</td>
<td>0.67 (0.52-0.86)</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>1.30 (0.94-1.81)</td>
<td>1.05 (0.83-1.33)</td>
</tr>
<tr>
<td>OGTT 2-h glucose</td>
<td>1.43 (1.07-1.91)</td>
<td>1.23 (0.97-1.56)</td>
</tr>
<tr>
<td>Fasting insulin</td>
<td>1.13 (0.92-1.39)</td>
<td>1.25 (0.99-1.59)</td>
</tr>
<tr>
<td>Fasting proinsulin</td>
<td>1.28 (1.02-1.61)</td>
<td>1.27 (1.02-1.60)</td>
</tr>
<tr>
<td>Fasting 32-33 split proinsulin</td>
<td>1.22 (0.96-1.54)</td>
<td>1.22 (0.97-1.55)</td>
</tr>
<tr>
<td>HOMA insulin resistance index</td>
<td>1.10 (0.86-1.41)</td>
<td>1.13 (0.88-1.45)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>1.37 (1.12-1.68)</td>
<td>1.38 (1.11-1.72)</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>1.40 (1.13-1.74)</td>
<td>1.44 (1.14-1.82)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HOMA, homeostasis model assessment; HR, hazard ratio; OGTT, oral glucose tolerance test.

* Cox proportional hazards ratios for a 1-SD increase in continuous variables or transfer from one level to another of categorical variables, adjusted for established risk factors (see Table 2 footnote for definition) and interim myocardial infarction.

### Table 4. Heart Failure Incidence in Relation to Established Risk Factors and Glucometabolic and Anthropometric Variables in a Subsample of Elderly Men Without Diabetes at Baseline (\( n=1061 \))

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted</th>
<th>Adjusted for Established Risk Factors†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established risk factors for CHF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior MI</td>
<td>3.22 (1.85-5.63)</td>
<td>2.88 (1.54-5.40)</td>
</tr>
<tr>
<td>Hypertension prevalence</td>
<td>2.89 (1.50-5.59)</td>
<td>2.63 (1.30-5.31)</td>
</tr>
<tr>
<td>Electrocardiographic LVH</td>
<td>3.23 (1.78-5.86)</td>
<td>2.17 (1.14-4.15)</td>
</tr>
<tr>
<td>Current cigarette smoking</td>
<td>1.49 (0.91-2.43)</td>
<td>1.86 (1.12-3.10)</td>
</tr>
<tr>
<td>Serum cholesterol</td>
<td>0.94 (0.76-1.14)</td>
<td>0.94 (0.74-1.19)</td>
</tr>
<tr>
<td>Glucometabolic variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clamp glucose disposal rate</td>
<td>0.66 (0.52-0.83)</td>
<td>0.68 (0.53-0.88)</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>1.07 (0.86-1.32)</td>
<td>1.04 (0.82-1.32)</td>
</tr>
<tr>
<td>OGTT 2-h glucose</td>
<td>1.34 (1.08-1.66)</td>
<td>1.23 (0.97-1.57)</td>
</tr>
<tr>
<td>Fasting insulin</td>
<td>1.24 (1.00-1.53)</td>
<td>1.20 (0.95-1.51)</td>
</tr>
<tr>
<td>Fasting proinsulin</td>
<td>1.37 (1.12-1.68)</td>
<td>1.30 (1.03-1.64)</td>
</tr>
<tr>
<td>Fasting 32-33 split proinsulin</td>
<td>1.32 (1.07-1.63)</td>
<td>1.26 (1.00-1.59)</td>
</tr>
<tr>
<td>HOMA insulin resistance index</td>
<td>1.16 (0.93-1.44)</td>
<td>1.15 (0.90-1.46)</td>
</tr>
<tr>
<td>Anthropometric variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td>1.42 (1.16-1.72)</td>
<td>1.36 (1.10-1.69)</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>1.41 (1.15-1.74)</td>
<td>1.38 (1.10-1.74)</td>
</tr>
</tbody>
</table>

Abbreviations: CHF, congestive heart failure; CI, confidence interval; HOMA, homeostasis model assessment; HR, hazard ratio; LVH, left ventricular hypertrophy; MI, myocardial infarction; OGTT, oral glucose tolerance test.

* Cox proportional hazards ratios for a 1-SD increase in continuous variables or transfer from one level to another of categorical variables.

† See Table 2 footnote for definition of established risk factors. Values shown for the established risk factors are from a multivariable model incorporating only these variables.

The variables describing impaired glucose regulation and obesity were highly correlated (Pearson \( r=-0.60, P<.001 \) for clamp glucose disposal rate vs both BMI and waist circumference). In the models including obesity variables, diabetes plus established risk factors, and clamp glucose disposal rate, the obesity variables were no longer significant, whereas clamp glucose disposal rate remained significant (Table 6). When performing the same analyses in the subsample excluding participants with diabetes at baseline and in the subsample of nonobese men, the same patterns were observed but with larger CIs, rendering some associations borderline significant (Table 6). None of the interaction terms were significant.

**COMMENT**

In this community-based sample of elderly men free of CHF and valvular disease at baseline, insulin resistance predicted CHF incidence independently of diabetes and other established risk factors for CHF. Furthermore, our observations indicate that the previously described association between obesity and subsequent CHF may be mediated partly by insulin resistance.

**Previous Studies**

Several previous longitudinal studies have shown an association between diabetes and CHF. In the present study, clamp glucose disposal rate and fasting proinsulin level, mainly reflecting insulin resistance, were the strongest glucometabolic predictors of CHF, both when adjusting for diabetes and in a subsample without diabetes. To our knowledge, this is the first study to demonstrate a relation between milder states of impaired glucose regulation and CHF incidence. Because information about diabetes incidence during follow-up was not collected in a systematic manner, it is possible that impaired glucose regulation at baseline was a sign of impending diabetes, which is a known risk factor for CHF. Still, we show that impaired glucose regula-
tion in healthy participants without diabetes or obesity at baseline is a strong predictor of subsequent CHF, independent of established risk factors. Our observations may indicate that the risk for CHF is already increased in the long subclinical phase of impaired glucose regulation that precedes clinically manifest diabetes.

**Possible Mechanisms**

In previous studies, signs of impaired glucose regulation have been related to both left ventricular systolic and diastolic dysfunction and left ventricular remodeling. There are numerous possible explanations for the observed relation of insulin resistance to CHF incidence: (1) The formation of advanced glycosylation end products is greatly accelerated in patients with diabetes, which in the myocardium leads to increased collagen cross-linking and myocardial stiffness. Ventricular function can be improved and collagen stiffness reversed in diabetic dogs when they are treated with a collagen cross-link breaker such as metformin. (2) Insulin may act as a growth factor in the myocardium, which is supported by the experimental observation that sustained hyperinsulinemia leads to increased myocardial mass and decreased cardiac output in rats. (3) Hyperinsulinemia leads to sodium retention, which may lead to decompensation in persons with otherwise subclinical myocardial dysfunction due to volume expansion. (4) Hyperinsulinemia also leads to sympathetic nervous system activation, which is a presumed causal factor for CHF. (5) Insulin resistance is related to an increased pressor response to angiotensin II and has recently been demonstrated to increase the stimulating effects of angiotensin II on cellular hypertrophy and collagen production in individuals with hypertension, leading to myocardial hypertrophy and fibrosis and likely subsequent CHF.

**Obesity as a Risk Factor for CHF**

Obesity as a risk factor for CHF has been established within the last decade. In the present study, BMI and waist circumference were strong predictors of CHF independently of established risk factors for CHF. This demonstrates that both truncal and overall obesity increase the risk of CHF to about the same degree. However, as obesity is also strongly associated with diabetes and insulin resistance, we investigated whether the relation between obesity and CHF may be mediated by insulin resistance. When clamp glucose disposal rate was included in the multivariable models with BMI and waist circumference, the obesity variables were no longer significant predictors of CHF. This observation would be expected if insulin resistance were in the causal pathway between obesity and CHF, which was our hypothesis. Furthermore, in the subsample of nonobese men, clamp glucose disposal rate was a significant predictor of subsequent CHF independent of established risk factors, whereas the obesity variables were no longer significant predictors of CHF. These findings demonstrate that insulin resistance is a risk factor for CHF independent of both truncal and overall obesity. It may imply either that insulin resistance forgoes obesity in a causal pathway leading to CHF, or simply that the relation of obesity to CHF is circumstantial and that obesity in this case may be regarded as an indicator of the more important trait, insulin resistance. It should be noted that it is not possible from our data to definitely disentangle the causative relations between obesity, insulin resistance, and CHF, but our data do add an important piece of knowledge and should stimulate further research in the area.

**Strengths and Limitations**

The strengths of this study include the large, community-based population, the long follow-up period, and the detailed metabolic characterization of the cohort. To our knowledge, the Uppsala Longitudinal Study of Adult Men co-

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**Table 5. Heart Failure Incidence in Relation to Established Risk Factors and Glucometabolic and Anthropometric Variables in a Subsample of Nonobese Elderly Men (n = 1034)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted HR (95% CI)</th>
<th>Adjusted for Diabetes HR (95% CI)</th>
<th>Adjusted for Established Risk Factors† HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established risk factors for CHF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior MI</td>
<td>2.60 (1.41-4.81)</td>
<td>2.55 (1.38-4.71)</td>
<td>2.40 (1.20-4.79)</td>
</tr>
<tr>
<td>Hypertension prevalence</td>
<td>2.25 (1.22-4.16)</td>
<td>2.21 (1.19-4.08)</td>
<td>2.56 (1.26-5.21)</td>
</tr>
<tr>
<td>Diabetes prevalence</td>
<td>1.67 (0.86-3.25)</td>
<td>NA</td>
<td>1.29 (0.58-2.83)</td>
</tr>
<tr>
<td>Electrocardiographic LVH</td>
<td>2.44 (1.25-4.78)</td>
<td>2.38 (1.21-4.67)</td>
<td>1.69 (0.82-3.50)</td>
</tr>
<tr>
<td>Current cigarette smoking</td>
<td>1.89 (1.16-3.05)</td>
<td>1.91 (1.18-3.09)</td>
<td>2.45 (1.47-4.06)</td>
</tr>
<tr>
<td>Serum cholesterol</td>
<td>1.01 (0.81-1.26)</td>
<td>1.02 (0.82-1.27)</td>
<td>0.98 (0.77-1.25)</td>
</tr>
<tr>
<td>Glucometabolic variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clamp glucose disposal rate</td>
<td>0.69 (0.55-0.88)</td>
<td>0.71 (0.55-0.91)</td>
<td>0.74 (0.56-0.98)</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>1.22 (1.02-1.47)</td>
<td>1.25 (0.92-1.71)</td>
<td>1.28 (0.87-1.88)</td>
</tr>
<tr>
<td>OGTT 2-h glucose</td>
<td>1.37 (1.12-1.68)</td>
<td>1.46 (1.09-1.96)</td>
<td>1.37 (0.99-1.90)</td>
</tr>
<tr>
<td>Fasting insulin</td>
<td>1.16 (0.93-1.44)</td>
<td>1.13 (0.90-1.41)</td>
<td>1.10 (0.86-1.41)</td>
</tr>
<tr>
<td>Fasting proinsulin</td>
<td>1.28 (1.04-1.58)</td>
<td>1.25 (0.98-1.59)</td>
<td>1.22 (0.93-1.59)</td>
</tr>
<tr>
<td>Fasting 32-33 split proinsulin</td>
<td>1.20 (0.96-1.51)</td>
<td>1.16 (0.91-1.48)</td>
<td>1.13 (0.87-1.48)</td>
</tr>
<tr>
<td>HOMA insulin resistance index</td>
<td>1.18 (0.94-1.46)</td>
<td>1.12 (0.88-1.42)</td>
<td>1.11 (0.84-1.45)</td>
</tr>
<tr>
<td>Anthropometric variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td>1.29 (1.03-1.63)</td>
<td>1.27 (1.01-1.61)</td>
<td>1.23 (0.95-1.60)</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>1.34 (1.06-1.68)</td>
<td>1.32 (1.04-1.66)</td>
<td>1.28 (0.99-1.67)</td>
</tr>
</tbody>
</table>

Abbreviations: CHF, congestive heart failure; CI, confidence interval; HOMA, homeostasis model assessment; HR, hazard ratio; LVH, left ventricular hypertrophy; MI, myocardial infarction; NA, not applicable; OGTT, oral glucose tolerance test.

*See Table 2 footnote for definition of established risk factors. Values shown for the established risk factors are from a multivariable model incorporating only these variables.

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Table 6. Heart Failure Incidence in Relation to Obesity Variables Assessed by Multivariable Models Including Clamp Glucose Disposal Rate in the Total Cohort (N = 1187) and in Subsamples Without Diabetes (n = 1061) and Without Obesity (n = 1034)

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI) Model With BMI†</th>
<th>HR (95% CI) Model With Waist Circumference†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Cohort</td>
<td>Subsample Without Diabetes</td>
</tr>
<tr>
<td>Prior MI</td>
<td>3.04 (1.76-5.25)</td>
<td>2.90 (1.55-5.43)</td>
</tr>
<tr>
<td>Hypertension prevalence</td>
<td>2.37 (1.17-4.81)</td>
<td>2.19 (1.07-4.46)</td>
</tr>
<tr>
<td>Diabetes prevalence</td>
<td>0.92 (0.48-1.76)</td>
<td>0.87 (0.42-1.67)</td>
</tr>
<tr>
<td>Electrocardiographic LVH</td>
<td>2.14 (1.19-3.85)</td>
<td>2.27 (1.19-4.32)</td>
</tr>
<tr>
<td>Current cigarette smoking</td>
<td>2.33 (1.47-3.68)</td>
<td>1.93 (1.15-3.22)</td>
</tr>
<tr>
<td>Serum cholesterol</td>
<td>0.93 (0.75-1.15)</td>
<td>0.95 (0.75-1.19)</td>
</tr>
<tr>
<td>Clamp glucose disposal rate</td>
<td>0.74 (0.55-1.00)</td>
<td>0.76 (0.56-1.02)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>1.17 (0.92-1.50)</td>
<td>1.17 (0.90-1.53)</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; LVH, left ventricular hypertrophy; MI, myocardial infarction; NA, not applicable.

*Adjusted for clamp glucose disposal rate plus diabetes and other established risk factors (prior acute MI, hypertension, electrocardiographic LVH, smoking, and serum cholesterol level).
†Cox proportional hazards ratios for a 1-SD increase in continuous variables or transfer from one level to another of categorical variables.

Insulin resistance predicted CHF incidence independently of established risk factors in our large community-based sample of elderly men. The previously described association between obesity and subsequent CHF may be mediated largely by insulin resistance. Further studies are needed to confirm our findings.

Conclusions

Insulin resistance predicted CHF incidence independently of established risk factors in our large community-based sample of elderly men. The previously described association between obesity and subsequent CHF may be mediated largely by insulin resistance. Further studies are needed to confirm our findings.

Author Contributions: Dr Ingelsson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Ingelsson, Sundström, Åmlov, Lind.

Acquisition of data: Ingelsson.

Analysis and interpretation of data: Ingelsson, Sundström, Åmlov, Zethelius, Lind.

Drafting of the manuscript: Ingelsson.

Critical analysis of the manuscript for important intellectual content: Ingelsson, Sundström, Åmlov, Zethelius, Lind.

Statistical analysis: Ingelsson.

Administrative, technical, or material support: Zethelius.

Study supervision: Sundström, Åmlov, Zethelius, Lind.

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Role of the Sponsors: The funding sources had no role in the design and conduct of the study; the collection, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript.

REFERENCES

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The responsibility of a writer is to excavate the experience of the people who produced him.
—James Baldwin (1924-1987)