Prevalence, metabolic features and prognosis of metabolically healthy obese Italian individuals: the Cremona Study

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Running title: Prognosis of metabolically healthy subjects

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**Objective** Some obese individuals have normal insulin sensitivity. It is controversial whether this phenotype is associated with increased all-cause mortality risk.

**Research Design and Methods** Fifteen-year all-cause mortality data were obtained through the Regional Health Registry in 2,011 out of 2,074 Caucasian middle-aged individuals of the Cremona Study, a population study on the prevalence of diabetes mellitus in Italy. Individuals were divided in four categories according to BMI (non-obese: < 30 kg/m\(^2\); obese: ≥ 30 kg/m\(^2\)) and estimated insulin resistance (insulin-sensitive: HOMA-IR < 2.5; insulin-resistant ≥ 2.5).

**Results** Obese insulin-sensitive subjects represented 11% (95%CI: 8.1-14.5%) of the obese population. This phenotype had similar BMI, but lower waist circumference, blood pressure, fasting glucose, triglycerides and fibrinogen, and higher HDL-cholesterol than obese insulin-resistant subjects. In the fifteen-year follow-up 495 deaths (CVD: 221, cancer: 180) occurred. All-cause mortality adjusted for age and sex was higher in the obese insulin-resistant (HR: 1.40; 95% CI: 1.08-1.81; P=0.01) but not in the obese insulin-sensitive (HR: 0.99; 95% CI: 0.46-2.11; P=0.97) when compared to non-obese insulin-sensitive subjects. Also mortality for CVD and cancer was higher in the obese insulin-resistant but not in the obese insulin-sensitive when compared to non-obese insulin-sensitive subjects.

**Conclusion** In contrast to obese insulin-resistant subjects, metabolically healthy obese individuals are less common than previously thought, and do not show increased all-cause, cancer and CVD mortality risks in a 15-year follow-up study.

Metabolically healthy obese (MHO) individuals are considered as a subset of obese subjects without metabolic abnormalities (such as insulin resistance, pro-atherogenic lipoprotein profile, pro-inflammatory state or hypertension), and a model for better understanding the pathogenesis of insulin resistance (1-3). The prevalence of the MHO phenotype in the general population, the reasons for not developing metabolic alterations, and the less aggressive therapeutic approach with respect to obese with metabolic abnormalities are currently debated (4,5). In the Framingham Offspring Study, Meigs et al. (6) found that MHO individuals do not have increased risk of incident diabetes and CVD. Conversely, in the Third National Health and Nutrition Examination Survey (NHANES III) Kuk et al. (7) reported increased all-cause mortality associated with the MHO phenotype. Finally, in a Scandinavian study middle-aged overweight/obese subjects without metabolic syndrome also had increased risk of CVD when compared to normal-weight individuals without metabolic syndrome (8). The present study shows the prevalence of the MHO phenotype, its metabolic features, and 15-year all-cause, CVD and cancer mortality rates in the Caucasian population of the Cremona Study (9,10).

**METHODS**

**Study Cohort and Follow-up.** The Cremona Study is a population survey
carried out in 1990-91 in the Health District of Cremona (Lombardia, Italy) to determine the prevalence of diabetes mellitus according to the Oral Glucose Tolerance Test and WHO criteria (8,9). 2,074 individuals were enrolled. Past medical history, anthropometric measures and clinical data of subjects were collected by trained interviewers using standardized procedures. A venous blood sample was collected after 12-h overnight fast, and thereafter a 75-g oral glucose monohydrate was given. An additional blood sample was collected 2 hrs later. Heart rate and blood pressure were recorded twice, at the beginning and at the end of the visit, in the sitting position and after at least 10 min rest using a full automatic non-invasive sphygomanometer. The lowest figure was considered. Further details concerning the study protocol were previously described (8,9). Vital status and time of death were acquired from the Regional Health Registry (updated to December 31, 2005), and causes of death were classified using the International Classification of Diseases, Ninth Revision (death codes for CVD from 401 to 448 and cancer from 140.0 to 208.9). Median follow-up was 180 months and median follow-up of those still alive 182 months (98% of the still-alive had a minimum follow-up period of 174 months). Data for 2,011 out of 2,074 individuals were available.

Definition of study groups. Study subjects were divided in four categories based on BMI (non-obese: < 30 kg/m²; obese; ≥ 30 kg/m²) and estimated insulin resistance (insulin-sensitive: HOMA-IR < 2.5; insulin-resistant ≥ 2.5). This cut-off of 2.5 for HOMA-IR was chosen to compare our data with those recently published by Kuk et al (7). Therefore the four categories were: 1) the non-obese subjects with normal insulin sensitivity, 2) the obese but insulin-sensitive subjects, 3) the non-obese but insulin-resistant subjects and 4) the obese and insulin-resistant subjects. The features of these subgroups are summarized in Table 1.

**Definition of diabetes, impaired glucose tolerance (IGT) and metabolic syndrome**

Diabetes was defined according to the use of oral hypoglycemic agents or insulin and according to the WHO diagnostic criteria for the OGTT (basal plasma glucose > 7.8 mmol/L or > 11.1 mmol/L after 2-hr oral glucose load). Patients with manifest diabetes did not undergo the OGTT. IGT was defined as basal plasma glucose < 7.8 mmol/L and plasma glucose > 7.8 but < 11 mmol/L after 2-hr oral glucose load. Metabolic syndrome was defined accordingly to the definition of the NCEP Adult Treatment Program III.

**Analytical Determinations.** Blood, serum and plasma measurements were done as previously described (8,9).

**Calculations.** BMI was calculated as weight in kilograms divided by the square of height in meters, and alcohol consumption as grams of alcohol (glass of wine=20 grams, glass of aperitif=30 grams and glass of liquor=80 grams). HOMA-IR was calculated as previously described (11), and LDL-cholesterol using the Friedwald formula.

**Statistical Analysis.** Data are presented as mean±SD unless differently stated. Serum insulin, triglycerides, fibrinogen and glucose had a skewed distribution therefore, log-transformed values were used in the analysis. ANOVA and Tukey post-hoc analysis was used for comparison between groups. Differences in proportion between groups were tested by the Chi-square test. The associations of each investigated risk factor with all-cause, CVD and cancer mortality were estimated by the Cox proportional hazard
model with adjustments for age and sex. Multivariate Cox regression analysis was performed in order to adjust the comparisons of mortality among the different sub-groups for possible confounding factors. Hazard ratios (HR) and 95% Confidence Intervals (95% CI) are presented. 95% CI of proportions were calculated using the normal approximation or the exact method. Kaplan and Meier curves for all-cause mortality were plotted for the four groups, as previously described. P-value <0.05 indicated statistical significance. Analyses were performed using the Statistical Analysis System (SAS) Software (v.9.1).

RESULTS
Prevalence of the obese insulin-sensitive phenotype. Out of 2,011 subjects, 708 were non-obese insulin-sensitive, 923 non-obese insulin-resistant, and 337 obese insulin-resistant. Obese insulin-sensitive individuals were 43, representing 11.0% (CI 8.1-14.5%) of the obese population and 2.1% (CI 1.6-2.9%) of the entire population.

Anthropometric and metabolic features of the obese insulin-sensitive individuals. The features of the four groups are summarized in Table 1. Sex distribution did not differ among all groups, whereas cigarette smoking was more frequent in non-obese insulin-sensitive subjects than all other groups.

Systolic and diastolic blood pressure, heart rate, plasma glucose, insulin, total cholesterol, HDL-cholesterol, triglycerides, transaminases, γGT, ALP, and fibrinogen did not differ between the two insulin-sensitive groups. Individuals in the insulin-sensitive groups were younger, had lower heart rate, higher plasma HDL-cholesterol and lower fibrinogen and triglycerides, as well as a lower prevalence of diabetes and metabolic syndrome than insulin-resistant groups.

Waist circumference was higher in obese insulin-sensitive than non-obese insulin-resistant, but lower than obese insulin-resistant subjects. Systolic and diastolic blood pressure, plasma transaminases, γGT and ALP were higher in the two groups of insulin-resistant than non-obese insulin-sensitive subjects.

Mortality in the cohort. During the 15-year observation period 495 deaths occurred. 221 deaths were CVD-related and 180 were cancer-related. Age and sex were associated with higher all-cause mortality (age: HR 1.11; 95% CI: 1.10-1.12; p<0.0001, female sex: HR 0.42; 95% CI: 0.35-0.50; p<0.0001), mortality for CVD (age: HR 1.15; 95% CI: 1.13-1.17; p<0.0001, female sex: HR 0.40; 95% CI: 0.31-0.53; p<0.0001), and mortality for cancer (age: HR 1.07; 95% CI: 1.06-1.09; p<0.0001, female sex: HR 0.39; 95% CI: 0.29-0.52; p<0.0001). All-cause mortality was higher in the obese insulin-resistant (31%) in comparison with the reference group of non-obese insulin-sensitive subjects (20%) (age and sex adjusted HR: 1.4; p=0.01, Table 2, fig 1) but not in the obese insulin-sensitive subjects (12%; age and sex adjusted HR: 0.99; p=0.97; Table 2, fig 1) and in the non-obese insulin-resistant (26%; age and sex adjusted HR: 1.11; p=0.35; Table 2, fig 1). Also mortality for CVD (15%; p=0.015) and cancer (12%; p=0.04; Table 2) was higher in the obese insulin-resistant but not in the obese insulin-sensitive (CVD-related: 5%; p=0.66 and cancer-related: 7%; p=0.95) and in the non-obese insulin-resistant (CVD-related: 12%; p=0.29 and cancer-related: 9%; p=0.64) when compared to non-obese insulin-sensitive subjects (CVD-related: 8% and cancer-related: 7%).
Since the prevalence of cigarette smoking habit and the baseline plasma LDL-cholesterol were different among the groups we performed the analysis adjusting also for these two factors. All-cause mortality remained higher in the obese insulin-resistant (HR: 1.66; 95% CI: 1.12-2.46; p=0.011) but not in the obese insulin-sensitive subjects (HR: 0.79; 95% CI: 0.19-3.28; p=0.75) and in the non-obese insulin-resistant (HR: 1.22; 95% CI: 0.88-1.70; p=0.23) when compared to the non-obese and insulin-sensitive subjects.

The analysis was also repeated after the exclusion of diabetic patients. When compared to non-obese insulin-sensitive (reference group), all-cause mortality tended to be higher in obese insulin-resistant (HR 1.29, CI 0.96-1.73, p=0.087), but was again not different in obese insulin-sensitive (HR 1.01, CI 0.47-2.17, p=0.97) and non-obese insulin-resistant subjects (HR 1.00, CI 0.80-1.25, p=0.98). Similarly, mortality for CVD and cancer tended to be higher in obese insulin-resistant (CVD: HR 1.40, CI 0.94-2.11, p=0.071; cancer: HR 1.46, CI 0.94-2.27, p=0.097), but was not different in obese insulin-sensitive (CVD: HR 0.76, CI 0.197-3.11, p=0.71; cancer: HR 1.05, CI 0.33-3.56, p=0.94) and non-obese insulin-resistant subjects (CVD: HR 1.09, CI 0.77-1.54, p=0.65; cancer: HR 1.01, CI 0.93-2.27, p=0.95) than non-obese insulin-sensitive subjects.

Finally, instead of the preselected HOMA-IR of 2.5, we repeated the analysis using cut-off values (top tertile and top quartile) for HOMA-IR obtained from the present study. Even in this case, the results did not change (see the online appendix available at http://care.diabetesjournals.org).

DISCUSSION

The 15-year follow-up of the Cremona Study demonstrates that obese insulin-sensitive individuals, also known as metabolically healthy obese: a. have a prevalence of 11% in the obese, and 2% in the entire population; b. have less features of the metabolic syndrome, when compared to obese insulin-resistant; c. do not have increased all-cause, CVD, and cancer mortality, when compared to non-obese insulin-sensitive (reference group).

Major findings and comparison with the literature. The prevalence of the obese insulin-sensitive phenotype (11%) in our obese cohort was lower than reported by Iacobellis et al (27.5%) in a cohort of 681 obese individuals living in Rome and surrounding areas (3). The discrepancy may be related to the different regional habits of the Italian cohorts but most likely to the different definition of metabolically healthy obese. Iacobellis et al based their definition mainly on the metabolic syndrome meanwhile our definition was centered on HOMA-IR, a surrogate index of insulin resistance, in order to compare our results with those recently published by Kuk and Ardern (7) who analyzed the NHANES III Survey in US using HOMA-IR<2.5 as the cut-off. Interestingly, they reported a prevalence of metabolically healthy of 6%. Our finding is in line with this report, therefore we think that the frequency of this phenotype is lower than previously thought.

The present study has also clearly shown that the obese insuli-sensitive phenotype carries less features of the metabolic syndrome. These subjects were characterized by lower waist circumference, blood pressure, circulating triglycerides, transaminases and GGT (as a surrogate markers of fatty liver) and fibrinogen (as a surrogate marker of low grade inflammation), when compared to
the obese insulin-resistant subjects, in
de spite of similar BMIs. Not surprisingly,
they had a lower prevalence of the
metabolic syndrome (7% in comparison
to the observed 41% in the obese insulin-
resistant) and of diabetes (0% vs. 28% of
the obese insulin-resistant). We think
therefore that the deleterious metabolic
features associated with obesity are
largely related to the presence of insulin
resistance rather than obesity per se.
The third aim was to establish the
prognosis of the metabolically healthy
obese subjects. The present study has
also shown that all-cause mortality is
significantly higher in obese insulin-
resistant, but not obese insulin-sensitive,
when compared to non-obese insulin-
sensitive individuals (considered as reference group). These findings were
confirmed when the analysis was
adjusted for LDL-cholesterol and cigarette
smoking (risk factors not related to
metabolic syndrome). However, our
findings are in contrast with recent data
from a US population suggesting
increased all-cause mortality in
metabolically healthy obese subjects
(defined according to the same BMI and
HOMA-IR criteria we use here) (7). The
potential explanations for this discrepancy are: number of events; reference HR; and
different ethnicity. Even though our
population was smaller, the number of
events was higher (495 vs. 292, or 25%
vs. 5%). This was likely due to the longer
observational period (15 vs. 8.7 years). It
is important to point out that a 10-15-yr
follow-up may be the least to see the
effects of metabolic risk factors on
mortality (8,11). Regarding reference HR,
we have used non-obese insulin-sensitive
individuals, which also includes
overweight individuals with BMI ranging
between 25-29.9 kg/m², whereas Kuk et
al (7) have used normal weight insulin-
sensitive subjects with BMI <25 kg/m².
Our finding is also in contrast with
another report by Arnlov et al (8) in a
Scandinavian population in which
overweight and obese individuals without
the metabolic syndrome showed a higher
mortality when compared to normal
weight and insulin-sensitive individuals.
We believe that the reason for this
discrepancy could be due to gender
differences, since our study included both
males and females, whereas only males
were included in the Scandinavian study.
This is worth mentioning, since male
gender was a significant risk factor for all-
cause mortality in our study.
We used all-cause mortality as primary
outcome (since this variable is less
affected by errors in reporting), whereas
CVD and cancer mortality were
considered secondary outcomes.
Mortality for CVD and cancer, as for all-
cause mortality, were also higher in
obese insulin-resistant individuals, but not
in the metabolically healthy obese
subjects.

**Strengths and Limitations.** The major
strengths of the present study are: 1)
population-based study including both
males and females 2) careful and
homogeneous acquisition of the
anthropometric parameter of interest; 3)
the robust end-point (all-cause mortality)
whose ascertainment was based on the
Regional Health Registry; 4) the long
follow-up period (15 years).

The limitations are: 1) the small sample
size of the group of obese insulin-
sensitive (n=43) due to its low prevalence
in the cohort (2%) could represent a
problem because of the consequent small
number of events even if it was similar to
previously reported data (8); 2) the lack of
collection of intermediate data points
about the parameters of interest during
the 15-year observation period; 3) the glucose clamp technique is the golden standard for the assessment of insulin sensitivity and HOMA is inferior, nevertheless it was suggested that HOMA appeared to be specifically suited to large-scale epidemiologic studies in which only fasting glucose and insulin concentrations were available (12); 4) the lack of collection of the dietary habits and habitual physical activity, known to have a well recognized impact on insulin sensitivity.

Pathogenic remarks. It is presently unclear why these metabolically healthy obese subjects may be protected. It was reported that a lower amount of visceral fat content may contribute to the favourable metabolic profile (1, 6). Fitting this view the waist circumference was lower in the metabolically healthy obese subjects than in the obese insulin-resistant; on the other hand it was higher in comparison to the non-obese and insulin-sensitive group (Table 1), in spite of a not different all-cause mortality. We speculate that visceral fat and insulin resistance may in combination explain the difference and the trends observed between groups in our study and in addition an undetectable effect of ectopic fat accumulation in the skeletal muscle (13) and the liver (14) should be considered. In particular the potential, but yet to be demonstrated, role of the liver (see the profile of surrogate markers of fatty liver) in mediating the increased CVD mortality may be hypothesized based on the pro-inflammatory and pro-atherosclerotic profile of individuals with NAFLD but also based on some initial epidemiological data (15).

CONCLUSIONS
All-cause mortality in obese insulin-resistant subjects but not in metabolically healthy obese subjects is higher when compared to non-obese insulin-sensitive subjects. The effect of obesity on the increasing risk is strongly related with insulin resistance and we therefore agree with Bonora E et al (16) and McLaughlin T et al (17) that it is important not to limit our risk evaluation to the identification of obesity alone, but to put more efforts on identifying those at higher risk, the insulin-resistant, obese individuals.

Author Contributions: G.C. researched data, contributed to discussion, wrote manuscript, reviewed/edited manuscript. G.L. researched data, reviewed/edited manuscript. L.P. contributed to discussion, reviewed/edited manuscript. M.P.G.: researched data, reviewed/edited manuscript. F. R. researched data, reviewed/edited manuscript. M.V. researched data, reviewed/edited manuscript. S.M. researched data, reviewed/edited manuscript. P.C. researched data, reviewed/edited manuscript. E.B. contributed to discussion, reviewed/edited manuscript. G.R. contributed to discussion, reviewed/edited manuscript. G.P. contributed to discussion, wrote manuscript, reviewed/edited manuscript.

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This work was selected for Poster Presentation (and new this year for Q&A sessions) at the American Diabetes Association’s 70th Scientific Sessions,
REFERENCES


## Table 1. Baseline anthropometric, clinical and laboratory features of study groups

<table>
<thead>
<tr>
<th></th>
<th>Non-obese insulin-sensitive</th>
<th>Obese insulin-sensitive</th>
<th>Non-obese insulin-resistant</th>
<th>Obese insulin-resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anthropometric parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (F/M)</td>
<td>708 (392F/316M)</td>
<td>43 (31F/12M)</td>
<td>923 (512F/411M)</td>
<td>337 (191F/146M)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>55 ± 11 ^†</td>
<td>55 ± 9</td>
<td>59 ± 11 °</td>
<td>59 ± 10 **</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.8 ± 2.8 ^°†</td>
<td>32.5 ± 4.3 *†</td>
<td>25.8 ± 2.3 °^</td>
<td>33.3 ± 3.4 °†</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>82 ± 9 ^°†</td>
<td>94 ± 4 ^°†</td>
<td>89 ± 10 °^</td>
<td>104 ± 11 °†</td>
</tr>
<tr>
<td>Actual smoking n (%)</td>
<td>201 (28%) §</td>
<td>8 (19%)</td>
<td>177 (19%)</td>
<td>64 (19%)</td>
</tr>
<tr>
<td>Alcohol (gr/day)</td>
<td>44 ± 59</td>
<td>39 ± 45</td>
<td>42 ± 59</td>
<td>39 ± 54</td>
</tr>
<tr>
<td>Systolic bp (mm Hg)</td>
<td>139 ± 20 ^†</td>
<td>143 ± 23 ^</td>
<td>147 ± 21 **</td>
<td>154 ± 20 °^</td>
</tr>
<tr>
<td>Diastolic bp (mm Hg)</td>
<td>77 ± 11 ^†</td>
<td>79 ± 13 ^</td>
<td>81 ± 12 ^</td>
<td>85 ± 12 °°</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>73 ± 11 ^†</td>
<td>72 ± 10</td>
<td>76 ± 13 °</td>
<td>77 ± 11 °</td>
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<tr>
<td><strong>Biochemical lab parameters</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Glucose (mmol/L)</td>
<td>4.83 ± 0.50 ^†</td>
<td>4.83 ± 0.33 †^</td>
<td>5.44 ± 1.05 **^</td>
<td>6.00 ± 1.67 °†</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>5.92 ± 1.09 ^†</td>
<td>6.20 ± 1.19</td>
<td>6.20 ± 1.14 *</td>
<td>6.10 ± 1.14</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>1.52 ± 0.36 ^°^</td>
<td>1.50 ± 0.34 ^°†</td>
<td>1.29 ± 0.36 °^</td>
<td>1.21 ± 0.34 °^</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L)</td>
<td>3.90 ± 1.03 ^°†</td>
<td>4.13 ± 1.00</td>
<td>4.19 ± 1.03 *</td>
<td>4.11 ± 1.06 *</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.15 ± 0.63 ^°†</td>
<td>1.26 ± 0.58 ^°</td>
<td>1.56 ± 1.04 °</td>
<td>1.72 ± 0.94 °°</td>
</tr>
<tr>
<td>ALT (U/I)</td>
<td>21 ± 14 ^†</td>
<td>23 ± 12 ^</td>
<td>27 ± 22 ^°</td>
<td>31 ± 26 °°</td>
</tr>
<tr>
<td>AST (U/I)</td>
<td>26 ± 12 ^</td>
<td>25 ± 8</td>
<td>28 ± 13</td>
<td>30 ± 19 °</td>
</tr>
<tr>
<td>GGT (U/I)</td>
<td>31 ± 38 ^°†</td>
<td>33 ± 41</td>
<td>42 ± 58 °</td>
<td>50 ± 82 °</td>
</tr>
<tr>
<td>ALP (U/I)</td>
<td>169 ± 64 ^°†</td>
<td>159 ± 52 ^</td>
<td>180 ± 66 °</td>
<td>187 ± 76 °°</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>271 ± 66 ^°†</td>
<td>274 ± 48 ^°</td>
<td>286 ± 74 °°</td>
<td>302 ± 76 °°</td>
</tr>
<tr>
<td><strong>Hormones</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin (pmol/L)</td>
<td>50 ± 13 ^†</td>
<td>56 ± 13 °^</td>
<td>112 ± 70 °°</td>
<td>154 ± 89 °°</td>
</tr>
<tr>
<td><strong>Insulin sensitivity, metabolic syndrome &amp; diabetes status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.80 ± 0.45 ^†</td>
<td>2.00 ± 0.43 †^</td>
<td>4.65 ± 3.70 °^</td>
<td>7.18 ± 5.57 °°</td>
</tr>
<tr>
<td>Metabolic syndrome (n%)</td>
<td>37 (5%)</td>
<td>3 (7%)</td>
<td>218 (24%) ‡</td>
<td>139 (41%) ‡</td>
</tr>
<tr>
<td>Diabetes (n%)</td>
<td>16 (2%)</td>
<td>0 (0%)</td>
<td>98 (11%) ‡</td>
<td>74 (28%) ‡</td>
</tr>
</tbody>
</table>

Average ± standard deviation

One way ANOVA and Tukey post hoc for continuous variable

* indicates p < 0.05 vs. non-obese insulin-sensitive

° indicates p < 0.05 vs. obese insulin-sensitive

^ indicates p <0.05 vs. obese insulin-resistant

† indicates p < 0.05 vs non-obese insulin-resistant

Chi square for categorical variables § indicates p < 0.05 vs. all; ‡ indicates p < 0.05 vs. non-obese and obese insulin-sensitive.
Table 2. Cox proportional hazard model adjusting for age and sex. Number of events/n, hazard ratio (HR) and 95% CI with respect to non-obese insulin-sensitive subjects are presented.

<table>
<thead>
<tr>
<th>All-cause mortality</th>
<th># events/n</th>
<th>HR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-obese insulin-sensitive</td>
<td>141/708</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Obese insulin-sensitive</td>
<td>7/43</td>
<td>0.99</td>
<td>0.46 – 2.11</td>
<td>0.97</td>
</tr>
<tr>
<td>Non-obese insulin-resistant</td>
<td>241/923</td>
<td>1.11</td>
<td>0.90 – 1.36</td>
<td>0.35</td>
</tr>
<tr>
<td>Obese insulin-resistant</td>
<td>106/337</td>
<td>1.40</td>
<td>1.08 – 1.81</td>
<td>0.01</td>
</tr>
<tr>
<td>CVD mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Non-obese insulin-sensitive</td>
<td>58/708</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Obese insulin-sensitive</td>
<td>2/43</td>
<td>0.73</td>
<td>0.18 – 3.00</td>
<td>0.66</td>
</tr>
<tr>
<td>Non-obese insulin-resistant</td>
<td>112/923</td>
<td>1.19</td>
<td>0.86 – 1.64</td>
<td>0.29</td>
</tr>
<tr>
<td>Obese insulin-resistant</td>
<td>49/337</td>
<td>1.61</td>
<td>1.10 – 2.36</td>
<td>0.015</td>
</tr>
<tr>
<td>Cancer mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-obese insulin-sensitive</td>
<td>51/708</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Obese insulin-sensitive</td>
<td>3/43</td>
<td>1.04</td>
<td>0.32 – 3.30</td>
<td>0.95</td>
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<td>Non-obese insulin-resistant</td>
<td>85/923</td>
<td>1.09</td>
<td>0.78 – 1.52</td>
<td>0.64</td>
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<tr>
<td>Obese insulin-resistant</td>
<td>41/337</td>
<td>1.52</td>
<td>1.02 – 2.26</td>
<td>0.04</td>
</tr>
</tbody>
</table>

**FIGURE LEGEND**

**Figure 1.** Survival by Kaplan-Meier estimates of all-cause mortality. Follow-up period was 15 years (180 months). Subjects were divided according to BMI (non-obese: < 30 kg/m², obese; ≥ 30 kg/m²) and estimated insulin resistance (insulin-sensitive: HOMA-IR < 2.5; insulin-resistant ≥ 2.5). At bottom the detailed figures of the number at risk for each sub groups of individuals.

NOb-IS indicates the non-obese insulin-sensitive subjects (the reference)
Ob-IS indicates obese insulin-sensitive
NOb-IR indicates the non-obese insulin-resistant subjects
Ob-IR indicates the obese insulin-resistant subjects
Prognosis of metabolically healthy subjects

Figure

![Survival graph showing follow-up months and number at risk for different groups: Non-obese insulin sensitive (708), Non-obese insulin resistant (637), Obese insulin sensitive (43), Obese insulin resistant (337).](image)