Prognostic implications for insulin-sensitive and insulin-resistant normal-weight and obese individuals from a population-based cohort1–3

Simona Bo, Giovanni Musso, Roberto Gambino, Paola Villois, Luigi Gentile, Marilena Durazzo, Paolo Cavallo-Perin, and Maurizio Cassader

ABSTRACT

Background: There are few prospective data on the prognosis of insulin-sensitive and insulin-resistant normal-weight (NW) or obese individuals.

Objectives: The estimated liver fat content, incidences of hyperglycemia and cardiovascular disease, and all-cause and cardiovascular mortality rates were investigated in a population-based cohort of 1658 individuals who were categorized according to BMI and insulin resistance as defined by HOMA-IR values ≥2.5 and the presence of metabolic syndrome.

Design: This was a prospective cohort study with a 9-y follow-up. Anthropometric values, blood pressure, and blood metabolic variables were measured, and information on vital status was collected from demographic files at follow-up.

Results: A total of 137 of 677 NW individuals (20%) were classified as insulin resistant and normal weight (IR-NW), and 72 of 330 obese individuals (22%) were classified as insulin sensitive and obese (IS-obese). Incidences of diabetes, impaired fasting glucose, and cardiovascular events were 0.4%, 6.3%, and 3.3%, respectively, in insulin-sensitive and normal-weight (IS-NW) individuals (reference category); 5.8%, 10.2%, and 6.6%, respectively, in IR-NW individuals; and 5.6%, 8.3%, and 8.3%, respectively, in IS-obese individuals. In a multiple logistic regression model, risks of incident hyperglycemia and cardiovascular events increased in both groups compared with in the reference category [HR (95% CI): 2.54 (1.42, 4.55) and 1.98 (0.86, 4.54) in IR-NW subjects; 2.16 (1.01, 4.63) and 2.76 (1.05, 7.28) in IS-obese subjects]. The estimated liver fat content significantly increased during follow-up only in the IR-NW group in the same model. Cardiovascular mortality was 2–3-fold higher in IR-NW and IS-obese than in IS-NW individuals in a Cox regression model.

Conclusions: Our data refute the existence of healthy obese phenotypes because IS-obese individuals showed increased cardiometabolic risk. The existence of unhealthy NW phenotypes is supported by their increased risk of incident hyperglycemia, fatty liver, cardiovascular events, and death. Am J Clin Nutr 2012;96:962–9.

INTRODUCTION

It is well known that not all obese individuals exhibit a cluster of metabolic and cardiovascular risk factors, and not all individuals with normal weight (NW)4 have a healthy metabolic and disease-free profile (1). On this basis, 2 categories of metabolically healthy obese (2) and metabolically obese NW subjects have been recently proposed (3). The former group exhibit BMI (in kg/m²) >30 but less frequently display obesity-related metabolic abnormalities and are relatively insulin sensitive (IS) (1, 2, 4). The latter group, despite having NW and normal BMI, show a cluster of metabolic disturbances, which are defined as metabolic syndrome, that are typical of obese individuals, including central adiposity, low concentrations of HDL cholesterol, hypertriglyceridemia, hyperglycemia, and hypertension (3–6), and these individuals are insulin resistant (IR). The prevalence of these categories of individuals varies greatly depending on the definition used (7).

Both insulin-resistant and normal-weight (IR-NW) and insulin-sensitive and obese (IS-obese) individuals have been described and cross-sectionally characterized at metabolic, behavioral, and lifestyle levels (1–4), but few studies have prospectively evaluated the prognosis of these individuals (5, 8–11). Conversely, the favorable outcomes of IS-obese patients are currently debated because not all studies confirmed the benign prognosis of this phenotype, which suggests that either body weight per se (8, 9, 12) or the insulin resistance associated with obesity (5, 10, 11, 13) is the most important determinant of the metabolic and cardiovascular consequences of obesity.

Nonalcoholic fatty liver disease (NAFLD), which is an excessive accumulation of fat in the liver, is a condition closely associated with insulin resistance and obesity and has a high prevalence in the general population and can be easily predicted with noninvasive tools (14). Two cross-sectional studies have examined the estimated liver fat percentage (15) and ectopic fat percentage in the liver by using magnetic resonance imaging (16) in insulin resistant and obese (IR-obese) and IS-obese individuals.

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4 Abbreviations used: ALT, alanine aminotransferase; CRP, C-reactive protein; GGT, γ-glutamyl transferase; ICD, International Classification of Diseases; IFG, impaired fasting glucose; IR, insulin resistant; IR-NW, insulin resistant and normal weight; IR-obese, insulin resistant and obese; IS, insulin sensitive; IS-NW, insulin sensitive and normal weight; IS-obese, insulin sensitive and obese; NAFLD, nonalcoholic fatty liver disease; NW, normal weight.

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and have shown lower liver fat percentages in the IS-obese patients.

The aims of the present study were as follows: 1) to evaluate in a population-based cohort of middle-aged individuals the prevalence of IS-obese and IR-obese overweight and NW individuals and the corresponding clinical correlates; 2) to prospectively analyze the incidence of hyperglycemia and cardiovascular disease, the estimated liver fat content, and the cardiovascular risk score in each group; and 3) to investigate all-cause and cardiovascular mortality in each group.

SUBJECTS AND METHODS

White patients (n = 1877), aged 45–64 y, of 6 family physicians were invited to participate in a metabolic screening in 2001–2003. These subjects were representative of the Local Health Units of the province of Asti (Northwestern Italy) (17). Of these individuals, 1658 subjects (88.3%) provided written informed consent to participate in the study, and 219 patients declined. Both participants and nonparticipants were similar to the resident population of a corresponding age range with respect to the percentage of men, level of education, prevalence of known diabetes, and residence in a rural area (17). The study was approved by the local ethics committee. All procedures conformed to the principles of the Helsinki Declaration.

Methods

In the morning and after fasting, weight, height, waist circumference, and blood pressure were measured, and glucose, insulin, total cholesterol, HDL-cholesterol, triglycerides, alanine aminotransferase (ALT), γ-glutamyl transferase (GGT), uric acid, and high-sensitivity C-reactive protein (CRP) concentrations were determined. If the serum glucose concentration was ≥6.1 mmol/L, a second fasting glucose determination was performed. Two blood pressure measurements were performed by using mercury sphygmomanometers and the appropriate cuff sizes after a 10-min rest in the sitting position, and the value reported was the mean of the 2 measurements. Waist circumference was measured by using a plastic tape meter at the level of the umbilicus.

Patients completed the Minnesota Leisure Time Physical Activity questionnaire (18) and the semiquantitative food-frequency questionnaire used in the European Prospective Investigation into Cancer and Nutrition studies (19). Each nutrient was adjusted for total energy by using the residual method (20). The physical activity level was calculated as the product of the estimated of the metabolic equivalent of the activity, and summed across the activities performed.

From January to November 2011, patients were submitted to a follow-up visit. Deaths occurred in 188 of 1658 subjects (11.3%) during follow-up. Information on the vital status of each patient and the causes of death of patients who died was collected from the demographic files of the towns of residence or death.

The laboratory methods have been described previously (17, 21). All samples were run blindly.

Definitions

The presence of insulin resistance and metabolic syndrome was considered for categorizing IR and IS individuals in line with other population-based studies (5, 8, 10, 22–24). The HOMA-IR (25) was used to estimate insulin resistance, and a cutoff of 2.5 mmol · L⁻¹ · μU⁻¹ · mL⁻¹ was chosen according to recently published studies (8, 10) and because this value approximated the upper quartile of HOMA-IR values in our population-based cohort (ie, 2.4 mmol · L⁻¹ · μU⁻¹ · mL⁻¹).

Hyperglycemia included both diabetes and impaired fasting glucose (IFG), which were defined according to published recommendations (26).

Metabolic syndrome was defined, in line with the Harmonization definition, by the presence of 3 of the following 5 components: waist circumference ≥94 cm (men) or ≥80 cm (women), triglyceride concentration ≥1.7 mmol/L, HDL-cholesterol concentration <1.0 mmol/L (men) or <1.3 mmol/L (women), systolic blood pressure ≥130 mm Hg and/or diastolic blood pressure ≥85 mm Hg and/or antihypertensive drug therapy, and fasting glucose concentration ≥5.6 mmol/L or hypoglycemic therapy (6).

The cardiovascular risk score was estimated by using the Framingham risk score (27). NAFLD was estimated by using the NAFLD liver fat score (14).

The diagnosis of cardiovascular disease was based on documented events that were recorded by the family physician (ie, angina, previous myocardial infarction, a coronary artery bypass graft or other invasive procedure to treat coronary artery disease, a transient ischemic attack, stroke, gangrene, amputation, vascular surgery, intermittent claudication, absent foot pulses and abnormal brachial and posterior tibial blood pressure by using Doppler techniques, and heart failure that required pharmacologic treatment or hospital admission).

The underlying cause of death was available for all deceased patients and was derived from the death certificate and coded according to the International Classification of Diseases (ICD), Ninth Revision. Cancer deaths corresponded to ICD codes 140–239, and deaths that were due to cardiovascular diseases corresponded to ICD codes 410–414 (coronary artery diseases), 430–438 (strokes), 440 (peripheral artery diseases), and others between 390–459 and 798.1 (other cardiovascular diseases).

Statistical analyses

With consideration of a type I error of 0.05 and type II error of 0.90, a minimum of 550 NW subjects needed to be enrolled to detect a significant difference in incident hyperglycemia between IS and IR individuals. Because distributions of alcohol intake, NAFLD score, cardiovascular risk score, triglyceride, fasting insulin, HOMA-IR, ALT, GGT, and CRP values were highly skewed, their values were log transformed to obtain a normal distribution. In all analyses, log-transformed values were used. For easy interpretation, untransformed values are reported in Tables 1–5.

A Student’s t test and a chi-square-test were performed to assess differences in continuous and categorical variables, respectively, by comparing IS with IR individuals in each BMI category.
A 2-factor ANOVA for continuous variables and a logistic regression model for dichotomous variables were performed, with insulin status (IR or IS) and BMI classes (<25, 25–30, and >30) as the 2 factors; one model for each variable, which was considered a dependent variable, and insulin status and BMI classes were the 2 factors. One model for each variable was performed.

A multiple logistic regression analysis was used to estimate the odds of incident hyperglycemia and incident cardiovascular disease according to BMI phenotypes after adjustment for age, sex, fiber intake, exercise level, smoking habits, cardiovascular risk score, and waist-circumference values. A multiple regression analysis was performed to assess the association between BMI phenotypes and variations from baseline to follow-up (values at follow-up minus values at baseline) in the estimated liver fat content and cardiovascular risk score after adjustment for age, sex, fiber intake, exercise level, and waist-circumference values. Multivariate Cox proportional hazards models were performed to estimate the probability of dying as a result of any cause and because of cardiovascular diseases by BMI phenotypes after adjustment for age, sex smoking habits, cardiovascular risk score, and waist circumference. Adjusted HRs and 95% CIs are presented. In all analyses, IS individuals with normal BMIs were considered the reference group, and the other groups were introduced as dummy variables (STATISTICA software 5.1; Statsoft Italia).

RESULTS

Baseline clinical, nutritional, and laboratory characteristics of subjects by BMI class and insulin sensitivity are shown in Tables 1 and 2. As expected, IR individuals within each group exhibited higher insulin and HOMA-IR values than did corresponding IS individuals (Table 2). IR individuals also displayed higher waist circumference and systolic blood pressure values; a worse metabolic pattern; increased uric acid, ALT, GGT concentrations; and significantly higher NAFLD and cardiovascular risk scores (Table 2).

After a mean follow-up time of 9 y, few NW subjects [5 of 677 subjects (0.7%)] developed obesity, and almost all them were IR individuals, whereas 105 of 651 overweight individuals (16.1%) developed obesity (Table 3). New cases of diabetes and IFG were as follows: 1.5% and 7.1%, respectively, in the NW group; 4.8% and 10.0%, respectively, in the overweight group; and 9.4% and 13.3%, respectively, in obese individuals (P-trend < 0.001 for diabetes and P = 0.001 for IFG). BMI classes and insulin status were significantly associated with incident hyperglycemia (Table 3). In a logistic regression model after adjustment for multiple confounders, incident hyperglycemia occurred more frequently in each group, with the exception of IS-overweight individuals (either IR or IS) than in the reference group (Table 4).

Incident cardiovascular events occurred in 4.0% of NW individuals (27 of 677 subjects), 5.7% of overweight individuals (37 of 651 subjects), and 8.5% of obese individuals (28 of 330 subjects) (P-trend = 0.004), and differences in the incidence of events between IR and IS subjects progressively reduced with increasing BMI (Table 3). In a logistic regression model, risk of incident cardiovascular events was >2-fold higher in obese individuals (either IR or IS) than in the reference group (Table 4).

Increments from baseline to follow-up in the cardiovascular risk score were significantly higher in all groups compared with the reference category in a multiple regression model (Table 4). The NAFLD score significantly increased in only the group of IS-normal weight (IS-NW) group (reference category) (Table 4).

During the 9-y observation period, 188 deaths occurred, and 81 deaths were due to cardiovascular diseases. The all-cause mortality and cardiovascular mortality rates increased with
increasing BMI as follows 6.2% and 2.4%, respectively, in the NW group; 11.1% and 4.5%, respectively, in the overweight group; and 22.4% and 10.9%, respectively, in the obese group (Table 5). In a Cox proportional hazard model that was adjusted for age, sex, smoking habits, cardiovascular risk score, and waist-circumference values, all-cause mortality and cardiovascular mortality were not significantly associated with overweight status or obesity [HR (95% CI): 1.20 (0.83, 1.57) and 1.12 (0.53, 1.70), respectively, in overweight individuals and 1.25 (0.80, 1.70) and 1.20 (0.53, 1.87), respectively, in obese patients).

The all-cause mortality and cardiovascular mortality rates tended to be higher in all categories of patients, except in the IS-

### TABLE 2
Baseline anthropometric and laboratory variables by BMI and insulin sensitivity

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>&lt;25</th>
<th>25–30</th>
<th>&gt;30</th>
<th>Insulin status</th>
<th>BMI classes</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>540</td>
<td>137</td>
<td>289</td>
<td>362</td>
<td>72</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>80.3 ± 9.1</td>
<td>87.6 ± 8.2</td>
<td>90.8 ± 7.7</td>
<td>95.9 ± 7.7</td>
<td>103.6 ± 11.0</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>126.8 ± 14.6</td>
<td>136.3 ± 13.6</td>
<td>134.1 ± 14.7</td>
<td>139.7 ± 16.5</td>
<td>138.4 ± 14.6</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>79.3 ± 8.3</td>
<td>83.8 ± 7.9</td>
<td>81.7 ± 8.0</td>
<td>86.3 ± 9.1</td>
<td>85.7 ± 10.1</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.2 ± 0.6</td>
<td>6.1 ± 1.7</td>
<td>5.3 ± 0.6</td>
<td>6.6 ± 2.5</td>
<td>5.2 ± 0.4</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.2 ± 0.6</td>
<td>1.9 ± 1.9</td>
<td>1.3 ± 0.5</td>
<td>2.0 ± 1.1</td>
<td>1.3 ± 0.7</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.7 ± 0.4</td>
<td>1.5 ± 0.3</td>
<td>1.6 ± 0.3</td>
<td>1.4 ± 0.3</td>
<td>1.6 ± 0.4</td>
</tr>
<tr>
<td>Fasting insulin (pmol/L)</td>
<td>39.3 ± 5.4</td>
<td>62.2 ± 44.9</td>
<td>41.2 ± 6.8</td>
<td>57.9 ± 24.9</td>
<td>46.1 ± 8.6</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>1.6 ± 4.6</td>
<td>3.1 ± 6.9</td>
<td>2.0 ± 3.1</td>
<td>3.3 ± 7.8</td>
<td>3.7 ± 6.1</td>
</tr>
<tr>
<td>Metabolic syndrome (%)</td>
<td>0</td>
<td>73.7</td>
<td>1.6 ± 0.3</td>
<td>2.9 ± 2.1</td>
<td>1.8 ± 0.3</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>0.6</td>
<td>7.4</td>
<td>0.4</td>
<td>11.6</td>
<td>1.4</td>
</tr>
<tr>
<td>IFG (%)</td>
<td>6.1</td>
<td>23.4</td>
<td>5.2</td>
<td>26.2</td>
<td>4.2</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>2.8</td>
<td>6.6</td>
<td>4.5</td>
<td>6.6</td>
<td>5.6</td>
</tr>
<tr>
<td>NAFLD score</td>
<td>−3.3 ± 1.0</td>
<td>−1.6 ± 1.4</td>
<td>−3.0 ± 0.6</td>
<td>−1.4 ± 1.3</td>
<td>−3.0 ± 0.6</td>
</tr>
<tr>
<td>Cardiovascular risk score</td>
<td>8.6 ± 5.1</td>
<td>13.9 ± 8.7</td>
<td>9.2 ± 5.5</td>
<td>14.0 ± 8.9</td>
<td>10.5 ± 5.2</td>
</tr>
</tbody>
</table>

1 P values for insulin status (insulin resistant and insulin sensitive) and BMI classes (<25, 25–30, and >30 kg/m²) were evaluated by using 2-factor ANOVA for continuous variables or logistic regression for dichotomous variables. Each variable listed was considered a dependent variable, and insulin status and BMI classes were the 2 factors. One model for each variable was performed. ALT, alanine aminotransferase; BP, blood pressure; CRP, C-reactive protein; GGT, γ-glutamyl transferase; IFG, impaired fasting glucose; NAFLD, nonalcoholic fatty liver disease.

| Mean ± SD (all such values). |

1 2 4 P values were evaluated by using ANOVA or the chi-square test for comparison of insulin-resistant with insulin-sensitive individuals in each BMI category: *P < 0.01, **P < 0.05.

### TABLE 3
Metabolic outcomes, NAFLD score, and cardiovascular risk score at follow-up by BMI and insulin sensitivity

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>&lt;25</th>
<th>25–30</th>
<th>&gt;30</th>
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<tbody>
<tr>
<td>n</td>
<td>540</td>
<td>137</td>
<td>289</td>
<td>362</td>
<td>72</td>
</tr>
<tr>
<td>New obesity (%)</td>
<td>0.2</td>
<td>2.9</td>
<td>13.5</td>
<td>18.2</td>
<td>—</td>
</tr>
<tr>
<td>New diabetes (%)</td>
<td>0.4</td>
<td>5.8</td>
<td>2.1</td>
<td>6.9</td>
<td>5.6</td>
</tr>
<tr>
<td>New IFG (%)</td>
<td>6.3</td>
<td>10.2</td>
<td>7.6</td>
<td>11.9</td>
<td>8.3</td>
</tr>
<tr>
<td>New cardiovascular events (%)</td>
<td>3.3</td>
<td>6.6</td>
<td>4.2</td>
<td>6.9</td>
<td>8.3</td>
</tr>
<tr>
<td>2011 NAFLD score</td>
<td>−1.9 ± 0.8</td>
<td>0.2 ± 1.1</td>
<td>−1.7 ± 0.8</td>
<td>0.1 ± 1.2</td>
<td>−1.4 ± 0.9</td>
</tr>
<tr>
<td>2011 cardiovascular risk score</td>
<td>18.9 ± 10.9</td>
<td>28.7 ± 16.0</td>
<td>20.9 ± 12.5</td>
<td>28.0 ± 15.3</td>
<td>26.1 ± 12.5</td>
</tr>
</tbody>
</table>

1 P values for insulin status (insulin resistant and insulin sensitive) and BMI classes (<25, 25–30, and >30 kg/m²) were evaluated by using 2-factor ANOVA for continuous variables or logistic regression for dichotomous variables. Each variable listed was considered a dependent variable, and insulin status and BMI classes were the 2 factors. One model for each variable was performed. IFG, impaired fasting glucose; NAFLD, nonalcoholic fatty liver disease.

1 2 4 P values were evaluated by using ANOVA or the chi-square test for comparison of insulin-resistant with insulin-sensitive individuals in each BMI category: *P < 0.01, **P < 0.05.

| Mean ± SD (all such values). |
overweight group, compared with the reference category in a Cox regression model after adjustment for age, sex, and smoking habits. Associations were reduced after additional adjustments for the cardiovascular risk score and waist-circumference values (Table 5).

The data did not change significantly after adjustment for BMI changes, education level, alcohol intake, or CRP values. Similarly, the results did not change if we used other definitions of metabolic syndrome (such as the definitions of the National Cholesterol Education Program–Adult Treatment Panel III and the International Diabetes Federation) (6).

DISCUSSION

Approximately one-fifth of NW adults from the population-based cohort were IR-NW and approximately one-fifth of obese individuals were IS-obese patients. IR-NW individuals showed an increased incidence of hyperglycemia, greater increments in liver fat estimates and cardiovascular scores, and an increased cardiovascular mortality after the 9-y follow-up. IS-obese individuals displayed a better metabolic profile than did corresponding IR-obese individuals but showed increased risk of incident hyperglycemia, cardiovascular disease, and cardiovascular mortality compared with the reference group, which thereby challenged the hypothesis that obesity without metabolic abnormalities is a benign condition. Overweight status conferred intermediate risk, which was increased by the presence of insulin resistance or metabolic syndrome.

Prevalence of BMI phenotypes

IR-NW and IS-obese individuals constituted 20.2% of NW patients and 21.8% of obese patients and 8.3% and 4.3% of the entire cohort, respectively. The prevalence of these 2 groups widely varied in previous studies and ranged from ~3% to 30% in IR-NW patients (1,3,5,9,15,28) and from ~2% to 40% in IS-obese patients (2,8,10,15,16,28–30), depending on the different criteria adopted and on age, sex, and anthropometric differences of studied populations. Our data confirmed that these phenotypes represent a nonnegligible proportion of the general population and are worthy of being subjected to preventive and therapeutic interventions.

TABLE 5

Outcomes at follow-up by BMI and insulin sensitivity at baseline in a multiple regression model

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>&lt;25</th>
<th>25–30</th>
<th>&gt;30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin sensitive</td>
<td>Insulin resistant</td>
<td>Insulin sensitive</td>
<td>Insulin resistant</td>
</tr>
<tr>
<td>Incident hyperglycemia</td>
<td>Reference category 2.54 (1.42, 4.55)</td>
<td>1.39 (0.82, 2.37)</td>
<td>2.48 (1.57, 3.91)</td>
</tr>
<tr>
<td>Incident cardiovascular disease</td>
<td>Reference category 1.98 (0.86, 4.54)</td>
<td>1.18 (0.56, 2.50)</td>
<td>1.77 (0.93, 3.37)</td>
</tr>
<tr>
<td>Change in cardiovascular risk score</td>
<td>Reference category 3.58 (2.01, 5.15)</td>
<td>1.41 (0.16, 2.66)</td>
<td>2.62 (1.33, 3.91)</td>
</tr>
<tr>
<td>Change in NAFLD score</td>
<td>Reference category 0.42 (0.07, 0.77)</td>
<td>−0.19 (-0.44, 0.06)</td>
<td>−0.07 (-0.31, 0.17)</td>
</tr>
</tbody>
</table>

1 Values are HRs; 95% CIs in parentheses. Multiple regression model after adjustment for age, sex, fiber intake, exercise level, smoking habits, waist circumference, and cardiovascular risk score values.

2 Values are βs; 95% CIs in parentheses. Multiple regression model after adjustment for age, sex, fiber intake, exercise level, and waist-circumference values.

3 NAFLD, nonalcoholic fatty liver disease.

TABLE 4

Outcomes at follow-up by BMI and insulin sensitivity at baseline in a multiple regression model

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>&lt;25</th>
<th>25–30</th>
<th>&gt;30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin sensitive</td>
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<td>Insulin sensitive</td>
<td>Insulin resistant</td>
</tr>
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1 Values are HRs; 95% CIs in parentheses. Multiple logistic regression model after adjustment for age, sex, fiber intake, exercise level, smoking habits, waist circumference, and cardiovascular risk score values.

2 Values are βs; 95% CIs in parentheses. Multiple regression model after adjustment for age, sex, fiber intake, exercise level, and waist-circumference values.

3 NAFLD, nonalcoholic fatty liver disease.
Incidence of hyperglycemia

With the exception of the IS-overweight group, all other categories showed a higher risk of incident hyperglycemia than the reference group. Even when individuals were IS, obese subjects showed an ~2-fold higher metabolic risk. This finding is in line with literature and guidelines (5, 30, 31) that have suggested that obesity is diabetogenic regardless of insulin resistance.

Our IR-NW individuals showed ~2-fold higher risk of incident diabetes compared with that of corresponding NW individuals, which was consistent with previous data (5). IR-NW subjects were described as having higher visceral fat mass, lower fat-free mass, and reduced insulin sensitivity (3, 4). Our IR-NW individuals showed a significantly higher waist circumference and a worse metabolic profile both at baseline and at follow-up. Our data highlight the limitations of BMI as a metabolic predictor because BMI cannot discriminate fat from muscle and does not account for body fat distribution and suggest the need for a simple, inexpensive tool that can differentiate NW individuals who carry an increased metabolic risk.

Estimated liver fat

NAFLD patients experienced higher risk of incident diabetes, cardiovascular disease, and total mortality compared with that of the general population (32). Obesity is a strong risk factor for NAFLD in the general population of northern Italy (33), and only a few studies have evaluated whether IS-obese patients are at increased risk of developing NAFLD (15, 16, 34). The IS-obese group showed a lower percentage of liver fat compared with that of IR-obese patients (16) or IR-NW individuals (15) but a higher percentage compared with that of IS-NW individuals (34). It is intriguing that the change in the NAFLD score was significantly higher in our IR-NW subjects only. It is possible that the liver is the primary site of ectopic fat accumulation in the absence of obesity, which would drive increased cardiometabolic risk in IR-NW subjects. With increasing adiposity, factors other than liver fat might contribute to increased risk.

Cardiovascular risk and mortality

With regard to cardiovascular risk, the existence of a healthy subtype of obesity is a highly debated topic (5, 8–11, 35). IS-obese individuals were reported to show reduced risk of cardiovascular disease and all-cause and cardiovascular mortality (5, 10, 11) or a similar risk of cardiovascular events (8, 9, 36) to that of corresponding IR-obese individuals. Attempts to disentangle the effects of obesity from those of its strongly associated conditions seem less useful. Furthermore, differences between studies may depend on the reference category used. For example, when IS-obese individuals were compared with IR-obese patients (5, 36), IR-NW individuals (15, 37), and IS-NW individuals (9, 30), lower, comparable, and increased cardiovascular risks, respectively, were shown. We showed a significant increase in the cardiovascular risk score and cardiovascular mortality in all groups except in IS-overweight subjects and an increased incidence of cardiovascular events in both IS-obese and IR-obese individuals. Accordingly, the apparently healthy obese subjects have been shown to exhibit subclinical vascular diseases (12, 38). IS-obese patients probably underwent adverse changes associated with obesity over time with a delayed onset of cardiovascular events; therefore, a longer follow-up is required to document adverse events, and the potential clinical benefits of diagnosing IS-obesity might be limited (9, 12). The increased cardiovascular risk we showed in our IR-NW individuals is in line with the results of most studies (1, 3, 11) and suggests the need for early identification, follow-up monitoring, and preventive approaches (ie, increased exercise and a balanced diet) for these individuals who are less likely to be submitted to lifestyle recommendations because of their normal BMI.

All-cause mortality

Death rates were higher in obese individuals in our study, regardless of whether they were IR or IS, whereas the IR-NW individuals and IR-overweight subjects showed intermediate risk. The associations were reduced after adjustment for the cardiovascular risk score. Data on mortality are sparse and discordant (8–10): IS-obese individuals did not show increased all-cause mortality in an Italian study (10), but in this cohort, IS-obese individuals showed significantly lower waist-circumference values than IS-obese individuals in the current study (94 compared with 104 cm). Other prospective studies have shown an association between IS-obesity and increased mortality (8, 9). This finding is in accordance with guidelines that recommend that all obese subjects are at risk and should be treated (31).

Pathogenetic considerations

The following effects have been reported as putative contributors to insulin resistance in NW subjects: reduced physical activity, lower peak oxygen uptake, less dietary restraint (4, 39), increased accumulation of visceral adipose tissue (2, 16, 39, 40), low fiber intake (41), high concentrations of free fatty acids and oxidized LDL (41, 42), impaired compensatory insulin secretion (42), altered proinflammatory and antiinflammatory cytokine action (41, 43–45), increased oxidative stress (46, 47), and reduced insulin-like growth factor I values (48). In particular, increased visceral fat has been associated with a higher free fatty acid flux to the liver, steatosis, and hepatic insulin resistance (40). Increased plasma proinflammatory cytokine values may result from the larger visceral fat mass (41, 43). Note that even IS-obese individuals have been reported to display increased concentrations of inflammatory markers compared with those of IS-NW individuals (44), which has provided a pathogenetic basis for our results in IS-obese subjects.

Limitations and strengths

Our study may have been underpowered to detect differences in the incidence of cardiovascular events or mortality in the groups compared. Despite the low number of events, risk of cardiovascular deaths was significantly higher in the IR-NW group than in corresponding IS-NW individuals, in line with literature (9). The definition of IR-NW was arbitrary; nevertheless, this classification effectively discriminated future risks in our cohort. Finally, the HOMA-IR index is not the best method to evaluate insulin sensitivity because it is strongly dependent on the precision of the insulin assay; however, it has been validated and proposed for large epidemiologic studies (49). The strengths of this study included its population-based nature, the duration and
completeness of the follow-up, and the centralized measurements performed.

In conclusion, the commonly used term healthy obesity is misleading because healthy obese individuals are probably on their way to becoming unhealthy individuals. Therefore, the clinical usefulness of stratifying obese individuals into subgroups of risk seems questionable. Otherwise, NW individuals are a highly heterogeneous category in terms of their cardiometabolic prognosis, and an accurate but simple tool to stratify risk for these individuals is warranted.

The authors’ responsibilities were as follows—SB: conception and design of the study, supervision of data collection, data analysis, interpretation of study findings, and manuscript writing and revision; GM: data analysis, interpretation of study findings, and manuscript writing and revision; RG: data analysis, interpretation of study findings, and manuscript writing and revision; PV and LG: data collection, interpretation of study findings, and manuscript revision; MD and PC-P: interpretation of study findings and manuscript writing and revision; and MC: conception and design of the study, interpretation of study findings, and manuscript writing and revision. All authors read and approved the final manuscript. None of the authors had a conflict of interest.

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