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Normal weight obese (NWO) women: An evaluation of a candidate new syndrome

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Abstract *Background and aims:* Obesity, an independent risk factor for cardiovascular disease (CVD), has been associated with the early development of coronary atherosclerosis in adolescents and young men. A subset of metabolically obese but normal weight individuals was identified, with potentially increased risks for development of the metabolic syndrome despite their normal body mass index. We determined the relationship among body fat distribution and selected CVD risk factors to distinguish normal weight obese from controls with normal metabolic profiles.
Methods and results: We analysed anthropometric variables, body composition by DXA, RMR by indirect calorimetry and bioumoral variables of 74 clinically healthy Caucasian Italian women. Significant differences were observed in the biochemical HDL-chol values between NWO and controls and pre-obese-obese. Significant correlations were found among cardiovascular risk indexes, LEAN of the right part of the trunk and TC/HDL ($R = -0.69$, $p < 0.001$) and LDL/HDL ($R = -0.72$, $p < 0.001$), and LEAN and RMR ($R = 0.44$, $p = 0.022$) of NWO women.
Conclusions: In normal weight obese women the cardiovascular risk indexes are related to metabolic variables and to body fat mass distribution. NWO individuals showed a relationship between the decrease in LEAN of the left leg and an increase in CVD risk factors. We suggest that LEAN distribution seems to be a potential predictor of CVD.

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Introduction

Obesity, an independent risk factor for cardiovascular disease [1], has been recently associated with the early development of coronary atherosclerosis in adolescents and young adult men [2]. The World Health Organization (WHO) defines obesity as an excessive accumulation of fat to an extent that health may be impaired [3]. Assessment of overweight and obesity includes the examination of body mass component distribution and risk factors for diseases, such as: type 2 diabetes, dyslipidaemia, impaired glucose tolerance and cardiovascular diseases (CVD). It has been reported that the risk of coronary artery disease increases with the severity of obesity, especially abdominal, when the waist to hip ratio (WHR) is >0.90 in males and >0.85 in females [4,5]. However, as shown by Busetto et al. [6], WHR cannot be considered an index of visceral/subcutaneous fat distribution in obese patients, especially in obese women. In any case, according to Lakka et al. a waist circumference in men >0.93 m is associated with an increase in carotid artery thickness, indicating that obesity is associated with an accelerated progression of atherosclerosis [7]. The distribution of body fat is as important as that of lipid and glucose values in predicting mortality and morbidity from cardiovascular diseases, including coronary heart disease (CHD). An increase in total body fat mass results in a higher increase in visceral adipose tissue (VAT) relative to total body fat, regardless of race and age; although African-American women maintain lower VAT levels across time [8]. Central obesity is a major contributor to the development of metabolic syndrome (MS), which has been defined as the cluster of cardiovascular disease risk factors such as dyslipidaemia, hypertension, glucose intolerance and hyperinsulinaemia [9]. In 2001, the National Cholesterol Education Program (NCEP) defined the criteria to diagnose MS [10]. Three or more of the following risk components are necessary: (1) waist circumference greater than 1.02 m for men and 0.88 m for women; (2) triglyceride (TG) levels of 150 mg/dl or more; (3) high density lipoprotein cholesterol (HDL-chol) levels less than 40 mg/dl for men and less than 50 mg/dl for women; (4) blood pressure of 130/85 mmHg or higher; (5) fasting glucose levels of 110 mg/dl or more. In addition, several studies have shown that high cholesterol levels (greater than 200 mg/dl) contribute to a high risk of both cardiovascular diseases and mortality [10]. To date, three subtypes of obese individuals have been individualized: ''at risk'' of obesity with metabolic syndrome (MS), metabolically healthy but obese individuals (MHO), metabolically obese normal weight (MONW) individuals [11,12]. MONW individuals, first described and re-examined by Ruderman [13–15] represent a subset of individuals who have normal weight and body mass index (BMI) of 18–25 kg/m^2, but display a cluster of metabolic characteristics that may increase the development of metabolic syndrome. MONW individuals are not obese but characterized by an excess of visceral fat [16]. Interestingly, they are a group where genetic factors predispose to insulin resistance, dyslipidaemia, hypertension and cardiovascular diseases, as noted in syndrome X [17,18]. Differences in body fat and fat mass (FM) distribution could play a role in CVD risk factors.

The purpose of our study was to define an early metabolic profile, and to evaluate the relationships between lean body mass and fat body mass distribution, resting metabolic rate (RMR) and selected lipid indexes associated with increased CVD in women with normal weight obese (NWO) syndrome, in comparison with controls and pre-obese-obese women. Using the criteria proposed in published data [19,20,21], we identified the best simple lipid indexes that are associated with increased cardiovascular diseases and mortality [22,23].

Therefore, we attempted to define early indicators of disease as significant prognostic parameters for CVD and metabolic syndrome risks.

Methods

Participants

This study comprised 74 Caucasian Italian women, subdivided into three groups: 28 NWO individuals ($BMI = 22.94 \pm 1.38\ kg/m^2$ and FM percentage, $FM\% = 38.80 \pm 6.1$), 26 age-matched pre-obese-obese individuals ($BMI = 30.10 \pm 5.75\ kg/m^2$ and $FM\% = 52.95 \pm 5.01$) and 20 control age-matched women ($BMI = 20.33 \pm 1.96\ kg/m^2$ and $FM\% = 20.01 \pm 4.33$). None of the individuals had either impaired glucose tolerance and diabetes or clinical history of CVD. No individuals were taking any medication. Participants were randomly selected among about 3000 participants to the studies on body composition and energy metabolism at the Unit of Human Nutrition of the Tor Vergata University (Rome, Italy).

Informed consent was obtained from all the participants before the beginning of the study, according to Medical Ethics Committee Guidelines of the University.

Anthropometric measurements

We measured anthropometric variables in all participants according to standard methods [24]. Individuals were instructed to remove their shoes and undress before any measurements were taken. Body weight (kg) was measured to the nearest 0.01 kg, using a balance scale (Invernizzi, Rome, Italy). Height (m) was measured using a stadiometre to the nearest 0.01 m (Invernizzi, Rome, Italy). Two circumferences (waist and hip) were measured to the nearest 0.01 m using a flexible steel metric tape. Abdominal circumference was defined as the horizontal distance around the abdomen at the umbilicus. Hip circumference (*H*) was measured as the distance passing horizontally through the two superior iliac bones. Body mass index (BMI) was calculated using the formula (kg)/height (m^2).

Dual X-ray absorptiometry (DXA)

Total body composition was assessed by dual-energy X-ray absorptiometry (DXA) (Lunar DPX). This technique combines a total body scanner, an X-ray source, an internal wheel to calibrate the bone mineral compartment, and an external lucite/aluminium phantom to calibrate the fat compartment. Standard DXA quality control and calibration measures were performed prior to each testing session. Individuals were required to remove all clothing including shoes, socks and jewels except undergarments, prior to being positioned on the DXA table. Scans were performed with individuals in a supine position. The entire body was scanned beginning from the top of the head and moving in a rectilinear pattern. Mean measurement time was 15 min. Radiation exposure was <0.8 mSv.

Resting metabolic rate (RMR) measurement

Resting metabolic rate (RMR) was measured by indirect calorimetry after a 12 h fast. The volumes of both oxygen (VO_2) and carbon dioxide (VCO_2) were measured using a canopy system for 30 min (Sensormedic 2900, California, USA). The first 10 min were considered a period of acclimatisation, while the last 20 min were used for analysis. RMR was calculated from oxygen consumption and carbon dioxide production according to Weir's equation [25]:

$$\mathrm{RMR} = 1.44 \times [3.91 \times \mathrm{VO_2(ml)} + 1.106 \times \mathrm{VCO_2(ml)}]$$

Calculation of RMR was made using only data of individuals with seemingly steady-state conditions (i.e. VO_2 and VCO_2 did not vary more than 5% from the mean value of the 20 min measurement period).

Individuals were instructed to drink only water, not to consume alcohol, no proteins for 12 h before testing and refrain from smoking and engaging in physical activities for 24 h before testing. Prior to the RMR measurements, individuals were supine for 25–30 min in a quiet room. All tests were performed on individuals while in a supine position. Room temperature of the room was set at an average of 22 °C. For additional quality control two different certified oxygen/carbon dioxide gas mixtures (SIAD Ltd Co, Rome, Italy) were used.

Analysis of blood samples

Blood samples were put into EDTA-treated collection tubes via venipuncture early in the morning (07:00 ÷ 09:00 h) after an overnight fast (12 h). After centrifugation for 10 min at 4 °C, plasma samples were stored at −80 °C. Plasma was obtained by centrifugation at 1500 rpm for 10 min and analysed on the day of collection. Plasma total cholesterol (TC), high density lipoprotein-cholesterol (HDL-chol), low density lipoprotein-cholesterol (LDL-chol), and triglycerides (TG) concentrations were determined from standard enzymatic colorimetric techniques (Roche Modular P800, Roche Diagnostics, Indianapolis, IN). Plasma glucose concentrations were measured using the glucose oxidase method with automated glucose analyser (Cobas Integra 400, Roche Diagnostics, Indianapolis, IN). Analysis were done at the accredited Clinical Chemical Laboratories of the Vergata Tor Policlinic (VTP) of Rome, Italy.

Indexes

Leg index consisted of Leg Index = LEANLEGS (kg):legs FM (kg). CVD risk indexes consisted of TC/HDL-chol = total cholesterol (mg/dl):HDL-cholesterol (mg/dl), LDL/HDL-chol = LDL cholesterol (mg/dl):HDL-cholesterol (mg/dl), TG/HDL-chol = triglycerides (mg/ml):HDL-cholesterol (mg/dl).

Statistical analysis

Descriptive values are expressed as mean± standard deviation (SD). Multiple comparisons by post hoc Tukey and Bonferroni tests were made with one-way ANOVA. Linear regression and correlation were used to evaluate the relationships among variables. Discriminate analysis and Pearson's correlation were performed using the SPSS statistical package (SPSS Chicago, IL) [26]. A value of $p < 0.05$ was considered significant.

Results

Characteristics of the 74 Caucasian Italian women (16–54 years old) examined are shown in Table 1. The participants were classified as control or pre-obese-obese according to the National Cholesterol Education Program NCEP criteria [9]. BMI values for the entire group identified 48 women with a BMI $18 \div 25$ kg/m^2, and 26 pre-obese-obese women with BMI>25 kg/m^2 (30.1 ± 5.75 kg/m^2). In the former group NWO women were distinguished from control women on the basis of their FM distribution using DXA, adopting as criteria of classification the % of FM. The original women with BMI $<$ 25 kg/m^2 were subdivided into two subgroups: (a) 20 women with BMI $<$ 25 kg/m^2 (20.33 ± 1.96 kg/m^2) and FM $<$ 30% (20.01 ± 4.33%); (b) 28 NWO women with BMI $<$ 25 kg/m^2 (22.94 ± 1.38 kg/m^2), but FM $>$ 30% (38.8 ± 6.13%). The FM percentage of pre-obese-obese women was $>$30% (52.95 ± 5.01%). All the descriptive characteristics of body composition variables were compared between the three groups: women with and without NWO syndrome and pre-obese-obese women (Fig. 1). The means of age, weight, height, BMI, tissue body composition (Tissue), waist (*W*) and hip (*H*) circumferences and waist to hip ratio (*W*/*H*) were similar in both the NWO and controls. As expected, the percentage of FM (FM%) (52.95 ± 5.01%), BMI (30.10 ± 5.75 kg/m^2) were higher in the pre-obese-obese group when NWO and pre-obese-obese women were compared. Significant differences were seen comparing NWO vs pre-obese-obese women, control vs pre-obese-obese women for weight ($p < 0.001$), BMI ($p < 0.001$), FM ($p < 0.001$), FM% ($p < 0.001$), *W* ($p < 0.001$) and *H* ($p < 0.001$) circumferences, total mass of tissue ($p < 0.001$) values. Despite their BMI values, NWO women showed a high body fat mass percentage (38.80 ± 6.13%) associated with a reduction of the body lean mass (LEAN $= 35.22 \pm 2.93$ kg) compared with controls (LEAN $= 39.57 \pm 3.99$ kg) ($p = 0.017$ by Tukey test, $p = 0.019$ by Bonferroni test). NWO individuals showed significant ($p = 0.01$ by Tukey test, $p = 0.011$ by Bonferroni test) reductions of lean leg mass (LEANLEGS) (LEANLEGS $= 12.25 \pm 1.11$ kg), compared to controls (LEANLEGS $= 13.87 \pm 1.87$ kg); while no significant difference was observed comparing NWO with pre-obese-obese group (LEANLEGS $= 12.99 \pm 1.78$ kg) (Fig. 2). A significant difference ($p = 0.003$ by Tukey test, $p = 0.004$ by Bonferroni test) between the NWO left leg lean mass (LEANLEGL) value (LEANLEGL $= 6.08 \pm 0.54$ kg) and controls (LEANLEGL $= 6.97 \pm 0.90$ kg) was observed (Fig. 3). The NWO leg index (1.44 ± 0.27), the lean and fat mass of leg ratio (LEANLEGS/FM), is lower than controls (2.24 ± 0.34) and higher than pre-obese-obese (0.98 ± 0.23) values, with significant differences between the three groups ($p < 0.001$ by Tukey and Bonferroni tests). No significant difference in resting metabolic rate (RMR) values was

Table 1 Body composition parameters of NWO, controls and pre-obese-obese women (Pre ob-Ob)

Value	Controls ($n = 20$)		NWO ($n = 28$)		Pre-Ob-Ob ($n = 26$)		NWO vs controls (p)*	NWO vs Pre-Ob-Ob (p)*	Controls vs Pre-Ob-Ob (p)*
	Mean	SD	Mean	SD	Mean	SD			
Age (years)	27.23	6.03	32.95	11.89	33.26	10.38	NS	NS	NS
Weight (kg)	55.32	6.57	59.42	4.93	77.43	15.37	NS	<0.001	<0.001
Height (cm)	164.96	7.48	160.90	5.63	160.35	6.05	NS	NS	NS
BMI (kg/m^2)[a]	20.33	1.96	22.94	1.38	30.10	5.75	NS	<0.001	<0.001
FAT (kg)[a]	13.12	2.75	21.30	3.55	36.57	10.53	0.003	<0.001	<0.001
LEAN (kg)	39.57	3.99	35.22	2.93	37.80	6.06	0.017 (0.019)**	NS	NS
LEANLEGS (kg)	13.87	1.87	12.25	1.11	12.99	1.78	0.01 (0.011)**	NS	NS
LEANLEGL (kg)	6.97	0.90	6.08	0.54	6.48	0.88	0.003 (0.004)**	NS	NS
FAT (%)[a]	20.01	4.33	38.8	6.13	52.95	5.01	<0.001	<0.001	<0.001
TISSUE (kg)	52.68	6.25	56.52	4.73	74.38	15.37	NS	<0.001	<0.001
WAIST (cm)	67.92	4.37	72.15	4.82	87.56	14.23	NS	<0.001	<0.001
HIP (cm)	93.5	5.09	96.05	8.21	111.76	12.88	NS	<0.001	<0.001
W/*H*	0.72	0.05	0.76	0.09	0.78	0.06	NS	NS	NS

Differences between pairs of means by post hoc Tukey and Bonferroni tests. *p value paired with a post hoc Tukey and Bonferroni tests. **p value paired with Bonferroni adjustment. NS, not significant value; NWO, normal weight obese women; controls, control women; Pre-Ob-Ob, pre-obese-obese women; BMI, body mass index; FAT, fat body composition; LEAN, lean body composition; LEANLEGS, lean of the legs; LEANLEGL, lean of left leg; FAT%, fat percentage; TISSUE, tissue body composition; WAIST, circumference of waist; HIP, circumference of hip; *W*/*H*, ratio waist to hip.

[a] FAT%, BMI, FAT represented selection criteria for the NWO, controls and pre-obese-obese.

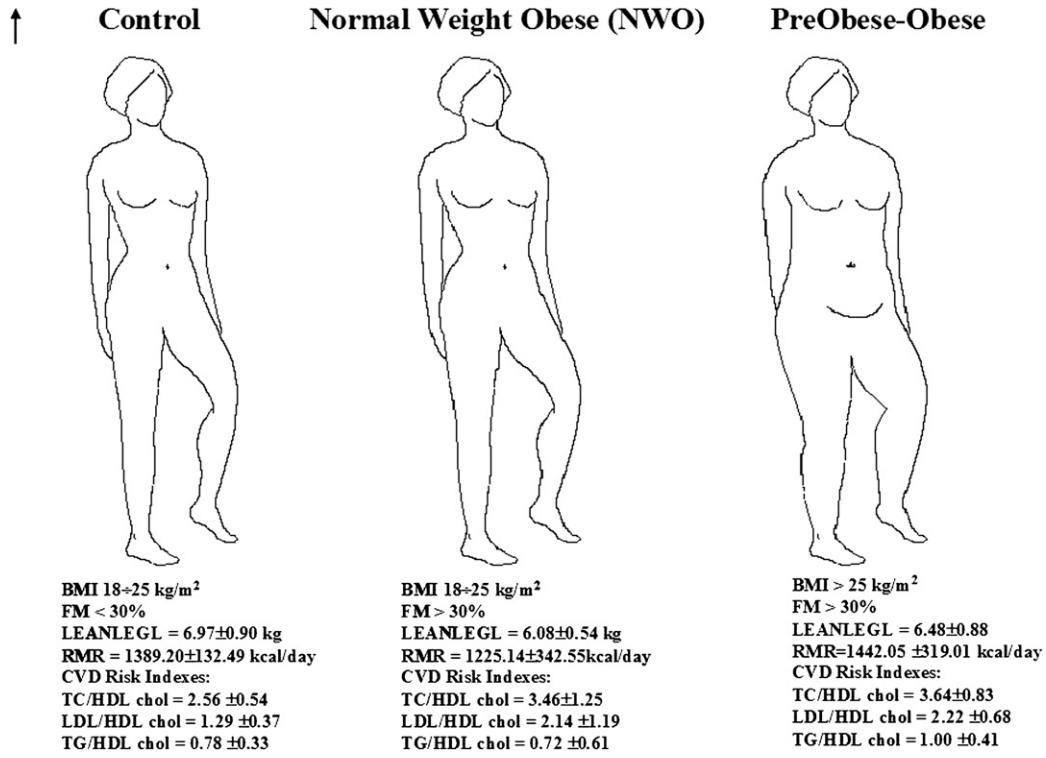

Figure 1 Different characteristics in normal, normal weight obese (NWO), and pre-obese-obese women. BMI, body mass index; FM, fat mass; LEANLEGL, lean of left leg; RMR, resting metabolic rate; CVD risk indexes, cardiovascular diseases risk indexes; TC, total cholesterol, HDL chol, high density lipoprotein cholesterol, LDL chol, low density lipoprotein, TG, triglycerides.

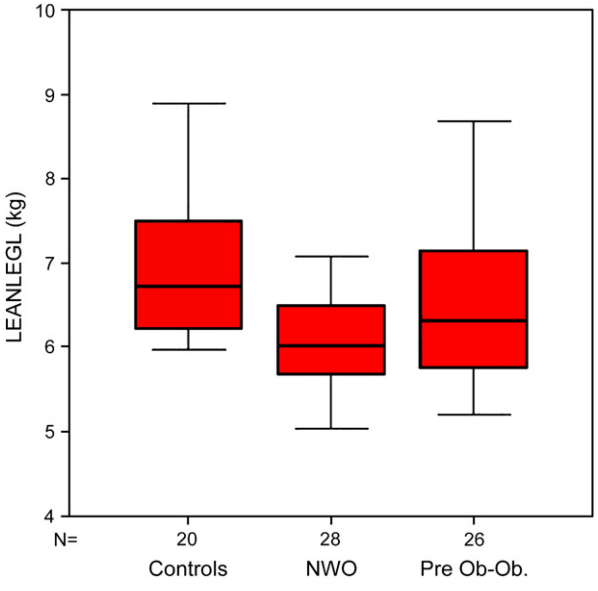

Figure 2 Differences of mean values, standard deviation (SD), standard error of LEANLEGL in controls, NWO, and pre-obese-obese (Pre-Ob-Ob) women. LEANLEGL, lean of left leg.

observed between NWO women (RMR = 1225.14 ± 342.55 kcal/day) and controls (RMR = 1389.2 ± 132.19 kcal/day). Significant difference ($p = 0.037$ by Tukey's test, $p = 0.043$ by Bonferroni test) was obtained comparing NWO RMR with pre-obese-obese RMR (RMR = 1442.05 ± 319.01 kcal/day). However, no significant differences were observed between controls and pre-obese-obese women RMR (Table 2). Linear regression analysis showed a significant relationship between RMR and LEANLEGL in all individuals ($R = 0.45$, $p < 0.001$) (Fig. 4). Serum fasting glucose levels were in the reference range in NWO (4.81 ± 0.42 mmol/l), controls (4.80 ± 0.57 mmol/l) and pre-obese-obese (4.92 ± 0.68 mmol/l) women (Table 3). Total cholesterol (TC) values of NWO women (4.90 ± 1.03 mmol/l) were not significantly different with respect to controls (5.18 ± 1.58 mmol/l) and pre-obese-obese women (5.10 ± 1.08 mmol/l). No significant differences were observed in triglyceride (TG) values of NWO women (1.24 ± 0.76 mmol/l) with respect to either controls (1.14 ± 0.41 mmol/l) or pre-obese-obese (1.37 ± 0.54 mmol/l) women. However, high density lipoprotein cholesterol (HDL-chol) levels were significantly different in NWO (1.92 ± 0.36 mmol/l) vs controls (1.57 ± 0.33 mmol/l) ($p = 0.006$), and in controls vs pre-obese-obese

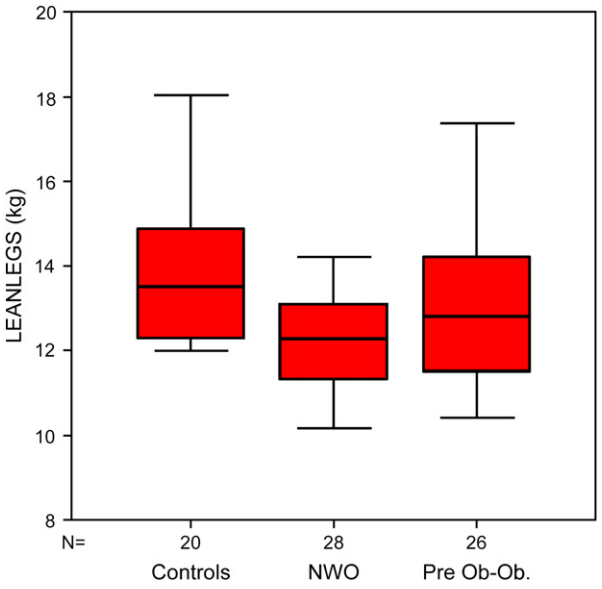

Figure 3 Differences of mean values, standard deviation (SD), standard error of LEANLEGS in NWO, controls and pre-obese-obese (Pre-Ob-Ob) women. Description of mean value, SD, standard error from LEANLEGS of NWO, normal and pre-obese-obese women. LEANLEGS, lean of legs.

women (1.40 ± 0.26 mmol/l) ($p < 0.001$), while no significant difference was observed between NWO and pre-obese-obese women. Also no significant difference was observed in low density lipoprotein cholesterol (LDL-chol) levels of NWO (2.48 ± 0.84 mmol/l), controls (3.18 ± 1.55 mmol/l), and pre-obese-obese women (3.03 ± 0.86 mmol/l). No significant differences were observed in triglyceride values of NWO (1.24 ± 0.76 mmol/l), controls (1.14 ± 0.41 mmol/l) and pre-obese-obese women (1.37 ± 0.54 mmol/l). Regarding CVD risk indexes, the TC/HDL-chol ratio of NWO (3.46 ± 1.25) was not significantly different than that of controls (2.56 ± 0.54) and pre-obese-obese women (3.64 ± 0.83). Significant difference was observed between this CVD risk index of controls vs pre-obese-obese women ($p = 0.020$ by Tukey test, $p = 0.022$ by Bonferroni test). A significant difference ($p = 0.041$ by Tukey test, $p = 0.047$ by Bonferroni test) was observed in the LDL/HDL-chol ratio of NWO vs controls, yet no significant difference between NWO and pre-obese-obese women emerged. A significant difference was observed between controls and pre-obese-obese women ($p = 0.028$ by Tukey test, $p = 0.032$ by Bonferroni test). The TG/HDL-chol CVD risk index was not significant for any group. To examine the possible relationships among CVD risk indexes and left leg lean mass of (LEANLEGL) in the three groups, Pearson correlation analysis was performed. As discussed later, some significant relations were obtained (Table 4). The LEANLEGL value of NWO individuals was significantly related to RMR ($R = 0.410$, $p = 0.046$) and hip circumference ($R = 0.40$, $p < 0.033$). Similar results were obtained for pre-obese-obese individuals, showing a significant relationship between LEANLEGL and oxygen consumption ($R = 0.59$, $p < 0.003$), carbon dioxide production ($R = 0.65$, $p < 0.001$), RMR ($R = 0.62$, $p < 0.002$), waist ($R = 0.580$, $p = 0.005$); and hip ($R = 0.6$, $p < 0.004$). No significant relations were observed in control individuals (Table 4). In NWO individuals inverse correlations were observed between the lean mass of the right part of the trunk (LEANTRUR) and TC/HDL-chol ($R = -0.69$, $p < 0.001$), and between LEANTRUR and LDL/HDL-chol ($R = -0.72$, $p < 0.001$). A significant inverse correlation was also observed between LDL/HDL-chol and LEANLEGL ($R = -0.34$, $p = 0.04$). In addition, we estimated the relationship between the TC/HDL-chol, and the LDL/HDL-chol CVD risk indexes and LEANLEGL. Linear regression ($R = -0.35$, $p = 0.007$) showed a strong inverse association between the TC/HDL-chol CVD risk index and LEANLEGL in all individuals (Fig. 5), as follows: TC/HDL-chol CVD risk index $= (-0.451 \times \text{LEANLEGL}) + 6.255$ (± 1.045).

Linear regression analysis also indicated a strong inverse association between the LDL/HDL-chol and

Table 2 Metabolic parameters of NWO, controls and pre-obese-obese women ('Pre-Ob-Ob)

Value	Controls ($n = 20$)		NWO ($n = 28$)		Pre-Ob-Ob ($n = 26$)		NWO vs Controls (p)*	NWO vs Pre-Ob-Ob (p)*	Controls vs Pre-Ob-Ob (p)*
	Mean	SD	Mean	SD	Mean	SD			
RMR (kcal/day)	1389.20	132.19	1225.14	342.55	1442.05	319.01	NS	0.037 (0.043)**	NS
VO_2 (ml)	193.15	19.44	173.96	48.96	205.26	46.59	NS	0.037 (0.043)**	NS
VCO_2 (ml)	184	24.89	149.37	43.55	174.04	40.50	0.03 (0.034)**	NS	NS
RQ	0.96	0.12	0.87	0.15	0.85	0.13	NS	NS	NS

Differences between pairs of means by post hoc Tukey and Bonferroni tests. *p value paired with post hoc Tukey and Bonferroni tests. **p value paired with Bonferroni adjustment. NWO, normal weight obese women; controls, control women; Pre-Ob-Ob, pre-obese-obese women; RMR, resting metabolic rate; VO_2, oxygen consumption; VCO_2, carbon dioxide production; RQ $= VO_2/VCO_2$.

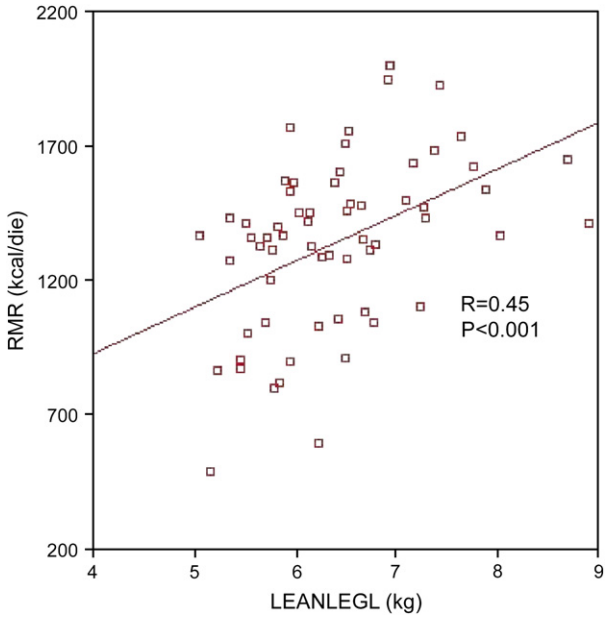

Figure 4 Linear regression from RMR and LEANLEGL in all individuals. RMR, resting metabolic rate; LEANLEGL, lean of left leg.

LEANLEGL in all individuals ($R = -0.37$, $p = 0.004$) (Fig. 6).

Discussion

According to National Institute of Statistics (ISTAT) data, 33.1% (41% males and 25.7% females) of the Italian population is overweight with a BMI higher than 25 kg/m^2, with a fat mass percentage over 25% in males and 35% in females: 9.7% of population is obese according to BMI diagnostic criteria [27]. However, as already demonstrated also by De Lorenzo et al. [28,29], a considerable number of individuals cannot be classified as obese on the basis of their BMI alone. Misclassification could occur if body fat mass percentage is not used to evaluate obesity. A previous study reported that 24% of the American population developed metabolic syndrome within the various BMI categories [30]. The prevalence of metabolic syndrome focusing on individuals with normal BMI and those slightly overweight should have been examined. It has been found that, depending on sex and ethnicity, the prevalence of metabolic syndrome increases from 0.9—3% at 18.5÷20.9 kg/m^2 BMI to 9.6—22.5% at 25÷26.9 kg/m^2 BMI [31]. Therefore, screening for body fat distribution in individuals with normal or slightly elevated BMI is an important contribution to the prevention of diabetes and cardiovascular diseases. The prevalence of obesity among adults overall in the USA increased from 22.9% during 1988—1994 to 30.5% during 1999—2002 [32]. The prevalence of obese diabetic adults reached 54.8% during 1999—2002. Weight management can help reduce the number of people at risk for diabetes and the risk for complications or premature mortality. Central obesity and excessive gain in abdominal fat, correlate closely with both hyperinsulinaemia and insulin resistance and with the possibility of developing type 2 diabetes and coronary heart disease in both obese and metabolically obese individuals [33,34]. Also a high serum level of triglycerides and low HDL cholesterol as well as high systolic and diastolic blood pressure correlate with hyperinsulinaemia [35]. Population studies have demonstrated that MS plays a pivotal role in the occurrence of cardiovascular disease [36,37]. The risk of coronary artery disease increases with the severity of

Table 3 Blood lipid values of NWO, controls and pre-obese-obese women (Pre-Ob-Ob)

Value	Controls ($n = 20$)		NWO ($n = 28$)		Pre-Ob-Ob ($n = 26$)		NWO vs controls (p)*	NWO vs Pre-Ob-Ob (p)*	Controls vs Pre-Ob-Ob (p)*
	Mean	SD	Mean	SD	Mean	SD			
Fasting glucose (mmol/l)	4.80	0.57	4.81	0.42	4.92	0.68	NS	NS	NS
Total cholesterol (mmol/l)	5.18	1.58	4.90	1.03	5.10	1.08	NS	NS	NS
HDL cholesterol (mmol/l)	1.57	0.33	1.92	0.36	1.40	026	0.006	NS	<0.001
LDL cholesterol (mmol/l)	3.18	1.55	2.48	0.84	3.03	0.86	NS	NS	NS
Triglycerides (mmol/l)	1.14	0.41	1.24	0.76	1.37	0.54	NS	NS	NS
TG/HDL cholesterol	0.78	0.33	0.72	0.61	1.00	0.41	NS	NS	NS
LDL/HDL cholesterol	1.29	0.37	2.14	1.19	2.22	0.68	0.041 (0.047)**	NS	0.028 (0.032)**
TC/HDL cholesterol	2.56	0.54	3.46	1.25	3.64	0.83	NS	NS	0.02 (0.022)**

Differences between pairs of means by post hoc Tukey and Bonferroni tests. *p value paired with post hoc Tukey and Bonferroni tests. **p value paired with Bonferroni adjustment. NS, not significant value; NWO, normal weight obese women; controls, control women; Pre-Ob-Ob, pre-obese-obese women; HDL cholesterol, high density lipoprotein cholesterol; LDL cholesterol, low density lipoprotein cholesterol; TG, triglycerides; TC, total cholesterol.

Table 4 Pearson correlations were performed to examine the relation between TC/HDL chol, LDL/HDL chol, LEANLEGL and body composition in the three groups (NWO, controls, pre-obese-obese women)

		Controls ($n = 20$)				NWO ($n = 28$)				Pre-Ob-Ob ($n = 26$)				Total ($n = 74$)			
		LDL/HDL chol	TC/HDL chol	LEANLEGL	LEAN	LDL/HDL chol	TC/HDL chol	LEANLEGL	LEAN	LDL/HDL chol	TC/HDL chol	LEANLEGL	LEAN	LDL/HDL chol	TC/HDL chol	LEANLEGL	LEAN
LEAN	R	−0.40	−0.22	0.85	1	−0.35	−0.34	0.87	1	−0.22	−0.17	0.92	1	−0.30	−0.27	0.90	1
	p	NS	NS	<0.001	0.000	NS	NS	<0.001	0.000	NS	NS	<0.001	0.000	0.019	<0.001	<0.001	0.000
LEANTRUR	R	−0.24	−0.22	0.44	0.82	−0.72	−0.69	0.57	0.74	−0.22	−0.18	0.86	0.98	−0.50	−0.45	0.70	0.87
	p	NS	NS	NS	0.001	<0.001	<0.001	<0.001	<0.001	NS	NS	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
LEANLEGL	R	−0.49	−0.28	1	0.85	−0.34	−0.34	1	0.87	−0.31	−0.27	1	0.92	−0.37	−0.35	1	0.90
	p	NS	NS	0.000	<0.001	NS	NS	0.000	<0.001	NS	NS	0.000	<0.001	0.004	0.007	0.000	<0.001
VO_2	R	0.15	0.20	−0.08	0.04	0.13	0.12	0.31	0.42	−0.36	−0.38	0.59	0.52	−0.02	−0.04	0.42	0.45
	p	NS	NS	NS	NS	NS	NS	NS	<0.001	NS	NS	0.003	0.012	NS	NS	0.001	<0.001
VCO_2	R	0.09	0.35	0.27	0.54	0.08	0.09	0.36	0.49	−0.49	−0.53	0.65	0.52	−0.13	−0.13	0.52	0.54
	p	NS	NS	NS	0.052	NS	NS	NS	0.010	0.035	0.021	0.001	0.011	NS	NS	<0.001	<0.001
RMR	R	0.15	0.27	0.01	0.20	0.12	0.12	0.41	0.44	−0.39	−0.42	0.62	0.53	−0.05	−0.06	0.45	0.48
	p	NS	NS	NS	NS	NS	NS	0.046	0.022	NS	NS	0.002	0.009	NS	NS	<0.001	<0.001
WAIST	R	−0.39	−0.14	0.49	0.79	0.00	0.05	−0.11	0.00	−0.29	−0.35	0.58	0.75	0.07	0.08	0.27	0.47
	p	NS	NS	NS	0.002	NS	NS	NS	NS	NS	NS	0.005	<0.001	NS	NS	0.034	<0.001
HIP	R	−0.23	−0.14	0.47	0.82	−0.03	−0.04	0.40	0.42	−0.29	−0.37	0.60	0.70	0.05	0.04	0.36	0.50
	p	NS	NS	NS	0.001	NS	NS	0.033	0.028	NS	NS	0.004	<0.001	NS	NS	0.004	<0.001

NWO, normal weight obese women; controls, control women; Pre-Ob-Ob, pre-obese-obese women; LEANTRUR, lean of trunk of the right part of the body; LEANLEGL, lean of left leg; LEAN, lean body composition; RMR, resting metabolic rate; VO_2, oxygen consumption; VCO_2, carbon dioxide production; WAIST, circumference of waist; HIP, circumference of hip; *W*/*H*, ratio waist to hip; NS, not significant value.

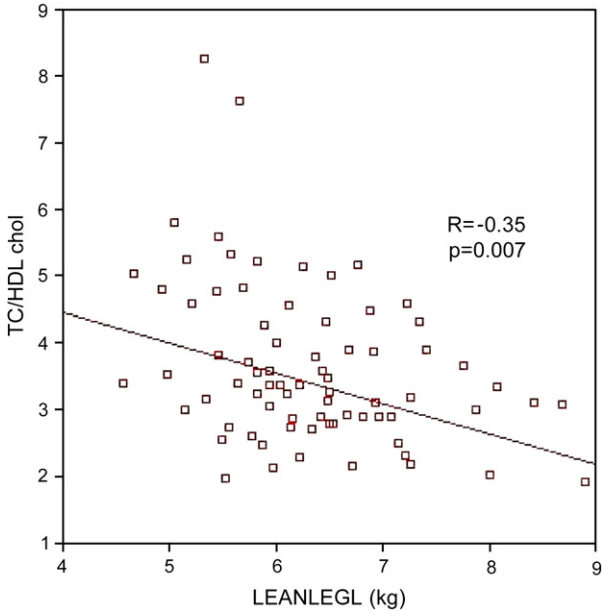

Figure 5 Linear regression from TC/HDL chol and LEANLEGL in all individuals. LEANLEGL, lean of left leg.

obesity especially for abdominal obesity, at the same time the insulin resistance syndrome has been associated with visceral obesity and triglyceride fatty acid content [38]. It has also been demonstrated that visceral adipose tissue (VAT) secretes adipocytokines, and their circulating levels are correlated with the development of insulin resistance and with the occurrence of cardiovascular diseases. Hyperleptinaemia has also been found to be an independent risk factor for coronary artery disease [39]. Suh et al. [40] showed that lumbar region mass distribution, as measured by DXA, is a better predictor of VAT than the waist circumference, WHR or BMI in obese postmenopausal women. It has also been shown that DXA, when combined with anthropometry, offers a good alternative to computed tomography (CT) for the prediction of visceral fat even in the elderly [41], and it provides an accurate measurement of VAT in addition to the total body composition determination in obese individuals [42]. Using a region of interest (ROI), selected by conventional whole body DXA (L2-4, L2-upper iliac), some advantages were obtained over waist circumference, CT or magnetic resonance imaging (MRI) as a means of assessing both VAT and adipose tissue distribution. DXA ROI fat distribution estimates may be useful in the early detection of individuals with abdominal/visceral obesity [43].

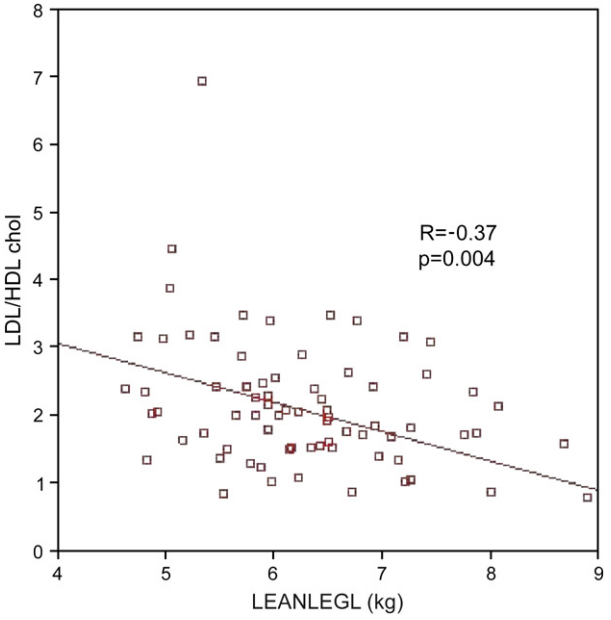

Figure 6 Linear regression from LDL/HDL chol and LEANLEGL in all individuals. LEANLEGL, lean of left leg.

In the present study, body composition variables for all participants were measured using dual X-ray absorptiometry (DXA), as the accuracy of waist and hip circumference ratio (WHR) has not been clearly established in the assessment of visceral/subcutaneous abdominal fat distribution in Italian obese population [6]. Individuals were classified not only according to their body mass index, but also according to their body fat distribution measured by DXA. Fig. 1 well describes the study results: in the 74 Caucasian Italian women we identified controls and NWO women with the BMI in the same range of normality, but with different fat mass distributions, and pre-obese-obese women with both higher BMI and FM. It was observed that NWO women were seemingly healthy because, despite a reference body weight, and a BMI in the normality range (18—25 kg/m^2), they showed a cluster of risky composition characteristics. This same group showed some characteristics of metabolic syndrome such as dyslipidaemia risk factors, as seen in pre-obese-obese women, although they belonged to a different metabolic profile. These results are in accordance with the report that shows the incidence of diabetes, hypertension and coronary heart disease increase well above the normal BMI cut-off of 25.0 kg/m^2 [44].

A significant reduction ($p = 0.01$ by Tukey test, $p = 0.011$ by Bonferroni test) in the lean mass of the legs was found in NWO women in comparison to controls. There was a significant reduction ($p = 0.003$ by Tukey test, $p = 0.004$ by Bonferroni test) in the lean of the left leg of NWO (6.08 ± 0.54 kg) (Fig. 1) in comparison with controls (6.97 ± 0.90 kg), meaning a reduction in muscle functions. The effects of body composition on resting metabolic rate (RMR) of NWO women

were demonstrated by comparing the RMR of controls, pre-obese-obese women and NWO. As reported in Fig. 1, a significant reduction ($p = 0.037$ by Tukey test, $p = 0.043$ by Bonferroni test) of about 200 kcal/day of RMR was observed between NWO and pre-obese-obese women, due to a reduction in metabolically active fat free mass. Finally, there was also a significant correlation between the lean mass of the left leg and RMR ($R = 0.45$, $p < 0.001$), and lean body composition and RMR ($R = 0.48$, $p < 0.001$) in all individuals examined. Thus, the measurement of energy expenditure normalised to metabolically active mass should provide a tool to identify hyper- and hypo-metabolic states at an early stage. Although in NWO women blood glucose, triglycerides, total cholesterol, and HDL-cholesterol were within a range of normality, the CVD risk index LDL/HDL-chol was significantly different between NWO ($p = 0.041$ by Tukey test, $p = 0.047$ by Bonferroni test) and controls. NWO were similar to pre-obese-obese women not only for lean body mass distribution, but also for CVD risk indexes values. Pearson correlations were performed to examine the relations between CVD risk indexes and LEANLEGL in the three groups. Data demonstrated an inverse association of CVD risk indexes and lean mass distribution, particularly in the lean of trunk of the right part of the body and lean of the left leg of NWO women. The present study has the following limitations, which require further investigation. First, due to the role of blood lipid abnormalities in diabetes and cardiovascular diseases, insulin resistance and hyperinsulinaemia should be identified as risk factors for CVD and recognized as a cluster of other abnormalities associated with increased risk of CVD in NWO women. Second, both systolic and diastolic blood pressure should be evaluated to better define the metabolic and vascular profile of NWO women. Despite these limitations, these preliminary data support the hypothesis that NWO women can be considered a subgroup of individuals with reference weight and BMI, although they display obesity-related abnormalities, as observed in MONW individuals [13]. Among reference weight individuals, the increased risk of metabolic syndrome and cardiovascular diseases may have a genetic origin or be a consequence of body composition abnormalities. Due to the peculiarity of the relationship between lean distribution and CVD risk indexes, NWO could be considered an additional metabolic subset of obesity. Furthermore, identification of phenotypes components and their expressions in NWO individuals may be helpful to understand the aetiology of cardiovascular diseases.

In conclusion, screening for CVD risk indexes, trunk and leg lean mass distribution, and metabolic abnormalities in individuals with a BMI in a range of normality may be beneficial in the prevention of both metabolic syndrome related and cardiovascular diseases.

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