Markers of metabolic and cardiovascular health in adults: Comparative analysis of DEXA-based body composition components and BMI categories

Pierre-Olivier Lang (MD, MPH, PD, PhD)\textsuperscript{a,b,*}, Christophe Trivalle (MD)\textsuperscript{c}, Thomas Vogel (PhD)\textsuperscript{d}, Jacques Proust (MD)\textsuperscript{b}, Jean-Pierre Papazian (MD)\textsuperscript{e}

\textsuperscript{a} Translational Medicine Research Group, Cranfield Health, Cranfield University, Cranfield, UK
\textsuperscript{b} Nescens Centre of Preventive Medicine, Clinic of Genolier, Genolier, Switzerland
\textsuperscript{c} Pôle Gériatrie, Hôpitaux Universitaires de Paris-Sud, Hôpital Paul Brousse, Assistance-Publique Hôpitaux de Paris, Villejuif, France
\textsuperscript{d} Pôle de Gériatrie, Hôpitaux Universitaires de Strasbourg, Strasbourg, France
\textsuperscript{e} Centre of Nuclear Medicine, Clinic of Genolier, Genolier, Switzerland

\textbf{A R T I C L E  I N F O}

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\textbf{A B S T R A C T}

\textbf{Objectives:} To investigate how body composition components fit body mass index (BMI) categories and whether they could be considered as markers of metabolic and cardiovascular health.

\textbf{Design:} Prospective study.

\textbf{Setting:} A center for preventive medicine.

\textbf{Participants:} Six hundred and sixteen consecutive outpatients: mean age of 56.0 ± 10.0 years; 74.6% aged ≥ 50 years and 61.4% were females.

\textbf{Measurements:} Fat mass (FM) and muscle mass (MM) were obtained by dual energy X-ray absorptiometry analyses. Metabolically unhealthy individuals were defined as people with biological features of dyslipidemia, hyperuricemia, diabetes, and/or hepatitis steatosis. Documented hypertension and/or atherosclerosis of one major artery, at least, defined individuals with cardiovascular complications.

\textbf{Results:} According to BMI categories, 45.8% of the sample was of normal weight, while 19.2% and 16.5% were classified as overweight and obese. A total of 78.0% and 86.3% of overweight and obese individuals were metabolically unhealthy respectively, 46.8% and 52.6% of subjects classified into normal and underweight BMI categories were also diagnosed. Cardiovascular complications mainly concerned the two highest BMI groups (78.2%). In multifactorial analyses the overweight and obese BMI categories were predictive of health outcomes [respectively, odds ratio (OR) = 8.05, 95% confidence interval (CI): 4.23–12.07 and 5.74, 95% CI: 3.41–8.98]. FM and MM indexes were significantly associated with metabolic (OR = 1.30, 95% CI: 1.19–1.47; and 0.84, 95% CI: 0.78–0.91) and cardiovascular (OR = 1.22, 95% CI: 1.13–1.32; and 0.72, 95% CI: 0.65–0.80) health respectively, and FM/MM (respectively, OR = 15.45, 95% CI: 11.77–20.17; and 16.61, 95% CI: 10.49–21.33) as well.

\textbf{Conclusion:} Our findings suggest that FM and MM readouts are important measurements of nutritional status and they extend the analysis of its impact on health outcomes to all BMI categories. Moreover, they highlight the interest of measuring body composition in medical check-ups to predict metabolic and cardiovascular diseases.

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\section*{Introduction}

The question of how adult weight may influence the risk of metabolic and cardiovascular health and inversely may promote longevity has profound health, social, and economic implications for individuals, communities, and the population as a whole [1]. In almost all epidemiological studies, the degree of overweight is simply defined by means of the body mass index (BMI) or Quetelet’s
index [2]. Expressed as the relationship between the total body mass (in kg) and stature (in m²), it is the most widely used indicator of nutritional status in the general population. It was in 1997 that a World Health Organization consultation on obesity defined
pre-obesity (overweight) as a BMI ≥ 25 kg/m², and class I, II, and III obesity as BMI ≥ 30, 35, and 40 kg/m² respectively.

BMI has, however, some limitations in estimating health-related risks [2,3]. Indeed, the relationships of the total body weight and the development of major health complications are strongly linked to the degree of adiposity. However, while it appeared obvious to establish normal weight as a function of height, this measurement accounts only for about two-thirds of the between-individual variation in total adiposity [4]. Furthermore, BMI does not account for sex, age, and fitness differences in fat mass (FM) even at the same body weight [5,6]. In addition, with aging, the decrease in stature, accumulation of fatty tissues, and reduction in lean mass (i.e. bone + muscle mass) further consider BMI as a problematic readout of total body weight and its health-related risks [1].

Dual energy X-ray absorptiometry (DEXA) is becoming a validated, reliable, and safe technique to assess the body composition. It uses the equivalent of less than 10% of one day’s exposure to natural background radiation (0.001 mSv) which corresponds to lower level of radiation than a standard X-ray (0.1 mSv) [7]. Thus, natural background radiation (0.001 mSv) which corresponds to It uses the equivalent of less than 10% of one day’s exposure to natural background radiation (0.001 mSv) which corresponds to

The results of the check-up are detailed and discussed during the medical consultation conducted before is dedicated to radiological, and functional investigations. Thus, blood test analyses, including in part the biological data of interest (see Table 1 for details), are carried out as well as a large panel of radiology exams such as DEXA-scan, angio-computed tomography (CT)-scans of the supra-aortic and coronary arteries, and total body CT-scan (256-row detector CT-scan). In addition, a cardiologist conducts a stress test on an electronically braked cycle ergometer in addition to a Doppler echocardiography. In order to avoid any interference due to injection of iodine-based contrast products used for the angio- and total body CT-scan, DEXA-scans were systematically carried out first. The data of interest were retrospectively collected from medical folders between April 1, 2013 and May 31, 2013. The study protocol was approved by the local ethics commit-tee.

Materials and methods

Study population and design

The sample study was recruited at the Clinic of Genolier (Switzerland) and consisted of 616 consecutive ambulatory patients consulting the Center for Preventive Medicine (www.nescens.com) for a medical check-up between January 1, 2009 and December 31, 2012. Pregnant women and/or individuals with self-reported cardiac failure, who had a cardiac pacemaker, or who had previously undergone limb amputation were not consid-ered. In addition, there were not any exclusion criteria.

Briefly, Nescens medical check-ups are designed in three steps. The first and third steps are dedicated to medical consultations, which are conducted before and after all the complementary investigations. The medical consultation conducted before is dedicated to personal and family medical histories, medications, current complaints and symptoms, and a complete medical examination is also performed. In the course of the first consultation, patients were informed about the protocol prior to signing informed consent. The results of the check-up are detailed and discussed during the second consultation. The second step is composed of biological, radiological, and functional investigations. Thus, blood test analyses, including in part the biological data of interest (see below and Table 1 for details), are carried out as well as a large panel of radiology exams such as DEXA-scan, angio-computed tomography (CT)-scans of the supra-aortic and coronary arteries, and total body CT-scan (256-row detector CT-scan). In addition, a cardiologist conducts a stress test on an electronically braked cycle ergometer in addition to a Doppler echocardiography. In order to avoid any interference due to injection of iodine-based contrast products used for the angio- and total body CT-scan, DEXA-scans were systematically carried out first. The data of interest were retrospectively collected from medical folders between April 1, 2013 and May 31, 2013. The study protocol was approved by the local ethics commit-tee.

Data collection

Assessment of body composition

The assessment of body composition was performed with a DEXA scan (Hologic Discovery; Hologic Inc., Bedford, MA, USA) [8]. The instrument was calibrated by using a spine phantom daily and a step phantom weekly. All scans were performed 4–5 h after the last meal, at least, and before CT-scans. DEXA represents a three-compartment model for estimating body composition, because it can divide the body into three compartments: fat, bone mineral, and all other fat-free mass that does not include bone. Thus, unlike two-compartment models, DEXA is not subject to errors caused by variations in bone density among different ethnicities. DEXA thus provides bone density estimates, and regional estimates of body composition (i.e. it can estimate the body composition of individual parts of the body), by measuring the body’s absorbance of X-rays at two different energies. Fat, bone mineral, and fat-free soft tissue have different absorption properties. As shown in Fig. 1, DEXA gets estimates of the body composition by scanning the entire body in 5–10 min. Data obtained were analyzed by a trained technician with an automated software (Vertec Scientific Ltd., Reading, BERKS, UK).

Body-composition variables chosen for the present study included two measures of total adiposity, namely the percentage of body fat and FM, and three measures of lean mass, namely percentage of body muscle mass, the bone mass, and MM. Subsequent to the measurement of individuals’ height, height-adjusted indexes were considered. Thus, height raised to the power of 2 was used to calculate BMI [weight (kg)/height² (m²)], FM index [FM = FM (kg)/height (m²)], and MM index [MM = MM (kg)/height (m²)].

According to BMI values, for descriptive purposes, individuals were classified as underweight (<18 kg/m²), normal weight (18–24.9 kg/m²), overweight (25–29.9 kg/m²), or obese (≥30 kg/m²) [1]. For statistical analyses, 18–24.9 kg/m² was used as reference group because it considers normal weight individ-uals. Body heights were measured to the nearest 0.5 cm and total body weight to the nearest 0.1 kg with calibrated digital scales (Seca Corp. Scale, Hamburg, Germany).

Biochemical markers

All biochemical markers considered in the study (see Table 1) were measured at the laboratory of the Clinic of Genolier (Synlab® Suisse – www.synlab.ch), which is accredited according to the international standards (ISO/CEI 15189 STS 497). Fasting blood samples were collected on peripheral venipuncture before all imagery investigations. Serum levels of total cholesterol (C), high-density lipoprotein-C, low-density lipoprotein C (LDL-C), triglycerides, and uric acid were measured using enzymatic methods with Combas Integra® 400 (Hoffmann-La Roche Ltd., Basel, Switzerland). Blood glucose was measured with hexoki-nase method; and blood glycated hemoglobin (Hb) A1c determined by IFCC (International Federation of Clinical Chemistry and Labor-atory Medicine) standardized immunoturbidimetric method with Combas Integra® 400. The serum homocysteine and lipoprotein (a) levels were measured with nephelometric immuno-assays on latex particles using BN ProSpec® (Siemens AG, Munich, Germany) and Combas Integra® 400, respectively.

Outcomes of interest

Metabolic health

Metabolically unhealthy individuals were defined as participants who demonstrate biological features of dyslipidemia (i.e. total and/or LDL hypercholesterolemia and/or hypertriglyc-eridemia), and/or hyperuricemia and/or a diagnosis of diabetes defined as a level of HbA1c above 6.5% [9]. A diagnosis of hepatic
steatosis was also part of the definition. The ratio of liver-to-spleen (L/S) Hounsfield units (HU) <1.0 and liver attenuation <40 HU on the abdomen 256-row detector CT-scan was used for diagnosing hepatic steatosis [10]. The normal serum values for biological markers were those given by the laboratory (www.synlab.ch): total cholesterol <5.2 mmol/L; LDL cholesterol <3.7 mmol/L; triglycerides <1.7 mmol/L; 210 ≤ uric acid ≤ 420 for men and 150 ≤ uric acid ≤ 360 for women; and 4.0 ≤ HbA1c ≤ 6.0 for both genders.

Table 1
Characteristics of the individuals comprising the sample study according to BMI categories (N = 616).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total</th>
<th>BMI &lt; 18</th>
<th>18 ≤ BMI &lt; 24.9</th>
<th>25 ≤ BMI &lt; 29.9</th>
<th>BMI ≥ 30</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td>378 (61.4)</td>
<td>106 (93.0)</td>
<td>188 (66.7)</td>
<td>40 (33.9)</td>
<td>44 (43.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>56.0 ± 10.0</td>
<td>51.8 ± 8.9</td>
<td>55.4 ± 9.4</td>
<td>58.0 ± 12.2</td>
<td>60.1 ± 8.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Country of origin, n (%)</td>
<td>68 (11.0)</td>
<td>28 (24.6)</td>
<td>28 (9.9)</td>
<td>4 (3.4)</td>
<td>8 (7.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Personal history, n (%)</td>
<td>70 (11.4)</td>
<td>2 (1.7)</td>
<td>22 (7.8)</td>
<td>26 (22.0)</td>
<td>20 (19.6)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>116 (18.8)</td>
<td>0 (0.0)</td>
<td>28 (9.9)</td>
<td>48 (40.7)</td>
<td>40 (39.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Risk factor for cardiovascular diseases, n (%)</td>
<td>46 (7.5)</td>
<td>0 (0.0)</td>
<td>10 (3.6)</td>
<td>16 (13.6)</td>
<td>20 (19.6)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Family history</td>
<td>286 (46.4)</td>
<td>36 (31.6)</td>
<td>134 (47.5)</td>
<td>52 (44.1)</td>
<td>64 (62.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>Tobacco consumption</td>
<td>200 (32.5)</td>
<td>12 (10.5)</td>
<td>70 (24.8)</td>
<td>54 (45.8)</td>
<td>64 (62.8)</td>
<td>&lt;0.00005</td>
</tr>
<tr>
<td>MUH, n (%)</td>
<td>372 (60.4)</td>
<td>60 (52.6)</td>
<td>132 (46.8)</td>
<td>92 (78.0)</td>
<td>88 (86.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HbA1c [14]</td>
<td>214 (34.7)</td>
<td>22 (19.3)</td>
<td>54 (19.1)</td>
<td>78 (76.5)</td>
<td>78 (76.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Known hypercholesterolemia, n (%)</td>
<td>196 (31.8)</td>
<td>0 (0.0)</td>
<td>76 (26.9)</td>
<td>60 (50.8)</td>
<td>60 (58.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Taking of cholesterol-lowering drugs, n (%)</td>
<td>66 (10.7)</td>
<td>0 (0.0)</td>
<td>18 (6.4)</td>
<td>24 (20.3)</td>
<td>24 (23.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diagnosis of diabetes, n (%)</td>
<td>24 (3.9)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>6 (5.1)</td>
<td>18 (17.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total cholesterol m ± SD</td>
<td>5.9 ± 1.1</td>
<td>5.8 ± 0.9</td>
<td>5.9 ± 1.2</td>
<td>5.9 ± 1.2</td>
<td>5.7 ± 1.1</td>
<td>NS</td>
</tr>
<tr>
<td>≥ 5.2 mmol/L, n (%)</td>
<td>174 (28.3)</td>
<td>32 (28.1)</td>
<td>42 (30.0)</td>
<td>30 (25.4)</td>
<td>14 (27.4)</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol m ± SD</td>
<td>1.7 ± 0.5</td>
<td>1.9 ± 0.4</td>
<td>1.9 ± 0.5</td>
<td>1.5 ± 0.4</td>
<td>1.2 ± 0.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cholesterol/HDL</td>
<td>16 (2.6)</td>
<td>0 (0.0)</td>
<td>4 (1.4)</td>
<td>6 (5.1)</td>
<td>6 (5.9)</td>
<td>0.08</td>
</tr>
<tr>
<td>LDL cholesterol m ± SD</td>
<td>3.7 ± 1.0</td>
<td>3.5 ± 0.9</td>
<td>3.6 ± 1.1</td>
<td>3.8 ± 0.9</td>
<td>3.9 ± 0.9</td>
<td>NS</td>
</tr>
<tr>
<td>≥ 3.7 mmol/L, n (%)</td>
<td>318 (51.8)</td>
<td>60 (52.6)</td>
<td>124 (44.3)</td>
<td>68 (57.6)</td>
<td>66 (64.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides m ± SD</td>
<td>1.1 ± 0.6</td>
<td>0.8 ± 0.2</td>
<td>1.0 ± 0.4</td>
<td>1.4 ± 0.6</td>
<td>1.7 ± 0.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥ 1.7 mmol/L, n (%)</td>
<td>92 (15.0)</td>
<td>0 (0.0)</td>
<td>18 (6.4)</td>
<td>36 (30.5)</td>
<td>38 (37.2)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>HbA1c [15]</td>
<td>5.5 ± 0.7</td>
<td>5.4 ± 0.4</td>
<td>5.3 ± 0.4</td>
<td>5.6 ± 0.6</td>
<td>6.3 ± 1.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥ 6.5%, n (%)</td>
<td>38 (6.23)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>6 (5.1)</td>
<td>32 (31.4)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>hs-CRP [16]</td>
<td>2.0 ± 3.1</td>
<td>1.0 ± 0.9</td>
<td>1.4 ± 1.1</td>
<td>2.3 ± 2.0</td>
<td>4.6 ± 4.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ferritin [17]</td>
<td>139.8 ± 92.9</td>
<td>128.7 ± 85.5</td>
<td>130.5 ± 88.1</td>
<td>169.4 ± 116.9</td>
<td>146.5 ± 79.6</td>
<td>NS</td>
</tr>
<tr>
<td>Uric acid [18]</td>
<td>281.4 ± 94.4</td>
<td>211.8 ± 40.9</td>
<td>253.0 ± 74.5</td>
<td>321.0 ± 94.6</td>
<td>381.2 ± 78.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hyperuricemia [19]</td>
<td>64 (11.3)</td>
<td>0 (0.0)</td>
<td>10 (4.0)</td>
<td>20 (18.2)</td>
<td>34 (33.3)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Homocystine [20]</td>
<td>10.5 ± 3.1</td>
<td>12.3 ± 0.7</td>
<td>10.2 ± 3.4</td>
<td>11.2 ± 3.2</td>
<td>9.9 ± 2.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lp(a) [21]</td>
<td>253.6 ± 272.6</td>
<td>302.6 ± 154.8</td>
<td>232.8 ± 207.8</td>
<td>234.9 ± 352.9</td>
<td>279.2 ± 351.2</td>
<td>0.02</td>
</tr>
</tbody>
</table>

BMI, body mass index (kg/m²); m: SD, mean standard deviation; MUH, metabolically unhealthy is defined by the presence of at least one metabolic disorder (hyper-LDL, hypertriglyceridemia, and/or HbA1c > 6.5%) and/or a diagnosis of hepatic steatosis; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA1c, glycosylated hemoglobin; hs-CRP, high-sensitivity C-reactive protein.

p-Values < 0.05 indicates that the candidate variable is associated with the BMI categories, when it is >0.05 then “NS” is mentioned.

* From other origin means: Algeria – 4 (0.6%), Belgium – 16 (2.5%), China – 8 (1.3%), Dubai – 2 (0.4%), Egypt – 2 (0.4%), Iraq – 4 (0.6%), Kuwait – 2 (0.4%), Monaco – 6 (1.0%), Saudi Arabia – 24 (3.8%), and Sweden – 2 (0.4%).

+ Any vascular diseases = suffering at least from any coronaropathy (symptomatic or not), and/or a stenosis of supra aortic trunk (with or without symptoms or complication), and/or an arteriopathy of the lower limbs.

# Hepatic steatosis = diagnosed by ultrasound of the abdomen and defined as a liver hyperechogenicity.

< Hyper-LDL, hypertriglyceridemia, and/or HbA1c > 6.5%.
Cardiovascular disease

Medical data and diagnostics of interest leading to identify individuals suffering from metabolic-related cardiovascular complications were collected throughout the two medical consultations from previous reports, personal medical history, and the result of the tests performed during the check-up. Thus, individuals who demonstrate documented hypertension (under treatment or not) and/or a significant coronaryopathy (symptomatic or not), atherosclerosis of at least one of the supra-aortic arteries (symptomatic or not), and/or one large arteries of the body were considered as having cardiovascular diseases [9].

Statistical analyses

For descriptive analysis, numerical variables are presented as mean ± standard deviation (m ± SD) and for categorical variables as number and percentage. Statistical tests used for the unifactorial comparative analysis were chosen according to the type of variable, the sample size under consideration, and the number of groups compared. Thus, numerical outcomes were compared using analysis of variance or Kruskal–Wallis test (when greater than two groups), and Student’s t or Mann–Whitney test (when two groups). For categorical outcomes, \( \chi^2 \) (Chi²) or Fisher’s exact test was used. Linear Pearson correlation coefficients (\( r \)) were calculated using a linear regression model to measure the strengths and directions of the linear relationships between the BMI values and the different anthropometric and biological data.

To investigate the respective relationship between the different anthropometric readouts of interest and the two main health outcomes independent multifactorial logistic models have been computed. In each model, gender and age were systematically considered as adjustment variables, and tobacco consumption (i.e. smoking) as a potential confounder for cardiovascular health only. The results of these analyses are presented in the form of adjusted ORs and 95% confidence intervals (95% CI). The Hosmer–Lemeshow test was used to assess whether the observed event rates match
expected event rates in subgroups of the model population. The goodness of fit of the logistic models was considered as good when the p value was >0.05. All these statistics were performed with SAS® software (version 9.3 – SAS System, SAS Institute Inc., Cary, NC, USA). The level of significance was set at p = 0.05.

Results

The socio-demographic characteristics and medical data retrospectively collected from the 616 consecutive adults comprising the sample study are presented according to BMI categories in Table 1. Two thirds of the sample study group were female (61.4%). The average age was 56.0 ± 10.0 years and 74.6% of the sample group were aged over 50 years. Two thirds of the analytic sample study group were diagnosed as being metabolically unhealthy (n = 372) while 20.0% had already at least one cardiovascular complication (n = 124). According to BMI categories, 45.8% of the analytic sample study group were considered to be of normal weight (BMI < 25 kg/m²), while 19.2% and 16.5% were classified as overweight (25 ≤ BMI < 29 kg/m²) and obese (BMI ≥ 30 kg/m²), respectively. When the individuals were classified as underweight (18.5% – BMI < 18 kg/m²), the vast majority was aged between 40 and 69 years (89.4%) and 93.7% were women. Patients with higher BMI were significantly older. Interestingly, when the metabolic status was then considered, 78.0% and 86.3% of overweight and obese individuals were metabolically unhealthy respectively, 46.8% and 52.6% of subjects classified into normal and underweight BMI category were also considered as being biologically unhealthy. Similarly, cardiovascular complications mainly concerned the overweight and obese sub-samples (78.2%).

Anthropometric data across BMI categories are detailed in Tables 2 and 3. While the average height was similar across BMI categories, obviously, all anthropometric parameters increased with the BMI values and categories. One interesting finding was that while all estimates of the fat compartments were positively correlated with BMI categories, the percentage of MM was negatively correlated with BMI values (r = −0.49; p < 0.0001) and this across all BMI categories. Mean MM and MMI values were higher within the highest BMI categories (p < 0.0001) and in metabolic and cardiovascular healthy subgroups respectively in underweight and in normal weight groups according to the BMI value (p = 0.001). In particular, when the body composition of normal and overweight individuals according to BMI classification was analyzed, the results demonstrated that the unhealthy sub-sample had a lower MM and a relative excess of FM compared to the healthy one. These findings

Table 2
Result of the descriptive analysis of the anthropometric data according to BMI categories (N=616).

<table>
<thead>
<tr>
<th>Anthropometric data</th>
<th>Total</th>
<th>BMI &lt; 18</th>
<th>18 ≤ BMI &lt; 24.9</th>
<th>25 ≤ BMI &lt; 29.9</th>
<th>BMI ≥ 30</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm)</td>
<td>169.7 ± 9.5</td>
<td>168.7 ± 7.5</td>
<td>168.9 ± 9.1</td>
<td>172.6 ± 10.7</td>
<td>169.5 ± 10.6</td>
<td>NS</td>
</tr>
<tr>
<td>Total body mass (kg)</td>
<td>68.6 ± 18.1</td>
<td>49.7 ± 4.8</td>
<td>61.5 ± 9.6</td>
<td>81.3 ± 11.3</td>
<td>94.4 ± 12.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.7 ± 5.5</td>
<td>17.4 ± 0.5</td>
<td>21.4 ± 1.9</td>
<td>27.2 ± 1.5</td>
<td>32.9 ± 3.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Bone mass (g)</td>
<td>2311.2 ± 493.5</td>
<td>2005.0 ± 270.8</td>
<td>2255.4 ± 425.6</td>
<td>2529.1 ± 537.1</td>
<td>2567.3 ± 576.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Bone mass index (kg/m²)</td>
<td>0.8 ± 0.1</td>
<td>0.7 ± 0.07</td>
<td>0.8 ± 0.1</td>
<td>0.8 ± 0.1</td>
<td>0.9 ± 0.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Muscle mass (g)</td>
<td>47,095.3 ± 12,197.7</td>
<td>35,101.2 ± 3526.1</td>
<td>44,683.9 ± 9523.9</td>
<td>55,465.5 ± 10,127.9</td>
<td>57,484.2 ± 12,386.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Muscle mass index (kg/m²)</td>
<td>16.2 ± 3.1</td>
<td>12.3 ± 0.9</td>
<td>15.5 ± 2.0</td>
<td>18.4 ± 1.8</td>
<td>19.8 ± 2.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Muscle mass (%)</td>
<td>69.2 ± 8.0</td>
<td>70.7 ± 4.9</td>
<td>72.3 ± 7.1</td>
<td>67.9 ± 6.7</td>
<td>60.5 ± 7.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fat mass (g)</td>
<td>19,135.8 ± 9261.5</td>
<td>12,623.2 ± 3144.3</td>
<td>14,497.8 ± 4567.7</td>
<td>23,342.6 ± 5727.0</td>
<td>34,369.6 ± 7246.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fat mass index (kg/m²)</td>
<td>6.7 ± 3.4</td>
<td>4.4 ± 0.9</td>
<td>5.1 ± 1.7</td>
<td>7.9 ± 2.0</td>
<td>12.2 ± 3.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fat mass (%)</td>
<td>27.2 ± 8.4</td>
<td>25.2 ± 5.1</td>
<td>23.9 ± 7.4</td>
<td>28.9 ± 6.8</td>
<td>36.8 ± 8.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fat mass/Muscle mass</td>
<td>0.4 ± 0.2</td>
<td>0.4 ± 0.1</td>
<td>0.3 ± 0.1</td>
<td>0.4 ± 0.1</td>
<td>0.6 ± 0.2</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

BMI, body mass index (kg/m²); m ± SD = mean ± standard deviation.

p-Value <0.05 indicates that the candidate variable is associated with the BMI value within the whole sample or within the BMI category considered, when it is >0.05 then “NS” is mentioned.
were observed whatever the health outcomes (metabolic and cardiovascular) and the muscle and fat readouts considered (p < 0.01).

Results of multifactorial logistic models, systematically adjusted for individuals’ age and gender, and smoking for any cardiovascular complications are presented in Table 4. Only overweight and obese BMI categories were significantly associated with metabolic and cardiovascular complications with, respectively, OR 6.84 (95% CI: 3.03–10.46) and 8.05 (95% CI: 4.23–12.07) and 5.10 (95% CI: 3.79–8.76) and 5.74 (95% CI: 3.41–8.98). In all models, every body weight component was significantly predictive of metabolic and cardiovascular health independently or combined except total FM and MM; FM and MM readouts were however inversely associated with the two outcomes. FM and MM indexes, which are equivalent concepts to BMI, were also significantly but inversely associated with metabolic disease (respectively, OR = 1.30, 95% CI: 1.19–1.47; and 0.84, 95% CI: 0.78–0.91) and cardiovascular complications (OR = 1.22, 95% CI: 1.13–1.32; and 0.72, 95% CI: 0.65–0.80). Thus, while increasing values of percentage of FM and MM adversely impacted metabolic and cardiovascular health, inversely increasing values for MMI and percentage of MM positively interfered with these health-related risks. The FM/MM, taking into account the two components together was also significantly associated with the two outcomes of interest (respectively, OR = 15.45, 95% CI: 11.77–20.17; and 16.61, 95% CI: 10.49–21.33).

Discussion

The main finding of this study is that all readouts of the two major components of the total body weight predicted significantly the metabolic and cardiovascular health. Thus, the total and percentage of FM and MM, the FM and MM indexes were independent predictive markers of the body composition changes related to health. Moreover, the FM/MM, taking into account simultaneously these two components was also significantly identified. The BMI value was significantly associated with such health risks, but the significant association was only observed with highest categories (i.e. overweight and obese). These findings are of particular interest when we consider that among individuals classified within normal and even underweight population according to BMI categorization, the prevalence of metabolic and cardiovascular complications are far from negligible in our analytic sample study group (see Table 1) and as also depicted by others [1,11,12].

The major shortcoming of the BMI is that the actual composition of body weight is not taken into account. Indeed, excess of body weight may be made up of adipose tissue or conversely muscle hypertrophy both of which situations will be judged as “excess mass.” Conversely a deficit of BMI may be due to a MM deficit or a mobilization of adipose tissue or both combined. Consequently, considering that BMI is the sum of FM and MM, an increase (or a decrease) in BMI may be accounted for by a rise (or a drop) in one component or in the other, or in both components. The advantage of the combined use of these indices is that one can judge whether the deficit or excess of body weight is selectively due to a change in FM vs. MM or both combined [13]. This is furthermore of interest when we consider that these two components may have a completely opposite and independent impact on metabolic risks and subsequently cardiovascular complications [1,14–19]. The association of overweight–overfat and the development of major complications is strongly linked to adiposity and its associated chronic inflammation and insulin resistance (IR) [1,15,20]. The utility of measuring fat mass index vs. BMI in the screening of metabolic syndrome, has been recently demonstrated by Liu et al. [3] in 1698 subjects (aged 20–79 years) who participated in annual health check-ups in Beijing, China. However, while the increase in body fat is the most common explanation for the occurrence of IR [15], over the past few years it has become evident that changes in the metabolic function of muscles played also a direct role [14,16–18]. Regardless of the specific intracellular mechanisms at the molecular level [21–23], it is clear that IR and ultimately diabetes are not simply the result of increased FM but rather related to alterations in the metabolic function of muscle and reduced MM [14,19,23].

Partitioning BMI into MM and FM is however not possible without associated measurement of body composition. Using this two-compartment model merits however a reappraisal. It appears to be of high interest to better identify how adult weight may interfere with health by more precisely exploring the wide range from underweight/underlean to overweight/overfat individuals [13]. It may also improve overweight and obesity management. Thus, while for many physicians and people goals of overweight/obesity therapy are to reduce body weight and maintain a lower body weight for the long-term, our findings underline the imperative
need to increase, or at least to maintain, regular physical activity practice in addition to long-term nutritional adjustments. Exercise improves muscle function and, in some circumstances, increases muscle mass as well. Improved function is not limited to the contractile properties but also muscle metabolism [19] and hence enhances insulin sensitivity [24]. However exercise seems to be more effective at preventing loss of muscle and improving functionality [19, 25] than of restoring lost muscle mass. Finally, exploring body composition through this two-compartment model should be not only part of the initial assessment of overweight and obese individuals but should be part of a periodic follow-up. Thus the impact of weight-loss programs on both FM and MM can be estimated and subsequently the level of caloric restriction and physical activity periodically re-adjusted accordingly.

Our study had some limitations. First, the study design limits our ability to draw causal inferences from the relationships observed. Thus, our study investigated neither adipokines to differentiate metabolically healthy from unhealthy individuals nor the mode of transition to observe the impact of adiposity-related chronic inflammation on metabolic and health outcomes. Indeed, whether theoretically metabolically healthy overweight (MHO) and metabolically unhealthy overweight (MUHO) represent distinct subtypes that could be predetermined genetically to confer differing metabolic and cardiovascular risks [26], these two entities may also represent transition phases in the natural course of obesity, with MHO individuals ultimately turning into MUHO [15, 27]. Thus investigating the chronic state of low-grade inflammation usually described as associated with fat deposition should be investigated. These measurements would have probably helped to better extend risk prediction beyond BMI scores [2] by identifying MUHO who do not yet exert overweight–obesity metabolic pattern and/or cardiovascular complications [15]. However, while this would help to better define metabolic risk across the different BMI categories this would have led to increase the number of individuals at risk and subsequently the strength of the observed associations.

Second, DEXA scan was used to estimate both fat and muscle mass and like other estimation techniques, DEXA has sources of error. There can be inconsistent results between different scans from different manufacturers, and even different results between machines from the same manufacturer. All DEXA-based body composition measurements considered in our study were made on the same machine (model Discovery W, Hologic) that is the only one to incorporate the National Health and Nutrition Examination Survey (NHANES) whole body composition reference data [28]. While it is usually believed that software upgrades may change the algorithm used to calculate body composition, the different upgrades performed during the study period have always been made to update the same mode of functioning. Moreover multiple controls have certified the reproducibility of the measurements. Another source of error with the use of DEXA scan is that it relies on the relationship between body composition and body water content. Indeed, this may be disturbed in pathological states that increase whole body water, such as acute cardiac or renal failure. While this point is more particularly a concern when trying to measure change over time, individuals with heart failure were not considered in our analytic sample study group and in individuals with chronic renal disease, in whom muscle mass would be overestimated [16].

Third, our analytic sample study group is not representative of a homogenous population. It is more representative of the international community visiting Switzerland for medical care than people of strictly Swiss nationality. This is due to the heterogeneity of the population consulting our clinic (i.e., one third of the sample were of non-Swiss origin) and that one composing the districts of the towns of Lausanne and Geneva (Switzerland) [13]. It has been demonstrated that there is a discrepancy between average BMI and average relative body fat in certain ethnic groups [29]. For example, a higher percentage body fat for the same BMI was observed in a Chinese population compared to Caucasians. This indicates that fat-mass index will be higher at the same BMI compared to other populations. This finding also means that population-specific BMIs need to be developed when body composition is unknown, whereas population-specific FM or MM indexes may be less warranted [30, 31].

**Conclusion**

Despite limitations, our findings suggest that considering the two components of the body weight (i.e., FM and MM) are important and complementary measurements in the evaluation of an individual’s nutritional status. These results may extend the exploration of its impact on metabolic and cardiovascular health to normal and underweight BMI categories and not only restrain it to overweight and obese populations. Finally, these findings also underline the interest of measuring body composition components in medical check-ups to predict metabolic and cardiovascular diseases.

The interest of considering FM and MM index as well as FM/MM to predict metabolic-associated health outcomes still needs, however, to be further explored on the basis of longitudinal studies. Similarly how changes in body composition over time affect metabolic patterns, Cardiovascular complications, and survival should also be investigated. Moreover, cut-off values have still to be determined as a function of age and gender and probably ethnic origin as well. Finally, due to DEXA-associated costs and its limited accessibility, the accuracy and reliability of alternative techniques in measuring body composition components should also be further explored.

**Conflict of interest**

The authors have no conflicts of interest for this article. The financial sponsors did not play any role in the design, execution, analyses and interpretation of data, or writing of the manuscript.

**Authors’ contributions**

P.-O. Lang: conceived the study. He computed statistical analyses and has contributed to interpretation of data, and to writing the manuscript. T. Vogel: contributed to drafting the manuscript. J. Proust: contributed to acquisition of subjects and data, and J.-P. Papazian: contributed to acquisition of subjects and data.

**References**


