Biomarkers, 2011; 16(3): 243–251

ISSN 1354-750X print/ISSN 1366-5804 online
DOI: 10.3109/1354750X.2010.547948

informa
healthcare

RESEARCH ARTICLE

Immunologic profile of excessive body weight

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Abstract

The purpose of this paper is to identify immunologic hallmarks of excessive bodyweight. The analysis is based on 176 adults (106 women, 70 men) who participated in a nested case-control study in Italy. All participants were healthy at the time of blood collection and aged between 36 and 75 years. We employed multivariate analysis of variance and a nonparametric Bayesian additive regression tree approach along with a receiver operating characteristic (ROC) curve analysis to determine the immunologic signature of excessive body weight (i.e., obesity and overweight). Interleukin 8 (IL-8), IL-10, interferon γ, and inducible protein 10 were shown to be predictive of excessive body weight with an area under the ROC curve of 71% ($p < 0.0002$). We propose that by using this profile-based approach to define immunologic signatures, it might be possible to identify unique immunologic hallmarks of specific types of obesity.

Keywords: Obesity/diabetes, growth factors/cytokines/inflammatory, mediators, proteomics

Introduction

Obesity is a complex and incompletely understood disorder (WHO, 2000). According to the World Health Organization (WHO), overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health, leading to reduced life expectancy (WHO, 2000). Obesity and overweight are associated with many health problems, including breathing difficulties during sleep and osteoarthritis, and are considered major risk factors for a number of chronic diseases, including diabetes, cardiovascular diseases and cancer. Obesity is a leading preventable cause of death worldwide with increasing prevalence in adults and children. Obesity is now considered one of the most serious public health problems of the 21st century (Barness et al., 2007). Since 1980, obesity rates have been rising with alarming trends in several parts of the world. It is estimated that overweight and obesity are responsible for more than 1 million deaths and 12 million life-years of ill health every year in the WHO European Region (WHO, 2000; Katz et al., 2005; Branca et al., 2007).

Obesity and overweight are usually measured by anthropometry indices. Body mass index (BMI), weight in kilograms divided by height squared in meters, is commonly used to classify adults into underweight, overweight and obese categories (Ezzati et al., 2002). Other measures are waist circumference (WC), hip circumference (HC) and waist-to-hip ratio (WHR). The WHO defines a BMI less than 18.5 kg/m^2 as underweight, a BMI between 18.5 and 24.9 kg/m^2 as normal, a BMI 25.0–29.9 kg/m^2 as overweight and a BMI more than 30 kg/m^2 as obese, which in turn is divided into further classes of obesity (2000, Gallagher et al., 2000; James et al., 2001). The association between BMI and risk of death has often been described as J-shaped or U-shaped (Lew and Garfinkel, 1979; Schroll, 1981; Vandenbroucke et al., 1984; Manson et al., 1987; Tuomilehto et al., 1987; Lindsted et al., 1991; Stevens et al., 1992; Lee et al., 1993;

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(Received 03 September 2010; revised 10 December 2010; accepted 10 December 2010)

Seidell et al., 1996; Troiano et al., 1996; Diehr et al., 1998; Durazo-Arvizu et al., 1998; Yuan et al., 1998; Calle et al., 1999; Baik et al., 2000). The literature suggests an increasing risk of mortality and other adverse health effects with BMI ≥ 25 kg/m² as well as WHR ≥ 0.95 for men and WHR ≥ 0.80 for women (Björntorp, 1985; Bray, 1989; Crepaldi et al., 1991; Folsom et al., 1993; Alberti and Zimmet, 1998; Kalmijn et al., 1999; Baik et al., 2000; Folsom et al., 2000; Visscher et al., 2001; Katzmarzyk et al., 2002; Lahmann et al., 2002; Bigaard et al., 2003; Hu et al., 2004; Dolan et al., 2007; Simpson et al., 2007; Zhang et al., 2007).

Over the past decade, we have been witnessing substantial progress into the understanding of physiologic processes regulating the balance of energy (Flier, 2004). A burgeoning of research on cytokines has been made possible since the pure recombinant cytokines and molecular probes for their genes became available (Balkwill and Burke, 1989). Also, it is not a long time ago that adipose tissue began to be viewed as an active organ in hormonal regulation (Zhang et al., 1994). Obesity is associated with substantial macrophage infiltration into adipose tissue (Weisberg et al., 2003; Xu et al., 2003; Curat et al., 2004; Herder et al., 2007). It seems that there is a considerable overlap between the biology of adipocytes and of innate immune cells such as macrophages (Wellen and Hotamisligil, 2005). A number of molecules involved in glucose homeostasis, vascular biology, tumor development, lipoprotein metabolism and inflammation that are derived from adipose tissue have already been identified (Rajala and Scherer, 2003). This growing body of information indicates a broad range of overlapping cell regulatory activities both *in vitro* and *in vivo* and may require systems biology approaches (Sauer et al., 2007) to make better sense of the observations (Balkwill and Burke, 1989).

Here we examine the association of plasma levels of 11 cytokines, 4 chemokines and 1 adhesion molecule with bodyweight indicators (i.e., BMI, WHR) and we propose hallmarks of excessive body weight resulting from perturbations in immunologic factors.

Materials and methods

Study population

The study is based on 176 adults (106 women, 70 men) who participated in a case-control study nested in the Italian European Prospective Investigation into Cancer and Nutrition (EPIC) whose original aim was to explore the association of plasma cytokine and chemokine levels with increased risk of non-Hodgkin lymphomas (NHL) (Hosnijeh et al., 2010b). All participants were healthy at the time of blood collection and aged between 36 and 75 years. EPIC, the European network of prospective cohorts, was designed to investigate the relationships between diet, nutritional status, lifestyle and environmental factors and the incidence of cancer and other chronic diseases (Riboli and Kaaks, 1997). EPIC-Italy recruited 47,749 volunteers (15,171 men, 32,578 women, aged 35–65 years) in 1993–1998 from five different administrative centers covered by cancer registries, including Varese (12,083 volunteers) and Turin (10,604) in the Northern part of the country; Florence (13,597) in Central Italy and Ragusa (6403) and Naples (5062 women) in Southern Italy. The nested case-control study included 88 cases (53 women, 35 men) diagnosed with NHL before the end of 2004 according to the ICD-O-3 classification of diseases. For each case, one control subject was selected out of all cohort members on a random basis, using the following criteria: alive and free of cancer at the time of diagnosis of the index case, matched by center, gender, date of recruitment, age at diagnosis and age at recruitment (±3 years). Here we present results for cases and controls ($n = 176$) together and also separately for the controls ($n = 88$).

Measures of anthropometry, physical activity and smoking

Weight, height, WC and HC were measured by trained personnel at the time of recruitment. WC was measured at the torso circumference (at the point where the front profile was narrowest) and HC was measured at the widest circumference (below the iliac crest and above the great trochanter where the front profile is wider). BMI was calculated as a person's body weight (in kilograms) divided by squared height (in meters). WHR is the ratio of WC to HC.

Information related to physical activity was collected [the type of physical activity at work, physical exercise to keep fit and vigorous physical activity, time spent on specific activities including walking, cycling, gardening, housework and number of stairs climbed per day (Riboli et al., 2002)]. Energy expenditure values were assigned using a standardized coding system developed by the Compendium of physical activities (Ainsworth et al., 2000). Depending on the duration and the type of recreational and household activity reported on the baseline questionnaire, the average of metabolic equivalent-hours (MET-hr) was assigned separately in winter and summer. Occupational activity has been coded as sedentary occupation, standing occupation, manual work, heavy manual work, unemployed or missing, as reported in the questionnaire. Subjects were cross-classified based on sex-specific quartiles of recreational and household activity and on categories of occupational work to generate a total physical activity variable coded as inactive, moderately inactive, moderately active and active (Friedenreich et al., 2005). Smoking status was coded as never-smoker, former smoker and current smoker.

Laboratory assay

Citrate plasma samples (50 μl) were used to measure eleven cytokines, that is, interleukin 1α (IL-1α), IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12, IL-13, interferon γ (IFN-γ) and tumor necrosis factor α (TNF-α); four chemokines, that is, IL-8, RANTES (regulated upon activation, normal T-cell expressed, and secreted), Eotaxin and inducible protein 10 (IP-10), and one adhesion molecule (ICAM).

We used the Luminex multianalyte profiling technology (Lab-MAP™) according to the protocol described by de Jager et al. (2003) except that instead of a 1 h incubation, an overnight incubation at 4°C was used (Hosnijeh et al., 2010a). Median time interval between sample collection and freezing was 4 h.

Due to the case-control study design, all samples were run in duplicate with matched case-control sets assayed in the same batch. Quality control sets (low and high concentration cytokines quality control samples) were run in duplicate with the case-control sets in each batch. The median intrabatch coefficient of variation for all cytokines based on these quality control duplicate sets was 6.7% (4.3–30) and the median interbatch coefficient of variation was 30.7% (9.6–110). The lower limits of detection were.24 (pg/ml) for IL4;.61(pg/ml) for IL-12; 1.22 (pg/ml) for IL-1β, IL-2, IL-5, IL-6, IL-8, IL-10, IL-13, IFN-γ and TNF-α; 2.44 (pg/ml) for IL-1α, RANTES and Eotaxin; 4.88 (pg/ml) for IP-10; and 73.24 (pg/ml) for ICAM (Hosnijeh et al., 2010b).

Statistical analysis

Outliers were removed (using Box-plot) before further statistical analysis. Numbers of missing values, including deleted outliers, varied from 19 to 26 depending on the model and the type of cytokines included in the model.

Multivariate analysis of variance

We classified individuals into two groups of normal (optimal) weight and excessive weight using the anthropometry indices. Cutoff point for BMI was set at 25 kg/m^2, for WC at 94 cm in men and 80 cm in women, and for WHR at 0.95 in men and 0.79 in women according to guidelines and the literature (Alberti and Zimmet, 1998; James et al., 2001). For HC, the cutoff point was set at 98.4 in men and 98.8 in women based on the median of the HC in each gender. The grouping of individuals by bodyweight indices was used to calculate the (adjusted) odds ratios (logistic regression) for cytokines, smoking status, physical activity and case/control status in relation to bodyweight. The grouping was used to carry out multivariate analysis of variance (MANOVA) with one dichotomous independent variable (e.g., BMI) and multiple dependent variables. The statistics that are normally used for MANOVA, that is, Wilks' lambda, Lawley–Hotelling trace, Pillai's trace, Roy's largest root, yielded similar results. The final selection of variables in the model was based on the impact of each variable on the separation of classes (loadings) and the overall statistical significance of the model. To perform MANOVA, we normalized the data to address the differences in variability in each marker, by dividing each variable by its standard deviation (univariate scaling).

BART, logistic regression, and 10-fold cross validation

We employed a nonparametric Bayesian additive regression tree (BART) analyses (Chipman et al., 2008) that uses dimensionally adaptive random basis elements and enables full posterior inference including point and interval estimates of the unknown regression function as well as the marginal effects of potential predictors. We used BART to predict two classes of BMI (i.e., BMI ≥ 25 kg/m^2 and BMI < 25 kg/m^2), WC, WHR and HC (the same cutoff points as MANOVA) based on different sets of predictors. We used 10-fold cross validation (in each iteration, 90% of the dataset was used to build the BART model and 10% was used to predict the classes). Subsequently, a receiver operating characteristic curve (ROC) (Fawcett, 2006; Linden, 2006) was used to measure the Area-under-ROC curve (AUC). Initially, we included all the variables such as age, physical activity and smoking status. However, these variables were removed after showing no added prognostic value. BART takes into account nonlinear associations as well as all potential interactions. We employed BART based on the assumption that immunologic complex systems consist of networks of interconnected and interactive elements with linear and nonlinear associations. We also employed logistic regression with 10-fold cross validation.

MANOVA analyses were carried out using Stata (SE 10.1 for Windows). BART and ROC analyses were based on freely available R packages: BART (Chipman et al., 2008; Chipman and McCulloch, 2009; Pocernich, 2010).

Results

Table 1 shows the characteristics of the study population stratified by cases and controls. Only immunologic elements with a statistically significant effect in our analysis are shown. There were altogether 70 men and 106 women in our study. IL-8, IL-10 and IP-10 together with gender, included in a MANOVA model ($p < 0.0003$), best separated individuals with BMI above and below 25 kg/m^2. Among the predictors, IP-10 ($p < 0.001$), IL-8 ($p < 0.017$) and IL-10 ($p < 0.026$) had significant impact on separating the classes, with IP-10 having the most significant impact. Table 2 shows the results of MANOVA analysis for two classes of normal versus excessive weight (i.e., BMI > 25 kg/m^2) individuals. BMI is a crude measure of fatness in both genders, while WHR is more representative of the common type of obesity, central adiposity. A MANOVA model ($p = 0.0003$) including IL-4, IL-8, IL-12, IL-13, IP-10 and gender best separated two classes of WHR groups (i.e., above and below 0.95 in men and 0.79 in women), in which IL-13 ($p = 0.003$), IL-8 ($p = 0.014$), IL-12 ($p = 0.018$), IP-10 (0.038) and IL-4 ($p = 0.043$) had significant impact.

An ROC curve based on 10-fold cross validated BART analyses provided prognostic values for the candidate cytokines, that is, IL-8, IL-10, IFN-γ and IP-10 for BMI, as shown in Figure 1, with AUC of 0.69 (95% CI: 0.67, 0.71), and $p < 0.00004$. When the same analysis was repeated by limiting the data to BMI ≥ 23.5, the prediction improved marginally adding 2% to AUC. Similar to MANOVA model, the set of IL-4, IL-8, IL-12, IL-13, IP-10 significantly ($p = 0.005$) separated two classes of WHR groups using the same cutoff points (Figure 2).

Table 1. Characteristics of the study population stratified by cases and controls.

	Controls			Cases		
	Men	Women	Both	Men	Women	Both
Age	53.6 (SD: 7.4)	54.0 (SD: 8.3)	53.8 (SD: 7.9)	53.4 (SD: 7.7)	54.5 (SD: 8.6)	54.1 (SD: 8.2)
Physical act	2.6 (SD: 1.0)	2.6 (SD: 0.9)	2.6 (SD: 0.9)	2.4 (SD: 0.9)	2.7 (SD: 0.9)	2.6 (SD: 1.0)
BMI	26.2 (SD: 3.0)	25.5 (SD: 3.6)	25.7 (SD: 3.4)	25.7 (SD: 3.4)	25.8 (SD: 4.3)	25.8 (SD: 3.9)
WHR	0.9 (SD: 0.1)	0.8 (SD: 0.1)	0.8 (SD: 0.1)	0.9 (SD: 0.1)	0.8 (SD: 0.1)	0.8 (SD: 0.1)
IL-4	−0.7 (SD: 1.1)	−0.7 (SD: 1.3)	−0.7 (SD: 1.2)	−0.8 (SD: 1.1)	−1.1 (SD: 1.2)	−1.0 (SD: 1.2)
IL-6	0.4 (SD: 1.8)	0.4 (SD: 2.1)	0.4 (SD: 2.0)	0.8 (SD: 1.8)	0.7 (SD: 2.0)	0.7 (SD: 1.9)
IL-8	4.5 (SD: 1.9)	3.7 (SD: 1.9)	4.0 (SD: 2.0)	3.8 (SD: 2.3)	3.1 (SD: 2.4)	3.4 (SD: 2.4)
IL-10	2.5 (SD: 1.7)	3.5 (SD: 2.1)	3.1 (SD: 2.0)	2.8 (SD: 2.2)	3.0 (SD: 2.4)	2.9 (SD: 2.3)
IL-12	5.6 (SD: 1.9)	6.6 (SD: 2.6)	6.2 (SD: 2.4)	5.2 (SD: 2.7)	6.1 (SD: 2.9)	5.7 (SD: 2.8)
1L-13	1.8 (SD: 1.3)	1.7 (SD: 1.3)	1.8 (SD: 1.3)	1.8 (SD: 1.2)	1.6 (SD: 1.4)	1.7 (SD: 1.3)
IP-10	3.6 (SD: 0.6)	3.9 (SD: 0.7)	3.8 (SD: 0.7)	3.7 (SD: 0.7)	4.0 (SD: 0.9)	3.9 (SD: 0.9)

BMI, body mass index; SD, standard deviation; WHR, waist-to-hip ratio.

Table 2. MANOVA for two classes of normal versus excessive weight (i.e., BMI > 25 kg/m^2) individuals.

	Statistic	*p* Value
MANOVA		
W	0.851	0.0003
P	0.149	0.0003
L	0.175	0.0003
R	0.175	0.0003
lnil8		
W	0.9373	0.0165
P	0.0627	0.0165
L	0.0669	0.0165
R	0.0669	0.0165
lnil12		
W	0.9532	0.0255
P	0.0468	0.0255
L	0.0491	0.0255
R	0.0491	0.0255
lnip10		
W	0.9326	0.0008
P	0.0674	0.0008
L	0.0723	0.0008
R	0.0723	0.0008
Sex		
W	0.9674	0.0296
P	0.0326	0.0296
L	0.0337	0.0296
R	0.0337	0.0296

BMI, body mass index; L, Lawley–Hotelling trace; MANOVA, multivariate analysis of variance; R, Roy's largest root; P, Pillai's trace; W, Wilks' lambda.

The 10-fold cross validated logistic regression analysis indicated an AUC of 0.65 (0.63, 0.67), $p = 0.0006$. A higher AUC derived from the BART model is consistent with our assumption about the complexity and nonlinearity of the immunologic network, particularly with regard to obesity.

The ROC curves derived after a BART model based on either control subjects (shown in Figure 2) or based on cases only (not shown) are comparable with each other and with the model including all subjects. In addition, examining the binary outcome of case/control status for NHL by using age-adjusted logistic regression, we found that there was no statistically significant difference between NHL cases and controls with regard to BMI and other anthropometric measures as well as the set of the predictors (IL-8, IL-10, IFN-γ, IP-10), nor was the logistic model itself statistically significant ($p = 0.1997$).

Discussion

Ideally, during the analysis of the associations between a complex condition such as obesity and a set of variables such as immunological factors, which constitute a complex network of interconnected elements, we would like to infer a full model of all possible immunological variables and all possible interactions between them. In practice, this is computationally impossible, and conceptually it would be difficult to interpret such a model. Here we suggest that it may be useful to look at the combination of immunologic changes that take place in obesity, and identify a set of predictor variables covering a network of linear and/or nonlinear associations. Within this context, we propose the concept of "immunological signature" of a pathological condition such as obesity. To our knowledge, this approach has not been applied in this field yet.

The MANOVA analyses indicated that IP-10, IL-8 and IL-10 have a significant impact on separation of the two classes of bodyweight based on BMI. IL-13, IL-8, IL-12, IP-10 and IL-4 had the maximum impact on the separation of WHR-based classes of bodyweight.

The BART enabled us to cross validate the prediction and measure the AUC. Tenfold cross validation of the BART model using various combinations of the predictors (cytokines) led to a highly significant prediction (AUC > 0.69%, $p < 0.00004$) using a set of IL-8, IL-10, IP-10 and IFN-γ, as shown in Figure 1. This is the same set of predictors (except IFN-γ in MANOVA) that we observed through MANOVA. This level of consistency reassures about the solidity of our findings. Among the predictors, IP-10 had the maximum prognostic value (IP-10 nearly 62%, IL-8 nearly 2%, IL-10 nearly 3% and IFN-γ nearly 1%).

We repeated all calculations in controls and cases separately and found similar predictive results (although with a slightly lower statistical power).

Concepts such as the "immunological signature" and "metabonomic fingerprint" have already been developed in genomic and metabonomic investigations (Lindon et al., 2003) of various diseases and there are similar examples in proteomics and lipidomics (Watson, 2006; Weiss et al., 2006; Drake and Ping, 2007; Tegnér et al., 2007). Here we have taken initial steps in a similar direction by introducing an immunologic profile or immunologic signature of excessive bodyweight based on our data.

Overall, our proposed approach, including MANOVA and BART analyses, showed significant impacts of IL-10, IP-10 and IL-8 and IL-4, IL-8, IL-12, IL-13 and IP-10 in separating BMI and WHR classes, respectively. Both predictive models of, i.e., BMI and WHR classes share IL-8 and IP-10 between the set of their predictors.

IP-10 belongs to the CXC superfamily (Farber, 1997). Monocytes, endothelial cells and fibroblasts express IP-10 (CXCL10) (Luster et al., 1985; Farber, 1997). The expression and secretion of IP-10 by human monocytic cells are selectively increased by leptin. IP-10 levels are positively associated with leptin levels (Meier et al., 2003). Therefore, the observed predictive role of IP-10 in our study might indicate increased levels of plasma leptin. In this regard, the observed association between female gender and higher levels of IP-10 is consistent with the fact that in general women have higher levels of leptin (Considine et al., 1996; Isidori et al., 2000; Marshall et al., 2000). An enhanced expression of IP-10 has been reported among coronary heart disease (CHD) patients (Fernandes et al., 2004; Rothenbacher et al., 2006), which is consistent with the well-established association of CHD and excessive body weight (Hubert et al., 1983; Harris et al., 1988; Kannel et al., 1991; Manson et al., 1995; Rimm et al., 1995; Shinton et al., 1995; Willett et al., 1995; Jousilahti et al., 1996; Kahn et al., 1996; Kannel et al., 1996; Spataro et al., 1996; Walker et al., 1996; Seidell, 1997; Shaper et al., 1997; Eckel and Krauss, 1998; Rexrode et al., 1998; Singh and Lindsted, 1998; Stevens et al., 1998; Baik et al., 2000; Field et al., 2001; Rao et al., 2001; Wilson et al., 2002; Zhou et al., 2002; Jensen et al., 2003; Suk et al., 2003; Pérez et al., 2007; Whitlock et al., 2009).

While obesity is associated with increased risk of cancer, IP-10 inhibits bone marrow colony formation and has shown to have antitumor activity *in vivo* (Angiolillo et al., 1995) and may participate in the regulation of angiogenesis during inflammation and tumorigenesis (Angiolillo et al., 1995). IP-10 is chemoattractant for human monocytes, activates T cells and a number of other cells. Moreover, it promotes T cell adhesion to endothelial cells (Angiolillo et al., 1995; Dufour et al., 2002). Thus, despite adverse effects of IP-10 on coronary events, its rising levels might hypothetically be beneficial in contrasting

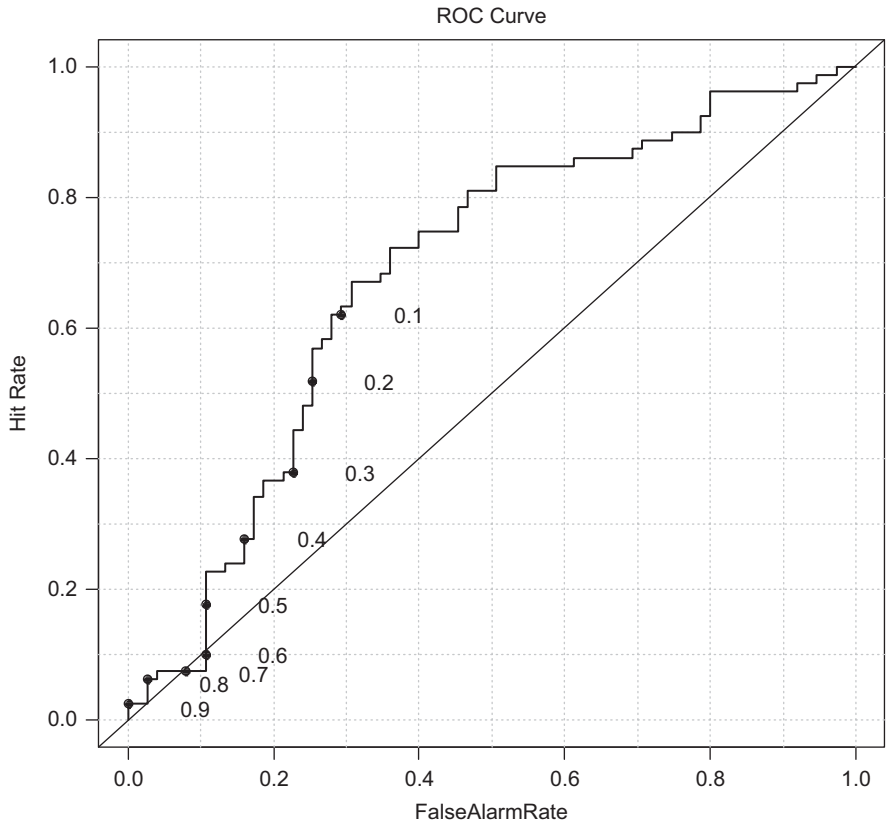

Figure 1. Receiver operating characteristic (ROC) curve of 10-times cross validated Bayesian additive regression tree prediction of body mass index classes (i.e., above or below 25 kg/m^2); AUC > 69%, and p value < 0.00004; total observations: 154; events: 79; nonevents: 75; predictors: IL-8, IL-10, IP-10 and IFN-γ.

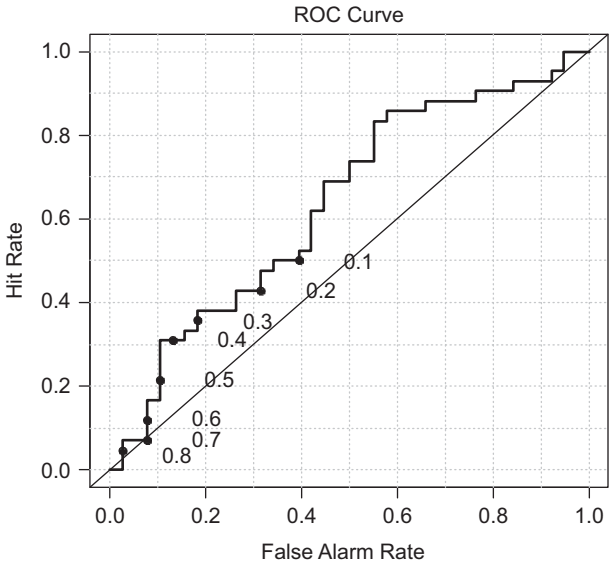

Figure 2. As in Figure 1, but controls only, AUC curve 63%, $p = 0.019$.

the cancer risk of obese people and could be viewed as a compensatory defense mechanism (Angiolillo et al., 1995).

The association of IL-8 with BMI (Straczkowski et al., 2002),WHR (Straczkowski et al., 2002) and WC (Kim et al., 2006) has been indicated in the literature. Scientific evidence based on *in vitro* experiments has shown that adipocytes produce IL-8 in human (Bruun et al., 2000; Bruun et al., 2001). IL-8 has already been introduced as a potential candidate linking obesity with obesity-related metabolic complications (Kim et al., 2006). Moreover, circulating levels of IL-8 were associated with BMI and WHR (Kim et al., 2006).

IL-10 is an anti-inflammatory cytokine that can inhibit production of proinflammatory cytokines like IFN-γ, IL-2, IL3 and TNF-α by macrophages and the type I T helper cells. There is evidence that leptin may promote an optimal proinflammatory response because, on one hand, it plays a pivotal role in the systemic inflammatory response and, on the other hand, restrains the inflammatory response via IL-10 production (Bracho-Riquelme et al., 2008). Therefore, we hypothesize the key role of leptin in pathogenesis of obesity, and its association with various cytokines indirectly has been reflected in the results of our analyses. Also the role of adiponectin and its association with cytokines need to be considered. Adiponectin is an adipocyte-derived protein and its levels are inversely related to the degree of adiposity (Nedvídková et al., 2005). Decreased plasma adiponectin levels were reported in insulin-resistant states such as obesity and type 2 diabetes and in patients with coronary artery diseases (Shimada et al., 2002; Hulthe et al., 2003). Adiponectin and leptin perform complementary actions and can have additive effects (Shimada et al., 2002). Scientific evidence suggests a critical relevance of adiponectin for regulation of cytokine in obesity. Adiponectin has been shown to induce the production of IL-10 in primary human monocytes, monocyte-derived macrophages and dendritic cells and to significantly impair the production of IFN-γ in human macrophages (Wolf et al., 2004). Thus, the significant effect of adiponectin in changing the production of IL-10 and IFN-γ in human and its critical role in energy balance might be a potential explanation of the predictive value of IL-10 and IFN-γ in our analysis.

In summary, our analyses suggest that IL-8, IL-10, IFN-γ and IP-10 together are an overall predictor (immunologic profile) of obesity (BMI) with up to 71% area-under-ROC curve. Changes of these immunological factors are likely to be mediated by leptin and adiponectin. We also propose that further studies are needed to determine the immunologic profiles of specific subgroups of overweight/obese individuals with regard to their underlying causes [e.g., those with known polymorphisms that are associated with both obesity and cytokine production (García et al., 2006; Strandberg et al., 2006; Suzuki et al., 2009; Manica-Cattani et al., 2010), those on high fat diet, those on diets used for weight loss, those who recently gained/lost weight]. Most likely, these specific subgroups of obese/overweight individuals will have their unique pattern of immunologic profiles with the same applications as lipidomics, genomics and metabonomics. Ultimately, this approach (based on human and/or animal research) could pave the way for integrating immunologic research into wider systems biology investigations (Sauer et al., 2007).

Declaration of interest

The study was funded by the "Determinants of obesity and its prevention" project, Regione Umbria, Direzione Regionale Sanità e Servizi Sociali, and by ECNIS.

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