AGE
DOI 10.1007/s11357-012-9483-x

Metabolic syndrome in the offspring of centenarians: focus on prevalence, components, and adipokines

R. Ostan · L. Bucci · E. Cevenini · M. G. Palmas · E. Pini · M. Scurti · R. Vescovini · C. Caruso · D. Mari · G. Vitale · C. Franceschi · D. Monti

Received: 4 May 2012 / Accepted: 17 October 2012

Abstract With aging, an increased prevalence of a clustering of metabolic abnormalities has been observed. These abnormalities include obesity, dyslipidemia, hypertension, and insulin resistance and are collectively known as metabolic syndrome (MetS), a low-grade, systemic, inflammatory condition associated with an increased risk of cardiovascular disease, diabetes, and other adverse health outcomes. A number of studies have demonstrated that centenarians' offspring have a significant survival advantage and a lower risk of developing the most important age-related diseases. They therefore represent one of the best models with which to study the familiar component of human longevity. The aim of this study was to determine if the offspring of centenarians (n=265 subjects) showed a different prevalence of MetS in comparison to the offspring of non-long-lived parents (controls, n=101 subjects). In addition, we assessed whether centenarians' offspring showed particular features of MetS and a distinct regulation of circulating adipokines, cytokines, and metabolic mediators. Although the prevalence of MetS was quite similar both

R. Ostan · L. Bucci · E. Cevenini · M. G. Palmas · E. Pini · M. Scurti · C. Franceschi
Department of Experimental Pathology,
University of Bologna,
Via San Giacomo, 12,
40126 Bologna, Italy

R. Vescovini
Department of Internal Medicine and Biomedical Sciences,
University of Parma,
Via Gramsci, 14,
43126 Parma, Italy

C. Caruso
Immunosenescence Unit, Department of Pathobiology and Biomedical Methodologies, University of Palermo,
Corso Tukory, 211,
90100 Palermo, Italy

D. Mari · G. Vitale
Department of Medical Sciences, University of Milan,
Via F. Sforza, 35,
20122 Milano, Italy

D. Mari
Geriatric Unit IRCCS Ca' Granda Foundation Maggiore Policlinico Hospital,
20122 Milan, Italy

G. Vitale
IRCCS Istituto Auxologico Italiano,
Milan, Italy

D. Monti (✉)
Department of Experimental Pathology and Oncology,
University of Florence,
Viale Morgagni, 50,
50134 Florence, Italy
e-mail: daniela.monti@unifi.it

Published online: 09 November 2012

in the offspring of centenarians and the controls, MetS-affected centenarians' offspring seemed healthier, more functionally fit, and had lower resistin levels. MetS prevalence did not change in centenarians' offspring across resistin, IGF-1, and resistin/IGF-1 ratio tertiles. On the other hand, in controls, MetS prevalence strongly increased across resistin tertiles and in the third resistin/IGF-1 ratio tertile, indicating a dramatic increase in MetS prevalence when the ratio between these two factors is unbalanced, with high levels of resistin and low levels of IGF-1.

Keywords Metabolic syndrome · Aging · Inflammaging · Centenarians' offspring · Adipokines

Introduction

With aging, there is a profound modification within the cytokine network, characterized by a general increase in plasma levels and cell capability to produce pro-inflammatory cytokines. This leads to a chronic, low-grade, pro-inflammatory status known as *inflammaging* (Franceschi et al. 2000a, b). This peculiar pro-inflammatory condition could be the cause or the effect of the increased prevalence of a clustering of metabolic abnormalities characterized by an inflammatory pathogenesis such as obesity, dyslipidemia, hypertension, insulin resistance, and type 2 diabetes. Together, these abnormalities constitute the metabolic syndrome (MetS) (Das 2004). All the single components of MetS and MetS itself are associated with an increased risk of developing cardiovascular disease, stroke, brain infarction, diabetes mellitus, and other age-related diseases (Haffner 2006; Kwon et al. 2006). It is unclear which of the risk factors that constitute the MetS contributes most strongly to these adverse outcomes, although it has been suggested that obesity or insulin resistance might be responsible (DeStefano et al. 1993; Sattar et al. 2008). In fact, fat mass accumulation is associated with an elevation of inflammatory markers, since adipose tissue, and in particular the visceral fat, is now considered an endocrine organ. Mature adipocytes are involved in the secretion of a large number of multifunctional molecules, collectively termed "adipokines" (Yudkin et al. 1999) able to physiologically modulate the energetic balance of the organism, lipid and glucose metabolism, immune response, and reproductive functionality (Chaldakov et al. 2003; Rajala and Scherer 2003; Gnacinska et al. 2009). Furthermore, macrophages residing in the adipose tissue may also be a source of pro-inflammatory factors and may modulate the secretory activity of adipocytes (Xu et al. 2003). Therefore, adipose tissue and its age-associated redistribution (Arai et al. 2011) could play a role in inflammaging by affecting the adipokines' network.

Recently, it has been shown that familiar factors may play an important role in the onset of MetS. In fact, the offspring of long-lived parents (nonagenarians and centenarians) have a moderately lower prevalence of MetS and retain improved glucose tolerance and enhanced insulin sensitivity (Rozing et al. 2009, 2010; Wijsman et al. 2011; Barzilai et al. 2003) compared to age-matched controls. These observations suggest that a protective phenotype against MetS and insulin resistance could be inherited from long-lived parents and be relevant to healthy aging.

The aim of this study was to determine if centenarians' offspring, who are characterized by "better" aging (Terry et al. 2004a, b; Atzmon et al. 2004; Vitale et al. 2012; Gentilini et al. 2012), showed a different prevalence of MetS in comparison to age-matched offspring of non-long-lived parents. In addition, we evaluated whether MetS-affected centenarians' offspring displayed particular features of this metabolic/pro-inflammatory syndrome and a peculiar regulation of circulating adipokines, cytokines, and metabolic mediators, in order to identify a phenotype that could influence their overall health status.

Materials and methods

Study design and participants

A total of 366 subjects were enrolled from five Italian cities (Bologna, Milan, Florence, Parma, and Palermo) and the surrounding areas. The group of centenarians' offspring consisted of 265 subjects (108 males and 157 females, mean age 70.2±6.6 years) with one centenarian parent (born in Italy between 1900 and 1908). The control group consisted of 101 subjects (52 males and 49 females, mean age 70.9±6.0 years) with both parents (born in Italy between 1900 and 1908) dead before the average life expectancy at 15 years of age (67 years for the father and 72 years for the mother) according to

Italian mortality tables (see website "Human Mortality Database" of the Max Planck Institute for Demography, Rostock, Germany: http://www.mortality.org). All the centenarians' offspring and offspring of non-long-lived parents were free living and recruited from Italian population according the above-mentioned strict demographic criteria. The study protocol was approved by the Ethical Committee of Sant'Orsola-Malpighi University Hospital (Bologna, Italy).

After obtaining written informed consent, a standard questionnaire was administered by trained physicians and nursing staff to collect demographic and lifestyle data, anthropometric measurements, functional, cognitive and health status, clinical anamnesis, and details on drug use. Subjects affected by malignant neoplasia and/or those in therapy with immunosuppressor drugs (like cyclosporine, methotrexate, glucocorticoids, etc.) or anticoagulant drugs were excluded from the study.

Data collection

Body weight was measured using standard weighing scales (SECA Mod. 761) calibrated in kilograms. Height was measured at head level to the nearest centimeter with the subject standing barefoot, feet together, using a standard tape measure calibrated in centimeters. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters (kg/m^2). Waist circumference was measured to the nearest centimeter by wrapping a flexible steel tape at the level of the umbilicus at the end of exhalation, with the subject standing.

Past and current disease history was accurately recorded by addressing the major age-related pathologies: myocardial infarction, stroke, cerebral thrombosis and hemorrhage, hypertension, chronic obstructive pulmonary disease, hypercholesterolemia, diabetes, cancer, and chronic renal insufficiency.

Current use of medication (including inspection of the drugs by the interviewer) was recorded, and the drugs were grouped into four main categories: cardiovascular (antiarrhythmic and/or vasodilator and/or thrombolytic drugs), antihypertensive (calcium channel blockers and/or ACE inhibitors and/or diuretics and/or beta blockers), lipid-lowering (statins and/or fibrates and/or other hypolipidemic agents), and antidiabetic (sulfonylureas and/or biguanides and/or insulin and insulin analogs and/or other oral antidiabetic association) therapies.

Physical performance was assessed using the Chair Stand Test protocol to evaluate leg strength and endurance by measuring the time it takes to perform five repetitions of sit-to-stand (Csuka and McCarty 1985). On the basis of the result obtained, participants were divided into two groups (able or unable to complete the test).

Laboratory measurements

Overnight fasting blood samples were obtained early in the morning. Serum was removed after clotting and centrifugation at $760\times g$ for 20 min, rapidly frozen and stored at −80 °C. Serum total and HDL cholesterol, triglycerides, and glycemia were measured using standard hematology methods. Serum LDL concentration was calculated using the Friedewald equation: LDL = total cholesterol−HDL−(triglycerides / 5). Serum insulin was measured using a chemiluminescent immunoassay (LIAISON® Insulin assay, DiaSorin, Saluggia, Italy), and samples were analyzed on the LIAISON® Analyzer (DiaSorin). Insulin resistance status was assessed using the homeostasis model assessment of insulin resistance (HOMA-IR), according to the previously described formula (Matthews et al. 1985): insulin (in microunits per milliliter) × glucose (in millimoles per liter)/22.5. Total IGF-I was assayed using a one-step sandwich chemiluminescence immunoassay after prior separation of IGF-I from binding proteins on the LIAISON® analyzer.

Plasma was obtained from blood within 2 h of venipuncture by centrifugation at $2{,}000\times g$ for 20 min. It was rapidly frozen and stored at −80 °C. Plasma levels of IL-6, IL-10, TNF-α trimer, serum amyloid A, adiponectin, leptin, and resistin were measured by multiplex sandwich ELISA technology (SearchLight, Aushon Biosystems, Billerica, MA) according to the manufacturer's instructions. Samples, standards, and reagents were dispensed in the plates using a standardized technique employing a robotic liquid handling system with 16 channels (Microlab® STAR, Hamilton Robotics, Reno, NV). Plasma TGF-β1 concentration was determined using a commercial ELISA kit (DRG Instruments GmbH, Marburg, Germany), according to the manufacturer's instructions. TGF-β1 concentration was detected and quantified using a Synergy™ HT Multi-Detection Microplate Reader (BioTek® Instruments, Winooski, VT). Plasma fibrinogen was measured using a fibrin polymerization assay (Boehringer Biochemia). Plasminogen activator inhibitor type 1 activity (PAI-1) was

measured using a chromogenic method (Biopool, Umea, Sweden).

Subjects who have recently (1 week prior to the study) used medication that could influence the inflammatory response, such as steroid or nonsteroidal anti-inflammatory drugs and immunomodulant agents, were excluded from adipokine and cytokine analysis.

Definition of MetS

MetS was defined according to the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP-ATP III) criteria (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults 2001). Based on this definition, the subjects with MetS were identified as having any combination of three or more of the following components: abdominal obesity (waist circumference >102 cm for men and >88 cm for women), high triglycerides (plasma triglycerides ≥150 mg/dl or subjects on lipid-lowering therapy), low HDL cholesterol (<40 mg/dl for men and <50 mg/dl for women), hypertension (blood pressure ≥130 or ≥85 mmHg or subjects on hypotensive treatment), and hyperglycemia (fasting plasma glucose ≥110 mg/dl or subjects on antidiabetic therapy).

Statistical analysis

A preliminary evaluation of the differences between MetS-affected centenarians' offspring and offspring of non-long-lived parents was performed using the chi-square test for categorical variables and the independent samples' *t* test or nonparametric Mann–Whitney *U* test for continuous variables (data not shown). Binary logistic regression was performed to examine the relationship between dichotomized variables (MetS prevalence, MetS components, ability to perform chair stand test, prevalence of past and current diseases, and drug therapies) and offspring status. The univariate general linear model was used to examine the relationship between continuous variables (BMI, lipids, metabolism, insulin resistance, and inflammatory markers) and offspring status. Multiple regression model was used to test the association between metabolic mediators and prevalence of MetS adjusted for BMI. All analyses were executed using SPSS 19.0 for windows (SPSS Inc., Chicago, IL, USA).

Results

Table 1 displays the baseline characteristics of the study population. No difference in age or gender distribution was observed between centenarians' offspring and offspring of non-long-lived parents (controls). BMI was higher in the controls ($p=0.003$), while no differences were observed in the distribution of the NCEP-ATP III criteria in the entire population. Ninety-four MetS-affected centenarians' offspring and 34 MetS-affected controls were identified, and the prevalence of the MetS was found to be quite similar in the two groups (35.5 vs. 33.7 %, $p=0.910$).

Table 2 shows the baseline and lifestyle features of the MetS-affected subjects. The MetS-affected centenarians' offspring and MetS-affected controls were comparable in age (71.1±5.6 vs 72.2±5.7 years, $p=0.329$), gender distribution ($p=0.745$), level of education ($p=0.307$), BMI ($p=0.066$), proportion of current and former smokers ($p=0.473$ and $p=0.969$, respectively), and proportion of subjects consuming alcohol ($p=0.642$).

The health status of MetS-affected centenarians' offspring and controls was therefore compared (Table 3). The MetS-affected centenarians' offspring had a significantly lower prevalence of past cardiovascular events (myocardial infarction, stroke, cerebral thrombosis/hemorrhage; $p=0.033$), hypercholesterolemia ($p=0.015$), and renal insufficiency ($p=0.027$) than the MetS-affected controls. The prevalence of hypertension ($p=0.066$), chronic obstructive pulmonary disease ($p=0.201$), and past cancer ($p=0.152$) was also lower in the MetS-affected centenarians' offspring, but these differences were not statistically significant. Moreover, in MetS-affected centenarians' offspring, the mean number of prescribed drugs was significantly lower ($p=0.000$); in particular, a significantly lower percentage of subjects on cardiovascular ($p=0.005$) and lipid-lowering therapy ($p=0.000$) was found. The percentage of MetS-affected centenarians' offspring on hypertensive therapy was also lower but this difference was not significant. Considering physical performance, a higher percentage of MetS-affected centenarians' offspring was able to perform chair stand test ($p=0.002$) (Table 3).

Thus, given that MetS-affected centenarians' offspring appeared healthier and more functionally fit than MetS-affected controls, we evaluated the constituents of the MetS affecting these subjects by analyzing the distribution of the NCEP-ATP III criteria (Fig. 1). Within the MetS-affected centenarians' offspring group,

Table 1 Distribution of MetS components and prevalence of MetS in centenarians' offspring and controls

	Centenarians' offspring	Controls	O.R. (95 % C.I.)	*p* value
n	265	101		
Age, years ± S.D.	70.2±6.6	70.9±6.0	0.98 (0.95–1.02)	0.338
Females, *n* (%)	157 (59.2)	49 (48.5)	1.54 (0.97–2.45)	0.065
BMI, kg/m^2, mean ± S.D.[a]	26.5±4.4	28.1±4.2	1.08 (1.03–1.14)	0.003
Hypertension, *n* (%)[a]	224 (84.5)	88 (87.1)	0.80 (0.41–1.57)	0.522
High triglycerides, *n* (%)[a]	96 (36.2)	46 (45.5)	0.67 (0.42–1.06)	0.088
Abdominal obesity, *n* (%)[a]	92 (35.2)	43 (43.0)	0.66 (0.41–1.07)	0.089
Low HDL cholesterol, *n* (%)[a]	81 (31.0)	22 (22.2)	1.49 (0.86–2.57)	0.154
Hyperglycemia, *n* (%)[a]	40 (15.1)	19 (18.8)	0.77 (0.42–1.40)	0.389
MetS prevalence, *n* (%)[a]	94 (35.5)	34 (33.7)	1.03 (0.63–1.68)	0.910

O.R. odds ratio, *C.I.* confidence interval

[a] Gender-adjusted

hypertension ranked the highest (95.6 %), followed by high plasma triglycerides (71.3 %), abdominal obesity and low HDL cholesterol (68.8 and 67.0 %, respectively), and high fasting glucose/antidiabetic medications use (36.2 %). Hypertension also ranked the highest (97.1 %) in the MetS-affected controls, but it was followed by abdominal obesity (85.3 %), high plasma triglycerides (79.4 %), low HDL cholesterol, and high fasting glucose/antidiabetic medications use (48.5 and 41.2 %, respectively). In particular, a lower percentage of abdominal obesity and a higher proportion of low HDL were found in MetS-affected centenarians' offspring even if this difference was not statistically significant (p=0.070 and p=0.060, respectively).

Table 4 shows the lipid profile, insulin resistance markers, inflammatory profile, and metabolic mediators (adipokines) in MetS-affected centenarians' offspring and controls. MetS-affected centenarians' offspring had lower levels of HDL cholesterol and higher levels of LDL cholesterol, while there were no differences in total cholesterol, triglycerides, insulin, glycemia, and HOMA between the two groups. MetS-affected centenarians' offspring had lower levels of resistin in comparison to MetS-affected controls (p=0.008), while no differences in the inflammatory parameters (C-reactive protein, fibrinogen, PAI-1, serum amyloid A protein, IL-6, and TNF-α, TGF-β1), adiponectin, leptin, IGF-1, leptin/adiponectin, and resistin/IGF-1 ratio were found.

To investigate whether the higher abdominal obesity observed in controls may play a role in the increased levels of resistin found in these subjects, a linear regression analysis was performed between plasma levels of resistin and waist circumference. In

Table 2 Baseline features of MetS-affected centenarians' offspring and controls

	MetS-affected centenarians' offspring	MetS-affected controls	*p* value
n	94	34	
Age, years, mean ± S.D.	71.1±5.6	72.2±5.7	0.329
Females, *n* (%)	61 (64.9)	21 (61.8)	0.745
Education, years, mean ± S.D.	9.9±5.1	9.0±3.5	0.307
BMI, kg/m^2, mean ± S.D.	29.2±4.2	30.8±4.3	0.066
Lifestyle			
Current smokers, *n* (%)	14 (15.2)	7 (20.6)	0.473
Former smokers, *n* (%)	43 (55.1)	15 (55.6)	0.969
Daily alcohol consumption, *n* (%)	44 (48.4)	17 (53.1)	0.642

Table 3 Prevalence of major age-related diseases, pharmacological therapies, and physical performance in MetS-affected centenarians' offspring and controls

	MetS-affected centenarians' offspring	MetS-affected controls	O.R. (95 % C.I.)	*p* value
n	94	34		
Pathologies				
Past myocardial infarction, stroke, cerebral thrombosis/hemorrhage, *n* (%)	10 (10.8)	9 (26.5)	0.33 (0.12–0.92)	0.033
Hypertension, *n* (%)	58 (61.7)	27 (79.4)	0.42 (0.16–1.06)	0.066
Chronic obstructive pulmonary disease, *n* (%)	3 (3.2)	3 (8.8)	0.34 (0.15–0.97)	0.201
Hypercholesterolemia, *n* (%)	35 (37.2)	21 (61.8)	0.37 (0.16–0.82)	0.015
Diabetes, *n* (%)	22 (23.4)	9 (26.5)	0.85 (0.34–2.09)	0.721
Past cancer, *n* (%)	8 (8.5)	6 (17.6)	0.43 (0.14–1.36)	0.152
Chronic renal insufficiency, *n* (%)	1 (1.1)	4 (11.8)	0.08 (0.01–0.75)	0.027
Pharmacological therapy				
Number of prescribed medicines, mean ± S.D.	3.4±2.4	6.2±2.7	0.68 (0.57–0.81)	0.000
Cardiovascular therapy, *n* (%)	29 (30.9)	20 (58.8)	0.31 (0.14–0.70)	0.005
Anti-hypertensive therapy, *n* (%)	58 (61.7)	27 (79.4)	0.42 (0.16–1.06)	0.066
Lipid-lowering therapy, *n* (%)	27 (28.7)	22 (64.7)	0.22 (0.10–0.51)	0.000
Anti-diabetic therapy, *n* (%)	15 (16.0)	8 (23.5)	0.62 (0.23–1.62)	0.327
Physical performance				
Able to perform chair stand test, *n* (%)	87 (94.6)	24 (72.7)	6.52 (2.00–21.30)	0.002

controls, resistin was positively associated with waist circumference ($p=0.013$), while no association was found in centenarians' offspring ($p=0.244$) (Fig. 2).

In order to evaluate the influence of metabolic mediators on MetS prevalence in the two groups, subjects were stratified according to tertiles of leptin, adiponectin, leptin/adiponectin ratio, resistin, IGF-1, and resistin/IGF-1 ratio. As shown in Fig. 3, MetS prevalence progressively increased significantly across leptin tertiles in both groups ($p<0.001$), while it decreased across adiponectin tertiles in both groups, with a significant decrease observed only in the centenarians' offspring group ($p<0.001$). Moreover, MetS prevalence increased significantly across leptin/adiponectin ratio tertiles in both groups ($p<0.001$). As shown in Fig. 4, MetS prevalence did not change across resistin and IGF-1 tertiles in centenarians' offspring, while it increased significantly across the resistin tertile ($p<0.001$) and tended to decrease across IGF-1 tertiles in controls. MetS prevalence did not change in centenarians' offspring across resistin/IGF-1 ratio tertiles, while in controls, MetS prevalence strongly increased in the third tertile comprising the highest levels of resistin and the lowest levels of IGF-1 ($p<0.001$). All these associations remained significant after adjusting for BMI, except for leptin and resistin in controls probably due to the sample size.

Discussion

In this study, we show that the prevalence of MetS and all its components is quite similar in the population of centenarians' offspring and the population of offspring of non-long-lived parents we recruited. These data are in contrast with a previous study reporting that offspring of long-lived parents have a lower prevalence of MetS than their partners despite having a comparable body composition (Rozing et al. 2010). However, the results of the present paper show that in the presence of MetS, centenarians' offspring have a significantly lower prevalence of some important age-related

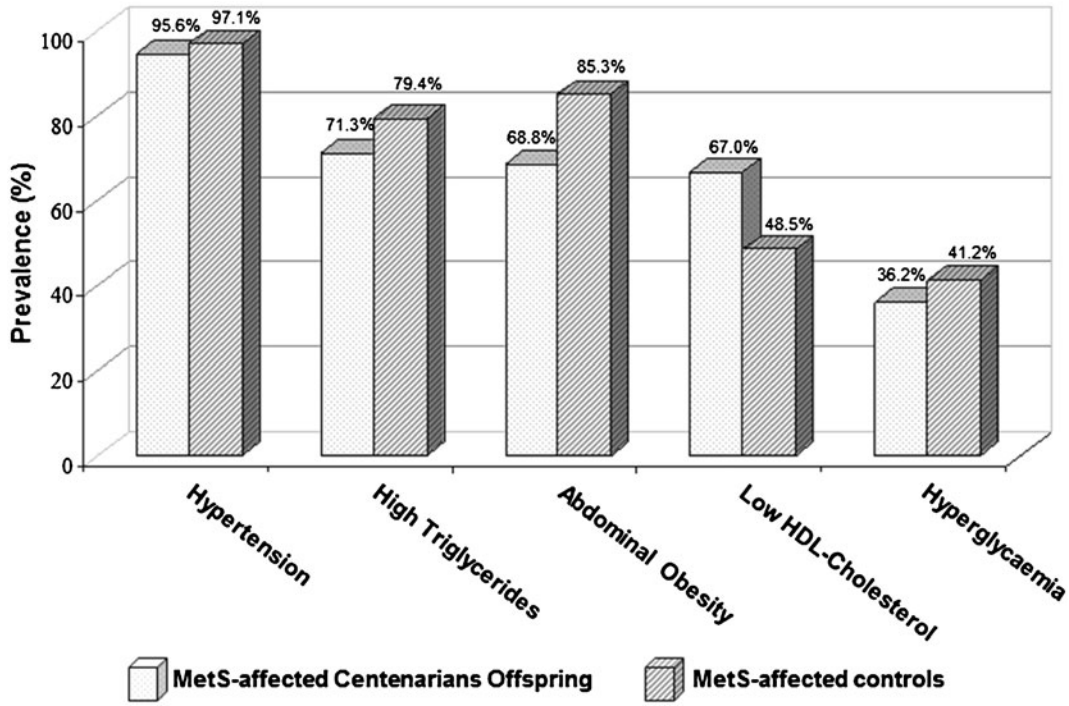


Fig. 1 Prevalence of MetS components in MetS-affected centenarians' offspring and controls. Data were expressed as percentage, and the statistical analysis was performed by chi-square test

diseases such as past cardiovascular events, hypertension, hypercholesterolemia, and renal insufficiency than do the offspring of non-long-lived parents. This is confirmed by the fact that MetS-affected centenarians' offspring took less drugs and, in particular, a lower percentage of them were on cardiovascular, lipid-lowering, and antihypertensive therapies. In addition, the chair stand test indicates that almost all the centenarians' offspring maintain good physical fitness even in the presence of MetS, while in controls, this percentage is significantly lower. These findings collectively indicate that MetS-affected centenarians' offspring are healthier and more functionally fit than MetS-affected controls, despite being comparable in age, gender distribution, and education level. Some studies report that centenarians generally avoid bad lifestyle habits (Galioto et al. 2008) and so too do their progeny, as demonstrated by Terry et al. (2007). In fact, the offspring of long-lived parents had a lower prevalence of some risk factors such as smoking. In contrast, in this study, no significant differences were found between groups with respect to lifestyle risk factors (smoking and alcohol consumption) showing that the better health status observed in MetS-affected centenarians' offspring might not depend on a healthier lifestyle transmitted from their centenarian parent.

Therefore, a possible explanation for the healthier condition of MetS-affected centenarians' offspring could be attributed to the composition of MetS. In fact, the prevalence of NCEP-ATP III criteria in MetS-affected centenarians' offspring and controls seems quite different and, in particular, we observed a trend towards a lower prevalence of abdominal obesity in centenarians' offspring with respect to controls. Abdominal obesity and the presence of visceral fat are increasingly recognized as major risk factors for cardiovascular diseases, and they also promote insulin resistance, dyslipidemia, and hypertension (Czernichow et al. 2011; de Koning et al. 2007). These observations, together with the fact that MetS-affected controls showed a higher proportion of past cardiovascular events, hypertension, and hypercholesterolemia, could suggest that a form of MetS where abdominal obesity is one of the major determinants could be associated with a worse outcome.

MetS-affected centenarians' offspring seem to have an unfavorable lipid profile, considering that they have

Table 4 Lipid profile, insulin resistance markers, metabolic mediators, and inflammatory profile of MetS-affected centenarians' offspring and controls

	MetS-affected centenarians' offspring	MetS-affected controls	O.R. (95 % C.I.)	*p* value
n	94	34		
Lipid profile				
Total cholesterol, mg/dl, mean (S.D.)	200.2 (43.5)	190.0 (36.4)	1.00 (1.00–1.02)	0.229
HDL cholesterol, mg/dl, median (25th–75th)	42.0 (35.0−50.0)	48.0 (38.5−71.0)	0.97 (0.94–0.99)	0.005
LDL cholesterol, mg/dl, mean (S.D.)	121.6 (41.8)	103.6 (34.3)	1.01 (1.00–1.02)	0.031
Triglycerides, mg/dl, mean (S.D.)	170.4 (82.2)	158.9 (69.0)	1.00 (1.00–1.01)	0.474
Insulin resistance markers				
Glycemia, mmol/l, mean (S.D.)	106.0 (42.3)	110.8 (41.0)	1.00 (0.99–1.01)	0.567
Insulin, μIU/ml, mean (S.D.)	17.2 (12.7)	13.4 (5.7)	1.05 (0.99–1.12)	0.106
HOMA-IR index, mean (S.D.)	4.5 (3.8)	3.8 (2.8)	1.06 (0.92–1.23)	0.407
Inflammatory profile[a]				
C-reactive protein, mg/l, mean (S.E.M.)	3.2 (0.5)	2.6 (0.4)	1.04 (0.92–1.18)	0.535
Fibrinogen, mg/ml, mean (S.E.M.)	3.6 (0.2)	3.1 (0.3)	1.27 (0.90–1.79)	0.173
PAI-1_{act}, IU/ml, mean (S.E.M.)	2.5 (0.2)	2.2 (0.3)	1.08 (0.78–1.50)	0.633
Serum amyloid A protein, μg/ml, mean (S.E.M.)	169.4 (22.6)	116.7 (20.4)	1.00 (1.00–1.01)	0.229
IL-6, pg/ml, mean (S.E.M)	36.9 (6.8)	52.9 (14.5)	1.00 (0.99–1.00)	0.283
TNF-α, pg/ml, mean (S.E.M)	39.7 (14.6)	67.7 (29.5)	1.00 (1.00–1.00)	0.383
IL-10, pg/ml, mean (S.E.M)	5.2 (0.8)	6.1 (1.0)	0.99 (0.94–1.04)	0.633
TGF-β1, pg/ml, mean (S.E.M.)	5.5 (0.4)	6.1 (1.0)	0.97 (0.89–1.07)	0.584
Metabolic mediators[a]				
Leptin, ng/ml, mean (S.E.M.)	33.1 (2.8)	35.7 (5.6)	1.00 (0.98–1.01)	0.649
Adiponectin, μg/ml, mean (S.E.M.)	31.6 (2.6)	35.7 (5.4)	0.99 (0.98–1.01)	0.454
Resistin, ng/ml, median (25th–75th)	8.7 (6.6–11.7)	11.4 (8.3–16.1)	0.87 (0.81–0.95)	0.008
IGF-1, ng/ml, mean (S.E.M.)	117.7 (4.9)	121.2 (9.4)	1.00 (0.98–1.01)	0.736
Leptin/adiponectin ratio, mean (S.E.M.)	2.1 (0.6)	1.8 (0.5)	–	0.767[b]
Resistin/IGF-1 ratio, mean (S.E.M.)	0.1 (0.0)	0.1 (0.0)	–	0.815[b]

[a] Five centenarians' offspring and four controls were excluded because they were using steroid or nonsteroidal anti-inflammatory drugs and/or immunomodulant agents the week before blood sampling. *p* values are obtained by regression analysis

p values are obtained by regression analysis and [b] Mann Whitney test

lower levels of HDL cholesterol and higher levels of LDL cholesterol in comparison to controls. These data are in contrast to the data obtained from a previous study which showed that the offspring of nonagenarian siblings displayed a more beneficial lipid profile (Vaarhorst et al. 2011). However, this result may be partly explained by the fact that less than half of the MetS-affected centenarians' offspring were on lipid-lowering therapy compared to the MetS-affected controls. This finding may indicate that in centenarians' offspring, a delayed onset or milder forms of hypercholesterolemia and hypertriglyceridemia can occur, which do not yet require pharmacological treatment with lipid-lowering agents.

In this study, we did not find significant differences in insulin resistance markers, in the prevalence of diabetes,

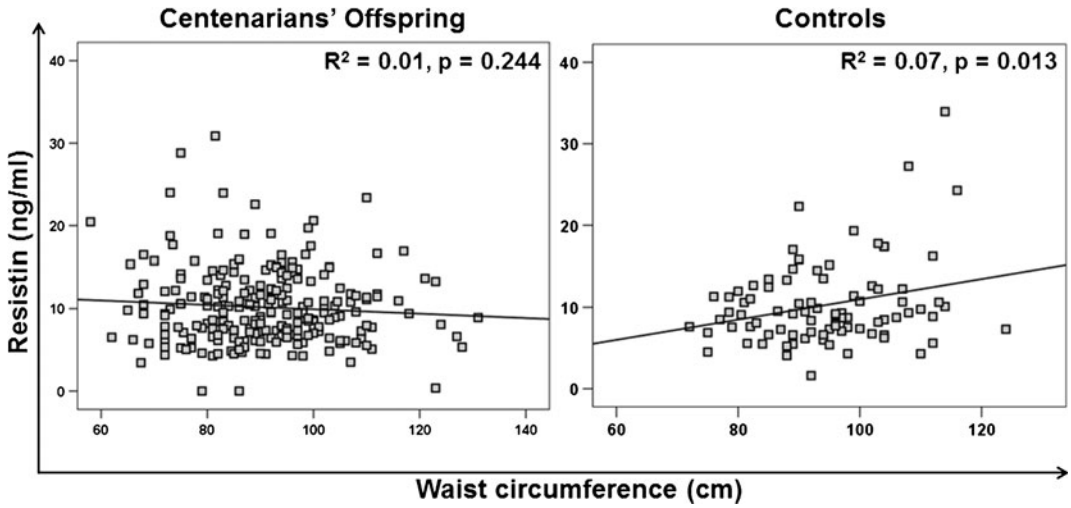
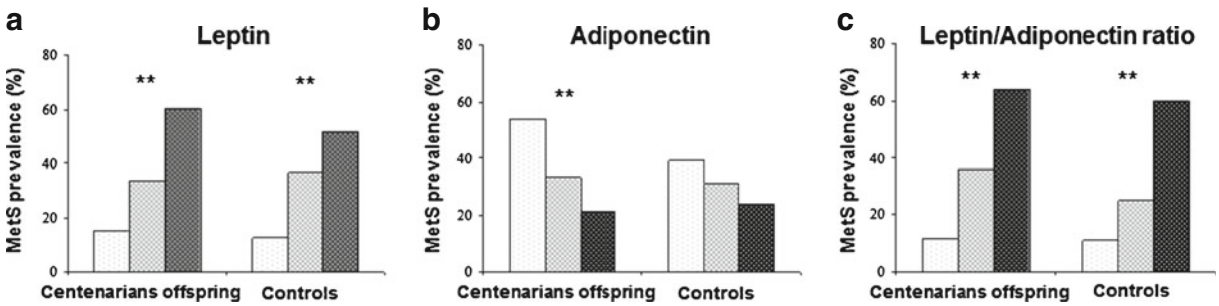


Fig. 2 Linear regression between resistin and waist circumference in centenarians' offspring and controls

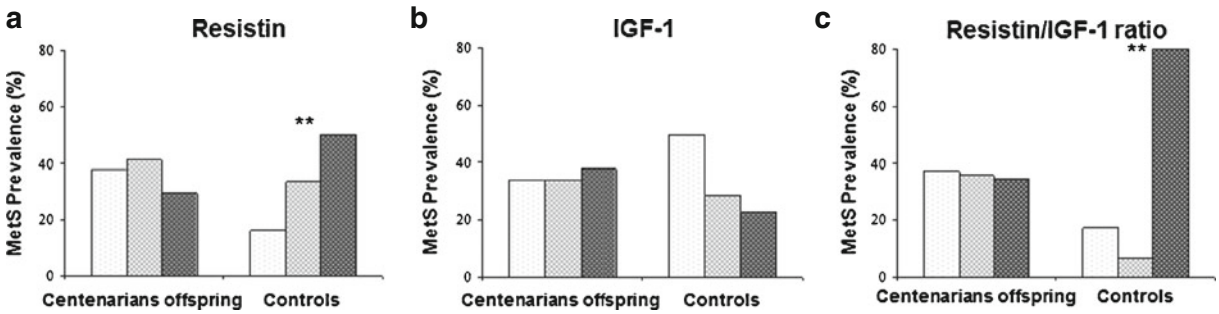
or in the use of antidiabetic therapy between centenarians' offspring and offspring of non-long-lived parents with MetS. A previous study demonstrated a preserved whole-body insulin sensitivity in healthy centenarians



d

	Centenarians offspring		Controls	
	p	O.R. (95% C.I.)	p	O.R. (95% C.I.)
Leptin				
1st Tertile (≤8.8 ng/ml)	1	-	1	-
2nd Tertile (8.9-23.6 ng/ml)	*0.053*	2.23 (0.99-5.01)	*0.323*	2.01 (0.50-8.09)
3rd Tertile (≥23.7 ng/ml)	*0.001*	4.36 (1.90-9.99)	*0.061*	3.85 (0.94-15.82)
Adiponectin				
1st Tertile (≤22.0 μg/ml)	1	-	1	-
2nd Tertile (22.1-48.2 μg/ml)	*0.002*	0.31 (0.15-0.66)	*0.423*	0.60 (0.18-2.07)
3rd Tertile (≥48.3 μg/ml)	*0.013*	0.38 (0.17-0.81)	*0.597*	0.71 (0.20-2.50)
Leptin/Adiponectin ratio				
1st Tertile (≤0.3)	1	-	1	-
2nd Tertile (0.4-0.8)	*0.016*	2.93 (1.23-7.01)	*0.423*	0.60 (0.18-2.07)
3rd Tertile (≥0.9)	*0.000*	6.57 (2.62-16.48)	*0.036*	5.09 (1.11-23.34)

Fig. 3 MetS prevalence for centenarians' offspring and controls in leptin (**a**), adiponectin (**b**), and leptin/adiponectin (**c**) ratio tertiles. $^{**}p<0.01$, for the chi-square test. **d** Multiple regression analysis showing the association between metabolic mediators tertiles and MetS prevalence adjusted for BMI. *O.R.* odds ratio, *C.I.* confidence interval



d

	Centenarians offspring		Controls	
	p	O.R. (95% C.I.)	p	O.R. (95% C.I.)
Resistin				
1st Tertile (≤7.6 ng/ml)	1	-	1	-
2nd Tertile (7.89-11.2 ng/ml)	*0.868*	1.06 (0.51-2.19)	*0.598*	1.46 (0.36-6.02)
3rd Tertile (≥11.3 ng/ml)	*0.233*	0.63 (0.30-1.34)	*0.090*	3.29 (0.83-13.04)
IGF-1				
1st Tertile (≤100.1 ng/ml)	1	-	1	-
2nd Tertile (100.2-136.7 ng/ml)	*0.437*	0.71 (0.30-1.68)	*0.176*	0.24 (0.03-1.88)
3rd Tertile (≥136.8 ng/ml)	*0.912*	1.05 (0.42-2.64)	*0.109*	0.23 (0.04-1.39)
Resistin/IGF-1 ratio				
1st Tertile (≤0.06)	1	-	1	-
2nd Tertile (0.07-0.11)	*0.939*	1.04 (0.37-2.94)	*0.189*	0.09 (0.00-3.22)
3rd Tertile (≥0.12)	*0.954*	1.03 (0.39-2.73)	*0.010*	19.13 (1.98-184.95)

Fig. 4 MetS prevalence for centenarians' offspring and controls in resistin (**a**), IGF-1 (**b**), and resistin/IGF-1 (**c**) ratio tertiles. $^{**}p<0.01$, for the chi-square test. **d** Multiple regression analysis showing the association between metabolic mediators tertiles and MetS prevalence adjusted for BMI. *O.R.* odds ratio, *C.I.* confidence interval

(Paolisso et al. 1996) and recent papers have reported that subjects with familial predisposition for healthy longevity showed enhanced glucose tolerance and higher whole-body insulin sensitivity when compared to a control group similar in age, sex, and body composition (Rozing et al. 2009, 2010; Wijsman et al. 2011). However, cross-sectional data from the Italian population showed the highest prevalence of insulin resistance (determined using the homeostasis model assessment) at 80–90 years (Paolisso et al. 2001). Therefore, a reevaluation of the parameters related to insulin resistance in the same subjects when older could reveal some significant differences.

The pathogenesis of MetS and of the metabolic abnormalities associated with it has a strong inflammatory component, and the presence and severity of this syndrome are tightly associated with markers of systemic inflammation. During aging, the fat redistribution and, in particular, the accumulation of central fat could contribute to the low-grade pro-inflammatory status mainly due to pro-inflammatory molecules (cytokines and adipokines) produced by adipocytes and by macrophages infiltrating adipose tissue (Arai et al. 2011; You et al. 2008). For this reason, we decided to evaluate the levels of the main pro- and anti-inflammatory markers. Moreover, Atzmon et al. (2008) demonstrated that adiponectin levels were significantly greater in ≥95-year-old subjects and their offspring compared to controls, suggesting that inherited factors play a role in determining adiponectin levels. In fact, a recent paper showed that the levels of some adipokines are significantly transmitted from parent to offspring (Al-Daghri et al. 2011).

The analysis of inflammatory and metabolic mediators showed that MetS-affected centenarians' offspring had lower levels of resistin in comparison to MetS-affected controls. In humans, data on the role of resistin

in insulin sensitivity and obesity are still controversial but a positive correlation has been found between this molecule and pro-inflammatory factors in adults with pathophysiological conditions such as atherosclerosis, renal disease, and obesity (Savopoulos et al. 2011). Furthermore, it has been tagged as a potential MetS marker. Since this pro-inflammatory and atherogenic adipokine is mostly produced by macrophages infiltrating visceral fat and is correlated with cardiovascular risk and insulin resistance, in the present paper, we showed that there was no association between the levels of resistin and abdominal obesity, as evaluated by waist circumference in centenarians' offspring. On the contrary, in the offspring of non-long-lived parents, resistin was positively associated with waist circumference. In view of this finding, we propose that abdominal fat tissue in the offspring of non-long-lived parents may have a different cellular composition, with a higher proportion of infiltrating macrophages. These subjects therefore have a greater predisposition to produce pro-inflammatory molecules such as resistin, thus explaining the increased prevalence of cardiovascular events, hypertension, and hypercholesterolemia in MetS-affected controls.

A plethora of data indicate the involvement of leptin and adiponectin in obesity, MetS, and cardiovascular disease. In particular, elevated leptin levels and decreased levels of adiponectin have been described in this context (Palomer et al. 2005; Bik and Baranowska 2009; Harwood 2012; Bremer et al. 2011; Cicero et al. 2011; You et al. 2008). We showed that the prevalence of MetS progressively increased across leptin levels and leptin/adiponectin ratio and decreased across adiponectin levels in both groups. These observations confirmed that high levels of leptin accompanied by low levels of adiponectin are associated with MetS and that these adipokines seem to influence MetS prevalence in a very similar way in centenarians' offspring and offspring of non-long-lived parents.

On the contrary, the analysis of MetS prevalence across resistin and IGF-1 tertiles revealed some intriguing differences between the two groups. While there was no change in MetS prevalence across the resistin and IGF-1 tertiles in centenarians' offspring, it increased significantly across the resistin tertiles in controls and tended to decrease across IGF-1 tertiles. Even though resistin has been recognized as an indicator of MetS in several studies (Malo et al. 2011; Gupta et al. 2011; Aquilante et al. 2008), high levels of resistin did not seem to influence the risk for this condition in centenarians' offspring. Recent papers have shown that lower levels of IGF-1 are associated with insulin resistance and MetS (Lam et al. 2010; Oh et al. 2012; Succurro et al. 2008; Arai et al. 2009). Whether this association is independent of adipokines and/or hormones remains controversial. In this paper, we show that while the resistin/IGF-1 ratio does not influence MetS prevalence in centenarians' offspring, an impaired balance among these mediators appears to greatly affect MetS prevalence in the offspring of non-long-lived parents. In particular, a dramatic increase of MetS prevalence was observed in controls with the resistin/IGF-1 ratio shifted towards high levels of resistin and low levels of IGF-1, even after adjusting for BMI. Despite the importance of resistin in determining insulin resistance and cardiovascular risk, relatively little is known about the effect of IGF-1 on the control of resistin production and action. Chen et al. (2005) demonstrated that IGF-1 is able to suppress resistin mRNA expression and protein release in 3T3-LI adipocytes in a dose- and time-dependent manner. In view of this finding, we hypothesized that in the MetS-affected offspring of non-long-lived parents belonging to the third tertile of the resistin/IGF-1 ratio, the low levels of IGF-1 may fail to inhibit resistin expression leading to increased level of resistin and contributing to the dramatic increase of MetS prevalence. On the contrary, in centenarians' offspring, peculiar genetic mechanisms could be involved in the fine regulation of the complex adipokine network and IGF-1 pathway. Further analyses are needed to fully understand the role of the balance between IGF-1 and resistin in MetS and related diseases taking into account the genetic background that seems to play a role on the modulation of the complex interaction between metabolism and inflammation.

Acknowledgments This research was funded by the European Union's Seventh Framework Programme (FP7/2007-2011) under grant agreement no. 259679 to CF and by the following Italian institutions: University of Florence and MIUR (PRIN 2006) to DM.

We also thank DiaSorin (Saluggia, Italy) for the insulin evaluation.

References

Al-Daghri NM, Al-Attas OS, Alokail MS, Alkharfy KM, Yakout SM, Sabico SB, Gibson GC, Chrousos GP, Kumar S (2011) Parent-offspring transmission of adipocytokine levels and

their associations with metabolic traits. PLoS One 6(4): e18182
Aquilante CL, Kosmiski LA, Knutsen SD, Zineh I (2008) Relationship between plasma resistin concentrations, inflammatory chemokines, and components of the metabolic syndrome in adults. Metabolism 57(4):494–501
Arai Y, Kojima T, Takayama M, Hirose N (2009) The metabolic syndrome, IGF-1, and insulin action. Mol Cell Endocrinol 299(1):124–128
Arai Y, Takayama M, Abe Y, Hirose N (2011) Adipokines and aging. J Atheroscler Thromb 18(7):545–550
Atzmon G, Schechter C, Greiner W, Davidson D, Rennert G, Barzilai N (2004) Clinical phenotype of families with longevity. J Am Geriatr Soc 52(2):274–277
Atzmon G, Pollin TI, Crandall J, Tanner K, Schechter CB, Scherer PE, Rincon M, Siegel G, Katz M, Lipton RB, Shuldiner AR, Barzilai N (2008) Adiponectin levels and genotype: a potential regulator of life span in humans. J Gerontol A Biol Sci Med Sci 63A:447–453
Barzilai N, Atzmon G, Schechter C, Schaefer EJ, Cupples AL, Lipton R, Cheng S, Shuldiner AR (2003) Unique lipoprotein phenotype and genotype associated with exceptional longevity. JAMA 290(15):2030–2040
Bik W, Baranowska B (2009) Adiponectin—a predictor of higher mortality in cardiovascular disease or a factor contributing to longer life? Neuro Endocrinol Lett 30(2):180–184
Bremer AA, Devaraj S, Afify A, Jialal I (2011) Adipose tissue dysregulation in patients with metabolic syndrome. J Clin Endocrinol Metab 96(11):E1782–E1788
Chaldakov GN, Stankulov IS, Hristova M, Ghenev PI (2003) Adipobiology of disease: adipokines and adipokine-targeted pharmacology. Curr Pharm Des 9:1023–1031
Chen YH, Hung PF, Kao YH (2005) IGF-I downregulates resistin gene expression and protein secretion. Am J Physiol Endocrinol Metab 288(5):E1019–E1027
Cicero AF, Magni P, Moré M, Ruscica M, Dozio E, Steffani L, Borghi C, Strollo F (2011) Adipokines and sexual hormones associated with the components of the metabolic syndrome in pharmacologically untreated subjects: data from the Brisighella Heart Study. Int J Endocrinol:724816
Csuka M, McCarty DJ (1985) Simple method for measurement of lower extremity muscle strength. Am J Med 78(1):77–81
Czernichow S, Kengne AP, Stamatakis E, Hamer M, Batty GD (2011) Body mass index, waist circumference and waist-hip ratio: which is the better discriminator of cardiovascular disease mortality risk?: evidence from an individual-participant meta-analysis of 82 864 participants from nine cohort studies. Obes Rev 12(9):680–687
Das UN (2004) Metabolic syndrome X: an inflammatory condition? Curr Hypertens Rep 6(1):66–73
de Koning L, Merchant AT, Pogue J, Anand SS (2007) Waist circumference and waist-to-hip ratio as predictors of cardiovascular events: meta-regression analysis of prospective studies. Eur Heart J 28:850–856
DeStefano F, Ford ES, Newman J, Stevenson JM, Wetterhall SF, Anda RF, Vinicor F (1993) Risk factors for coronary heart disease mortality among persons with diabetes. Ann Epidemiol 3(1):27–34
Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (2001) Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 285:2486–2497
Franceschi C, Bonafè M, Valensin S (2000a) Human immunosenescence: the prevailing of innate immunity, the failing of clonotypic immunity, and the filling of immunological space. Vaccine 18(16):1717–1720
Franceschi C, Valensin S, Bonafè M, Paolisso G, Yashin AI, Monti D, De Benedictis G (2000b) The network and the remodeling theories of aging: historical background and new perspectives. Exp Gerontol 35(6–7):879–896
Galioto A, Dominguez LJ, Pineo A, Ferlisi A, Putignano E, Belvedere M, Costanza G, Barbagallo M (2008) Cardiovascular risk factors in centenarians. Exp Gerontol 43(2):106–113
Gentilini D, Mari D, Castaldi D, Remondini D, Ogliari G, Ostan R, Bucci L, Sirchia SM, Tabano S, Cavagnini F, Monti D, Franceschi C, Di Blasio AM, Vitale G (2012) Role of epigenetics in human aging and longevity: genome-wide DNA methylation profile in centenarians and centenarians' offspring. Age. doi:10.1007/s11357-012-9463-1
Gnacińska M, Małgorzewicz S, Stojek M, Łysiak-Szydłowska W, Sworczak K (2009) Role of adipokines in complications related to obesity: a review. Adv Med Sci 54(2):150–157
Gupta V, Singh AK, Gupta V, Kumar S, Srivastava N, Jafar T, Pant AB (2011) Association of circulating resistin with metabolic risk factors in Indian females having metabolic syndrome. Toxicol Int 18(2):168–172
Haffner SM (2006) The metabolic syndrome: inflammation, diabetes mellitus, and cardiovascular disease. Am J Cardiol 97(2A):3A–11A
Harwood HJ Jr (2012) The adipocyte as an endocrine organ in the regulation of metabolic homeostasis. Neuropharmacology 63(1):57–75
Kwon HM, Kim BJ, Lee SH, Choi SH, Oh BH, Yoon BW (2006) Metabolic syndrome as an independent risk factor of silent brain infarction in healthy people. Stroke 37 (2):466–470
Lam CS, Chen MH, Lacey SM, Yang Q, Sullivan LM, Xanthakis V, Safa R, Smith HM, Peng X, Sawyer DB, Vasan RS (2010) Circulating insulin-like growth factor-1 and its binding protein-3: metabolic and genetic correlates in the community. Arterioscler Thromb Vasc Biol 30(7):1479–1484
Malo E, Ukkola O, Jokela M, Moilanen L, Kähönen M, Nieminen MS, Salomaa V, Jula A, Kesäniemi YA (2011) Resistin is an indicator of the metabolic syndrome according to five different definitions in the Finnish Health 2000 survey. Metab Syndr Relat Disord 9(3):203–210
Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC (1985) Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28(7):412–9
Oh J, Kim JY, Park S, Youn JC, Son NH, Shin DJ, Lee SH, Kang SM, Jee SH, Jang Y (2012) The relationship between insulin-like growth factor-1 and metabolic syndrome, independent of adiponectin. Clin Chim Acta 413(3–4):506–510
Palomer X, Pérez A, Blanco-Vaca F (2005) Adiponectin: a new link between obesity, insulin resistance and cardiovascular disease. Med Clin (Barc) 124(10):388–395

Paolisso G, Gambardella A, Ammendola S, D'Amore A, Balbi V, Varricchio M, D'Onofrio F (1996) Glucose tolerance and insulin action in healthy centenarians. Am J Physiol 270:E890–E894

Paolisso G, Barbieri M, Rizzo MR, Carella C, Rotondi M, Bonafè M, Franceschi C, Rose G, De Benedictis G (2001) Low insulin resistance and preserved beta-cell function contribute to human longevity but are not associated with TH-INS genes. Exp Gerontol 37(1):149–156

Rajala MW, Scherer PE (2003) Minireview: the adipocyte: at the crossroads of energy homeostasis, inflammation, and atherosclerosis. Endocrinology 144:3765–3773

Rozing MP, Westendorp RG, Frölich M, de Craen AJ, Beekman M, Heijmans BT, Mooijaart SP, Blauw GJ, Slagboom PE, van Heemst D, Leiden Longevity Study (LLS) Group (2009) Human insulin/IGF-1 and familial longevity at middle age. Aging (Albany NY) 1(8):714–22

Rozing MP, Westendorp RG, de Craen AJ, Frölich M, de Goeij MC, Heijmans BT, Beekman M, Wijsman CA, Mooijaart SP, Blauw GJ, Slagboom PE, van Heemst D, Leiden Longevity Study Group (2010) Favorable glucose tolerance and lower prevalence of metabolic syndrome in offspring without diabetes mellitus of nonagenarian siblings: the Leiden Longevity Study. J Am Geriatr Soc 58(3):564–9

Sattar N, McConnachie A, Shaper AG, Blauw GJ, Buckley BM, de Craen AJ, Ford I, Forouhi NG, Freeman DJ, Jukema JW, Lennon L, Macfarlane PW, Murphy MB, Packard CJ, Stott DJ, Westendorp RG, Whincup PH, Shepherd J, Wannamethee SG (2008) Can metabolic syndrome usefully predict cardiovascular disease and diabetes? Outcome data from two prospective studies. Lancet 371(9628):1927–1935

Savopoulos C, Michalakis K, Apostolopoulou M, Miras A, Hatzitolios A (2011) Adipokines and stroke: a review of the literature. Maturitas 70(4):322–327

Succurro E, Andreozzi F, Sciaqua A, Hribal ML, Perticone F, Sesti G (2008) Reciprocal association of plasma IGF-1 and interleukin-6 levels with cardiometabolic risk factors in nondiabetic subjects. Diabetes Care 31(9):1886–1888

Terry DF, McCormick M, Andersen S, Pennington J, Schoenhofen E, Palaima E, Bausero M, Ogawa K, Perls TT, Asea A (2004a) Cardiovascular disease delay in centenarian offspring: role of heat shock proteins. Ann N Y Acad Sci 1019:502–505

Terry DF, Wilcox MA, McCormick MA, Pennington JY, Schoenhofen EA, Andersen SL, Perls TT (2004b) Lower all-cause, cardiovascular, and cancer mortality in centenarians offspring. J Am Geriatr Soc 52(12):2074–2076

Terry DF, Evans JC, Pencina MJ, Murabito JM, Vasan RS, Wolf PA, Kelly-Hayes M, Levy D, D'Agostino RB Sr, Benjamin EJ (2007) Characteristics of Framingham offspring participants with long-lived parents. Arch Intern Med 167 (5):438–444

Vaarhorst AA, Beekman M, Suchiman EH, van Heemst D, Houwing-Duistermaat JJ, Westendorp RG, Slagboom PE, Heijmans BT, Leiden Longevity Study (LLS) Group (2011) Lipid metabolism in long-lived families: the Leiden Longevity Study. Age (Dordr) 33(2):219–27

Vitale G, Brugts MP, Ogliari G, Castaldi D, Fatti LM, Varewijck AJ, Lamberts SW, Monti D, Bucci L, Cevenini E, Cavagnini F, Franceschi C, Hofland LJ, Mari D, Janssen J (2012) Low circulating IGF-I bioactivity is associated with human longevity: findings in centenarians' offspring. Aging (Albany NY) 4(9):580–589

Wijsman CA, Rozing MP, Streefland TC, le Cessie S, Mooijaart SP, Slagboom PE, Westendorp RG, Pijl H, van Heemst D, Leiden Longevity Study group (2011) Familial longevity is marked by enhanced insulin sensitivity. Aging Cell 10(1):114–21

Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, Sole J, Nichols A, Ross JS, Tartaglia LA, Chen H (2003) Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J Clin Invest 112 (12):1821–1830

You T, Nicklas BJ, Ding J, Penninx BW, Goodpaster BH, Bauer DC, Tylavsky FA, Harris TB, Kritchevsky SB (2008) The metabolic syndrome is associated with circulating adipokines in older adults across a wide range of adiposity. J Gerontol A Biol Sci Med Sci 63(4):414–419

Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW (1999) C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? Arterioscler Thromb Vasc Biol 19:972–978