# Contributions of Cardiorespiratory Fitness and Visceral Adiposity to Six-Year Changes in Cardiometabolic Risk Markers in Apparently Healthy Men and Women

Caroline Rhéaume, Benoit J. Arsenault, Marie-Pierre Dumas, Louis Pérusse, Angelo Tremblay, Claude Bouchard, Paul Poirier, and Jean-Pierre Després

Department of Family and Emergency Medicine (C.R., M.-P.D.), Faculty of Medicine, Université Laval, Québec, Canada G1V 0A6; Centre de Recherche de l'Institut Universitaire de Cardiologie et de Pneumologie de Québec (C.R., B.J.A., A.T., P.P., J.-P.D.), Québec, Canada G1V 4G5; Division of Kinesiology (L.P., A.T., J.-P.D.), Department of Social and Preventive Medicine, Université Laval, Québec, Canada G1V 0A6; Pennington Biomedical Research Center, Baton Rouge (C.B.), Louisiana 70808; and Faculty of Pharmacy (P.P.), Université Laval, Québec, Canada G1V 0A6

**Context:** Both excess visceral adipose tissue (VAT) and low cardiorespiratory fitness (CRF) levels are associated with a deteriorated cardiometabolic risk profile.

**Objective:** The aim of the study was to examine the respective contributions of changes in VAT accumulation *vs.* changes in CRF to 6-yr longitudinal changes in cardiometabolic risk markers.

**Design, Settings, and Participants:** We conducted a prospective, population-based study with an average follow-up of 5.9 ± 0.8 yr. We followed 132 middle-aged participants from the Quebec Family Study (mean age, 35.3 ± 13.9 yr). VAT was measured by computed tomography, whereas the level of CRF was assessed by a submaximal physical working capacity test at baseline and at follow-up. A complete cardiometabolic risk profile, including systolic and diastolic blood pressure, fasting glucose and insulin levels, C-reactive protein (n = 72), as well as a standard lipoprotein-lipid profile, was obtained at baseline and at follow-up.

**Main Outcome Measures:** We measured changes in CRF, VAT, and cardiometabolic risk profile over 6 yr.

**Results:** After adjusting for age and sex, 6-yr changes in VAT were negatively correlated with changes in CRF (r = −0.38; $P < 0.001$). In a multivariate model that included age, sex, changes in VAT, changes in CRF, as well as baseline levels of the above cardiometabolic risk factors, 6-yr changes in VAT were the most important predictor of the change in the metabolic syndrome score ($R^2$ = 13.2%; $P < 0.001$). Adding 6-yr changes in CRF levels significantly improved the predictability of the model ($R^2$ = 19.7%; $P = 0.002$).

**Conclusions:** Changes in both VAT and CRF levels observed over 6 yr are associated with changes in parameters of the lipoprotein-lipid profile, glucose-insulin homeostasis, and inflammatory markers. Thus, maintaining a low level of VAT and a high level of CRF are important targets for maintenance of cardiometabolic health. (*J Clin Endocrinol Metab* 96: 1462–1468, 2011)

Abbreviations: CRF, Cardiorespiratory fitness; CRP, C-reactive protein; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; MetS, metabolic syndrome; PWC, physical working capacity; SBP, systolic blood pressure; VAT, visceral adipose tissue.

lthough controversy exists around the added value of a clinical diagnosis of the metabolic syndrome (MetS), available evidence has clearly shown that the simultaneous presence of the features of the MetS is associated with an increased relative risk of type 2 diabetes (3- to 5-fold increase) (1, 2) and cardiovascular disease (1.5- to 2-fold increase) (3–6) compared to individuals without MetS. Metabolic abnormalities considered as features of MetS are an atherogenic dyslipidemic state [elevated triglyceride and low high-density lipoprotein (HDL) cholesterol levels], systemic hypertension, insulin resistance, low-grade inflammation, and abdominal obesity (7–10).

It has been shown that weight gain is associated with MetS incidence (11). Although the etiology of the MetS is still a matter of debate, several lines of evidence suggest that irrespective of total body weight, a preferential accumulation of adipose tissue inside the abdomen, the so-called intraabdominal or visceral adipose tissue (VAT), is closely associated with the development of the MetS, independently of body weight, total body fat, or the content of other body fat compartments such as sc adipose tissue (12–15).

Numerous prospective studies have also reported that individuals with high levels of cardiorespiratory fitness (CRF) are at reduced risk of developing MetS (16–18) and of all-cause mortality (19–24). Previous cross-sectional studies from our laboratory have shown that independent of their CRF levels, individuals carrying a certain excess of VAT were nevertheless characterized by several features of the MetS such as dyslipidemia, insulin resistance, increased blood pressure, and low-grade inflammation (25, 26). However, whether maintaining a good level of CRF could protect against the development of the MetS among individuals increasing or decreasing VAT accumulation over time remains unclear. To the best of our knowledge, no study has yet evaluated the respective contributions of specific changes in VAT accumulation and CRF over time to longitudinal changes in cardiometabolic risk markers. The objective of this 6-yr longitudinal study was to test the hypothesis that individuals who would maintain adequate levels of both CRF and VAT would be able to maintain a healthy cardiometabolic risk profile over time.

## Subjects and Methods

### Study subjects

Study subjects were asymptomatic men and women who participated in the Québec Family Study (QFS), a longitudinal study including three phases: 1, 1980–1982; 2, 1989–1995; and 3, 1997–2001. We considered phase 2 as baseline. The mean duration of follow-up was 5.87 ± 0.84 yr. The study sample included healthy men and women with data on body composition, CRF, and plasma levels of cardiometabolic risk markers at base-

line and after the follow-up. Briefly, the QFS is a population-based study of French-Canadian families living in and around the Québec City area. The QFS was approved by the Medical Ethics Committee of Université Laval. Subjects were recruited through the media and gave their written informed consent to participate in the study. Only asymptomatic men and women, 18 to 65 yr of age, who were not under treatment for cardiovascular disease, diabetes, dyslipidemias, or endocrine disorders were considered for the present analyses.

### Anthropometric, body composition, and hemodynamic measurements

Height, body weight, and waist circumference were measured following standardized procedures. Body density was measured by the hydrostatic weighing technique (27). The mean of six measurements was used to calculate percentage body fat from body density using the equation of Siri (28). Fat mass was obtained by multiplying body weight by percentage body fat. Measurement of abdominal VAT areas was performed by computed tomography with a Siemens Somatom DHR scanner (Siemens, Erlanger, Germany). Briefly, participants were examined in the supine position with both arms stretched above the head. The scan was performed at the abdominal level (L4 and L5 vertebrae) using an abdominal scout radiograph to standardize the position of the scan to the nearest millimeter. Total adipose tissue area was calculated by delineating the abdominal scan with a graph pen and then by computing the total abdominal adipose tissue area with an attenuation range of $-190$ to $-30$ Hounsfield units. Abdominal VAT area was measured by drawing a line within the muscle wall surrounding the abdominal cavity. Abdominal sc adipose tissue area was calculated by subtracting the VAT area from the total abdominal adipose tissue area. Resting blood pressure was measured in the morning when participants were in the fasting state and in a sitting position after a 45-min rest using mercury sphygmomanometer (proper) and an appropriately sized cuff (Welch Allyn Tycos, Skaneateles Falls, NY), according to standard procedures. Participants were asked to refrain from smoking for 2 h before the procedure. Blood pressure values are the mean of two different measurements.

### Biochemical analyses

After a 12-h overnight fast, blood samples were collected from an antecubital vein into Vacutainer tubes containing EDTA (Miles Pharmaceuticals, Rexdale, Ontario, Canada) for the measurement of plasma lipid and lipoprotein levels. Plasma cholesterol and triglyceride concentrations were determined in plasma and lipoprotein fractions using a Technicon RA-500 analyzer (Bayer Corporation, Tarrytown, NY), and enzymatic reagents were obtained from Randox Laboratories Ltd. (Crumlin, UK). Plasma very low-density lipoproteins (LDLs) (density < 1.006 g/ml) were isolated by ultracentrifugation (29), and the HDL fraction was obtained after precipitation of LDLs in the infranatant (density > 1.006 g/ml) with heparin and $MnCl_2$ (30). The cholesterol content of the infranatant fraction was measured before and after the precipitation step, allowing the calculation of LDL-cholesterol. ELISAs were used to measure plasma adiponectin (B-Bridge International, Inc., San Jose, CA), IL-6, and TNF-$\alpha$ (R&D Systems Inc., Minneapolis, MN). Plasma C-reactive protein (CRP) levels were measured with a highly sensitive immunoassay that used a monoclonal antibody coated with polystyrene particles (high-sensitivity CRP); the assay was per-

formed with a Behring BN-100 nephelometer (Dade Behring, Deerfield, IL). Participants with plasma levels of CRP above 10 mg/dl were excluded from the analyses on inflammatory markers. Frozen plasma samples for the measurement of inflammatory markers before and after the follow-up were only available for 72 subjects. Plasma glucose was measured enzymatically, whereas plasma insulin was measured by RIA with polyethylene glycol separation (31). The homeostasis model assessment of insulin resistance (HOMA-IR) index was calculated as previously described for each participant (32).

## Assessment of CRF

CRF of each participant was assessed by a progressive submaximal physical working capacity (PWC) test performed on a modified Monark cycle ergometer (Stockholm, Sweden). Heart rate was measured through one electrocardiogram derivation and recorded during three consecutive 6-min workloads, each separated by a 1-min rest. The test was designed to exceed a heart rate of 150 beats per minute at the end of the last workload. $PWC_{150}$, which is the power output at 150 beats per minute, was then calculated from the linear relationship between heart rate and power output. To take into account the individual differences in body weight, $PWC_{150}$ was expressed by kilograms of body weight and was specifically used as the marker of CRF in the present study.

## Statistical analyses

Data are presented as mean ± SD or median (interquartile range) in Tables 1 and 2 and as mean ± SEM in Fig. 1. Baseline anthropometric and metabolic characteristics of participants are presented in men and women separately. Paired *t* tests were performed to compare baseline and follow-up levels of cardiometabolic risk markers and anthropometric parameters. Based on the changes in cardiometabolic risk markers over the follow-up period [systolic blood pressure (SBP), diastolic blood pressure (DBP), HOMA-IR index, as well as triglyceride and HDL cholesterol levels], a "metabolic syndrome score" was developed. Participants were allowed one point when a change in one of the above risk markers was equal to or above the 75th percentile of the distribution of changes observed over 6-yr in the whole cohort (equal to or below the 25th percentile for HDL cholesterol). Over the 6-yr follow-up period, the 75th percentile of changes corresponded to an increase in SBP of 6.0 mm Hg, an increase in DBP of 4.0 mm Hg, an increase in the HOMA-IR index of 1.26 U, and an increase in triglyceride levels of 0.23 mmol/liter; and finally, the 25th percentile of HDL cholesterol changes corresponded to a decrease in HDL cholesterol levels of −0.13 mmol/liter. Mean changes in cardiometabolic risk markers and in the MetS score were also obtained in participants classified on the basis of median changes in VAT and CRF (< or ≥ 11.83 cm² for VAT; and < or ≥ 1.0 kilopond per minute/kg for CRF). Because there was no important difference between either VAT or CRF variations over time in men and women, pooled analyses were conducted. Because plasma levels were available in a smaller proportion of the study sample, we did not include changes in inflammatory markers. Multiple regression analyses were also performed to quantify the respective contributions of changes in VAT and CRF to the variance in cardiometabolic risk variables over time. A P value <0.05 was considered to be statistically significant. All statistical analyses were performed with the SAS package (SAS Institute, Cary, NC).

## Results

A complete cardiometabolic risk profile was available for 132 participants at baseline and after a mean follow-up of 6 yr. Characteristics of the study participants before and after the follow-up period are presented in Table 1. During that timeframe, most men and women gained weight, and all body fatness indices were significantly increased at follow-up. CRF levels were higher after 6 yr than at the beginning of the study. Among the parameters of the lipoprotein-lipid profile, total and LDL cholesterol levels, as well as the total to HDL cholesterol ratio decreased. However, there were no changes in fasting triglycerides and HDL cholesterol levels, indicating that the change in the total to HDL cholesterol ratio is largely attributable to the decrease in non-HDL cholesterol levels. Most of the parameters of the glucose-insulin homeostasis were higher after the study follow-up. Although significant decreases were observed in plasma levels of adiponectin, changes in inflammatory markers were mostly inconsistent.

Based on the changes in cardiometabolic risk markers over the follow-up (SBP, DBP, insulin resistance, as well as triglyceride and HDL cholesterol levels), a MetS score was developed (see *Statistical analyses*). MetS score represents the change in the severity indices of our cardiometabolic risk variables as a function of changes in VAT and CRF.

Table 2 presents the results of multivariate regression analyses that considered the contributions of changes in VAT, changes in CRF, age, sex, and baseline levels of cardiometabolic risk markers to the variance in the response of the cardiometabolic risk markers and MetS score over time. Changes in VAT were associated with changes in SBP ($R^2$ = 16.0%; $P < 0.001$), DBP ($R^2$ = 10.9%; $P < 0.001$), HOMA-IR index ($R^2$ = 7.3%; $P < 0.05$), and CRP ($R^2$ = 17.9%; $P = 0.005$). Changes in CRF were associated with changes in HDL cholesterol ($R^2$ = 7.3%; $P < 0.05$). Changes in both VAT and CRF were associated with changes in the MetS score ($R^2$ = 13.2%, $P < 0.001$; and $R^2$ = 19.7%, $P = 0.002$, respectively).

Although changes in CRF and VAT were negatively correlated ($r = -0.38$; $P < 0.001$ after adjusting for age and sex), the correlation was of moderate magnitude. This moderate association suggests that several participants increased VAT over the follow-up period without concomitant changes in CRF, whereas other subjects decreased CRF without concomitant changes in VAT. Figure 1 illustrates mean changes in MetS score in participants classified on the basis of changes in VAT (below or equal or above median) and changes in CRF levels (below or equal or above median). Fig. 1 shows that individuals who increased their VAT and decreased their CRF had the most detrimental changes in indices of severity of MetS score

**TABLE 1.** Characteristics of men and women before and after the study follow-up

| | Men (n = 68) | | | | Women (n = 64) | | | |
|---|---|---|---|---|---|---|---|---|
| | Baseline | 6-yr follow-up | % change | P value | Baseline | 6-yr follow-up | % change | P value |
| Age (yr) | 36.9 ± 14.7 | 42.7 ± 14.7 | | | 33.7 ± 13.0 | 39.6 ± 12.9 | | |
| PWC (kpm/kg) | 11.0 ± 3.3 | 12.2 ± 3.3 | 10.9 | <0.001 | 7.3 ± 2.4 | 8.4 ± 2.9 | 15.1 | <0.001 |
| Body mass index (kg/m²) | 25.7 ± 4.3 | 26.5 ± 4.5 | 3.1 | 0.001 | 24.2 ± 4.5 | 25.3 ± 4.5 | 4.5 | <0.001 |
| Waist circumference (cm) | 88.6 ± 12.2 | 91.2 ± 12.8 | 2.9 | <0.001 | 75.5 ± 11.5 | 78.4 ± 12 | 3.8 | <0.001 |
| AT accumulation (cm²) | | | | | | | | |
| Total | 305.0 ± 184.3 | 329.6 ± 187.5 | 8.1 | 0.002 | 328.0 ± 162.7 | 371.5 ± 171.2 | 13.3 | <0.001 |
| Visceral | 105.0 ± 61.5 | 119.2 ± 74.7 | 13.5 | <0.001 | 69.9 ± 49.4 | 81.1 ± 51.4 | 16.0 | <0.001 |
| Subcutaneous | 200.0 ± 133.3 | 210.4 ± 126.5 | 5.2 | 0.04 | 258.1 ± 128.1 | 290.4 ± 132.3 | 12.5 | <0.001 |
| SBP (mm Hg) | 117 ± 11 | 116 ± 14 | −0.8 | 0.40 | 112 ± 12 | 113 ± 19 | 0.9 | 0.50 |
| DBP (mm Hg) | 73 ± 10 | 72 ± 12 | −1.4 | 0.22 | 69 ± 9 | 70 ± 13 | 1.4 | 0.68 |
| Total cholesterol (mmol/liter) | 4.85 ± 0.95 | 4.70 ± 0.91 | −3.1 | 0.04 | 4.78 ± 0.91 | 4.46 ± 0.96 | −6.7 | <0.001 |
| LDL cholesterol (mmol/liter) | 3.07 ± 0.77 | 2.92 ± 0.74 | −4.9 | 0.03 | 2.90 ± 0.78 | 2.58 ± 0.80 | −11.0 | <0.001 |
| HDL cholesterol (mmol/liter) | 1.15 ± 0.25 | 1.15 ± 0.24 | 0.0 | 0.98 | 1.36 ± 0.33 | 1.38 ± 0.32 | 1.5 | 0.60 |
| Total cholesterol/ HDL cholesterol | 4.41 ± 1.28 | 4.27 ± 1.19 | −3.2 | 0.10 | 3.67 ± 0.98 | 3.43 ± 1.03 | 6.5 | <0.001 |
| Triglycerides (mmol/liter) | 1.26 (0.90–1.71) | 1.31 (0.95–1.63) | 4.0 | 0.48 | 1.11 (0.86–1.38) | 0.99 (0.68–1.47) | −10.8 | 0.20 |
| Glucose (mmol/ liter) | 5.28 ± 0.73 | 5.72 ± 1.5 | 8.3 | <0.001 | 4.86 ± 0.42 | 5.10 ± 0.49 | 4.9 | <0.001 |
| Insulin (pmol/liter) | 46.5 (34.0–71.5) | 62.0 (44.5–85.5) | 33.3 | 0.06 | 47.5 (29.5–64.5) | 57.0 (31.5–71.5) | 20.0 | 0.05 |
| HOMA-IR | 1.85 (1.31–2.81) | 2.38 (1.70–3.58) | 28.6 | 0.01 | 1.71 (1.11–2.24) | 2.05 (1.21–2.75) | 19.9 | 0.006 |
| CRP (mg/liter)[a] | 0.74 (0.36–2.00) | 0.74 (0.27–1.22) | 0.0 | 0.08 | 1.56 (0.56–3.46) | 2.05 (0.57–3.24) | 31.4 | 0.65 |
| Adiponectin (µg/ml)[a] | 5.06 (3.57–6.98) | 4.37 (3.53–5.06) | −13.6 | 0.04 | 7.76 (5.32–9.88) | 5.60 (4.57–7.10) | −27.8 | <0.001 |
| IL-6 (pg/ml)[a] | 1.24 (0.93–1.62) | 1.12 (0.72–1.93) | −9.7 | 0.17 | 1.35 (1.00–2.26) | 1.25 (0.87–2.26) | −7.4 | 0.34 |
| TNF-α (pg/ml)[a] | 1.65 (1.35–2.02) | 1.58 (1.35–1.74) | −4.2 | 0.13 | 1.63 (1.39–1.89) | 1.44 (1.21–1.65) | −11.7 | 0.02 |

Data are presented as mean ± SD or median (interquartile range). AT, Adipose tissue.

[a] n = 72 (participants with CRP levels above 10 mg/ml at baseline or at follow-up were excluded).

compared with the other subgroups. Supplemental Fig. 1A (published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org) shows that although the relationship did not reach statistical significance, individuals who improved their CRF over the study follow-up appeared to have lowered their SBP, whereas those who decreased their CRF increased in their SBP, independently of their changes in VAT. Participants who had the lowest increase in VAT and the smallest decrease in CRF were the only subgroup who showed a decrease in DBP over the 6-yr follow-up (Supplemental Fig. 1B). As for the HOMA-IR index, only participants who had simultaneous increases in VAT and decreases in CRF levels showed an increase in the HOMA-IR index over the follow-up period (Supplemental Fig. 1C). Participants who did not increase their VAT showed no change in triglyc-

eride levels, whereas those who increased their VAT experienced a small increase in their triglyceride levels, but only in the presence of a simultaneous decrease in CRF (Supplemental Fig. 1D). Finally, individuals who had the smallest increase of VAT combined with an increase in CRF levels significantly increased their HDL cholesterol levels, with no changes observed in the other subgroups (Supplemental Fig. 1E).

## Discussion

In this 6-yr longitudinal study conducted in a population of asymptomatic men and women, we found that changes in VAT were associated with changes in SBP, DBP, HOMA-IR index, and CRP. On the other hand, only

**TABLE 2.** Multivariate regression analyses showing the contributions of changes in VAT, CRF, age, sex, and baseline levels of cardiometabolic risk markers to the variance of the cardiometabolic risk markers and MetS score

| Changes | Independent variables | Total $R^2$ (%) | *P* value |
|---|---|---|---|
| SBP | Age at baseline | 16.0 | <0.0001 |
| | + Changes in VAT | 20.7 | 0.006 |
| | + Triglycerides at baseline | 20.1 | 0.05 |
| DBP | DBP at baseline | 10.9 | <0.0001 |
| | + Changes in VAT | 16.8 | 0.003 |
| | + Age at baseline | 19.5 | 0.04 |
| HOMA-IR index | Changes in VAT | 7.3 | 0.002 |
| | + Age at baseline | 12.0 | 0.01 |
| | + HOMA-IR at baseline | 15.0 | 0.04 |
| Triglycerides | Triglycerides at baseline | 22.4 | <0.0001 |
| | + Age at baseline | 32.9 | <0.0001 |
| | + Sex | 34.3 | 0.10 |
| HDL cholesterol | HDL cholesterol at baseline | 12.6 | <0.0001 |
| | + Changes in CRF | 17.9 | 0.005 |
| | + Sex | 20.5 | 0.04 |
| | + SBP at baseline | 22.8 | 0.05 |
| MetS score | Changes in VAT | 13.2 | <0.0001 |
| | + Changes in CRF | 19.7 | 0.002 |
| | + HDL cholesterol at baseline | 22.6 | 0.03 |
| | + Age at baseline | 25.7 | 0.02 |
| | + DBP at baseline | 27.3 | 0.09 |
| CRP[a] | Changes in VAT | 17.3 | 0.0003 |
| | + Sex | 19.8 | 0.14 |
| Adiponectin[a] | HOMA-IR at baseline | 5.4 | 0.05 |
| IL-6[a] | SBP at baseline | 5.3 | 0.05 |
| TNF-$\alpha$[a] | Sex | 7.6 | 0.02 |
| | + SBP at baseline | 10.8 | 0.12 |

Variables included in the model were changes in VAT, CRF, sex, age, HOMA-IR index, SBP, DBP, triglycerides, and HDL cholesterol levels at baseline as well as baseline levels of VAT and CRF.

[a] n = 72 (participants with CRP levels above 10 mg/ml at baseline or at follow-up were excluded). +, Variables added in the model.

changes in CRF were independently associated with changes in HDL cholesterol levels. Changes in both VAT and CRF were associated with changes in the MetS score. We also found that individuals who increased their VAT and who decreased their CRF over time experienced the most detrimental changes in their cardiometabolic risk profile. Taken together, these observations provide for the first time longitudinal data suggesting that maintaining low levels of VAT and high levels of CRF are both important targets for the maintenance of a healthy cardiometabolic risk profile in asymptomatic individuals.

## Comparison with other studies

VAT is closely associated with the development of the MetS, independently of the other body fat compartments such as sc adipose tissue and specific measures of insulin resistance (12–15). Additionally, numerous prospective
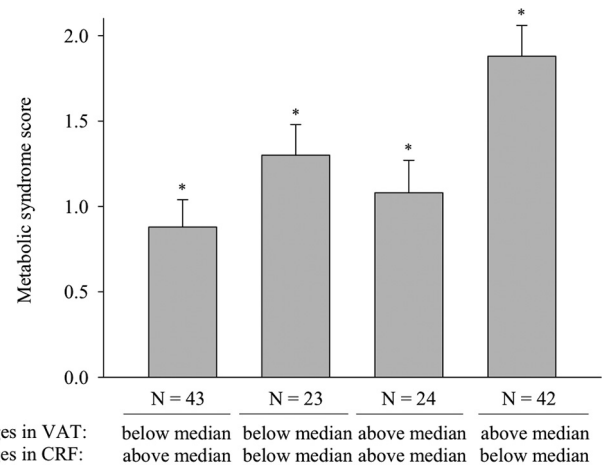


**FIG. 1.** Mean changes in indices of severity of MetS score in participants classified on the basis of changes in VAT accumulation (low = below median; high = above or equal to median) and changes in CRF levels (low = above or equal to median; high = below median). *, $P < 0.05$. See Supplemental Fig. 1 for changes in SBP (A), DBP (B), HOMA-IR index (C), plasma triglyceride levels (D) and plasma HDL cholesterol levels (E). §, $P < 0.10$ and $>0.05$ in Supplemental Fig. 1D.

studies have reported that high levels of CRF are associated with lower risk of MetS (16–18, 33) and all-cause mortality (19–24, 34). Previous cross-sectional studies from our laboratory have confirmed the notion that independent of CRF, individuals carrying a certain excess of VAT were simultaneously characterized by several features of the MetS such as dyslipidemia, insulin resistance, high blood pressure, and low-grade inflammation (26, 35). The present longitudinal study provides evidence that individuals with the largest increment of CRF and decrement in VAT had the most substantial improvements in their cardiometabolic risk factors/markers over a 6-yr follow-up period. In a previous cross-sectional study, we have suggested that the relationship between poor CRF and high blood pressure might be related to the fact that unfit individuals were most likely characterized by high VAT levels (26). We have also reported similar findings regarding other features of the MetS and plasma biomarkers of low-grade inflammation (25). We believe that this prospective study further reinforces the notion that apparently healthy individuals should be encouraged to maintain low levels of VAT and adequate levels of CRF to prevent them from the development of atherogenic and diabetogenic metabolic abnormalities.

## Pathophysiological consequences of high VAT and low CRF levels

Several pathophysiological mechanisms may contribute to explaining our observations that both VAT and CRF were associated with changes in the cardiometabolic risk profile. For instance, VAT secretes several adipokines that may impact numerous biological systems such as

plasma glucose-insulin homeostasis, lipoprotein-lipid metabolism, immune response, thrombosis, as well as regulation of blood pressure. This has led several investigators to suggest that adipose tissue, and especially VAT, is at the center of an important cross-talk among several other organs such as liver, skeletal muscle, heart, pancreas, and brain. It is also reasonable to believe that because most individuals with poor CRF levels concomitantly show elevated VAT levels, such an accumulation of VAT may represent an important biological mediator in the relationship between low CRF levels and a deteriorated cardiometabolic risk profile. However, our results suggest that the relationship between changes in CRF levels and specific cardiometabolic risk markers may well be partly independent of VAT. For instance, several studies have shown that increasing physical activity/CRF levels have beneficial HDL-raising effects (16, 36). Similar observations were also found for the relationship between CRF and blood pressure (37–39).

### Study strengths and limitations

An important strength of our study is that an extensive cardiometabolic risk profile was measured both at baseline and after the 6-yr follow-up period. Moreover, we have directly measured body fat distribution by computed tomography. However, it must be kept in mind that our study sample is of limited size and it only includes middle-aged Caucasians in whom the prevalence of MetS was somewhat low. This may limit our ability to translate our findings to other populations and ethnic groups with broader age ranges (40).

### Clinical implications

In primary care facilities, VAT is not routinely assessed by computed tomography. As an alternative, we believe that the measurement of waist circumference, a crude marker of visceral adiposity, could be used by primary care physicians to identify patients who are at high-risk for hypertension and/or MetS (41). In this regard, we also found that changes in SBP, triglyceride, HDL, insulin resistance, adiponectin, IL-6, and TNF-$\alpha$ were all significantly associated with 6-yr changes in waist circumference (data not shown). It is important to point out that the objective of our study was to investigate the "natural" evolution of the cardiometabolic risk profile associated with changes in VAT and CRF over time. We believe that intervention studies with specific measurements of fitness and visceral adiposity are required to properly investigate their association with the cardiometabolic risk profile. Additionally, because our results show that both VAT and CRF have a strong impact on the cardiometabolic risk profile, we believe that further studies are warranted to

investigate whether or not CRF and VAT both contribute to predicting cardiovascular endpoints and/or type 2 diabetes incidence.

In conclusion, our results suggest that VAT and CRF have additive and independent contributions to the variation in cardiometabolic risk factors over time. Therefore, targeting both VAT and CRF should be considered for the maintenance of a healthy cardiometabolic risk profile in primary care.

### Acknowledgments

### References

1. **Wilson PW, D'Agostino RB, Parise H, Sullivan L, Meigs JB** 2005 Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. Circulation 112:3066–3072
2. **Després JP, Cartier A, Côté M, Arsenault BJ** 2008 The concept of cardiometabolic risk: bridging the fields of diabetology and cardiology. Ann Med 40:514–523
3. **Després JP, Lemieux I, Bergeron J, Pibarot P, Mathieu P, Larose E, Rodés-Cabau J, Bertrand OF, Poirier P** 2008 Abdominal obesity and the metabolic syndrome: contribution to global cardiometabolic risk. Arterioscler Thromb Vasc Biol 28:1039–1049
4. **Grundy SM** 2004 Obesity, metabolic syndrome, and cardiovascular disease. J Clin Endocrinol Metab 89:2595–2600
5. **Galassi A, Reynolds K, He J** 2006 Metabolic syndrome and risk of cardiovascular disease: a meta-analysis. Am J Med 119:812–819

6. **Gami AS, Witt BJ, Howard DE, Erwin PJ, Gami LA, Somers VK, Montori VM** 2007 Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. J Am Coll Cardiol 49:403–414

7. **Ford ES** 2005 Risks for all-cause mortality, cardiovascular disease, and diabetes associated with the metabolic syndrome: a summary of the evidence. Diabetes Care 28:1769–1778

8. **Hunt KJ, Resendez RG, Williams K, Haffner SM, Stern MP** 2004 National Cholesterol Education Program versus World Health Organization metabolic syndrome in relation to all-cause and cardiovascular mortality in the San Antonio Heart Study. Circulation 110:1251–1257

9. **Rutter MK, Meigs JB, Sullivan LM, D'Agostino Sr RB, Wilson PW** 2004 C-reactive protein, the metabolic syndrome, and prediction of cardiovascular events in the Framingham Offspring Study. Circulation 110:380–385

10. **Després JP** 2006 Is visceral obesity the cause of the metabolic syndrome? Ann Med 38:52–63

11. **Carnethon MR, Loria CM, Hill JO, Sidney S, Savage PJ, Liu K** 2004 Risk factors for the metabolic syndrome: the Coronary Artery Risk Development in Young Adults (CARDIA) study, 1985–2001. Diabetes Care 27:2707–2715

12. **Tong J, Boyko EJ, Utzschneider KM, McNeely MJ, Hayashi T, Carr DB, Wallace TM, Zraika S, Gerchman F, Leonetti DL, Fujimoto WY, Kahn SE** 2007 Intra-abdominal fat accumulation predicts the development of the metabolic syndrome in non-diabetic Japanese-Americans. Diabetologia 50:1156–1160

13. **Fox CS, Massaro JM, Hoffmann U, Pou KM, Maurovich-Horvat P, Liu CY, Vasan RS, Murabito JM, Meigs JB, Cupples LA, D'Agostino Sr RB, O'Donnell CJ** 2007 Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. Circulation 116:39–48

14. **Carr DB, Utzschneider KM, Hull RL, Kodama K, Retzlaff BM, Brunzell JD, Shofer JB, Fish BE, Knopp RH, Kahn SE** 2004 Intra-abdominal fat is a major determinant of the National Cholesterol Education Program Adult Treatment Panel III criteria for the metabolic syndrome. Diabetes 53:2087–2094

15. **Smith SR, Lovejoy JC, Greenway F, Ryan D, deJonge L, de la Bretonne J, Volafova J, Bray GA** 2001 Contributions of total body fat, abdominal subcutaneous adipose tissue compartments, and visceral adipose tissue to the metabolic complications of obesity. Metabolism 50:425–435

16. **Lee S, Kuk JL, Katzmarzyk PT, Blair SN, Church TS, Ross R** 2005 Cardiorespiratory fitness attenuates metabolic risk independent of abdominal subcutaneous and visceral fat in men. Diabetes Care 28:895–901

17. **Lakka TA, Laaksonen DE, Lakka HM, Männikkö N, Niskanen LK, Rauramaa R, Salonen JT** 2003 Sedentary lifestyle, poor cardiorespiratory fitness, and the metabolic syndrome. Med Sci Sports Exerc 35:1279–1286

18. **Church TS, Finley CE, Earnest CP, Kampert JB, Gibbons LW, Blair SN** 2002 Relative associations of fitness and fatness to fibrinogen, white blood cell count, uric acid and metabolic syndrome. Int J Obes Relat Metab Disord 26:805–813

19. **Lee CD, Blair SN, Jackson AS** 1999 Cardiorespiratory fitness, body composition, and all-cause and cardiovascular disease mortality in men. Am J Clin Nutr 69:373–380

20. **Wei M, Gibbons LW, Kampert JB, Nichaman MZ, Blair SN** 2000 Low cardiorespiratory fitness and physical inactivity as predictors of mortality in men with type 2 diabetes. Ann Intern Med 132:605–611

21. **Blair SN, Kohl 3rd HW, Barlow CE, Paffenbarger Jr RS, Gibbons LW, Macera CA** 1995 Changes in physical fitness and all-cause mortality. A prospective study of healthy and unhealthy men. JAMA 273:1093–1098

22. **Blair SN, Kohl 3rd HW, Paffenbarger Jr RS, Clark DG, Cooper KH,** Gibbons LW 1989 Physical fitness and all-cause mortality. A prospective study of healthy men and women. JAMA 262:2395–2401

23. **Blair SN, Kampert JB, Kohl 3rd HW, Barlow CE, Macera CA, Paffenbarger Jr RS, Gibbons LW** 1996 Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. JAMA 276:205–210

24. **Katzmarzyk PT, Church TS, Janssen I, Ross R, Blair SN** 2005 Metabolic syndrome, obesity, and mortality: impact of cardiorespiratory fitness. Diabetes Care 28:391–397

25. **Arsenault BJ, Lachance D, Lemieux I, Alméras N, Tremblay A, Bouchard C, Pérusse L, Després JP** 2007 Visceral adipose tissue accumulation, cardiorespiratory fitness, and features of the metabolic syndrome. Arch Intern Med 167:1518–1525

26. **Rhéaume C, Arsenault BJ, Bélanger S, Pérusse L, Tremblay A, Bouchard C, Poirier P, Després JP** 2009 Low cardiorespiratory fitness levels and elevated blood pressure: what is the contribution of visceral adiposity? Hypertension 54:91–97

27. **Behnke AR, Wilmore JH** 1974 Evaluation and regulation of body build and composition. Englewood Cliffs, NJ: Prentice-Hall; 20–37

28. **Siri WE** 1956 The gross composition of the body. Adv Biol Med Phys 4:239–280

29. **Havel RJ, Eder HA, Bragdon JH** 1955 The distribution and chemical composition of ultracentrifugally separated lipoproteins in human serum. J Clin Invest 34:1345–1353

30. **Laurell CB** 1966 Quantitative estimation of proteins by electrophoresis in agarose gel containing antibodies. Anal Biochem 15:45–52

31. **Richterich R, Dauwalder H** 1971 [Determination of plasma glucose by hexokinase-glucose-6-phosphate dehydrogenase method]. Schweiz Med Wochenschr 101:615–618

32. **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 28:412–419

33. **Farrell SW, Cheng YJ, Blair SN** 2004 Prevalence of the metabolic syndrome across cardiorespiratory fitness levels in women. Obes Res 12:824–830

34. **Katzmarzyk PT, Church TS, Blair SN** 2004 Cardiorespiratory fitness attenuates the effects of the metabolic syndrome on all-cause and cardiovascular disease mortality in men. Arch Intern Med 164:1092–1097

35. **Arsenault BJ, Cartier A, Cote M, Lemieux I, Tremblay A, Bouchard C, Perusse L, Despres JP** 2009 Body composition, cardiorespiratory fitness, and low-grade inflammation in middle-aged men and women. Am J Cardiol 104:240–246.

36. **Fonong T, Toth MJ, Ades PA, Katzel LI, Calles-Escandon J, Poehlman ET** 1996 Relationship between physical activity and HDL-cholesterol in healthy older men and women: a cross-sectional and exercise intervention study. Atherosclerosis 127:177–183

37. **Sui X, LaMonte MJ, Blair SN** 2007 Cardiorespiratory fitness and risk of nonfatal cardiovascular disease in women and men with hypertension. Am J Hypertens 20:608–615

38. **Rankinen T, Church TS, Rice T, Bouchard C, Blair SN** 2007 Cardiorespiratory fitness, BMI, and risk of hypertension: the Hypgene Study. Med Sci Sports Exerc 39:1687–1692

39. **Carnethon MR, Gidding SS, Nehgme R, Sidney S, Jacobs Jr DR, Liu K** 2003 Cardiorespiratory fitness in young adulthood and the development of cardiovascular disease risk factors. JAMA 290:3092–3100

40. **Poirier P** 2008 Obesity, adiposity indices, and blood pressure; ethnicity does matter. Am J Hypertens 21:244

41. **Pouliot MC, Després JP, Lemieux S, Moorjani S, Bouchard C, Tremblay A, Nadeau A, Lupien PJ** 1994 Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. Am J Cardiol 73:460–468