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## Impact of Fitness Versus Obesity on Routinely Measured Cardiometabolic Risk in Young, Healthy Adults

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### Abstract

Obesity demonstrates a direct relation with cardiovascular risk and all-cause mortality, while cardiorespiratory fitness demonstrates an inverse relation. In clinical practice, several cardiometabolic (“CM”) risk factors are commonly measured to gauge cardiovascular risk yet the interaction between fitness and obesity with regard CM risk has not been fully explored. We studied 2,634 Brazilian adults referred for an employer-sponsored health exam. Obesity was defined as BMI >30 kg/m<sup>2</sup> or waist circumference > 102cm (men) or >88cm (women) when BMI 25–30kg/m<sup>2</sup>. Fitness was quantified by stage achieved on an Ellestad treadmill stress test, with those completing stage 4 considered fit. Hepatic steatosis was determined by ultrasound. We compared CM risk factors after stratifying patients into 4 groups: fit/normal weight, fit/obese, unfit/normal weight & unfit/obese. Approximately 22% of patients were obese; 12% were unfit. Fitness and obesity were moderately correlated ( $\rho=0.38-50$ ). 6.5% of the sample was unfit/normal weight, and 16% fit/obese. In overweight and obese patients, fitness was negatively associated with CM risk ( $p<0.01$  for all values). In fit patients, increasing BMI was positively associated with CM risk ( $p<0.01$  for all values). In instances of discordance between fitness and obesity, obesity was the stronger determinant of CM risk. Fitness and obesity are independently associated with CM risk. The effects of fitness and obesity are additive but obesity is more strongly associated with CM risk when fitness and obesity are discordant. These findings underscore the need for weight loss in obese individuals and suggest an unmeasured benefit of fitness.

### Keywords

fitness; obesity; metabolic syndrome; liver fat; inflammation

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Obesity has become one of the most pressing worldwide health issues. Obesity increases both all-cause and cardiovascular mortality. According to the World Health Organization, the prevalence of obesity doubled between 1980 and 2008 and now roughly half of a billion people worldwide are obese. The World Health Organization has estimated that 2.8 million people die each year as a result of being overweight or obese.<sup>1</sup> Many studies have shown that the mortality associated with obesity can be attenuated or even reversed with improved cardiorespiratory fitness (“fitness”).<sup>2-6</sup> These investigations have demonstrated that those who are fit yet obese have lower cardiovascular mortality than those who are lean but unfit. However, it is not clear if the benefits of improved fitness can be fully appreciated on routinely measured cardiometabolic (“CM”) risk panels. We sought to investigate the interaction of fitness and obesity with regard to routinely measured traditional and non-traditional CM risk factors to explore if the previously observed mortality benefit of fitness could be accounted for in routine CM risk assessment.

## Methods

A total of 2634 asymptomatic Brazilian men and women, who were free of known heart disease, were evaluated during an employer-sponsored clinical health examination at the Preventive Medicine Center of the Hospital Israelita Albert Einstein in São Paulo Brazil between November 2008 and July 2010. The examination consisted of a medical history questionnaire, laboratory evaluation of cardiovascular risk factors, an abdominal ultrasound for determination of liver fat, and a symptom-limited Ellestad treadmill test. A total of 2576 individuals (98%) had complete information on CM risk factors except for high-sensitivity C-reactive protein (“hs-CRP”), and these make up the primary study population. A total of 88% of individuals had measurements of hs-CRP and, these were retained in hs-CRP-specific analyses.

All participants had anthropomorphic measurements of obesity including height, weight and waist circumference. Obesity was defined using both BMI and waist circumference to measure central adiposity, adapted from the National Cholesterol Education Program Adult Treatment Panel III ranges for metabolic syndrome.<sup>7</sup> Obesity was present if BMI > 30 kg/m<sup>2</sup> or waist circumference >102cm for men or >88cm for women when BMI  $\geq$  25 kg/m<sup>2</sup>. Those who had a BMI between 25–30 kg/m<sup>2</sup> but did not meet the waist circumference cutoff for obesity were considered overweight.

Fitness was quantified by peak stage achieved on a maximal symptom-limited Ellestad treadmill stress test which ranged from 1.7 mph at a 10% grade (roughly 4.6 METS) to 8 mph at a 15% grade (roughly 21.5 METS). As such, fitness was considered an ordinal variable ranging from stage 1 through stage 7. Those who completed stage 4 (3 minutes at 5 mph at 10% grade or roughly 12.1 METS) were considered fit while those who could not, were considered unfit. Stage 4 was chosen as the fitness cutoff because it corresponds to the 125<sup>th</sup> percentile of predicted exercise capacity of our cohort given their average age.<sup>8</sup> Because of the small sample sizes at the extremes, we combined stages 1 and 2 and stages 6 and 7 for subsequent analyses after the basic correlation analysis. METS were calculated according to the guidelines for indirect oxygen consumption according to the American College of Sports Medicine.<sup>9</sup>

Blood specimens were collected after an overnight fast. Laboratory analysis included a standard lipid panel, fasting glucose, aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyl transpeptidase all of which were analyzed using a Vitros platform automated laboratory system (Johnson & Johnson Clinical Diagnostics). Hs-CRP levels were determined by immunonephelometry (Dade-Behring). Hepatic steatosis was assessed by

ultrasonography after at least a 6-hour fast using an ACUSON XP-10 (Mountain View, Ca) machine. The diagnosis was made by two board-certified radiologists, blinded to the results of the laboratory tests, via a pattern of bright liver with contrast between hepatic and renal parenchyma. This method is widely used and has been previously validated.<sup>10,11</sup> Metabolic syndrome was defined according to the International Diabetes Federation definition.<sup>12</sup>

Age, gender, CM risk factors, and 10 year Framingham risk score for the overall study population were determined by computing frequencies for categorical variables, means with standard deviations for normally distributed continuous variables, and medians with interquartile ranges for skewed, continuous variables. Pearson correlation coefficients were calculated to assess the relationship of stage achieved on the Ellestad treadmill stress test with BMI, waist circumference, and obesity.

In the subset of participants who were either overweight or obese (all participants with BMI >25kg/m<sup>2</sup>), the effect of increasing fitness level was determined by comparing CM risk factors across Ellestad stages using Pearson's  $\chi^2$  tests for categorical variables, 1-way analysis of variance (ANOVA) for continuous variables with normal distributions, and Kruskal-Wallis tests for continuous variables with skewed distributions. In the subset of participants who were defined as fit (Ellestad stage 4), the effect of increasing BMI was determined by comparing CM risk factors across BMI quartiles using Pearson's  $\chi^2$  tests, 1-way ANOVA, and Kruskal-Wallis tests.

To assess the effect of fitness on CM risk in the absence and presence of obesity, the total study population was divided into 4 groups: group 1, fit and not obese; group 2, unfit and not obese; group 3, fit and obese; group 4, unfit and obese. CM risk factors were compared across these 4 study groups using Pearson's  $\chi^2$  tests, 1-way ANOVA, and Kruskal-Wallis tests. CM risk in the unfit/not obese group was compared to the fit/obese group using the same tests. All analyses were performed using STATA, version 12 (College Station, TX).

## Results

The baseline characteristics of the study population are found in Table 1. The study population had a mean age of 42.8±8.7 years with an average BMI of 23.5±3.7 kg/m<sup>2</sup> for women and 26.9±3.5 for men. Obesity affected 11.6% of the female and 24.3% of the male participants. The average waist circumference was 78.7±9.5 cm for women and 94.8±9.8 cm for men. The mean calculated 10-year Framingham risk score was 3.8±4.3%.

Stage achieved on the Ellestad treadmill stress test was correlated with BMI, waist size, and obesity (Table 2). There was a greater correlation between fitness stage and obesity among men than women. Of the three anthropometric measures, waist size was most strongly correlated with fitness stage in both men and women.

In a cohort of overweight and obese participants (all participants with a BMI >25), increasing fitness levels demonstrated a progressively lower burden of CM risk factors (Table 3). All measured risk factors showed a progressive decrease across increasing fitness levels (p<0.001 for all). In fit individuals, ascending BMI quartiles demonstrated increasing levels of CM risk factors (Table 4). All measured risk factors increased as BMI quartile increased (p<0.001 for all).

Across the 4 fitness/obesity groups, the median or mean values of the 7 CM risk factors differed significantly (all p<0.001) (Table 5). All 7 risk factors were higher in the 2 groups with obesity than in the 2 groups without obesity. Specifically, improving fitness while worsening obesity increased cardiometabolic risk: all risk factor levels were significantly higher in the fit/obese group compared to the unfit/not obese group (all p<0.001). However,

improving fitness among individuals with the same level of obesity mildly decreased several CM risk factors. In the absence and presence of obesity, fit individuals compared to unfit individuals had significantly lower median hs-CRP, ( $p < 0.001$ ) and nonsignificantly lower metabolic syndrome prevalence. In the presence of obesity, fit individuals also had significantly lower mean systolic blood pressure than unfit individuals ( $p < 0.001$ ) and nonsignificantly lower mean glucose.

## Discussion

In this study, improved fitness among overweight and obese people was associated with an improvement in routinely measured CM risk factors (all  $p < 0.001$ ); in addition, among those who were fit, the BMI quartile predicted CM risk (all  $p < 0.001$ ). In general, we found that these effects were additive. However, the effect of fitness on the routine CM risk profile was minimal in a non-obese population. In discordant pairs (fit/obese and unfit/not obese) both fitness and obesity influence CM risk. However, obesity was a more important determinant of CM risk (all  $p < 0.001$ ); fitness did not reverse the effects of obesity with regard to CM risk.

Our study had a few limitations. First, our fitness variable relied on stage achieved on an Ellestad protocol stress test, allowing only seven possible values in our fitness variable. Also, because this cohort was a healthy, young population with a high degree of fitness, the degree to which this study can be generalized to a non-healthy population is unclear. Our population was so healthy that only 12% of our cohort was unable to achieve the equivalent of 12 METS. Based on the average age of our cohort, that is approximately 125% of the predicted fitness level.<sup>8</sup> Since this cohort was made up of only Brazilian men and women, the extent to which these findings can be generalized to other populations is unclear as well. Finally because this is a cross-sectional study that measured risk factors once, a causal relationship and lifetime patterns could not be determined.

Our study expands upon the knowledge regarding the interaction of obesity and fitness on measured cardiovascular risk. Strengths of our study included our population, which was a well-defined, young, healthy population free of known heart disease. Our study differed from previous cross-sectional studies in a few ways. First, few cross-sectional studies examining fitness/obesity discordance have used a measured fitness variable, instead using physical activity or questionnaires as a surrogate of fitness. The association of these surrogates with fitness is often modest.<sup>13</sup>

Of those studies that measured fitness most have involved a more limited list of risk factors or a smaller population. For instance, O'Donovan *et al.* had multiple cardiovascular risk factors but a small study population of 183 patients.<sup>14</sup> Similarly Hamer and Steptoe, Racette *et al.*, and Christou *et al.* had small study populations of 176, 407, and 135 patients respectively.<sup>15-17</sup> Wing *et al.* did have a large patient population of 5,145 but included relatively few cardiovascular risk factors including only measures of glucose tolerance, cholesterol and blood pressure.<sup>18</sup> Our analysis adds to the literature by including some commonly measured, emerging markers of CM disease such as hepatic steatosis, TG/HDL ratio, and a robust measure of inflammation, hs-CRP. Hepatic steatosis has been found to be an independent cardiac risk factor and correlated with coronary calcification.<sup>19, 20</sup> The TG/HDL ratio has been correlated to lipoprotein particle size, insulin resistance and findings on coronary angiography.<sup>21, 22</sup>

Despite the heterogeneity in how obesity and fitness are defined in the literature, our results are supported by available studies on cardiorespiratory fitness and CM risk in discordant populations. Cross-sectional studies consistently show a much stronger relationship between

CM risk and obesity than fitness, although both influence CM risk. Multiple studies of discordant pairs have shown that the fit/obese category has higher CRP,<sup>14,15</sup> worse glucose intolerance,<sup>14-16</sup> higher systolic blood pressure,<sup>17,23</sup> and worse HDL and LDL cholesterol<sup>17,23</sup> than the unfit/not obese category. However, there has been some mild variation in the results. For instance, O'Donovan *et al.* found that fitness and obesity had equivalent impact on HDL and LDL, although obesity was the main determinant of CRP, GGT and insulin resistance.<sup>14</sup>

Similarly, both maintenance of fitness and prevention of obesity are important to reduce CM risk over time. Again, obesity had a stronger influence on CM risk than changes in fitness. Lee *et al.* studied 3,148 healthy adults over a 6-year period measuring the impact of a change in fitness and obesity on hypertension, metabolic syndrome and hypercholesterolemia. Fat gain conferred an increased CM risk. However, this risk was partially but not completely attenuated when fitness was maintained or improved. Thus, although fitness was protective, these effects could not overcome the CM effects of increasing adiposity.<sup>24</sup> Similarly, the Quebec Family Study compared changes in visceral adiposity and cardiorespiratory fitness over time and found that changes in adiposity were the most important predictor in the change in metabolic syndrome score.<sup>25</sup> Thus over time, obesity continues to remain the most important determinant of CM risk.

From these data showing increased CM risk with obesity and our reliance on CM risk to estimate cardiovascular mortality, one would expect a higher cardiovascular mortality in the fit/obese compared to unfit/not obese. Studies that compared fitness, obesity, and cardiovascular mortality, however, present a different picture. Multiple studies have shown that in the discordant pairs, it is those who are fit and obese that have a lower cardiovascular mortality than unfit/not obese individuals; it is fitness that is protective against some, if not all of the mortality effects of obesity.<sup>2-6</sup> Although a causal relationship cannot be established by our data alone, our findings suggest that the protective effect of fitness on cardiovascular mortality in obese individuals is not due to better CM risk factors. This implies that the benefits of fitness are not captured in the routinely measured risk profiles. Possible mechanisms for this may include improvement of baseline cardiovascular hemodynamics including arterial elasticity and resting heart rate and warrant further investigation.

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**Table 1**

Baseline Characteristics of the Study Population (n=2,634)

Characteristic	Mean ± SD or Frequency
Age (years)	42.8 ± 8.7
Gender (women)	21.0%
Body Mass Index (kg/m <sup>2</sup> )	26.2 ± 3.8
Obesity <sup>a</sup>	21.7%
Systolic blood pressure (mm Hg)	116.8 ± 11.9
Diastolic blood pressure (mm Hg)	76.2 ± 7.8
Hypertension	12.4%
Fasting glucose (mg/dL)	89.8 ± 10.2
Diabetes mellitus	1.2%
Low-Density Lipoprotein	
(mg/dL)	131.1 ± 33.6
(mmol/L)	3.39 ± 0.87
High-Density Lipoprotein	
(mg/dL)	50.0 ± 13.5
(mmol/L)	1.29 ± 0.35
Triglycerides <sup>b</sup>	
(mg/dL)	116 (83–165)
(mmol/L)	1.31 (0.93–2.15)
Lipid lowering drugs	8.1%
Current smoker	8.3%
Alcohol use <sup>b,c</sup>	3 (2–6)
High sensitivity C-Reactive Protein (mg/L) <sup>b,d</sup>	1.2 (0.6–2.4)
Gamma-Glutamyl Transpeptidase (U/L)	38.3 ± 31.5
Hepatic steatosis	35.1%
Metabolic syndrome	17.3%
10 year Framingham risk (%)	3.8 ± 4.3

<sup>a</sup>Defined as BMI >30 kg/m<sup>2</sup> or waist circumference > 102cm (men) or >88cm (women) when BMI 25–30kg/m<sup>2</sup>

<sup>b</sup>Median (interquartile range).

<sup>c</sup>Measured by the Alcohol Use Disorders Identification Test.

<sup>d</sup>n=2576



**Table 2**

## The Correlation between Obesity and Fitness

Correlation Coefficient	Males	Females
$\rho$ Stage and BMI	- 0.423	- 0.390
$\rho$ Stage and waist size	- 0.503	- 0.401
$\rho$ Stage and obesity	- 0.376	- 0.307

All individual correlation coefficients were significant at  $p < 0.0001$ .

For men and women, respectively,  $n=2035$  and  $541$  for BMI and obesity and  $n=2034$  and  $540$  for waist size.

**Table 3**The Effect of Increasing Fitness in Overweight and Obese<sup>a</sup> Subjects

Ellestad Stage Achieved <sup>b</sup>	High-sensitivity C-reactive Protein <sup>b</sup> (mg/L) (median)	Triglyceride: High Density Lipoprotein Ratio (median)	Glucose (mg/dL)	Systolic Blood Pressure (mmHg)	Metabolic syndrome	Hepatic Steatosis	Gamma-Glutamyl Transpeptidase (IU/L)
<b>1 or 2</b> (n=17)	4.0	3.3	92.9	129.2	58.8%	58.8%	24.2
<b>3</b> (n=190)	2.3	3.3	93.8	124.1	37.9%	61.1%	41.9
<b>4</b> (n=918)	1.5	3.2	92.5	120.5	31.4%	57.1%	38.7
<b>5</b> (n=329)	1.2	2.6	90.8	118.2	15.2%	34.0%	25.3
<b>6 or 7</b> (n=84)	0.9	2.1	88.7	116.7	7.1%	19.1%	15.2
<b>p value</b>	<0.001	<0.001	0.001	<0.001	<0.001	<0.001	<0.001

<sup>a</sup>Includes all participants with a BMI > 25 regardless of waist circumference<sup>b</sup>Estimated METS (Kcal/kg<sup>#</sup>h) for stage 1 to 7 respectively: 4.6, 7.4, 9.6, 12.1, 16.4, 19.0, 21.5<sup>c</sup>n=182, 810, 283, and 73 for stages 3, 4, 5, and 6 or 7, respectively.

**Table 4**

The Effect of Increasing Body Mass Index in Fit Subjects

BMI quartile <sup>a</sup>	High-sensitivity C-reactive Protein <sup>b</sup> (mg/L) (median)	Triglyceride: High Density Lipoprotein Ratio (median)	Glucose (mg/dL)	Systolic Blood Pressure (mmHg)	Metabolic syndrome	Hepatic Steatosis	Gamma-Glutamyl Transpeptidase (IU/L)
1 <sup>st</sup> (n=586)	0.8	1.6	85.2	109.4	1.2%	6.5%	26.5
2 <sup>nd</sup> (n=610)	0.9	2.2	89.6	115.9	6.4%	24.4%	34.9
3 <sup>rd</sup> (n=571)	1.3	2.8	90.8	118.1	18.6%	39.4%	43.5
4 <sup>th</sup> (n=505)	1.8	3.4	93.8	123.0	41.2%	70.5%	49.7
<b>p value</b>	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

<sup>a</sup>BMI based on quartile 1<sup>st</sup> quartile: 15.8–23.6; 2<sup>nd</sup> quartile 23.7–25.8; 3<sup>rd</sup> quartile 25.9–28.3 and 4<sup>th</sup> quartile: 28.4 – 44.6

<sup>b</sup>n=508, 531, 503, and 440 for the 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup>, and 4<sup>th</sup> BMI quartiles, respectively.

**Table 5**

Cardiometabolic Risk Factors According to Fitness/Obesity Category

Fitness/Obesity Category	High-sensitivity C-reactive Protein <sup>a</sup> (mg/L) (median)	Triglyceride: High Density Lipoprotein Ratio (median)	Glucose (mg/dL)	Systolic Blood Pressure (mmHg)	Metabolic syndrome	Hepatic Steatosis	Gamma-Glutamyl Transpeptidase (IU/L)
Fit/not obese (n=1856)	1.0	2.2	88.7	114.9	9.8%	25.0%	35.9
Unfit/not obese (n=161)	1.4	1.9	87.5	113.1	10.6%	19.9%	29.8
Fit/obese (n=416)	1.9	3.4	93.8	123.0	42.8%	73.1%	48.5
Unfit/obese (n=143)	2.6	3.4	94.3	127.3	47.6%	72.0%	49.2
<b>p across all groups</b>	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
<b>p for unfit/not obese vs. fit/obese</b>	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

<sup>a</sup> n=1621, 153, 361, and 137 for the fit/not obese, unfit/not obese, fit/obese, and unfit/obese groups, respectively.