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The intriguing metabolically healthy but obese phenotype: cardiovascular prognosis and role of fitness

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Aims Current knowledge on the prognosis of metabolically healthy but obese phenotype is limited due to the exclusive use of the body mass index to define obesity and the lack of information on cardiorespiratory fitness. We aimed to test the following hypotheses: (i) metabolically healthy but obese individuals have a higher fitness level than their metabolically abnormal and obese peers; (ii) after accounting for fitness, metabolically healthy but obese phenotype is a benign condition, in terms of cardiovascular disease and mortality.

Methods and results Fitness was assessed by a maximal exercise test on a treadmill and body fat per cent (BF%) by hydrostatic weighing or skinfolds (obesity = BF% $\geq$25 or $\geq$30%, men or women, respectively) in 43 265 adults (24.3% women). Metabolically healthy was considered if meeting 0 or 1 of the criteria for metabolic syndrome. Metabolically healthy but obese participants (46% of the obese subsample) had a better fitness than metabolically abnormal obese participants ($P < 0.001$). When adjusting for fitness and other confounders, metabolically healthy but obese individuals had lower risk (30–50%, estimated by hazard ratios) of all-cause mortality, non-fatal and fatal cardiovascular disease, and cancer mortality than their metabolically unhealthy obese peers; while no significant differences were observed between metabolically healthy but obese and metabolically healthy normal-fat participants.

Conclusions (i) Higher fitness should be considered a characteristic of metabolically healthy but obese phenotype. (ii) Once fitness is accounted for, the metabolically healthy but obese phenotype is a benign condition, with a better prognosis for mortality and morbidity than metabolically abnormal obese individuals.

Keywords Cardiovascular diseases • Heart diseases • Metabolic syndrome • Mortality • Obesity • Physical fitness

Introduction

Obesity is a major public health concern in most developed and developing countries. It is well known that obesity is related to a large number of chronic diseases and metabolic abnormalities. However, a subset of obese people who seem to be protected against obesity-related metabolic complications has been identified.[1] These individuals are described as metabolically healthy but obese, having uncomplicated obesity, or having metabolically benign obesity.[2] This concept should not be mixed with a different concept and opposite health condition, the so-called metabolically obese but normal weight, which is defined as a subset of individuals who are not obese on the basis of height and weight, but who, like people with overt obesity, are hyperinsulinaemic, insulin resistant, and predisposed to type 2 diabetes, hypertriglyceridaemia, and premature coronary heart disease.[3] This study is focused on the metabolically healthy but obese phenotype.

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Primeau *et al.*[4] have recently reviewed the existing literature and reported a number of characteristics of the metabolically healthy but obese phenotype, including lower visceral fat accumulation, higher birth weight, adipose cell size, and gene expression-encoding markers of adipose cell differentiation. However, the authors did not consider that differences in the metabolic profile of obese individuals might be partially explained by differences in cardiorespiratory fitness (hereinafter fitness). There is strong evidence indicating that higher fitness levels are associated with fewer metabolic complications and lower prevalence of metabolic syndrome at any age and across different weight status groups.[4–9] Further research is needed to understand whether higher fitness is a common characteristic in metabolically healthy but obese individuals.

The extent to which metabolically healthy but obese people are at a lower risk for diseases or have a lower risk for mortality, compared with the rest of obese people, is currently under debate. While some studies observed a low risk for cardiovascular disease (CVD) incidence and mortality in this group of people (similar to that observed in metabolically healthy normal-weight people),[10–14] others suggested that obesity *per se* rather than the metabolic profile increased the risk of morbidity and mortality.[15,16] In this study, we refer to CVD in broad terms not meaning only atherosclerotic outcomes.

Obesity is internationally defined based on the body mass index (BMI); however, BMI is criticized for its lack of sensitivity to distinguish between the fat and lean mass. A recent meta-analysis has shown that BMI failed to identify half of the people with excess body fat per cent (BF%).[17] To better understand the metabolically healthy but obese phenotype and its prognosis, further research using more accurate measures of adiposity, e.g. BF% derived from skinfold thicknesses and/or hydrostatic weighing, is warranted. To the best of our knowledge, the long-term effect of the metabolically healthy but obese phenotype on mortality has not been examined using BF% to define obesity. In addition, only one previous study conducted in men by our group has considered fitness, a strong and well-known predictor of mortality,[18] as a potential confounder in the analyses of obesity and health outcomes.[19] The present study aimed to add to our previous study by: (i) including the measure of BF% in addition to BMI, (ii) doubling the sample size for obese people, which will allow us to have higher statistical power after dividing the sample into metabolically healthy vs. metabolically unhealthy obese; (iii) adding women to the study; (iv) increasing the follow-up period; (v) adding non-fatal CVD major events, in addition to CVD mortality, as outcomes; and (vi) adding cancer mortality as an outcome.

The present study aimed to test the following hypotheses: (i) metabolically healthy but obese individuals have a higher fitness level than their metabolically abnormal and obese peers; (ii) if the metabolically healthy but obese phenotype is a benign condition, these people should have lower risk of CVD and mortality compared with the 'theoretically unhealthiest group', i.e. metabolically abnormal and obese individuals, and a similar risk as the 'theoretically healthiest group', i.e. metabolically healthy and normal-weight individuals. We examined these hypotheses after controlling for relevant confounders, including fitness, and using both BMI and BF% to define obesity.

Methods

Study cohort

The Aerobics Center Longitudinal Study (ACLS) is a prospective epidemiological investigation of adult men and women.[20–22] The ACLS participants are mostly Caucasian (98%), well educated, and worked in executive or professional positions.[23] All participants completed a detailed questionnaire and underwent an extensive clinical evaluation, including a physical examination, fasting blood chemistry analyses, personal and family health history, body composition, smoking and alcohol use, and a maximal exercise treadmill test between 1979 and 2003. All participants provided written informed consent, and the study protocol was approved annually by the Institutional Review Board of the Cooper Institute.

Inclusion criteria for the present analysis were: (i) no existing CVD or cancer at baseline; (ii) achieving 85% or more of the individual's age-predicted maximal heart rate during the graded modified Balke treadmill exercise testing (considered a maximal test); (iii) BMI $\geq$18.5 kg/m^2, (iv) $\geq$1 year of follow-up; (v) complete data on BMI, BF%, fitness, metabolic syndrome traits, mortality outcomes, and all the confounders included in the study. A total of 43 265 participants (24.3% women) aged 20 years or older at baseline met all these criteria and were therefore included in the study.

Baseline examination

Previous reports have described the baseline examination in detail.[20,20] Briefly, height and weight were measured using a stadiometer and a standard scale. The waist circumference was obtained at the level of the umbilicus with a plastic anthropometric tape. The BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2), and participants were classed as normal weight (BMI = 18.5–24.9 kg/m^2), overweight (BMI = 25.0–29.9 kg/m^2), and obese (BMI $\geq$30 kg/m^2). Body fat per cent was assessed by hydrostatic weighing or the sum of seven skinfold measures, following standardized protocols.[24,25] Some participants chose to go through the underwater weighing assessment for hydrostatically estimated body density with a mathematical conversion to BF%, whereas other participants received a skinfold estimate of BF%. Standardized protocols used and specific procedures for the ACLS assessment of BF% were published elsewhere.[21,24,26,27] The correlations between hydrostatically estimated BF% and skinfold estimated BF% were $>$0.90 for participants who had both measurements.[26,27] When available, hydrostatically estimated per cent BF was always used in the analysis, i.e. hydrostatic weighing was available on 18 104 participants (42%) and the sum of seven skinfold measures in 25 161 participants (58%). Body fat per cent was further dichotomized based on standard clinical definitions for men (normal fat $<$25%, overfat $\geq$25%) and for women (normal fat $<$30%, overfat $\geq$30%),[17] which has shown to be associated with a higher risk for all-cause and CVD mortality.[21,24]

Cardio respiratory fitness was defined as the total time of a symptom-limited maximal treadmill exercise test, using a modified Balke protocol.[20,28] Total time of the test on this protocol correlates highly with measured maximal oxygen uptake (VO_{2max}) in both men (r = 0.92)[29] and women (r = 0.94).[30] The test endpoint was volitional exhaustion or when the physician stopped it for medical reasons. VO_{2max} was calculated from the final treadmill speed and grade.[31] Fitness was also expressed in metabolic equivalents (METs, 3.5 mL/kg/min of oxygen uptake). Information on smoking (never, former, and current smoker), alcohol consumption ($\geq$5 drinks/week or $<$5 drinks/week), and parental history of CVD was obtained from a standardized medical history questionnaire.

Systolic and diastolic blood pressures were obtained with a mercury sphygmomanometer and auscultory methods following the American Heart Association protocol.[32] A fasting blood sample was obtained by venipuncture, and serum triglycerides, HDL cholesterol, and plasma glucose were assayed with automated techniques at the Cooper Clinic Laboratory, which participates in and meets the quality control standards of the U.S. Centers for Disease Control and Prevention Lipid Standardization Programme.

Definition of metabolically healthy

We have followed the metabolic syndrome definition proposed in the latest joint statement by the International Diabetes Federation Task Force on Epidemiology and Prevention, National Heart, Lung, and Blood Institute, American Heart Association, World Heart Federation, International Atherosclerosis Society, and the International Association for the Study of Obesity.[33] Based on this definition, participants who met 0 or 1 of the criteria were classified as metabolically healthy. Consistent with previous literature on this topic,[4,16] the waist circumference was excluded as a criterion, since our main purpose was to study the prognosis of obese people who regardless of their adiposity levels (both total and central) have a better metabolic profile, i.e. metabolically healthy but obese phenotype. In the present study, >80% of the obese participants had a high waist circumference, i.e. ≥102 and ≥88 cm for men and women, respectively.

The rest of criteria used were: high blood pressure (≥130/85 mmHg), high triglycerides (≥150 mg/dL), low HDL cholesterol (<40 and 50 mg/dL in men and women, respectively), and high fasting glucose level (≥100 mg/dL).

Participants with normal blood pressure or fasting plasma glucose at the clinical evaluation who indicated a history of physician-diagnosed hypertension ($n = 1571$) or diabetes ($n = 482$) were also coded as positive for these risk factors, which increased the number of participants with metabolic syndrome by 635 ($n = 15\,648$ vs. $n = 16\,283$). The results obtained when these participants were excluded from all analyses were virtually identical to those reported here.

Assessment of outcomes

The participants were followed from the baseline examination until the date of death or 31 December 2003 (for mortality outcomes). Mortality surveillance was based on the national death index (NDI). The underlying cause of death was determined from the NDI report or by a nosologist's review of official death certificates obtained from the department of vital records in the decedent's state of residence. Cardiovascular disease mortality was defined by *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes 390 to 448.9 before 1999 and *Tenth Revision* (*ICD-10*) codes I00 to I78 during 1999–2003.[34] Cancer mortality was defined by *ICD-9* codes 140 to 208 and *ICD-10* codes C00 to C97.[34]

Data on non-fatal CVD events were additionally ascertained in a subsample of 18 430 individuals (77.5% men). Non-fatal CVD events were ascertained from responses to mail-back health surveys in 1982, 1999, and 2004. The aggregate survey response rate across all survey periods in the ACLS is ~65%. Non-response bias is a concern in epidemiological surveillance, and this issue has been investigated in the ACLS.[35] Baseline health histories and clinical measures were mostly similar between responders and non-responders and between early and late responders. Total mortality rates also have been similar between responders and non-responders (data not shown). We observed similar response rates between metabolically healthy but obese participants and metabolically abnormal obese participants (data not shown). On the other hand, metabolically healthy normal-fat participants had a 5% higher response rate than both obese groups (data not shown). This finding is consistent with previous epidemiological studies that reported increasing responding rates as BMI decreases.[36,37]

Non-fatal CVD endpoints were defined as diagnosis by a physician of myocardial infarction, stroke, or a coronary revascularization procedure (coronary artery bypass graft or percutaneous coronary intervention). In participants reporting multiple events, the first event was used for analysis. The primary outcome was all CVD events. Secondary outcomes were coronary heart disease events (myocardial infarction, coronary revascularization) and myocardial infarction and stroke as separate endpoints. In a random sample of these endpoints, we applied a standard definition for defining and adjudicating myocardial infarction, revascularization, and stroke.[38,39] The percentage of agreement between reported events and participants' medical records was 88, 100, and 89% for myocardial infarction, revascularization, and stroke, respectively.[40]

Statistical analysis

All statistical analyses were performed using PASW (Predictive Analytics Soft Ware, formerly SPSS), version 18.0 SPSS, Inc., Chicago, IL, USA. The level of significance was set at <0.05 for all the analyses. The characteristics of the study sample are presented as means and standard deviations or as frequencies and percentages, as appropriate. For the purposes of the present study, we focused the analyses on 3 × 2 study groups: the metabolically healthy but obese, metabolically abnormal obese ('unhealthiest group') and metabolically healthy normal weight/fat ('healthiest group'), using both BMI and BF% to define obesity. Since we aimed to compare the metabolically healthy but obese phenotype with the two 'extreme' groups defined above, 'middle' groups were not included in the analyses, i.e. overweight participants ($n = 17\,453$) and metabolically abnormal normal weight ($n = 4161$) /fat ($n = 9383$) participants.

Aim 1

Differences in baseline fitness among the three study groups were examined by one-way analysis of covariance, after adjustment for age, sex, examination year, smoking, and alcohol consumption.

Aim 2

We used Cox proportional hazards regression (two-sided tests) to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) according to exposure categories (aforementioned three study groups). The metabolically healthy but obese group was used as referent in the analyses. The main study outcomes were: all-cause mortality, CVD mortality, non-fatal CVD events, and cancer mortality. In secondary analyses, we also studied non-fatal coronary heart disease, myocardial infarction, and stroke separately. All the models were adjusted for age, sex, examination year, smoking, alcohol consumption, and fitness. Parental history of CVD was additionally included in all the models, except when the outcome was cancer. Proportionality assumption for Cox regression analyses was met in all the models studied.

Results

The baseline characteristics of the study sample are shown in *Table 1*. A total of 5649 (13.1%) and 12 829 (29.7%) participants were obese according to the standard BMI and BF% criteria, respectively. Within the obese participants, 30.8 and 46.3% of them, for BMI-based obesity and BF%-based obesity, respectively, were metabolically healthy. Metabolically abnormal obese

Table 1 Baseline characteristics of the study sample

	All (n = 43 265)	Men (32 764)	Women (10 501)
Age (years)	44.2 (9.9)	44.3 (9.6)	44.0 (10.5)
BMI (kg/m^2)	25.8 (4.0)	26.5 (3.7)	23.5 (4.0)
BF%	22.8 (6.8)	21.5 (6.3)	26.9 (6.8)
Waist circumference (cm)[a]	87.3 (19.3)	92.0 (16.5)	70.1 (19.3)
Triglycerides (mg/dL)	121.4 (73.5)	130.5 (76.6)	93.2 (53.9)
HDL cholesterol (mg/dL)	50.0 (14.5)	46.1 (11.9)	62.2 (15.0)
Glucose (mg/dL)	98.4 (15.6)	99.9 (15.9)	93.8 (13.4)
Systolic blood pressure (mmHg)	119.0 (14.0)	121.0 (13.3)	112.6 (14.3)
Diastolic blood pressure (mmHg)	79.9 (9.8)	81.2 (9.5)	75.9 (9.5)
VO_2 max (mL/kg/min)	39.8 (8.9)	41.7 (8.5)	34.0 (7.4)
Maximal METs	11.4 (2.5)	11.9 (2.4)	9.7 (2.1)
Cigarette smoking, n (%)			
Never	31 378 (72.5)	23 176 (70.7)	8202 (78.1)
Former	5541 (12.8)	4185 (12.8)	1356 (12.9)
Current	6346 (14.7)	5403 (16.5)	943 (9.0)
Alcohol consumption, n (%) of ≥5 drinks/week	19 328 (44.7)	16 058 (49.0)	7231 (68.9)
Parental history of CVD, n (%)	11 765 (27.2)	8954 (27.3)	2811 (26.8)
BMI-based obesity, n (%)	5649 (13.1)	4907 (15.0)	742 (7.1)
BF%-based obesity, n (%)[b]	12 829 (29.7)	9343 (28.5)	3516 (33.5)
Metabolically healthy, n (%)[b]	26 982 (62.4)	18 287 (55.8)	8695 (82.8)
Metabolically healthy among the BMI-based obese sample, n (%)[b]	1738 (30.8)	1381 (28.1)	357 (48.1)
Metabolically healthy among the BF%-based obese sample, n (%)[b]	5959 (46.3)	3548 (38.0)	1105 (31.4)

Data are means (standard deviations), unless otherwise indicated. BF%, percent body fat; BMI, body mass index; HDL, high-density lipoproteins; VO_2max, maximal oxygen consumption; METs, metabolic equivalents, 1 MET = 3.5 mL of oxygen uptake/ kg/min.
[a]This variable has 2979 missing values; for the rest of variables data are complete.
[b]BMI-based obesity was defined as BMI ≥30 kg/m^2; BF%-based obesity was defined as BF% ≥25% in men and BF% ≥30% in women; 'Metabolically healthy' was defined as meeting 0 or 1 of the criteria for metabolic syndrome.[33]

participants had higher BMI, BF%, and waist circumference than metabolically healthy but obese participants, regardless of the set of confounders (*Table 2*). The differences were attenuated after additional adjustment for fitness (data not shown).

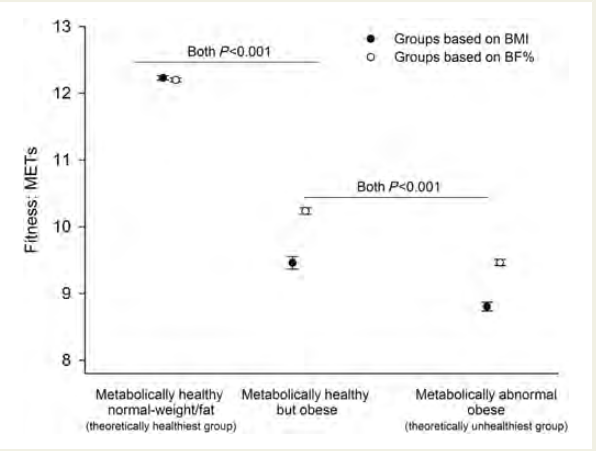

Figure 1 Differences in baseline fitness among the study groups using either body mass index or percent body fat to define obesity. The circled points and error bars represent adjusted means and 95% confidence intervals, respectively. The model (one-way analysis of covariance) was adjusted for age, sex, examination year, smoking, and alcohol consumption. Pair-wise comparisons were adjusted for the Bonferroni correction. METs, metabolic equivalents, 1 MET = 3.5 mL of oxygen uptake/kg/min.

The median (25–75th percentiles) follow-up period for mortality was 14.3 (6.0–19.8) years and for non-fatal CVD incidence was 7.9 (2.9–16.2) years. Frequency and percentage of deaths and incidence of non-fatal CVD events are shown in *Table 2*. A total of 1779 (4.1%) participants died during the study period; 546 of the deaths were caused by CVD and 698 by cancer. The incidence of non-fatal CVD events was 5.8%, being 1.7% due to myocardial infarction and 1.3% to stroke.

Figure 1 shows that metabolically healthy but obese participants had a better baseline fitness level than metabolically abnormal obese participants, after adjustment for the set of confounders, and when using either BMI or BF% to define obesity ($P < 0.001$). This difference was consistent in men and women, particularly when using BF%-based obesity ($P < 0.001$, data not shown). The results did not materially change when excluding class 3 obesity, i.e. BMI ≥ 40 kg/m^2, or when excluding participants with abnormal electrocardiogram (data not shown).

Hazards ratios and 95% CI of all-cause mortality, CVD mortality and non-fatal CVD incidence, and cancer mortality in the study groups are shown in *Tables 3–5*, respectively. When obesity was defined using BF% and the models were fully adjusted by the set of confounders including fitness, metabolically healthy but obese individuals had a 38% lower risk of all-cause mortality than their metabolically unhealthy obese peers, while no significant difference was observed between metabolically healthy but obese and metabolically healthy normal-fat participants (*Table 3*). This result was consistent for CVD mortality and incident non-fatal CVD (*Table 4*), as well as for cancer mortality (*Table 5*). Further analyses focused on coronary heart disease, myocardial infarction and stroke also showed similar results (data not shown). The risk difference between metabolically healthy but obese and metabolically

Table 2 Anthropometric and metabolic parameters according to study groups

	BMI-based groups			*P*-value*	BF%-based groups			*P*-value*
	Metabolically healthy and normal weight (*n* = 16 002) Mean (SEM)	Metabolically healthy but obese (*n* = 1738) Mean (SEM)	Metabolically abnormal and obese (*n* = 3911) Mean (SEM)		Metabolically healthy and normal fat (*n* = 21 023) Mean (SEM)	Metabolically healthy but obese (*n* = 5959) Mean (SEM)	Metabolically abnormal and obese (*n* = 6900) Mean (SEM)	
BMI (kg/m^2)	22.6 (0.0)	32.4 (0.1)	33.0 (0.0)	<0.001	23.8 (0.0)	28.1 (0.0)	30.0 (0.0)	<0.001
BF%	19.3 (0.0)	31.6 (0.1)	31.9 (0.1)	<0.001	19.4 (0.0)	29.9 (0.1)	30.5 (0.1)	<0.001
Waist circumference (cm)[a]	77.6 (0.1)	99.5 (0.4)	103.0 (0.3)	<0.001	81.3 (0.1)	92.4 (0.2)	97.9 (0.2)	<0.001
Triglycerides (mmol/L)	83.3 (0.4)	106.9 (1.2)	191.2 (0.8)	<0.001	86.8 (0.4)	102.3 (0.7)	182.3 (0.6)	<0.001
HDL cholesterol (mmol/L)	57.0 (0.1)	50.3 (0.3)	41.7 (0.2)	<0.001	55.4 (0.1)	52.1 (0.1)	42.4 (0.1)	<0.001
Glucose (mmol/L)	93.6 (0.1)	95.3 (0.3)	107.6 (0.2)	<0.001	94.3 (0.1)	95.0 (0.2)	106.3 (0.2)	<0.001
Systolic blood pressure (mmHg)	113.5 (0.1)	118.4 (0.3)	126.3 (0.2)	<0.001	114.8 (0.1)	116.6 (0.2)	125.7 (0.1)	<0.001
Diastolic blood pressure (mmHg)	75.9 (0.1)	80.5 (0.2)	86.2 (0.1)	<0.001	76.7 (0.1)	79.0 (0.1)	85.2 (0.1)	<0.001

BF%, percent body fat; BMI, body mass index; HDL, high-density lipoproteins; SEM, standard error of the mean.
[a]This variable has 2979 missing values; for the rest of variables data are complete.
*The model (one-way analysis of covariance) was adjusted for age, sex, examination year, smoking and alcohol consumption. Pairwise comparisons were adjusted for the Bonferroni correction and were significant among all the groups ($P < 0.001$).

abnormal obese patients ranged from 32 to 51% (*Tables 3–5*). Comparisons between models adjusted and non-adjusted for fitness allow exploring the role of fitness in these associations (*Tables 3–5*). The results did not materially change when excluding class 3 obesity, i.e. BMI $\geq$40 kg/m^2, or when excluding participants with abnormal electrocardiogram (data not shown).

If a more strict definition of 'metabolically healthy' was applied, i.e. meeting 0 metabolic syndrome criteria, the metabolically healthy but obese sample was reduced to one-third of the original sample ($n = 5959$ vs. $n = 2197$, 37%). When the same analyses were repeated using these new groups, almost identical findings were observed for all-cause mortality. Similar trends were also observed for CVD mortality and cancer mortality, though the differences between the metabolically healthy but obese group and the metabolically abnormal obese group were not significant, presumably due to the 63% reduction in the sample size and consequently reduced number of cases (deaths) of the main study group, i.e. metabolically healthy but obese (data not shown).

Discussion

The results of the present study suggest that: (i) metabolically healthy but obese individuals have better fitness than their metabolically abnormal obese peers, both in men and women and using BMI or BF% to define obesity; (ii) for a given fitness level, the metabolically healthy but obese phenotype is a benign condition, since these individuals had a lower risk for mortality and morbidity than that observed in metabolically abnormal obese individuals. In addition, we did not observe differences in the prognosis between metabolically healthy but obese individuals and metabolically healthy normal-fat individuals. These findings are consistent for all the outcomes studied, i.e. all-cause mortality, CVD mortality and morbidity, and cancer mortality. Although the prevalence of metabolically healthy but obese phenotype differs depending on the definition of metabolically healthy used and no standard definition is currently available,[4,41] the prevalence of metabolically healthy but obese participants observed in our study (~30%, based on BMI definition) is in agreement with that previously observed in US adults[42] and in other populations,[43–46] and supports the notion that this phenotype is a frequent condition.

The prevalence of obesity in the present study was 13% as defined by BMI and 30% as defined by BF%. This difference is in agreement with the findings from a recent meta-analysis that concluded that BMI ($\geq$30 kg/m^2) failed to identify half of the individuals with excess BF% (standard cut points used in the present study).[17] Based on this, the 'actual' number of obese people would be two times higher than that identified by BMI, which would result in a similar percentage observed in this study when using BF% (i.e. ~30%). In the remaining discussion, we focus on the BF%-based results rather than BMI, since it is a more accurate measure of adiposity and a major contribution of this study to the previous literature.

Differences in fitness between metabolically healthy but obese and metabolically abnormal obese individuals

In spite of the strong evidence indicating that higher fitness levels are related to lower metabolic complications and lower prevalence of metabolic syndrome,[5–9] a recent review[4] characterizing the metabolically healthy but obese phenotype did not mention the possibility that the better metabolic profile observed in this subset of obese people could be, at least in part, explained by fitness. Our study conducted on thousands of obese people supports that metabolically healthy but obese individuals have a better fitness level than the rest of obese individuals, regardless of a set of relevant confounders and using BF% to define obesity. Messier *et al.*[47] observed a higher

Table 3 Hazard ratios of all-cause mortality in metabolically healthy but obese individuals compared with metabolically abnormal obese and metabolically healthy normal-weight individuals, using both body mass index and per cent body fat to define obesity

	BMI-based obesity			BF%-based obesity		
	Cases (total)	HR (95% CI)[a]	Fitness-adjusted HR (95% CI)[b]	Cases (total)	HR (95% CI)[a]	Fitness-adjusted HR (95% CI)[b]
All-cause mortality						
Metabolically abnormal obese[c]	218 (3911)	1.61 (1.19–2.18)	1.44 (1.06–1.96)	436 (6900)	1.57 (1.32–1.85)	1.38 (1.16–1.63)
Metabolically healthy but obese	52 (1738)	1 (Ref.)	1 (Ref.)	216 (5959)	1 (Ref.)	1 (Ref.)
Metabolically healthy normal-weight/fat[d]	449 (16 002)	0.65 (0.48–0.87)	0.91 (0.67–1.24)	584 (21 023)	0.84 (0.72–0.99)	1.10 (0.92–1.30)

CI, confidence interval.
[a]Model adjusted for age, sex, examination year, smoking, alcohol consumption and parental history of CVD.
[b]Additional adjustment for fitness.
[c]Theoretically unhealthiest group.
[d]Theoretically healthiest group.

Table 4 Hazard ratios of cardiovascular disease mortality and incidence in metabolically healthy but obese individuals compared with metabolically abnormal obese and metabolically healthy normal-weight individuals, using both body mass index and body fat percentage to define obesity

	BMI-based obesity			BF%-based obesity		
	Cases (total)	HR (95% CI)[a]	Fitness-adjusted HR (95% CI)[b]	Cases (total)	HR (95% CI)[a]	Fitness-adjusted HR (95% CI)[b]
CVD mortality						
Metabolically abnormal obese[c]	81 (3911)	1.77 (1.05–2.99)	1.48 (0.87–2.52)	153 (6900)	1.76 (1.31–2.37)	1.44 (1.06–1.95)
Metabolically healthy but obese	17 (1738)	1 (Ref.)	1 (Ref.)	64 (5959)	1 (Ref.)	1 (Ref.)
Metabolically healthy normal-weight/fat[d]	98 (16 002)	0.41 (0.24–0.70)	0.73 (0.42–1.28)	144 (21 023)	0.74 (0.54–1.00)	1.13 (0.82–1.56)
Non-fatal CVD events[e]						
Metabolically abnormal obese[c]	107 (1300)	1.44 (0.96–2.17)	1.39 (0.92–2.10)	231 (2598)	1.61 (1.29–2.01)	1.51 (1.20–1.89)
Metabolically healthy but obese	30 (544)	1 (Ref.)	1 (Ref.)	123 (2340)	1 (Ref.)	1 (Ref.)
Metabolically healthy normal-weight/fat[d]	261 (7001)	0.58 (0.39–0.86)	0.78 (0.52–1.18)	353 (9263)	0.78 (0.63–0.96)	0.95 (0.76–1.20)

CI, confidence interval.
[a]Model adjusted for age, sex, examination year, smoking, alcohol consumption and parental history of CVD.
[b]Additional adjustment for fitness.
[c]Theoretically unhealthiest group.
[d]Theoretically healthiest group.
[e]Non-fatal CVD events include: myocardial infarction, stroke, and coronary revascularization (i.e. bypass, coronary angioplasty); data available in a subsample of 18 430 participants.

Table 5 Hazard ratios of cancer mortality in metabolically healthy but obese individuals compared with metabolically abnormal obese and metabolically healthy normal-weight individuals, using both body mass index and body fat percentage to define obesity

	BMI-based obesity			BF%-based obesity		
	Cases (total)	HR (95% CI)[a]	Fitness-adjusted HR (95% CI)[b]	Cases (total)	HR (95% CI)[a]	Fitness-adjusted HR (95% CI)[b]
Cancer mortality						
Metabolically abnormal obese[c]	74 (3911)	1.19 (0.75–1.89)	1.17 (0.73–1.88)	171 (6900)	1.40 (1.08–1.80)	1.32 (1.02–1.71)
Metabolically healthy but obese	24 (1738)	1 (Ref.)	1 (Ref.)	100 (5959)	1 (Ref.)	1 (Ref.)
Metabolically healthy normal-weight/fat[d]	194 (16 002)	0.56 (0.36–0.86)	0.61 (0.38–0.97)	237 (21 023)	0.76 (0.60–0.97)	0.84 (0.65–1.09)

CI, confidence interval.
[a]Model adjusted for age, sex, examination year, smoking, alcohol consumption.
[b]Additional adjustment for fitness.
[c]Theoretically unhealthiest group.
[d]Theoretically healthiest group.

fitness level (VO_2 peak) in metabolically healthy but obese women when using a definition based on hyperinsulinaemic–euglycaemic clamp, but not when using other definitions for metabolically healthy profile ($n = 113$). Brochu *et al.*[48] also observed a higher fitness level (VO_2 peak) in metabolically healthy (based on insulin sensitivity) but obese post-menopausal women compared with their metabolically abnormal obese peers, yet the difference was not significant, maybe due to the small sample size ($n = 43$ split into two groups) and consequent low statistical power. Similar findings, i.e. higher but not significantly higher fitness (VO_2 peak) in the metabolically healthy (based on hyperinsulinaemic–euglycaemic clamp) but obese group, were observed in another study conducted

on sedentary post-menopausal women ($n = 42$) by Karelis *et al.*[43] In a later study from the same authors that included a larger sample ($n = 137$) of overweight and obese sedentary post-menopausal women, the investigators observed a significantly higher fitness (VO_2 peak) in the metabolically healthy group, as well as a higher physical activity level in this group. Likewise, data from the National Health and Nutrition Examination Surveys 1999–2004 showed a higher physical activity level (fitness was not studied) in the metabolically healthy but overweight/obese group, compared with the metabolically abnormal overweight/obese group ($n = 1664$ obese participants).[42]

Long-term prognosis in metabolically healthy but obese individuals: role of fitness

Our study focused on two comparisons: (i) metabolically healthy but obese vs. metabolically abnormal obese ('theoretically unhealthiest group') individuals; and (ii) metabolically healthy but obese vs. metabolically healthy normal-weight/fat ('theoretically the healthiest group') individuals. The first comparison addressed in the present study provides for the first time evidence that metabolically healthy but obese individuals have a significantly better prognosis, in terms of mortality and morbidity, than the rest of obese individuals, after adjustment for fitness. The fact that metabolically healthy but obese participants have slightly lower levels of adiposity might have contributed to explain their better prognosis. The available literature from prospective studies has focused on the second comparison and provided mixed findings. Our results agree with those from three prospective studies that observed a similar risk between metabolically healthy but obese individuals and metabolically healthy normal-weight/fat individuals for: (i) incident ischaemic heart disease ($n = 1824$);[11] (ii) incident fatal and non-fatal CVD ($n = 2902$)[12]; and (iii) all-cause, CVD, and cancer mortality ($n = 2011$).[10] In contrast, two previous studies have suggested that compared with metabolically healthy normal-weight individuals, metabolically healthy but obese individuals have a higher risk of: (i) all-cause mortality ($n = 6011$)[16]; and (ii) all-cause mortality, CVD mortality and morbidity and cancer incidence ($n = 1758$).[15] Note that none of these studies included fitness as a potential confounder in the analyses, which could partially explain the discrepancies with the present study findings. Indeed, our non-adjusted for fitness models concur with the results observed in the two mentioned studies, but once fitness is accounted for, the metabolically healthy but obese group had no longer a higher risk compared with their normal-fat peers. This finding supports a major role of fitness in these associations and suggests that fitness should be included in future research on this topic as a relevant confounder.

Comparisons between models adjusted and non-adjusted for fitness allow for the further exploration of the role of fitness in these associations. We observed that fitness eliminated the risk for mortality and morbidity (all outcomes) associated with obesity, i.e. comparison of metabolically healthy but obese vs. metabolically healthy normal weight, in accordance with previous studies.[24,49] On the other hand, fitness attenuated but did not eliminate the risk of mortality and morbidity associated with an abnormal metabolic profile (all outcomes), i.e. comparison of metabolically healthy but obese vs. metabolically abnormal obese groups. An explanation could be that obesity plus metabolic syndrome is so adverse condition that cannot be fully counteracted by fitness. Nevertheless, it is important to note that adjusting for fitness lowered the risk of mortality and morbidity by 10–30%, indicating a beneficial effect also in this subgroup.

Limitations and strengths

A complex issue in the study of the metabolically healthy but obese phenotype is how to define the 'metabolically healthy' phenotype. Multiple definitions have been used, and can be classed into two groups: (i) those based on insulin resistance/sensitivity measurements or (ii) those based on metabolic syndrome criteria (excluding waist).[4,41] In the present study, we considered a participant as being 'metabolically healthy' if he/she met 0 or 1 of the updated criteria for metabolic syndrome.[33] Unfortunately, data on insulin resistance were not available in the ACLS sample. Nevertheless, we believe it is unlikely that the results could be largely influenced by using a different definition for metabolically healthy, since previous prospective studies observed consistent results using both insulin resistance and metabolic syndrome definitions.[12,15,16] Markers of systemic inflammation or detailed dietary measurements on the entire cohort were not available. Another limitation is the lack of information on the duration of obesity. Data from the NHANES have shown that not only the current BMI, but also the duration of obesity is an important predictor of metabolic risk in adults.[50] Note that the number of female participants is much lower than the number of male participants (24.3% of the participants were women), which precludes separate analyses for men and women. The participants were 98% Caucasian, well educated and with high professional positions, so we cannot know to which extent the present findings apply to other populations. The fact that measurement error for skinfolds is larger in obese population should be acknowledged.

Strengths of the present study are: (i) the inclusion of an accurate measure of BF% to define obesity; (ii) the inclusion of fitness and the study of its role in these associations; (iii) the complete set of major outcomes studied, i.e. all-cause mortality, CVD mortality and morbidity (total non-fatal CVD events, coronary heart disease events, myocardial infarction and stroke were analyzed separately) and cancer mortality; and (iv) the large sample size, particularly the large number of obese participants allowed power analyses on the obese subgroups.

Clinical implications

The results from the current study have important clinical implications. Our data suggest that accurate BF% and fitness assessment can contribute to properly define a subset of obese individuals who do not have an elevated risk of CVD or cancer. Fatness and fitness assessment provide useful information to clinicians about the severity of obesity and health-related problems. In this context, the Edmonton Obesity Staging System proposed by Sharma and Kushner[51] provide information on the presence or the extent of comorbidities or functional limitations that would guide clinicians' decision-making. Based on the findings of the present and other studies, staging systems should consider the

inclusion of fitness as an informative measure of the severity of obesity and functional limitations.

Conclusion

Our results suggest that: (i) better fitness should be considered a characteristic of metabolically healthy but obese phenotype. (ii) Once fitness is duly accounted for and an accurate measure of adiposity is used, the metabolically healthy but obese phenotype is a benign condition, with a better prognosis (30–50% lower risk) for mortality and morbidity than metabolically abnormal obese people. Interestingly, no difference in the prognosis is observed between metabolically healthy but obese individuals and metabolically healthy normal-fat individuals once fitness is accounted for, suggesting a key role of fitness in these associations.

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