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Body Mass Index, the Most Widely Used but also Widely Criticized Index: Would a Gold-Standard Measure of Total Body Fat be a Better Predictor of Cardiovascular Disease Mortality?

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Abstract

Objectives—To examine whether an accurate measure (using a gold-standard method) of total body fat (BF) would be a better predictor of cardiovascular disease (CVD) mortality than body mass index (BMI).

Participants and Methods—A total of 60,335 participants were examined between January 1, 1979, and December 31, 2003, and then followed-up for mean of 15.2 years. BMI was estimated by standard procedures. Indices of body composition [i.e. BF%, fat mass index (FMI), fat-free mass (FFM) and FFM index (FFMI)] were derived from either skinfold thicknesses or hydrostatic weighing. For exact comparisons, the indices studied were categorized identically using sex-specific percentiles.

Results—Compared with a medium BMI, a very high BMI was associated with hazard ratios (HR) of 2.7 (confidence interval, CI:2.1-3.3) for CVD mortality, a stronger association than for BF % or FMI; i.e. HR=1.6(CI:1.3-1.9) and 2.2(CI:1.8-2.7), respectively. Compared with a medium FFMI, a very high FFMI was associated with a HR of 2.2 (CI:1.7-2.7) for CVD mortality, with

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conflict of interest

The authors have declared that no competing interests exist.

these estimates being markedly smaller for FFM, i.e. HR=1.2(CI:0.9-1.6). When the analyses were restricted only to the sample with hydrostatic assessments (N=29,959), the results were nearly identical, with even slightly larger differences in favor of BMI, i.e. HR=3.0 (CI:2.2-4.0) compared with BF% and FMI, i.e. HR=1.5(CI:1.2-1.9) and 2.1(CI:1.6-2.7) respectively. We estimated Harrell c-index as an indicator of discriminant/predictive ability for these models and observed that the c-index in models including BMI was significantly higher than that in models including BF% or FMI (all P values <.005).

Conclusions—The simple and inexpensive measure of BMI can be as clinically important or even more than total adiposity measures assessed by accurate and expensive methods. Physiological explanations for these findings are discussed.

INTRODUCTION

Obesity is a major public health concern in most of countries around the world. There is a vast amount of data supporting an increased risk of cardiovascular disease (CVD) mortality and reduced survival associated with overweight and obesity. Although this notion is generally well-accepted in public health and clinical settings, literature on this topic is extremely controversial. In fact, a number of studies have recently reported that in certain conditions, especially in individuals with existing CVD, obesity might be related with a lower risk of mortality, the so-called “obesity-mortality paradox”[1]. In addition, the systematic review and meta-analysis conducted by Flegal and colleagues concluded that overweight is associated with a reduced risk of mortality compared with normal-weight, whereas mild or Class I obesity was associated with a trend for better survival [2]. Recently, Ahima and Lazar discussed this phenomenon and concluded that the impact of a high body mass index (BMI) on mortality is in question and that better metrics are needed [3]. Before investigating which are the best indexes to measure obesity in relation to future health, the fundamental question of what obesity really means deserves discussion. While many scientists and other readers would assert that obesity means an excess of adiposity, measured by body fat percentage (BF%), others would suggest that most of what we currently know about the adverse effects of obesity on health is actually based on BMI-defined obesity. Therefore, obesity could as well mean an excess of body weight, which is what BMI directly measures.

Although it is internationally and well-accepted that the definition of obesity is based on BMI (i.e. 30 kg/m^2 or higher), this traditional anthropometric index is strongly criticized for its lack of ability to distinguish between fat and lean tissues. There is no doubt that BMI includes an estimation error when assessing total adiposity. Based on this and on the assumption that it is the excess of adiposity that predicts mortality, it would be expected that more accurate measures of total adiposity, such as BF% or fat mass index [FMI, fat mass (kg) divided by squared height (m^2)] would be stronger predictors of death than BMI. We reviewed the literature on this topic and searched whether there was any study conducting a direct comparison of BMI and BF% as predictors of CVD mortality or all-cause mortality. We found that most longitudinal studies examining mortality outcomes have used BMI as an exposure, for a simple reason, weight and height are easy and inexpensive to measure. In addition, in order to conduct exact comparisons, both variables should be handled

statistically in an identical way (e.g. sex-specific centiles); using standard cut-points (e.g. BMI ≥30kg/m^2 and BF% ≥25 for men or ≥ 35 % for women for obesity) would lead to a different distribution of participants into the BMI and BF% groups, which would hamper accurate and direct comparisons. In this context, the Aerobics Center Longitudinal Study (ACLS) includes an accurate measure of total BF (i.e. using a gold-standard method in roughly 30,000 men and women) as well as BMI in the baseline examination [4-6], providing a unique opportunity to address this research question. The present study, therefore, aimed to examine whether an accurate measure of total BF would be a better predictor of CVD mortality and all-cause mortality than BMI. In addition, we tested which of the following conditions more strongly predict CVD mortality and all-cause mortality: an excess of body weight, an excess of BF or an excess of fat-free mass (FFM).

METHODS

Study Cohort

The ACLS is a prospective epidemiologic investigation of adult men and women [5,7,8]; participants are mostly Caucasian (98%), well-educated, and worked in executive or professional positions [9]. 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 January 1, 1979 and December 31, 2003. All participants provided written informed consent, and the study protocol was approved annually by the Institutional Review Board of the Cooper Institute. Exclusion criteria for the present analyses were: 1) existing CVD or cancer at baseline (n=1,021); 2) < 1 year of follow-up (n=1,064); 3) incomplete data on BMI, BF% and all the confounders (n=1,272). The rationale why participants with less than 1 year of follow-up were excluded is based on the fact that persons dying during the first year are likely to have a preexisting occult disease that confounds the relation between the risk factor under study and mortality. Excluding persons dying during the first years of follow-up purportedly reduces this confounding effect, and is a widely used technique especially in the field of obesity [10]. Based on these criteria, a total of 3,357 participants (5.3%) aged 20 years or older at baseline were excluded. The final sample included 60,335 participants (26.7% women) for the analyses.

Baseline Examination

As described previously [7], height and weight were measured using a stadiometer and a standard scale. Waist circumference was obtained at the level of the umbilicus with a plastic anthropometric tape. BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2); BF% was assessed by hydrostatic weighing or the sum of 7 skinfold measures, following standardized protocols [4,11]. Some participants had an underwater weighing assessment for hydrostatically estimated body density with a mathematical conversion to BF%, whereas other participants were assessed using standard skinfold thicknesses from which BF% was estimated. Standardized protocols used and specific procedures for the ACLS assessment of BF% were published elsewhere [4,5,12,13]. A large number of the participants (N=21,681) had both measurements, and the correlation between hydrostatically estimated BF% and skinfold estimated BF% was >0.90 [12,13]. When

available, hydrostatically estimated BF% was always used in the analysis, i.e. hydrostatic weighing was available on 52% of the sample. In the present study, the analyses were conducted for the whole sample (including participants assessed with both methods) and also for the sub-sample with hydrostatic weighing. For the purpose of this study and in order to conduct as exact as possible comparisons with BMI, we additionally computed FMI (kg/m^2), as fat mass expressed in kilograms divided by the square of height expressed in meters. For exploratory analyses, we also computed FFM expressed in kg by subtracting fat mass (kg) from total body weight (kg). Likewise, for exact comparisons with BMI, FFM index (FFMI, kg/m^2) was computed as FFM expressed in kilograms divided by the square of height expressed in meters. FMI and FFMI body composition indexes are widely used in the literature [14-16] and of special interest for this study, since they mirror the way BMI is computed and expressed, i.e. dividing weight, fat mass or FFM by squared height expressed in meters. Comparing the findings obtained for BMI, FMI and FFMI will allow testing of the following to determine what more strongly predicts CVD mortality and all-cause mortality: an excess of body weight, an excess of BF or an excess of FFM, which is the secondary aim of this study.

Information on risk factors such as smoking (current smoker or not current smoker), excessive drinking (defined as alcohol drinks >14 per week for men and >7 per week for women), physical inactivity (defined as no leisure-time physical activity during past three months) and having a parental history of CVD or cancer was obtained from a standardized medical history questionnaire. As described previously[7,17], cardiorespiratory fitness (CRF) was defined as the total time of a symptom-limited maximal treadmill exercise test, using a modified Balke protocol. Total time of the test on this protocol correlates highly with measured maximal oxygen uptake (VO_{2max}) in both men ($r = 0.92$)[18] and women ($r = 0.94$)[19]. 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[20].

As described previously[6,21], systolic and diastolic blood pressures were obtained with a mercury sphygmomanometer and auscultory methods following the American Heart Association protocol[22]. A fasting blood sample was obtained by venipuncture and serum total cholesterol was 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 Program.

Assessment of outcomes

The main outcome of this study is CVD mortality, yet results about all-cause mortality were also reported as Online-Only Supplemental Material in order to provide a broader picture about the association between body composition markers and mortality. The participants were followed from the baseline examination until the date of death or 31 December 2003. Mortality surveillance was based on the National Death Index (NDI). Participants not found to be deceased as of December 31, 2003 via the National Death Index were assumed to be alive. The underlying cause of death was determined from the NDI report or by a nosologist's review of official death certificates allobtained 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[23].

Statistical analysis

All statistical analyses were performed using IBM-SPSS, version 20.0 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. In order to address the main study aim, we used Cox proportional hazards regression (two-sided tests) to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) according to exposure categories. The main study outcome was CVD mortality, yet results for all-cause mortality are also provided in Supplemental Figure 1. The exposures/predictors studied were BMI, BF%, FMI, FFM and FFMI. They all were categorized using exactly the same procedures in order to allow exact comparisons among exposures. These variables were categorized based on sex-specific centiles as follows: Very low if < percentile 5^{th}, Low if percentile 5^{th}-15^{th}, Middle if percentile 15^{th}-85^{th}, High if percentile 85^{th}-95^{th} and Very high if above percentile 95^{th}. Percentiles 85^{th} and 95^{th} have been traditionally used to represent overweight and obesity respectively, so we used the same criteria for all the indices studied and mirrored the bottom extreme using percentiles 5^{th} and 15^{th}. The possibility of an interaction with sex was tested by entering interaction terms (e.g. sex×BMI) in all the models. Since no evidence of interaction with sex was observed for any of the models performed (all $P>.2$), all the analyses were conducted for the whole sample together. All the analyses were adjusted for age, sex, examination year, smoking, alcohol consumption, physical inactivity and parental history of CVD (and parental history of cancer, when all-cause mortality was the outcome studied). In order to test the discriminating ability of the predictive models used, we estimated the c-index as proposed by Harrell et al.[24,25] for each of the models including BMI, BF% and FMI and compared whether these c-indices were significantly different from each other using the "compareC" package in the R statistical software, following the method recently suggested by Kang and colleagues [26].

A number of sensitive/exploratory analyses were conducted, in order to test whether the results from the main analyses were altered in specific conditions/sub-groups of individuals: 1) in the subsample with hydrostatic weighing assessment; and 2) in a subsample of individuals with high WC. We also tested how additional adjustment for CRF, hypertension or hypercholesterolemia influenced the results.

RESULTS

Table 1 shows the descriptive characteristics of the study sample at baseline (N=60,355): 13% of the participants were obese and 18% of them centrally obese; 16% of the participants were smokers and 8% of them drank excessive alcohol. One third of them were inactive and one fourth had parental history of CVD disease. One fifth of the participants had hypertension or hypercholesterolemia. Over a mean follow-up period of 15.2 years, a total of 3,780 (6.3%) participants died, 1,359 due to CVD (2.3% of the total sample and 36% of the total number of deaths).

Compared with a medium BMI, a very high BMI was associated with 2.7-fold higher risk (CI:2.1-3.3) of CVD mortality (Figure 1). The corresponding HRs for CVD mortality for BF % and FMI were lower than for BMI, and were lower for BF% than for FMI, i.e. 1.6 (CI: 1.3-1.9) and 2.2 (CI:1.8-2.7) respectively. When the analyses were restricted only to the sample with hydrostatic assessments (N=29,595), the results were very similar (Figure 1) with even slightly larger differences in favor of BMI, i.e. HR=3.0 (CI:2.2-4.0) compared with BF% and FMI, i.e. HR=1.5(CI:1.2-1.9) and 2.1(CI:1.6-2.7) respectively. The diagnostic ability (c-index) of the multivariate model including BMI to predict CVD mortality was 0.844 in the whole sample, whereas the same multivariate model but with BF% was 0.839 ($P<0.001$ for c-index difference compared with the BMI model) and with FMI was 0.841 ($P=0.004$ for c-index difference compared with the BMI model). The corresponding c-indices for models including BMI, BF% and FMI in the subsample with hydrostatic weighing assessment were 0.828, 0.820 and 0.823 respectively; with c-indices of BF% and FMI being significantly different from those of BMI ($P<0.001$ and $P=0.005$ respectively).

Compared with a medium FFMI, a very high FFMI was associated with 2.2 (CI:1.7-2.7) higher risk of CVD mortality, with these estimates being markedly smaller for FFM, i.e. 1.2(CI:0.9-1.6); Figure 2. Similar results were obtained when the analyses were conducted on the sub-sample with hydrostatic assessments (Figure 2).

Table 2 shows the sex-specific (percentile-based) levels of weight, fat or FFM corresponding to the study groups used in this study. A very high (percentile 95^{th}) BMI was considered if a BMI equal or higher than $34 kg/m^2$ for men and $32 kg/m^2$ for women. A very high BF% was considered if a BF% equal or higher than 33% for men and 39% for women. A very high FMI was considered if a FMI equal or higher than 11 for men and 12 for women; and a very high FFMI was considered if a FFMI equal or higher than 25 for men and 21 for women. As shown in Figures 1 and 2, these cut-point values were associated with a higher risk of CVD mortality.

HRs and CIs for all-cause mortality are shown in Supplemental Figure 1as Online-Only Supplemental Material. Overall, the differences in HRs for BMI compared with BF% or FMI were smaller for all-cause mortality than for CVD mortality.

Sensitivity/exploratory analyses

We run the same models as in Figure 1 in a sub-sample of individuals with a high WC (i.e. n=7,887) in order to test whether the results would change in a sample of apple shaped individuals, in which body fat markers could potentially be more strongly related to the risk of CVD mortality. The differences between BMI and adiposity markers persisted, HRs (and its CIs) for very high BMI were markedly larger than those of very high levels of either BF % or FMI (See Supplemental Table 1). In addition, we tested whether the proportion of missing values for WC was equal in men and women, and it was not. There were more missing data (proportionally) in women (33%) than in men (24%), $P<0.001$. In order to test whether the missing data on WC could influence the main study findings, we run again all the main models in a subsample with valid data on WC, and also in the subsample assessed with hydrostatic assessment with valid data on WC. In all cases, the HRs associated with

CVD mortality were higher for very high BMI than for very high BF% or FMI, when compared with the respective middle groups.

We also run the models (same exposures and outcomes as in Figures 1 and 2) with additional adjustment for CRF (VO_2max). All the HRs were attenuated as a result of this additional adjustment (Supplemental Table 2); nevertheless, a very high BMI persisted associated with a 1.6 (CI: 1.3-2.1) higher risk of CVD mortality compared with middle levels of BMI, being the corresponding HRs for BF% 1.0 (CI: 0.9-1.3) and for FMI 1.3 (CI: 1.1-1.6). Interestingly, a very high FFM and FFMI also remained significantly related to higher CVD mortality after additional adjustment for CRF, i.e. HR=1.4 (CI: 1.0-1.8) and HR=1.6 (CI: 1.3-2.1) respectively. Likewise, additional adjustments for hypertension attenuated all the HRs, yet differences between BMI models and BF% or FMI persisted (See Supplemental Table 3). On the other hand, the results were not altered after additional adjustment for hypercholesterolemia (data not shown).

DISCUSSION

Main findings

The present study contributes to the existing knowledge with several major findings, which have implications for clinical practice and public health applications, as well as for the fundamental understanding of obesity and its adverse consequences. First, the main findings were directly related to daily clinical practice and epidemiology: a) BMI was a stronger predictor of CVD mortality than total adiposity markers, particularly BF% and FMI, assessed with accurate methods (including a gold-standard); b) if total adiposity is to be assessed, FMI is far more predictive of CVD mortality than BF%. Second, concerning our current understanding of what obesity means, this study provides the following novel findings: a) we used BMI, FMI and FFMI as indicators of body weight, fat and FFM, respectively normalized by height, and our results supported the notion that an excess of body weight is more associated with a worse CVD prognosis than is an excess of total BF; b) in addition, not only is an excess of BF related with higher risk of CVD mortality, but also and to a similar extent an excess of FFM increases CVD mortality risk. The results are very consistent and persisted in all the sensitivity/exploratory analyses conducted. The differences between the models including BMI and those including BF% or FMI were present: 1) when the analyses were conducted in the whole sample and in the sub-sample with hydrostatic weighing assessment, as well as in the sub-sample with a high WC. 2) after additional adjustment for CRF, hypertension or hypercholesterolemia. Finally, the fact that the c-index observed for the model including BMI was significantly higher than for the models including BF% or FMI, support the notion than BMI might be a stronger predictor of CVD mortality than markers of total adiposity measured using gold-standard methods.

Physiological interpretation of the findings

If body weight is the sum of fat mass plus FFM, and a high body weight (normalized by height, i.e. high BMI) predicted CVD mortality more strongly than a high fat mass (normalized by height, i.e. high FMI), the most logical explanation for this finding would be that the remaining part of body weight, i.e. the FFM, is also contributing to the larger effect

size associated with a high BMI. This notion is supported by our results by showing that a high FFMI (FFM normalized by height) was associated with higher risk of CVD mortality to a similar extent that a high FMI, so that high FMI plus high FFMI result in a high BMI that provides the strongest prediction of CVD mortality.

When interpreting these findings, it is important to bear in mind that obese individuals (defined by the internationally accepted BMI>30kg/m^2) are not only heavier and fatter than their normal-weight peers but also have higher levels of FFM [27-29], a human adaptation to the extra load (body weight) that these individuals have to carry during their daily life activities. This fact together with the principles of pathophysiology and hemodynamics of CVD in relation to obesity provide a solid mechanistic explanation to our findings. The higher FFM largely explains the higher circulating blood volume that has been observed in obese individuals. This increases the left ventricular stroke volume which in turns increases the cardiac output. These changes place an extra burden on the heart resulting in ventricular (both left and right) alterations that ultimately lead to ventricular (both left and right) hypertrophy and enlargement, predisposing obese people to heart failure. More detailed information about obesity and its relationship with pathophysiology and hemodynamics of CVD is provided elsewhere [1,30,31].

The role of high fat mass in CVD has been more extensively studied. First, it is well-known that this worsens most of the CVD risk factors, such as plasma lipids, blood pressure, glucose and inflammation. In addition, it increases the risk of sleep apnea, which ultimately is associated with right ventricular hypertrophy and enlargement, increasing the risk of right ventricular failure [1]. Our findings are supported by other studies that observed a positive association between FFM/lean mass and CVD risk factors in young people [32-35]. Bigaard and colleagues[36] observed a reversed J-shape association between FFMI and all-cause mortality, using bioelectrical impedance to assess body composition and additionally adjusting by FMI what could have attenuated the association since it is known that obese people have both high fat mass and high FFM. Recently, Moreno et al.,[37] have demonstrated that lean mass rather than fat mass is an independent determinant of carotid intima media thickness in obese subjects, which would contribute to explain the higher risk in CVD mortality observed in our study in individuals with a very high FFMI. Pooling all this evidence together, the accumulated physiological consequences of high FFM and high fat mass for CVD can explain why BMI, which includes both FFM and fat mass (in fact, BMI is the mathematical sum of FMI + FFMI), can be a stronger predictor than these two components of body composition separately. These findings and pathophysiology explanations might lead to a change in the understanding of obesity. Obesity might be considered as an excess of body weight (which includes the fat and non-fat components), rather than an excess of adiposity alone. In addition, BMI has been strongly criticized by its lack of ability to distinguish between fat and non-fat components; our findings, however, show that BMI, by including both components together, might be more clinically meaningful than accurate measures (including gold-standard methods) of the fat component alone. In line with our findings and interpretations, Dr. Wells, a well-known expert on body composition analysis, recently pointed out that “BMI is not a good index of adiposity, but might be a good index of cardio-metabolic risk” [38]. Figure 3 presents a graphical view of the main study findings, as well as our physiological interpretations.

Finally, it is important to mention that the interpretation of the findings largely differ when we are referring to apparently healthy people, as it is the case in our study in which people with diagnoses of CVD or cancer at baseline were excluded from the analyses, compared with when we are referring to CVD patients or referral populations at baseline [40]. In this second case, the so-called “obesity-mortality paradox” has been shown very consistently [1,40-44]. In the current study, having a very high FMI and very high FFMI were both associated with higher risk of CVD mortality and all-cause mortality, whereas previous studies conducted in patients with stable coronary heart disease have shown the opposite trend, with high body fat combined with high FFMI was associated with the lowest risk of mortality [45].

Practical and clinical implications

The present study supports the use of BMI, a combination of fat mass and FFM, as a predictor of CVD prognosis. Of note is that this simple index was a stronger predictor of CVD than accurate measures of body composition, even when using a gold-standard method. This strongly supports the use of BMI in clinical epidemiology, which is in line with the recent AHA/ACC/TOS Guidelines for the Management of Overweight and Obesity in Adults [46]. In order to do exact comparisons between the indexes used in this manuscript, we used our population-specific percentiles to define very high BMI. The percentile 95th used to define very high BMI corresponds with a BMI of 34 and 32kg/m^2 for men and women, respectively, which in men is near to the international definition of Class II obesity (i.e. BMI>35kg/m^2) and in women is near to Class I obesity (i.e. BMI>30kg/m^2).

In addition, our results support the use of FMI instead of BF% and also the use of FFMI instead of FFM, showing that normalizing body composition components by squared height markedly increased their predictive capacity for CVD mortality. Based on these findings, whenever body composition components are to be assessed in relation to CVD prognosis, the use of FMI and FFMI is preferred to other markers traditionally used, such as BF%. The current study provides (Table 2) cut-points values for FMI and FFMI associated with a higher risk of CVD mortality, i.e. FMI equal or higher than 10.4 kg/m^2 for men and 12.0 kg/m^2 for women; and FFMI equal or higher than 24.3 kg/m^2 for men and 20.6 kg/m^2 for women. Although these cut-points are population-specific, they seem to match well with those reported for other Caucasian populations [14,16]. The US-representative data from NHANES for a 25 year-old adult Caucasian individuals measured by Dual X-ray Absorptiometry (DEXA) for FMI equivalent to Class II obesity (BMI>35kg/m^2) was 11.9 kg/m^2 for men, while the FMI equivalent to Class I obesity (BMI>30kg/m^2) was 12.9 kg/m^2 for women [16]. Whenever possible, country-specific reference values are desired , and these NHANES cut-points [16] supported by the association with CVD mortality reported in the present study , which could be very useful for clinical practice in USA. Similarly, the reference data (including percentile 95th) for FMI and FFMI reported by Schutz et al. could be useful for European populations [14].

Limitations and strengths

The majority of the participants were Caucasian, well-educated and with high professional positions, so we cannot know to which extent the present findings apply to other

populations. Nevertheless, the main aim of the present study was to compare BMI with other body composition indexes in relation to CVD and all-cause mortality. Therefore, we believe that whether the study sample is more or less heavier and more or less fatter than the general US population or any other population is unlikely to have a major influence on the study conclusions. The number of women participating in the present study (N=16,101) is markedly smaller than the number of men (N=44,234), which is a limitation of the study. However, the fact that no interaction with sex was found suggests that the major findings hereby reported are consistent for both genders. We do not have information about where fat is located in the body, e.g. subcutaneous fat *versus* visceral fat what could influence CVD mortality. Since the methods used in this study do not allow to distinguish among different fat depots, we cannot examine whether all fat (e.g. intra-abdominal vs. subcutaneous) imparts the same risks.

The major strength of the present study is the use of a gold standard measure of body composition (i.e. hydrostatic weighing) in roughly 30,000 participants of whom a complete baseline examination and mortality outcomes were available. In addition, 21,681 participants were assessed with both methods (i.e. hydrostatic weighing and skinfolds) allowing to conduct cross-validation between methods (r>0.9) and resulting in good estimates of body composition for a sample of more than 60,000 participants. These data provided a unique opportunity to address the current study questions.

Conclusions

We make two major conclusions from these analyses:

1. Our data support that BMI is a stronger predictor of CVD mortality compared with accurate measures of adiposity, such as BF% and FMI. This suggests that the simple and inexpensive measure of BMI can be as clinically important measure or even more than total adiposity measures assessed by accurate, complex and expensive methods. Another major conclusion of this study is that FMI is a more informative measure of future CVD prognosis than is BF%. This has direct implications for clinical settings.
2. Considering a very high BMI as an indicator of an excess of body weight (normalized by height) and FMI as an indicator of an excess of BF (equally normalized by height), the results presented in this study suggest that an excess of body weight is a stronger predictor of CVD mortality than is an excess BF. In addition, our results support that an excess of FFM, and specially FFMI, is also associated with a higher risk of CVD mortality (as much as an excess of BF), which could explain why BMI (the mathematical sum of FMI + FFMI) can be a stronger predictor of CVD mortality than fat mass alone.

These findings have potentially important implications for current clinical practice, future research, as well as for general understanding obesity and its adverse consequences.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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LIST OF ABBREVIATIONS

BF%	body fat percentage
BMI	body mass index
CIs	95% confidence intervals
CVD	cardiovascular disease
FMI	fat mass index
FFM	fat-free mass
FFMI	fat-free mass index
HRs	hazard ratios

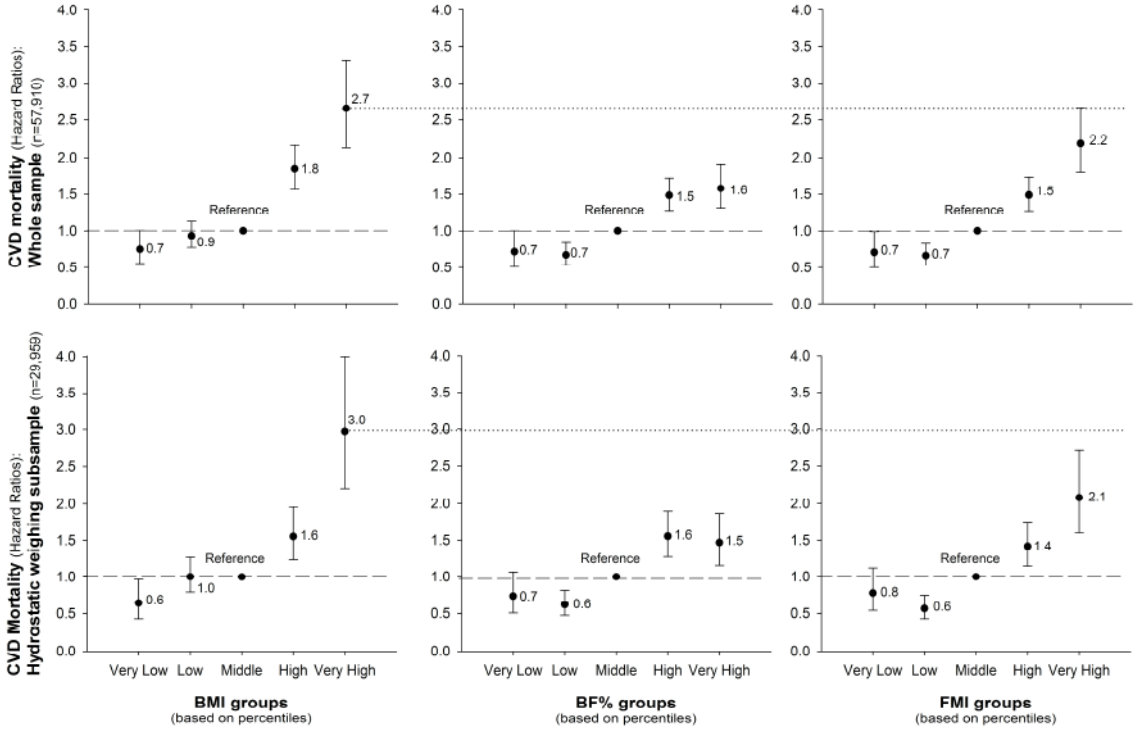

Figure 1. Hazard ratios for mortality due to cardiovascular disease (CVD) according to body mass index (BMI), percent body fat (BF%) and fat mass index (FMI) groups in the whole study sample (N=57,910) and in the sub-sample with hydrostatic weighing assessment (N=29,959)

Body weight/body fat groups were estimated based on sex-specific centiles: Very low if < percentile 5^{th}, Low if percentile 5^{th}-15^{th}, Middle if percentile 15^{th}-85^{th}, High if percentile 85^{th}-95^{th} and Very high if above percentile 95^{th}.

All the models were adjusted for age, sex, examination year, smoking, alcohol consumption, inactivity and parental history of CVD.

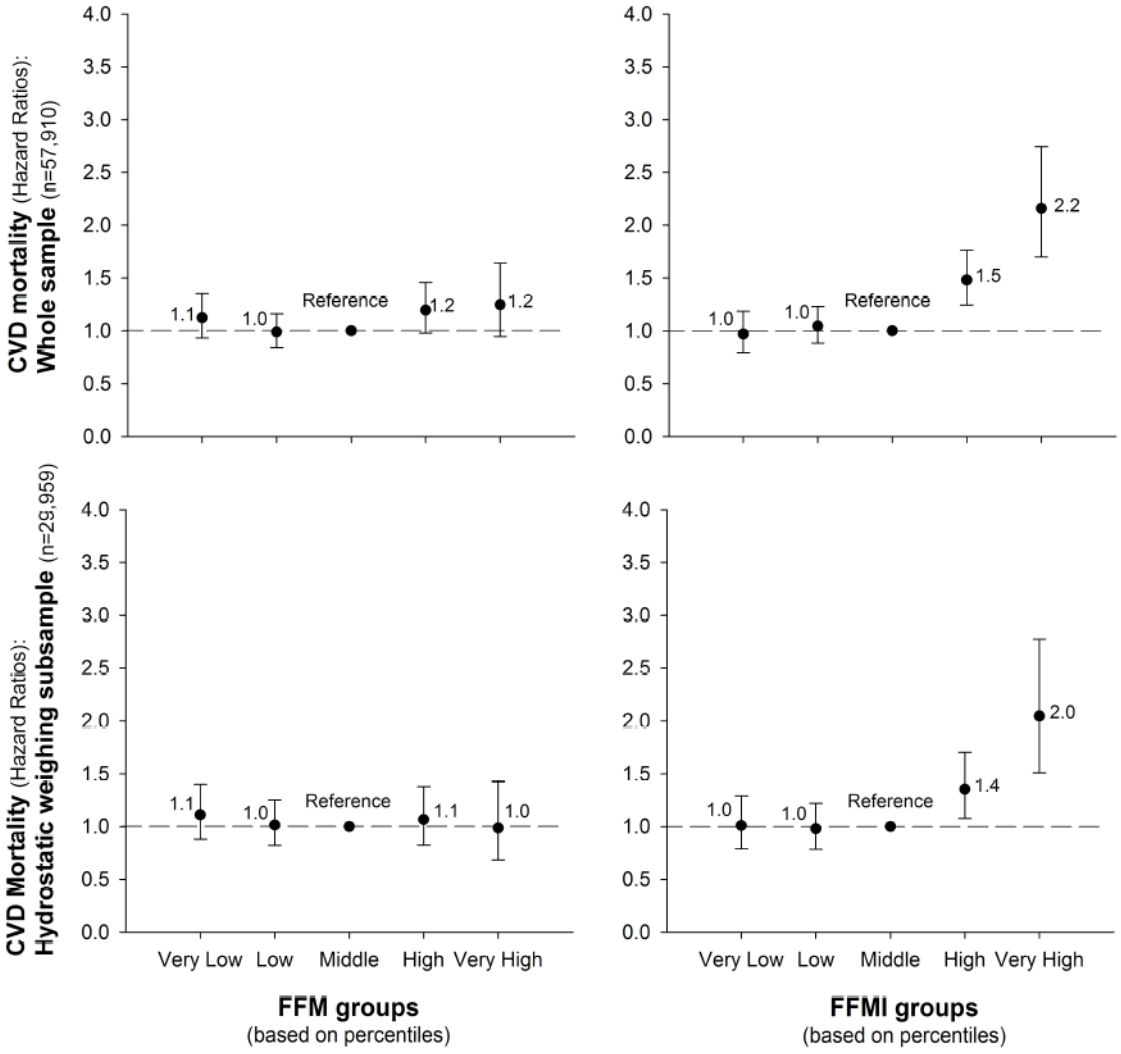

Figure 2. Hazard ratios for mortality due to cardiovascular disease (CVD), according to fat-free mass (FFM) and to fat-free mass index (FFMI) groups in the whole study sample (N=57,910) and in the sub-sample with hydrostatic weighing assessment (N=29,959)

FFM and FFMI groups were estimated based on sex-specific centiles: Very low if < percentile 5th, Low if percentile 5th-15th, Middle if percentile 15th-85th, High if percentile 85th-95th and Very high if above percentile 95th.

All the models were adjusted for age, sex, examination year, smoking, alcohol consumption, inactivity and parental history of CVD.

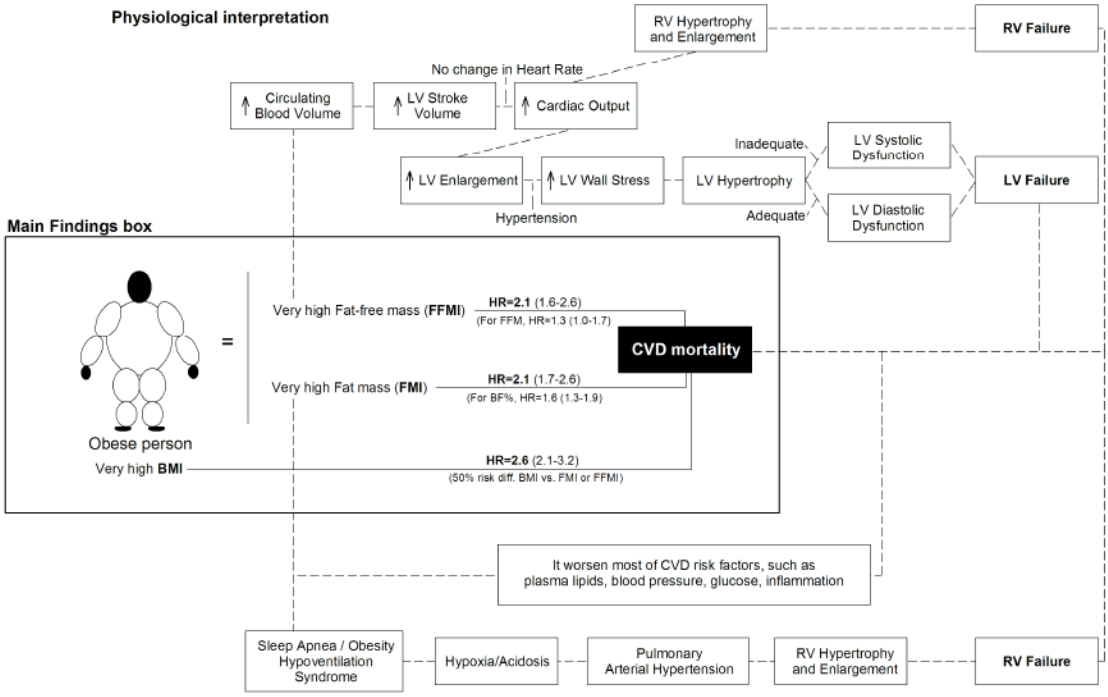

Figure 3. Graphical illustration of the main findings of the present study and plausible physiological interpretation

BMI indicates body mass index; BF%, percent body fat; FMI, fat mass index; FFM, fat-free mass; FFMI, fat-free mass index; CVD, cardiovascular disease; LV, left ventricular; RV, right ventricular. Part of the physiological interpretation shown is adapted with permission from Lavie et al. [30]. More detailed information about obesity and its relationship with pathophysiology and hemodynamics of CVD is provided elsewhere [1,30,39].

Table 1

Characteristics of the study population.

	All (N=60,335)		Men (44,234)		Women (16,101)	
Baseline data	***Mean***	***SD***	***Mean***	***SD***	***Mean***	***SD***
Age (years)	43.6	10.7	43.8	10.3	43.1	11.9
Height (cm)	175.0	9.2	178.9	6.7	164.4	6.3
Weight (kg)	79.3	16.8	85.2	14.0	63.0	12.4
Body mass index (BMI, kg/m^2)	25.7	4.3	26.6	3.9	23.3	4.4
Waist circumference (cm) *	89.2	14.2	94.1	11.2	73.9	11.1
Body fat percentage	22.7	7.3	21.4	6.7	26.3	7.5
Fat mass (kg)	18.4	8.3	18.8	8.4	17.2	7.8
Fat mass index (kg/m^2)	6.0	2.7	5.9	2.6	6.4	2.9
Fat-free mass (kg)	60.9	12.1	66.3	8.4	45.8	6.5
Fat-free mass index (kg/m^2)	19.7	2.7	20.7	2.1	16.9	2.1
Cardiorespiratory fitness (VO_2max, ml/kg/min) *	38.6	9.1	40.4	8.8	33.2	7.8
	n	*%*	*n*	*%*	*n*	*%*
Obesity (BMI>30kg/m^2)	8,091	13.4	6,862	15.5	1,229	7.6
Central obesity (WC>102cm in men, <88cm in women) *	7,887	17.6	6,721	19.9	1,166	10.7
Current smoker, n (%)	9,517	15.8	8,034	18.2	1,483	9.2
Excessive alcohol drinking, n (%) †	4,628	7.7	3,242	7.3	1,386	8.6
Inactivity, n (%) †	20,289	33.6	14,784	33.4	5,505	34.2
Hypertension, n (%)	16,952	28.1	14,118	31.9	2,834	17.6
Hypercholesterolemia, n (%)	15,688	26.0	12,353	27.9	3,335	20.7
Parental history of CVD, n (%)	15,316	25.4	11,444	25.9	3,872	24.0
Parental history of cancer, n (%)	1,874	3.1	1,228	2.8	646	4.0
Follow-up data	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Follow-up period (years)	15.2	8.5	15.8	8.5	13.6	8.2

	All (N=60,335)		Men (44,234)		Women (16,101)	
Baseline data	***Mean***	***SD***	***Mean***	***SD***	***Mean***	***SD***
	n	*%*	*n*	*%*	*n*	*%*
Number of deaths, n (%)	3,780	6.3	3,218	7.3	562	3.5
Number of CVD deaths, n (%)	1,359	2.3	1,208	2.7	151	0.9

Data are means (standard deviations), unless otherwise indicated. CVD indicates Cardiovascular disease.

*All variables have complete data (i.e. N=60,335), except for WC which was available in 44,724 participants and cardiorespiratory fitness that was available in 56,815 participants.

†Excessive drinking was defined as alcohol drinks >14 per week for men and >7 per week for women; physical inactivity was defined as no leisure-time physical activity during past three months.

Table 2

Descriptive information about the study groups.

Study groups	Statistics		BMI		BF%		FMI		FFM		FFMI	
			Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Very low (<Percentile 5th)	Minimum		13.8	14.3	2.0	2.3	0.4	0.4	58.3	39.8	18.7	15.1
	Maximum		21.5	18.4	10.1	14.6	2.3	2.8	74.6	51.5	22.7	18.7
	Percentiles	25	20.0	17.4	6.2	10.6	1.4	2.0	62.4	42.7	19.7	15.9
		50	20.7	17.9	8.0	12.6	1.8	2.4	65.8	45.0	20.5	16.6
		75	21.2	18.2	9.2	13.8	2.1	2.6	69.4	47.6	21.4	17.4
Low (Percentile 5th-15th)	Minimum		21.5	18.4	10.2	14.7	2.3	2.8	23.2	20.3	7.7	7.5
	Maximum		23.1	19.6	14.5	18.4	3.4	3.7	54.0	37.1	17.6	14.3
	Percentiles	25	22.1	18.8	11.6	15.8	2.7	3.1	48.8	34.3	16.4	13.4
		50	22.5	19.1	12.7	16.8	3.0	3.3	51.5	35.6	17.0	13.9
		75	22.8	19.4	13.7	17.7	3.2	3.5	52.9	36.5	17.4	14.1
Middle (Percentile 15th-85th)	Minimum		23.1	19.6	14.6	18.5	3.4	3.7	54.0	37.1	17.6	14.3
	Maximum		30.1	27.1	28.1	34.4	8.3	9.1	58.3	39.8	18.7	15.1
	Percentiles	25	24.6	20.9	18.5	22.7	4.6	4.8	55.5	38.0	18.0	14.6
		50	26.0	22.3	21.5	26.2	5.6	5.8	56.6	38.7	18.3	14.8
		75	27.6	24.0	24.4	29.8	6.6	7.1	57.5	39.3	18.5	15.0
High (Percentile 85th-95th)	Minimum		30.1	27.1	28.2	34.5	8.3	9.1	74.6	51.5	22.7	18.7
	Maximum		33.5	31.9	32.4	38.3	10.4	12.0	80.8	57.1	24.3	20.6
	Percentiles	25	30.7	27.9	28.9	35.3	8.6	9.6	75.6	52.5	23.0	19.0
		50	31.4	28.8	29.8	36.2	9.1	10.2	77.0	53.5	23.3	19.4
		75	32.2	30.1	31.0	37.2	9.7	10.9	78.6	55.0	23.7	19.9
Very high (>Percentile 95th)	Minimum		**33.5**	**31.9**	**32.5**	**38.4**	**10.4**	**12.0**	**80.8**	**57.1**	**24.3**	**20.6**
	Maximum		64.6	63.6	62.7	65.9	35.3	28.8	133.9	109.1	40.5	46.1
	Percentiles	25	34.4	33.1	33.4	39.1	11.0	12.7	82.3	58.9	24.7	21.1
		50	35.8	34.8	34.8	40.0	12.0	13.6	84.4	61.0	25.3	21.9
		75	38.4	38.0	37.1	42.3	13.5	15.0	88.3	65.4	26.3	23.5

BMI indicates body mass index; BF%, percent body fat; FMI, fat mass index; FFM, fat-free mass; and FFMI, fat-free mass index.

The study groups were created using sex-specific percentile using the full study sample (N=60,335; 44,234 men and 16,101 women). Numbers in bold font can be used as cut-point values associated with higher cardiovascular disease mortality (See Figure 1 and 2).