

Accepted Manuscript

Addition of Cardiorespiratory Fitness within an Obesity Risk Classification Model Identifies Men at Increased Risk of All-Cause Mortality

T. Alexander Ricketts, MSc, Xuemei Sui, MD, PhD, MPH, Carl J. Lavie, MD, Steven N. Blair, PED, Robert Ross, PhD

PII: S0002-9343(15)01113-4

DOI: [10.1016/j.amjmed.2015.11.015](https://doi.org/10.1016/j.amjmed.2015.11.015)

Reference: AJM 13272

To appear in: *The American Journal of Medicine*

Received Date: 31 October 2015

Revised Date: 5 November 2015

Accepted Date: 5 November 2015

Please cite this article as: Ricketts TA, Sui X, Lavie CJ, Blair SN, Ross R, Addition of Cardiorespiratory Fitness within an Obesity Risk Classification Model Identifies Men at Increased Risk of All-Cause Mortality, *The American Journal of Medicine* (2015), doi: 10.1016/j.amjmed.2015.11.015.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



Addition of Cardiorespiratory Fitness within an Obesity Risk Classification Model Identifies Men at Increased Risk of All-Cause Mortality

T. Alexander Ricketts MSc¹, Xuemei Sui MD,PhD,MPH², Carl J. Lavie MD³, Steven N. Blair PED^{2,4}, and Robert Ross PhD¹.

¹ School of Kinesiology and Health Studies, Queen's University, Canada.

² Department of Exercise Science, Arnold School of Public Health, University of South Carolina, USA.

³ Department of Cardiovascular Diseases, John Ochsner Heart and Vascular Institute, Ochsner Clinical School-the University of Queensland School of Medicine, New Orleans, USA

⁴ Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, USA.

All authors had access to the data and a role in writing the manuscript

Running Head: Cardiorespiratory Fitness, Obesity and Mortality

Keywords: Fitness, Obesity, Mortality, Health Risk

Word Count = 3206

Corresponding Author:

Robert Ross, PhD, R.Kin, FACSM, FAHA
Email: rossr@queensu.ca
School of Kinesiology and Health Studies,
28 Division Street, Kingston, ON,
Canada, K7L 3N6.

Abstract

Background: Guidelines for identification of obesity-related risk stratify disease risk using specific combinations of body mass index and waist circumference. Whether the addition of cardiorespiratory fitness, an independent predictor of disease risk, provides better risk prediction of all-cause mortality within current body mass index and waist circumference categories is unknown.

Objective: To determine whether the addition of cardiorespiratory fitness improves prediction of all-cause mortality risk classified by the combination of body mass index and waist circumference.

Methods: We performed a prospective observational study using data from the Aerobics Center Longitudinal Study (ACLS). A total of 31,267 men (mean age 43.9 [SD, 9.4] years) who completed a baseline medical examination during 1974-2002. The main outcome measure was all-cause mortality. Participants were grouped using body mass index- and waist circumference-specific threshold combinations: Normal body mass index: 18.5-24.9 kg/m², waist circumference threshold of 90 cm; overweight body mass index: 25.0-29.9 kg/m², waist circumference threshold of 100 cm, and obese body mass index: 30.0-34.9 kg/m², waist circumference threshold of 110 cm. Participants were classified using cardiorespiratory fitness as unfit or fit, where unfit was the lowest fifth of the age-specified distribution of maximal exercise test time on treadmill among the entire ACLS population.

Results: 1,399 deaths occurred over a follow-up of 14.1 ± 7.4 years, for a total of 439,991 person-years of observation. Males who were unfit and normal body mass index with waist circumference <90 cm and ≥90 cm had 95% (1.95, 1.34-2.83) [Hazard ratio,

95% confidence interval] and 163% (2.63, 1.58-4.40) higher mortality risk than males who were fit, respectively ($p<.05$). Males who were unfit and overweight had 41% (1.41, 1.04-1.90) higher mortality risk with a waist circumference <100 cm ($p<.05$), but were at no greater risk (1.30, 0.92-1.84) if their waist circumference was ≥ 100 cm ($p=.14$). Males who were unfit and obese were not at increased mortality risk (1.37, 0.90-2.09) with a waist circumference <110 cm ($p=.14$), but were at 111% (2.11, 1.31-3.42) increased risk with a waist circumference ≥ 110 cm ($p<.05$).

Conclusions: For most of the body mass index and waist circumference categories, inclusion of cardiorespiratory fitness allowed for improved identification of males at increased mortality risk.

Introduction

Health organizations worldwide recommend that body mass index and waist circumference be combined to estimate obesity related health risk [1], as these measures have independent associations with all-cause mortality [2], and the addition of waist circumference to body mass index has been shown to improve evaluation of cardiometabolic risk [3], cardiovascular disease, and diabetes [4].

At present, a single 102 cm waist circumference threshold is recommended for the identification of adult Caucasian males at elevated health risk within each body mass index category [1]. The 102 cm threshold was originally intended as a replacement of body mass index measurement to identify white male adults with a body mass index of $\geq 30.0 \text{ kg/m}^2$ [5]. Use of the 102 cm threshold classifies very few individuals with normal and overweight body mass index, and almost all individuals who are obese with high waist circumference based on this cut-point [6]. In response, Arden and colleagues proposed the use of waist circumference values specific to each body mass index category to identify coronary heart disease mortality risk that were developed and cross-validated using large representative samples [7].

Currently obesity risk classification models do not include cardiorespiratory fitness, a strong predictor of morbidity and mortality [8, 9] independent of body mass index and waist circumference [10-12]. Cardiorespiratory fitness protects against all-cause mortality even when body mass index, waist circumference, and percent body fat are elevated [13]. In that study the authors were unable to determine the effect of cardiorespiratory fitness across specific combinations of body mass index and waist circumference due to sample size limitations. Therefore, whether the addition of cardiorespiratory fitness improves prediction of mortality risk within a combined body

mass index and waist circumference model has potentially important implications for obesity risk management. Should cardiorespiratory fitness improve risk prediction, practitioners would have a behavioural measure which, when used in combination with body mass index and waist circumference, may be used to improve the management of obesity-related health risk.

We classified a large cohort of males enrolled in the Aerobics Center Longitudinal Study (ACLS) according to body mass index - and waist circumference - specific thresholds, and examined whether the addition of cardiorespiratory fitness improved the prediction of all-cause mortality.

Methods

Study Population

The ACLS is a prospective longitudinal study established in the 1970s to examine associations between health behaviours, risk factors for chronic disease, and morbidity and mortality [8]. The ACLS consists of patients attending the Cooper Clinic in Dallas, Texas for preventive medical examinations. The ACLS cohort consists of predominantly white, well-educated, United States residents from all 50 states, and from middle to upper socioeconomic stratum. Participants were aware of the purpose of the study, and provided written consent. The ACLS protocol is reviewed annually by the Cooper Institute's institutional review board.

All males with body mass index measurements between 18.5-34.9 kg/m² and a complete set of baseline data were included for the current analysis. Males with a body mass index ≥ 35.0 kg/m² and all females were excluded due to few events within some groups for all-cause mortality. Participants were excluded based on presence of

cardiovascular disease or cancer at baseline, or an abnormal exercise test electrocardiogram [14]. Participants with less than one year of follow-up, or who failed to achieve 85% of age-predicted exercise test maximal heart rate were excluded [8]. Using these criteria, 31 267 males having completed baseline medical examinations at the Cooper Clinic between 1974 and 2002 were included in the analysis.

Data Collection

After providing written consent, patients underwent a preventive medical examination, fasted blood chemistry analysis, personal and family health history assessment, anthropometry, resting blood pressure, electrocardiography measurement, and a maximal treadmill exercise test. Cigarette smoking (current smoker or not), alcohol intake (heavy drinking defined as >14 alcoholic drinks per week), and physical inactivity (defined as no reported physical activity during the previous 3 months) were determined by self-report. Parental history of cardiovascular disease was determined from family health history.

Mortality Surveillance

Mortality follow-up occurred from the date of baseline examination until the date of death, or December 31, 2003 for survivors. The National Death Index and state death certificates were used to determine survival status. Deaths were classified using the *International Classification of Diseases, Ninth Revision* for deaths occurring before 1999, and the *International Statistical Classification of Diseases, 10th edition*, for deaths occurring from 1999 to 2003.

Measurement and Classification of body mass index, waist circumference and cardiorespiratory fitness

Body mass index was calculated (weight (kg)/height (m)²) and participants were classified according to standard body mass index categories for normal (body mass index 18.5 to <25.0 kg/m²), overweight (body mass index 25.0 to <30.0 kg/m²), and obesity (body mass index 30.0 to <35.0 kg/m²).

Waist circumference was measured at the level of the umbilicus. Participants were classified as abdominally obese according to body mass index-specific thresholds derived by Arden et al [7]. Thresholds for males are: normal body mass index (18.5-24.9), waist circumference threshold of ≥ 90 cm; overweight body mass index (25.0-29.9), waist circumference threshold of ≥ 100 cm; and obese body mass index (30.0-34.9) waist circumference threshold of ≥ 110 cm. For the analysis involving waist circumference alone, a waist circumference threshold of 96 cm was used [7].

Cardiorespiratory fitness was determined using a modified Balke maximal treadmill exercise test [8, 15]. Treadmill speed was initially set at 88 m/min. Treadmill grade was initially set at 0% for the first minute, 2% for the second minute, and was increased by 1% each minute thereafter. The treadmill test continued until the patient reached volitional fatigue.

Maximal time on treadmill has been found to correlate highly with measured maximal oxygen uptake in males [16]. Metabolic equivalent (MET) levels were determined from end of test treadmill speed and grade to allow for comparison between patients. Patients were classified as fit or unfit based on the upper 80% (fit) and lower 20% (unfit) of the age-standardized cardiorespiratory fitness ACLS time on treadmill for the entire ACLS population. While a consensus definition for low cardiorespiratory fitness is lacking, previous ACLS reports using this method have demonstrated that low

cardiorespiratory fitness by this definition independently predicts risk of morbidity and mortality [8, 11, 12].

Rationale for the use of body mass index-specific thresholds

The 94 and 102 cm thresholds proposed by Han and colleagues were originally designed to identify males with a body mass index of ≥ 25.0 kg/m² and ≥ 30.0 kg/m² respectively, providing action levels for obesity treatment [5]. However, this results in very few individuals with a normal body mass index with a waist circumference over the 102 cm threshold, and few individuals who are obese with a waist circumference under the 102 cm threshold [6]. Indeed, in our cohort, only 15 males were classified as having a normal body mass index when waist circumference was greater than 102 cm (data not shown). The Arden waist circumference thresholds within each body mass index category were designed to maximize sensitivity and specificity for Framingham coronary heart disease risk, optimally identifying individuals at high risk of future coronary heart disease events.

Statistical Analysis

Group differences in baseline characteristics were compared using t-tests and analysis of variance for continuous, and χ^2 tests for categorical variables. Tukey's studentized range test was used post hoc to determine group differences in baseline characteristics between unfit and fit males within each body mass index and waist circumference group. Cox proportional hazards models were used to estimate hazard ratios and 95% confidence intervals of all-cause mortality risk for males who were unfit compared with the fit reference group within each of the combined body mass index and waist circumference groups. Each model was adjusted for age, year of baseline examination, and the following behaviours and conditions: smoking, alcohol intake,

physical inactivity, diabetes, hypertension, hypercholesterolemia, and parental history of cardiovascular disease. Models were checked to ensure that they did not violate the proportional hazards assumption. Statistical significance was set at $p < 0.05$.

Results

A total of 1,399 deaths occurred in 31,267 males followed for an average of 14.1 ± 7.4 years with a range of 1.0 to 29.3 years, for a total of 439,991 person-years of observation. Baseline characteristics for participants according to survival status are presented in **Table 1**. Mean age at baseline was 43.9 ± 9.4 years. Decedents were older, had greater waist circumference, lower cardiorespiratory fitness, and higher blood pressure, blood cholesterol, and blood glucose than survivors ($p < 0.05$). Survivors had greater cardiorespiratory fitness and time on treadmill than decedents ($p < 0.05$). Decedents were more likely to smoke, be physically inactive, and to have diabetes, hypertension, or parental history of cardiovascular disease ($p < 0.05$). Survivors were more likely to consume alcohol in excess of 14 alcoholic drinks per week ($p < 0.05$).

Baseline characteristics according to cardiorespiratory fitness within each body mass index and waist circumference group are presented in **Table 2**. Unfit participants within each body mass index and waist circumference group were generally younger, with higher body mass index and waist circumference, but had lower cardiorespiratory fitness and time on treadmill ($p < 0.05$). Unfit individuals were more likely to be smokers, physically inactive, and to have diabetes, hypercholesterolemia, or hypertension ($p < 0.05$).

For most body mass index and waist circumference groups, being unfit was associated with a higher risk of all-cause mortality after adjusting for covariates (**Table**

3). For males with normal body mass index, being unfit was associated with a 95% higher risk (1.95, 1.34-2.83) [Hazard ratio, 95% confidence interval] of all-cause mortality ($p<0.05$) for males with a waist circumference <90 cm, and a 163% higher risk (2.63, 1.58-4.40) of all-cause mortality ($p<0.05$) for males with a waist circumference ≥ 90 cm. For overweight males, being unfit was associated with a 41% higher risk (1.41, 1.04-1.90) of all-cause mortality for males with a waist circumference <100 cm ($p<0.05$), while there was no significant increase in risk (1.30, 0.92-1.84) for males who were unfit and overweight with a waist circumference ≥ 100 cm ($p=0.14$). Males who were unfit and obese were not at higher risk of all-cause mortality (1.37, 0.90-2.09) with a waist circumference <110 cm ($p=.14$), but were at 111% higher risk (2.11, 1.31-3.42) with a waist circumference ≥ 110 cm ($p<0.05$).

When grouped by body mass index or waist circumference alone, unfit males were at significantly greater mortality risk compared to fit males within each group (**Table 4**). When considering body mass index alone, unfit males were at 110%, 41%, and 65% greater risk of all-cause mortality compared with fit males if they had normal, overweight, or obese body mass index, respectively. When grouped according to waist circumference alone, unfit males were at 53% and 79% greater risk of all-cause mortality if they had waist circumference <96.0 cm or waist circumference ≥ 96.0 cm, respectively.

Discussion

Current obesity risk management guidelines do not recommend that cardiorespiratory fitness be measured along with body mass index and waist circumference [1]. Our primary observation is that for most combinations of body mass

index and waist circumference, males who were unfit were at significantly higher risk of all-cause mortality than males who were fit. These data suggest that the inclusion of cardiorespiratory fitness within current body mass index and waist circumference models will improve the ability of practitioners to identify males at higher mortality risk and thus, improve patient management.

That individuals who are unfit are at elevated mortality risk after grouping according to body mass index and waist circumference is consistent with a previous report demonstrating the protective effect of cardiorespiratory fitness on all-cause mortality risk when body mass index, waist circumference and/or percent body fat is elevated [13]. Our current findings extend these previous observations, as we have demonstrated the ability of cardiorespiratory fitness to determine mortality risk across a range of combined body mass index and waist circumference groups that are used to characterize obesity-related risk in clinical practise.

Contrary to our expectation, males who were unfit and overweight with waist circumference ≥ 100 cm and those who were unfit and obese with waist circumference < 110 cm were not at higher mortality risk compared with males who were fit within the same body mass index and waist circumference group. This does not appear to be a result of group differences in cardiometabolic risk factors, anthropometric measures, or exercise test results (**Table 2**). In fact, the trend for all obesity phenotypes appears to be toward a protective role of cardiorespiratory fitness (**Table 3**). In agreement with previous reports [10-12], all males grouped as unfit were at increased risk of mortality when cardiorespiratory fitness was added to body mass index or waist circumference alone.

Possible explanations for the protective role of cardiorespiratory fitness for a given obesity phenotype include lower levels of visceral or ectopic fat, and/or lower values of cardiometabolic risk factors [17]. Visceral (intra-abdominal) fat and ectopic fat depots, such as hepatic fat are established correlates of cardiometabolic health and morbidity [18, 19]. Cross-sectional analyses show that for a given body mass index, males who are fit have lower levels of visceral fat and lower cardiometabolic risk factor values than males who are unfit [20, 21]. Individuals who are fit have been shown to have lower total and abdominal fat for a given body mass index or waist circumference [22]. Furthermore, for a given waist circumference or amount of visceral fat, cardiorespiratory fitness is associated with lower values of cardiometabolic risk factors [23]. Finally, it has been demonstrated that physical activity interventions which improve cardiorespiratory fitness are associated with a reduction in both visceral fat and cardiometabolic risk factors, independent of change in weight [24].

Our findings have implications regarding effective obesity management. Obesity management guidelines that focus on reductions in body mass index and waist circumference alone require weight loss to determine treatment efficacy [25]. Inclusion of cardiorespiratory fitness in addition to body mass index and waist circumference to determine treatment success provides opportunities to counsel patients regarding risk reduction consequent to improvements in cardiorespiratory fitness regardless of change in body mass index or waist circumference. Accordingly the patient is encouraged to sustain healthy behaviours rather than discontinue them because s/he failed to achieve weight loss. Furthermore, evidence from numerous epidemiologic studies demonstrates that the major reduction in all-cause and cardiovascular disease mortality occurs when adults move from the least fit group (cardiorespiratory fitness < 5 METS) to

the next-least fit group. Relatively less is gained by increasing fitness between moderately fit and highly fit individuals. This has implications for physical activity counselling, given that considerable benefits are likely to occur by encouraging the most sedentary or low-fit individuals to engage in modest levels of activity. Indeed, approximately 150 minutes of weekly physical activity consistent with consensus recommendations is associated with substantial increases in cardiorespiratory fitness for most adults [26] in as little as 4 weeks [27]. While direct measurement of cardiorespiratory fitness may not be feasible in many clinical settings, non-exercise algorithms have been developed to estimate cardiorespiratory fitness using routinely collected clinical measures, and are associated with all-cause and coronary heart disease mortality [28, 29].

Strengths of the current study include a large, well-characterized cohort [8, 12, 14, 30, 31], with considerable follow-up, providing a large number of mortality events for analysis, as well as objectively measured cardiorespiratory fitness, body mass index, and waist circumference. The use of novel body mass index-specific waist circumference thresholds [7] permitted analysis of groups stratified according to body mass index, waist circumference, and cardiorespiratory fitness in combination. We controlled for confounding factors including age, year of baseline examination, smoking, and physical activity. The exclusion of individuals with pre-existing cardiovascular disease or cancer, with less than one year of follow-up, and those who failed to reach 85% of maximal predicted exercise test heart rate decreased the likelihood of other factors influencing the observed relationships [8, 14].

Limitations of the ACLS cohort are well described [8]. The cohort is predominantly white, well-educated, and from middle to upper socioeconomic stratum. Therefore, caution must be exercised when generalizing these findings to other populations. There were relatively few events in some groups despite large sample size thereby preventing analyses involving females, cause-specific mortality, and the classification of cardiorespiratory fitness across a gradient of low, moderate, and high cardiorespiratory fitness. There is a lack of sufficient data concerning medication use or dietary patterns, both of which could confound results. The Arden body mass index-specific waist circumference thresholds were developed using risk of coronary heart disease to determine the optimal waist circumference that indicated elevated risk [7]. Whether these thresholds are appropriate for all-cause mortality is uncertain, although our mortality data from ACLS supports this concept for all-cause mortality. Finally, the use of categorical analysis could be viewed as a limitation. We believe that the categorization of body mass index and waist circumference in this manner reflects how obesity risk estimation models are typically used in clinical settings, which strengthens our findings.

In summary, we report that for most body mass index and waist circumference groups, inclusion of cardiorespiratory fitness identifies males at increased mortality risk after classification according to novel body mass index-specific waist circumference values. These observations provide further support for the inclusion of cardiorespiratory fitness as a routine measure in health care settings to help identify and manage obesity-related risk.

Acknowledgements

We thank Dr. Kenneth Cooper for establishing the ACLS, the Cooper Clinic physicians, nurses, and technicians for collecting the data, and the staff at the Cooper Institute for data entry and management.

Funding Source

Supported by grants AG06945, HL62508, and DK099185 from the National Institutes of Health.

Disclosure

Conflicts of Interest: None to declare.

TAR and RR were responsible for conception and design of the research undertaken.

SNB was responsible for the acquisition of the data.

TAR, XS and RR were responsible for analysis and interpretation of the data.

TAR was responsible for drafting of the manuscript.

RR, XS, C JL, and SNB were responsible for critical revision of the manuscript for important intellectual content.

References

1. Jensen, M.D., et al., *2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society*. J Am Coll Cardiol, 2014. **63**(25 Pt B): p. 2985-3023.
2. Cerhan, J.R., et al., *A pooled analysis of waist circumference and mortality in 650,000 adults*. Mayo Clin Proc, 2014. **89**(3): p. 335-45.
3. Nazare, J.A., et al., *Usefulness of measuring both body mass index and waist circumference for the estimation of visceral adiposity and related cardiometabolic risk profile (from the INSPIRE ME IAA study)*. Am J Cardiol, 2015. **115**(3): p. 307-15.
4. Balkau, B., et al., *International Day for the Evaluation of Abdominal Obesity (IDEA): a study of waist circumference, cardiovascular disease, and diabetes mellitus in 168,000 primary care patients in 63 countries*. Circulation, 2007. **116**(17): p. 1942-51.
5. Lean, M.E., T.S. Han, and C.E. Morrison, *Waist circumference as a measure for indicating need for weight management*. BMJ, 1995. **311**(6998): p. 158-61.
6. Janssen, I., P.T. Katzmarzyk, and R. Ross, *Body mass index, waist circumference, and health risk: evidence in support of current National Institutes of Health guidelines*. Arch Intern Med, 2002. **162**(18): p. 2074-9.
7. Arden, C.I., et al., *Development of health-related waist circumference thresholds within BMI categories*. Obes Res, 2004. **12**(7): p. 1094-103.
8. Blair, S.N., et al., *Physical fitness and all-cause mortality. A prospective study of healthy men and women*. JAMA, 1989. **262**(17): p. 2395-401.
9. Kodama, S., et al., *Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis*. JAMA, 2009. **301**(19): p. 2024-35.
10. Barry, V.W., et al., *Fitness vs. fatness on all-cause mortality: a meta-analysis*. Prog Cardiovasc Dis, 2014. **56**(4): p. 382-90.
11. Lee, C.D., S.N. Blair, and A.S. Jackson, *Cardiorespiratory fitness, body composition, and all-cause and cardiovascular disease mortality in men*. Am J Clin Nutr, 1999. **69**(3): p. 373-80.
12. Wei, M., et al., *Relationship between low cardiorespiratory fitness and mortality in normal-weight, overweight, and obese men*. JAMA, 1999. **282**(16): p. 1547-53.
13. Farrell, S.W., et al., *Association of multiple adiposity exposures and cardiorespiratory fitness with all-cause mortality in men: the Cooper Center Longitudinal Study*. Mayo Clin Proc, 2014. **89**(6): p. 772-80.
14. Blair, S.N., et al., *Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women*. JAMA, 1996. **276**(3): p. 205-10.
15. Balke, B. and R.W. Ware, *An experimental study of physical fitness of Air Force personnel*. U S Armed Forces Med J, 1959. **10**(6): p. 675-88.
16. Pollock, M.L., et al., *A comparative analysis of four protocols for maximal treadmill stress testing*. Am Heart J, 1976. **92**(1): p. 39-46.
17. Gaesser, G.A., et al., *Fitness versus Fatness: Which Influences Health and Mortality Risk the Most?* Curr Sports Med Rep, 2015. **14**(4): p. 327-32.

18. Bastien, M., et al., *Overview of epidemiology and contribution of obesity to cardiovascular disease*. Prog Cardiovasc Dis, 2014. **56**(4): p. 369-81.
19. Tchernof, A. and J.P. Despres, *Pathophysiology of human visceral obesity: an update*. Physiol Rev, 2013. **93**(1): p. 359-404.
20. Arsenault, B.J., et al., *Visceral adipose tissue accumulation, cardiorespiratory fitness, and features of the metabolic syndrome*. Arch Intern Med, 2007. **167**(14): p. 1518-25.
21. Wong, S.L., et al., *Cardiorespiratory fitness is associated with lower abdominal fat independent of body mass index*. Med Sci Sports Exerc, 2004. **36**(2): p. 286-91.
22. Janssen, I., et al., *Fitness alters the associations of BMI and waist circumference with total and abdominal fat*. Obes Res, 2004. **12**(3): p. 525-37.
23. Lee, S., et al., *Cardiorespiratory fitness attenuates metabolic risk independent of abdominal subcutaneous and visceral fat in men*. Diabetes Care, 2005. **28**(4): p. 895-901.
24. Lee, S., et al., *Exercise without weight loss is an effective strategy for obesity reduction in obese individuals with and without Type 2 diabetes*. J Appl Physiol (1985), 2005. **99**(3): p. 1220-5.
25. Ross, R., et al., *Changing the endpoints for determining effective obesity management*. Prog Cardiovasc Dis, 2015. **57**(4): p. 330-6.
26. Stofan, J.R., et al., *Physical activity patterns associated with cardiorespiratory fitness and reduced mortality: the Aerobics Center Longitudinal Study*. Am J Public Health, 1998. **88**(12): p. 1807-13.
27. Ross, R., et al., *Effects of exercise amount and intensity on abdominal obesity and glucose tolerance in obese adults: a randomized trial*. Ann Intern Med, 2015. **162**(5): p. 325-34.
28. Artero, E.G., et al., *Longitudinal algorithms to estimate cardiorespiratory fitness: associations with nonfatal cardiovascular disease and disease-specific mortality*. J Am Coll Cardiol, 2014. **63**(21): p. 2289-96.
29. Nes, B.M., et al., *A simple nonexercise model of cardiorespiratory fitness predicts long-term mortality*. Med Sci Sports Exerc, 2014. **46**(6): p. 1159-65.
30. Lee, D.C., et al., *Long-term effects of changes in cardiorespiratory fitness and body mass index on all-cause and cardiovascular disease mortality in men: the Aerobics Center Longitudinal Study*. Circulation, 2011. **124**(23): p. 2483-90.
31. Sui, X., et al., *Cardiorespiratory fitness and adiposity as mortality predictors in older adults*. JAMA, 2007. **298**(21): p. 2507-16.

Table I. Baseline characteristics for all study participants and according to survival status.

	All Participants (n=31 267)	Survivors (n=29 868)	Decedents (n=1399)
Age (y)	43.9 ± 9.4	43.5 ± 9.2*	51.1 ± 10.6
Body mass index (kg/m ²)	26.2 ± 3.1	26.2 ± 3.1	26.2 ± 3.2
Waist Circumference (cm)	92.7 ± 9.5	92.7 ± 9.5*	94.1 ± 10.0
Cardiorespiratory Fitness (METs)	12.1 ± 2.4	12.2 ± 2.3*	10.8 ± 2.4
Time on Treadmill (min)	18.9 ± 4.7	19.0 ± 4.7*	16.2 ± 5.1
Fasting Glucose (mg/dL)	99.7 ± 54.2	99.5 ± 55.1*	104.3 ± 28.1
Fasting Total Cholesterol (mg/dL)	207.7 ± 43.6	207.3 ± 43.6*	216.3 ± 42.2
Resting SBP (mmHg)	120.4 ± 12.8	120.3 ± 12.7*	124.0 ± 14.5
Resting DBP (mmHg)	80.9 ± 9.3	80.8 ± 9.3*	82.4 ± 10.1
Current Smoker (%)	16.6	16.2*	26.7
Heavy Alcohol Intake (%)	8.1	8.2*	5.5
Physically Inactive ^a (%)	22.7	22.5*	26.9
Diabetes ^b (%)	3.8	3.6*	7.3
Hypercholesterolemia ^c (%)	27.2	27.1	29.2

Hypertension ^d (%)	28.3	27.7*	39.6
Parental History of CVD (%)	26.9	26.2*	41.5

Abbreviations: SBP, systolic blood pressure; DBP diastolic blood pressure; CVD cardiovascular disease.

Data presented as mean \pm standard deviation, unless otherwise indicated. * indicates a significant difference between survivors and decedents ($p < .05$).

^a Defined as no self-reported leisure-time physical activity within 3 months of baseline examination, as reported on the standardized medical history/health habits questionnaire.

^b Defined as history of physician diagnosed diabetes, use of insulin, or measured fasting glucose level ≥ 126 mg/dL.

^c Defined as history of physician diagnosis or measured fasting total cholesterol level ≥ 240 mg/dL.

^d Defined as history of physician diagnosis or measured resting systolic blood pressure ≥ 140 mmHg or measured resting diastolic blood pressure ≥ 90 mmHg.

Table 2. Baseline characteristics according to fitness status within each combined body mass index and waist circumference group.

	Normal Body Mass Index				Overweight Body Mass Index				Obese Body Mass Index			
	Normal WC		High WC		Normal WC		High WC		Normal WC		High WC	
	Unfit	Fit	Unfit	Fit	Unfit	Fit	Unfit	Fit	Unfit	Fit	Unfit	Fit
<i>N</i>	307	9217	176	2459	879	10860	569	2814	674	1966	520	783
Age (y)	41.6 ± 9.5	41.9 ± 9.8	44.0 ± 9.6	45.9 ± 9.4	41.9 ± 8.3*	44.1 ± 9.1	44.6 ± 8.8*	47.2 ± 9.0	42.4 ± 8.4	44.9 ± 8.7	44.5 ± 8.5*	47.2 ± 9.2
Body Mass Index (kg/m ²)	22.8 ± 1.5	23.0 ± 1.3	24.0 ± 0.8	24.1 ± 0.8	27.0 ± 1.3*	26.7 ± 1.2	28.5 ± 1.1*	28.2 ± 1.2	31.7 ± 1.2*	31.4 ± 1.1	32.9 ± 1.3*	32.6 ± 1.4
Waist Circumference (cm)	83.8 ± 5.2	83.0 ± 4.6	93.4 ± 3.1	92.8 ± 3.0	94.5 ± 4.2*	92.7 ± 4.8	104.2 ± 3.8*	103.2 ± 2.9	104.4 ± 4.6*	103.1 ± 5.8	114.9 ± 6.5*	113.6 ± 3.3
Cardiorespiratory Fitness (METs)	8.9 ± 1.1*	13.7 ± 2.3	8.7 ± 1.2*	12.2 ± 1.8	9.0 ± 1.0*	12.2 ± 1.8	8.7 ± 1.1*	11.1 ± 1.5	8.8 ± 1.0*	11.1 ± 1.4	8.5 ± 1.1*	10.4 ± 1.3
Time on Treadmill (min)	12.1 ± 2.4*	22.1 ± 4.3	11.7 ± 2.7*	19.2 ± 3.7	12.3 ± 2.1*	19.2 ± 3.8	11.6 ± 2.3*	16.8 ± 3.2	11.8 ± 2.1*	16.8 ± 3.0	11.1 ± 2.2*	15.4 ± 2.8
Resting SBP (mmHg)	115.3 ± 13.0	117.5 ± 12.4	119.3 ± 12.5	120.6 ± 13.1	119.9 ± 11.7	120.7 ± 12.5	123.0 ± 12.8	123.1 ± 13.0	125.0 ± 12.5	124.8 ± 12.5	126.1 ± 12.2	127.2 ± 13.0
Resting DBP (mmHg)	79.1 ± 8.7	77.8 ± 8.7	80.1 ± 9.0	81.5 ± 9.3	81.8 ± 8.9	81.1 ± 9.0	84.0 ± 9.4	83.2 ± 9.2	85.6 ± 9.3	85.0 ± 9.3	86.4 ± 9.1	86.5 ± 9.6
Fasting Total Cholesterol (mg/dL)	212.8 ± 40.4*	197.0 ± 46.3	209.8 ± 38.5	216.0 ± 40.5	221.9 ± 44.9*	209.5 ± 42.1	219.5 ± 41.4	215.8 ± 41.1	217.2 ± 39.3	212.7 ± 40.1	222.2 ± 45.6	214.6 ± 40.8
Fasting Blood Glucose (mg/dL)	97.3 ± 17.2	97.6 ± 96.6	102.4 ± 27.9	98.6 ± 13.5	102.1 ± 22.5	99.1 ± 12.9	103.6 ± 21.3	102.4 ± 15.8	105.2 ± 25.7	102.1 ± 16.6	110.8 ± 32.5	105.1 ± 18.7

Current Smoker (%)	41.7*	12.5	38.8*	14.6	36.6*	16.6	31.6*	16.8	25.5*	15.8	23.3*	12.9
Heavy Alcohol Intake (%)	8.5	6.8	9.0	7.9	6.9	8.8	7.7	9.0	6.2*	9.3	8.3	9.8
Physically Inactive ^a (%)	55.7*	14.1	59.6*	20.7	51.1*	19.5	54.1*	28.3	52.1*	23.2	54.8*	32.2
Diabetes ^b (%)	2.0	2.2	6.2*	2.7	4.0	3.2	7.2*	5.0	9.8*	6.1	14.2*	9.2
Hypercholesterolemia ^c (%)	28.0*	17.7	30.9	26.3	37.5*	29.0	37.1	34.6	38.9*	32.8	41.0	37.0
Hypertension ^d (%)	20.5	16.8	32.6*	24.2	30.6	28.2	43.2*	38.7	49.0	44.7	52.5	53.6
Parental History of Cardiovascular Disease (%)	22.8	23.6	34.8	30.1	29.8*	26.7	32.9	30.2	27.0	25.7	30.6	28.9

Abbreviations: WC, waist circumference; SBP, systolic blood pressure; DBP diastolic blood pressure.

Data presented as mean \pm standard deviation unless otherwise indicated. * indicates a significant difference between unfit and fit individuals within each BMI/WC group ($p < .05$).

^aDefined as no self-reported leisure-time physical activity within 3 months of baseline examination, as reported on the standardized medical history/health habits questionnaire.

^bDefined as history of physician diagnosed diabetes, use of insulin, or measured fasting glucose level ≥ 126 mg/dL.

^cDefined as history of physician diagnosis or measured fasting total cholesterol level ≥ 240 mg/dL.

^dDefined as history of physician diagnosis or measured resting systolic blood pressure ≥ 140 mmHg or measured resting diastolic blood pressure ≥ 90 mmHg.

Table 3. Hazard ratios for all-cause mortality between unfit and fit men within each combined body mass index and waist circumference group.

Body Mass Index	Waist Circumference	Unfit vs. Fit	p-value
Normal	<90 cm	1.95 (1.34-2.83)*	0.0005
	≥90 cm	2.63 (1.58-4.40)*	0.0002
Overweight	<100 cm	1.41 (1.04-1.90)*	0.0253
	≥100 cm	1.30 (0.92-1.84)	0.1426
Obese	<110 cm	1.37 (0.90-2.09)	0.1408
	≥110 cm	2.11 (1.31-3.42)*	0.0023

Data presented as Hazard Ratio (95% Confidence Interval), * indicates $p < .05$.

Model adjusted for age, year of baseline examination, smoking, alcohol intake, physical inactivity, diabetes, hypertension, hypercholesterolemia, and parental history of cardiovascular disease.

Normal BMI: 18.5 to <25 kg/m², Overweight BMI: 25 to <30 kg/m², Obese BMI: 30 to <35 kg/m².

Table 4. Hazard ratios for all-cause mortality between unfit and fit men grouped according to body mass index or waist circumference alone.

	Category	Unfit vs. Fit	<i>p</i> -value
Body Mass Index	Normal	2.10 (1.56-2.83)*	<.0001
	Overweight	1.41 (1.12-1.76)*	0.0030
	Obese	1.65 (1.22-2.24)*	0.0011
WC	WC < 96.0 cm	1.53 (1.18-1.99)*	0.0012
	WC ≥ 96.0 cm	1.79 (1.48-2.15)*	<.0001

Abbreviations: WC, waist circumference

Data presented as Hazard Ratio (95% Confidence Interval), * indicates $p < .05$.

Model adjusted for age, year of baseline examination, smoking, alcohol intake, physical inactivity, diabetes, hypertension, hypercholesterolemia, and parental history of cardiovascular disease.

Normal body mass index: 18.5 to <25 kg/m², Overweight body mass index: 25 to <30 kg/m², Obese body mass index: 30 to <35 kg/m².

Clinical Significance:

In 31,267 males with a total of 439,991 person-years of observation, for most combinations of body mass index and waist circumference, unfit men were at substantially higher risk of all-cause mortality than fit men.

Inclusion of cardiorespiratory fitness within current body mass index and waist circumference models substantially improves the ability of practitioners to identify men at higher mortality risk and thus, improves patient management.