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Fitness vs. Fatness on All-Cause Mortality: A Meta-Analysis

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ABSTRACT

The purpose of this study was to quantify the joint association of cardiorespiratory fitness (CRF) and weight status on mortality from all causes using meta-analytical methodology. Studies were included if they were (1) prospective, (2) objectively measured CRF and body mass index (BMI), and (3) jointly assessed CRF and BMI with all-cause mortality. Ten articles were included in the final analysis. Pooled hazard ratios were assessed for each comparison group (i.e. normal weight-unfit, overweight-unfit and -fit, and obese-unfit and -fit) using a random-effects model. Compared to normal weight-fit individuals, unfit individuals had twice the risk of mortality regardless of BMI. Overweight and obese-fit individuals had similar mortality risks as normal weight-fit individuals. Furthermore, the obesity paradox may not influence fit individuals. Researchers, clinicians, and public health officials should focus on physical activity and fitness-based interventions rather than weight-loss driven approaches to reduce mortality risk.

In the past 20 years many prospective studies have described the independent effects of cardiorespiratory fitness [1–8] (CRF) and obesity [9–14] on mortality. Two meta-analytical reviews of these studies reported an independent association of these exposures to mortality. [15,16] Specifically, these reviews found that obesity (assessed as body mass index; BMI) independently increased mortality risk by 20% and 28% in women and men, respectively, [16] while decreasing CRF by 1 MET value increased mortality risk by 13%. [15] Although the independent effects of CRF and obesity on mortality are well established, which factor is more "important" remains controversial and is often debated by researchers.

One theory is the fitness-fatness hypothesis, which suggests a higher level of CRF will substantially reduce the adverse effects of obesity on morbidity and mortality, making obesity a much less important factor for health than is generally believed. [17,18] Numerous studies, including two narrative reviews [18,19] have examined the joint association of CRF and fatness on mortality, [20–42] and the evidence strongly supports the hypothesis that CRF is much more important than fatness as a mortality risk indicator.

However, to our knowledge, no study in the current literature has assessed, meta-analytically, the joint association of CRF and BMI on mortality. Therefore, as suggested by the literature, we hypothesized that mortality levels would be highly correlated to CRF when CRF and BMI were jointly assessed. To quantify this hypothesis, an extensive literature review and meta-analysis was performed on observational studies examining the joint associations of fitness and fatness on all-cause mortality.

Statement of Conflict of Interest: see page 389.

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Abbreviations and Acronyms
BMI = body mass index
CRF = cardiorespiratory fitness
PA = physical activity

Methods

Literature review

The data collection and reporting process were completed following the Meta-analysis of Observational Studies in Epidemiology [43] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statements. [44] The review of the literature was performed through Pubmed, EBSCOhost, and ProQuest searches by the first author using keywords related to the joint association between CRF and BMI on mortality from all-causes ((“Cardiorespiratory fitness” OR “physical fitness” OR “fitness” OR “maximal oxygen consumption” OR “VO2max” OR “maximal oxygen uptake”) AND (“Body composition” OR “BMI” OR “body mass index” OR “obesity” OR “adiposity”) AND (“mortality” OR “mortalities” OR “death” OR “fatality” OR “fatal” OR “all-cause mortality”)) between January 1980 and May 2013. Articles were included in the analysis if 1) the design was prospective; 2) the main outcome was all-cause mortality; 3) CRF was assessed using a maximal or VO_2peak exercise test; 4) BMI was directly measured; 5) CRF and BMI were jointly assessed on all-cause mortality; and 6) the reference group was the normal weight and fit group. When assessing the ProQuest database, articles were then sorted by their “relevance” to the search terms and the first 300 studies were assessed. No other limits were applied during the search process. These criteria were used to target prospective studies that objectively assessed CRF and BMI and their joint association to all-cause mortality.

Following the database searches, references from relevant review articles and observational studies were assessed for additional reports on fitness and fatness in relation to mortality. Once the data were organized, specific authors were contacted for additional information including hazard ratio, 95% confidence intervals, and sample size and follow-up duration for each comparison group (e.g. normal weight-unfit group). After the data were received and an assessment of the full dataset was completed, three articles were excluded: two because BMI quintiles compared the heaviest quintile to the other four combined groups [34,35] and one for not being able to provide hazard ratios and 95% CI information upon request. [3] In total, 10 articles remained eligible for the current analysis (Fig 1). [27,28,30,32,33,37–41]

Cardiorespiratory fitness and body mass index

The exposure variables for this analysis, CRF and BMI, were categorized into 2 (i.e. unfit and fit) and 3 (i.e. normal weight, overweight, and obese) groups, respectively. The CRF and BMI categories were combined to make 5 comparison groups (i.e. normal weight-unfit, overweight-unfit, overweight-fit, obese-unfit and obese-fit) and a referent group (i.e. normal weight-fit).

Most of the articles in this analysis reported fit and unfit CRF categories. However, three articles further delineated CRF into low, moderate and high. [27,33,39] To account for three CRF groups, we used the Hamling method to combine the moderate and high fit groups. [45] All CRF data were then analyzed and reported in fit and unfit categories. Seven of the 10 included articles used CRF quintiles to define the unfit (1st quintile) and fit (2nd-5th quintile) categories. The three remaining articles determined this threshold using study specific criteria. [27,39,41]

The BMI categories related to normal weight, overweight and obese were <25 kg/m ^{2}, 25 – <30 kg/m ^{2}, and ≥ 30 kg/m ^{2}, respectively. All studies included in this analysis used these thresholds except one. This article, published in 1998, used slightly different threshold values (i.e. normal weight: 19 – <25; overweight: 25 – <27.8; obese: ≥ 27.8). [30] Furthermore, only eight of the 10 articles provided data for all three BMI categories. The remaining two articles provided data for the normal weight BMI category only. [37,38] This particular information (i.e. exposure categorization), along with sample size, number of deaths and average years of follow-up, etc., is found in Table 1.

Article quality assessment

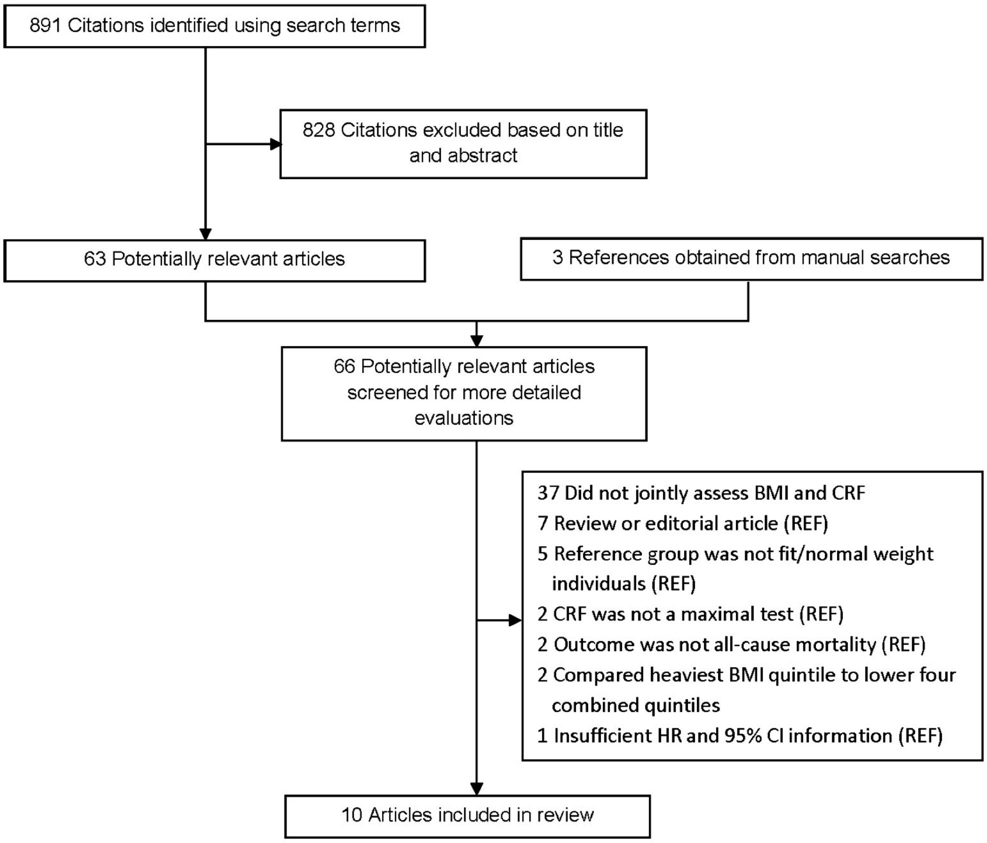
To assess article quality, studies were examined using the Quality Assessment Tool for Quantitative Studies. [41] Sections of this tool were modified to improve the assessment of observational studies. Two new sections were included (i.e. study sample and follow-up period), three sections were removed (i.e. study design, blinding, and withdrawals and drop-outs), and two sections were modified (i.e. confounders and data collection methods). Articles were scored by summing the numeric component ratings (i.e. 1 = weak, 2 = moderate, 3 = strong) and dividing by the highest possible score (i.e. 15).

Statistical analysis

Hazard ratios and 95% confidence intervals were gathered for the five comparison groups (i.e. normal weight-unfit, overweight-unfit, overweight-fit, obese-unfit, and obese-fit). Pooled hazard ratios were estimated using a random-effects model. This model was chosen because of the heterogeneity between studies. This observation was confirmed after calculating the Q score and I^2 statistic.

To assess for possible publication bias, the Begg and Egger tests [47,48] were performed. Furthermore, after completing the aforementioned literature review, data from two research databases (i.e. Aerobic Center Longitudinal Study [ACLS] and Veterans Exercise Testing Study) and one independent article met the inclusion criteria. To account for possible population overlap between studies, a sensitivity analysis was performed using each database or independent article as the unit of analysis. For this analysis two articles [32,40] were chosen from the ACSL dataset (i.e. different population: sex), as these articles provided the largest sample and follow-up years in a healthy population, making the number of studies in this analysis equal to four. [32,39–41]

To examine the effect of study characteristics on risk of all-cause mortality, multiple moderator analyses were performed on possible confounders (mean age [$\geq$50 years or



BMI indicates body mass index; CRF, cardiorespiratory fitness

Fig. 1 – Selection of articles for meta-analysis.

not], sex [men or not], chronic disease [yes or no], mean follow-up [≥12 years or not], confounder control, defined as adjusting for >3 of the American College of Sports Medicine's atherosclerotic cardiovascular disease risk factors [49] [yes or no], study data origin [ACLS or not], and article quality assessment score [≥90% or not]). A two-sided $P \leq 0.05$ was considered statistically significant. Data were analyzed using Comprehensive Meta Analysis version 2.2.050 (Comprehensive Meta Analysis, Englewood, New Jersey).

Results

Fig 1 shows the literature selection process. A total of 891 articles were retrieved from Pubmed, Ebscohost, and ProQuest searches. Sixty-six potentially relevant articles were further examined using abstract and full article assessments. Following this assessment, ten articles remained eligible for the current meta-analysis. When assessing for publication bias, however, there were no significant results. Figs 2, 3, and 4 present the findings from the meta-analysis comparing the joint association of fitness and fatness on mortality from all causes. The data for the figures were reported by six joint categories of BMI and CRF levels. Figs 2–4 show the hazard ratios and 95% confidence intervals of five groups (i.e., normal weight unfit, overweight unfit, overweight fit, obese unfit and obese fit) compared to the reference group (i.e., normal weight fit group). The figures also have a forest plot and a pooled hazard ratio.

After completing the meta-analysis on normal weight and unfit individuals, an increased risk of death was found (i.e. hazard ratio, 95% CI: 2.42, 1.96–2.99) compared to normal weight fit individuals (see Fig 2). This relationship was similar after adjusting for duplicate articles from the same database (i.e. 2.39, 1.62–3.52). We also assessed for seven moderators (i.e. age, sex, chronic disease status, mean follow-up, confounder control, data origin, and article quality) and found that chronic disease status and age significantly modified this relationship. Unfit normal weight individuals with a chronic disease had the largest risk of death in the whole analysis (i.e. 3.55, 2.37-5.31) while those without a chronic disease had lower mortality risk (i.e. 2.10, 1.70–2.61). Older (i.e. ≥50 year), normal weight and unfit adults were also more likely to die (i.e. 3.35, 2.20–5.12) than their younger counterparts (i.e. 2.03, 1.64–2.51).

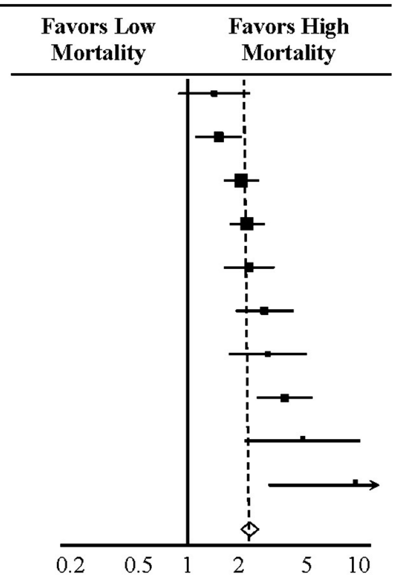
When assessing overweight unfit individuals, all the articles showed a significant mortality risk when compared to normal weight fit individuals. This elevated risk across all

Table 1 – Characteristics of Studies Included in the Meta-analysis. *

Article	No. of participants	Men (%)	Age (mean years)	Disease status	Study database	Follow-up (mean years)	Outcome (No. of deaths)	Exposures	
								CRF	BMI (kg/m ^{2})
Church et al. [27] 2004	2,196	100	49.3	Diabetes	ACLS	14.6	275	Fit: ≥8.8 METs Unfit: <8.8 METs	Normal weight: <25 Overweight: 25–29.9 Obese: ≥30
Farrell et al. [40] 2010	11,335	0	45	-	CCLS	12.3	292	Fit: 2nd–5th quintile Unfit: 1st quintile	Normal weight: 18.5–24.9 Overweight: 25–29.9 Obese: ≥30
Goel et al. [41] 2011	855	80.1	62.4	Coronary artery disease	Mayo Clinic	9.7	159	*Men,* Fit: ≥21.5 mL/kg/min Unfit: <21.5 mL/kg/min *Women* Fit: ≥16.8 mL/kg/min Unfit: <16.8 mL/kg/min	Normal weight: 18.5-24.9 Overweight: 25–29.9 Obese: ≥30
Lee et al. [30] 1998	21,856	100	43.9	-	ACLS	8.1	427	Fit: 2nd–5th quintile Unfit: 1st quintile	Normal weight: 19.0–<25.0 Overweight: 25.0–<27.8 Obese: ≥27.8
Lyerly et al. [37] 2009	3,044	0	47.4	Pre- and undiagnosed diabetes	ACLS	16	171	Fit: 2nd-5th quintile Unfit: 1st quintile	Normal weight: 19.0–<25.0
McAuley et al. [33] 2009	13,155	100	47.7	Hypertension	ACLS	12	883	Fit: 2nd–5th quintile Unfit: 1st quintile	Normal weight: 18.5–<25.0 Overweight: 25.0–<30.0 Obese: ≥30.0
McAuley et al. [39] 2010	10,965	100	57.3	-	VETS	7.7	2801	Fit: >5 METs Unfit: <5.0 METs	Normal weight: 18.5–<25.0 Overweight: 25.0–<30.0 Obese: ≥30.0
Sui et al. [28] 2007	2,603	80.2	64.4	-	ACLS	12.1	450	Fit: 2nd–5th quintile Unfit: 1st quintile	Normal weight: 19.0–<25.0 Overweight: 25.0–<30.0 Obese: 30.0–<35.0
Wei et al. [32] 1999	25,714	100	43.8	-	ACLS	10.1	1025	Fit: 2nd–5th quintile Unfit: 1st quintile	Normal weight: 19.0–<25.0 Overweight: 25.0–<30.0 Obese: ≥30.0
Wei et al. [38] 2000	1,263	100	50.2	Diabetes	ACLS	11.7	180	Fit: 2nd–5th quintile Unfit: 1st quintile	Normal weight: <25.0

* ACLS: Aerobics Center Longitudinal Study; CCLS: Cooper Clinic Longitudinal Study; VETS: The Veterans Exercise Testing Study; CRF: Cardiorespiratory Fitness; BMI: body mass index.

Study author/year	Hazard ratio
Lyerly et al. 2009	1.41 (0.87-2.30)
Farrell et al. 2010	1.50 (1.01-2.23)
McAuley et al. 2010	2.03 (1.60-2.58)
Wei et al. 1999	2.20 (1.73-2.80)
Lee et al. 1998	2.25 (1.59-3.18)
McAuley et al. 2009	2.77 (1.87-4.10)
Wei et al. 2000	2.90 (1.71-4.92)
Sui et al. 2007	3.63 (1.47-5.33)
Church et al. 2004	4.80 (2.31-9.96)
Goel et al. 2011	9.60 (2.90-31.79)
Overall	2.42 (1.96-2.99)
	I^2=65.4%;P=.002



* Compared to normal weight fit individuals

Fig. 2 – Meta-analysis of all-cause mortality on normal weight unfit individuals.

studies more than doubled the risk of mortality (i.e. 2.14, 1.77–2.58) in this population (see Fig 3) while overweight individuals who were fit did not experience significant risk (i.e. 1.13, 1.00–1.27). Mortality risk for fit individuals, after adjusting for population overlap, remained stable. An increase was found after adjusting for population overlap in unfit individuals (i.e. 2.39, 1.94–2.95). After assessing for potential moderators of this relationship, the article quality assessment and study data origin significantly altered mortality risk in overweight unfit and fit individuals, respectively. Higher quality articles showed a lower risk of death for unfit overweight individuals (i.e. higher quality articles: 1.86, 1.61–2.14; lower quality articles: 2.81, 1.92–4.10) while articles originating from the ACLS dataset had a lower risk of death for their fit counterparts (i.e. ACLS: 1.08, 0.96–1.21; other: 1.39, 1.13–1.71) than outcomes originating from different sources.

When assessing obese unfit individuals, all articles showed a significant relationship to all-cause mortality, except one (see Fig 4). The overall risk associated with this population was significantly elevated (i.e. 2.46, 1.92–3.14), while those who were obese and fit did not experience a significantly different mortality risk (i.e. 1.21, 0.95–1.52) compared to normal weight and fit individuals. Mortality risk was not stable for unfit individuals with changes occurring after the population overlap adjustments (i.e. 2.99, 2.56–3.49), but more stable for obese and fit individuals with only minor differences after adjusting for population overlap (i.e.1.28, 0.78–2.10). Mortality risk was modified significantly during the moderator analysis for both CRF categories. The significant moderators for unfit individuals were age and the article quality assessment. Studies with older, obese, and unfit populations had a lower morality risk (i.e. 1.66, 1.34–2.04) than studies with their younger counterparts (i.e. 2.83, 2.37–3.38) and higher quality studies reported a lower mortality risk (i.e. higher quality studies: 2.09, 1.54–2.84) than lower quality studies (i.e. lower quality studies: 3.10, 2.57–3.7). The only significant moderator for obese fit individuals was chronic disease status with individuals with disease more likely to die (i.e. 1.81, 1.41–2.32) than their more healthy equivalents (i.e. 1.03, 0.90–1.19) when comparing to normal weight fit individuals.

Discussion

After completing the meta-analysis on the joint association between CRF and BMI on mortality from all causes, the results indicate that the risk of death was dependent upon CRF level and not BMI. Therefore, fit individuals who are overweight or obese are not automatically at a higher risk for all-cause mortality. These findings are promising for all individuals, including those unable to lose weight or maintain weight loss, as all can experience significant health benefits by developing and maintaining a moderate level of CRF by participating regularly in physical activity (PA ;e.g. brisk walking, biking) at the level of PA currently recommended by the U.S. Physical Activity Guidelines. [50]

Earlier systematic review articles support the finding of this analysis [18,19]; however, neither quantified the joint association of CRF and body weight on all-cause mortality. The first review, by Pedersen et al., assessed the independent and joint associations of BMI and CRF on mortality. As concluded in several articles [1,27,35,51]; Pedersen et al. stated that a higher CRF level independently reduces mortality risk regardless of BMI. [19] In the second review, Fogelholm et al. concluded that individuals with elevated body weight and good CRF have a lower mortality risk than normal weight

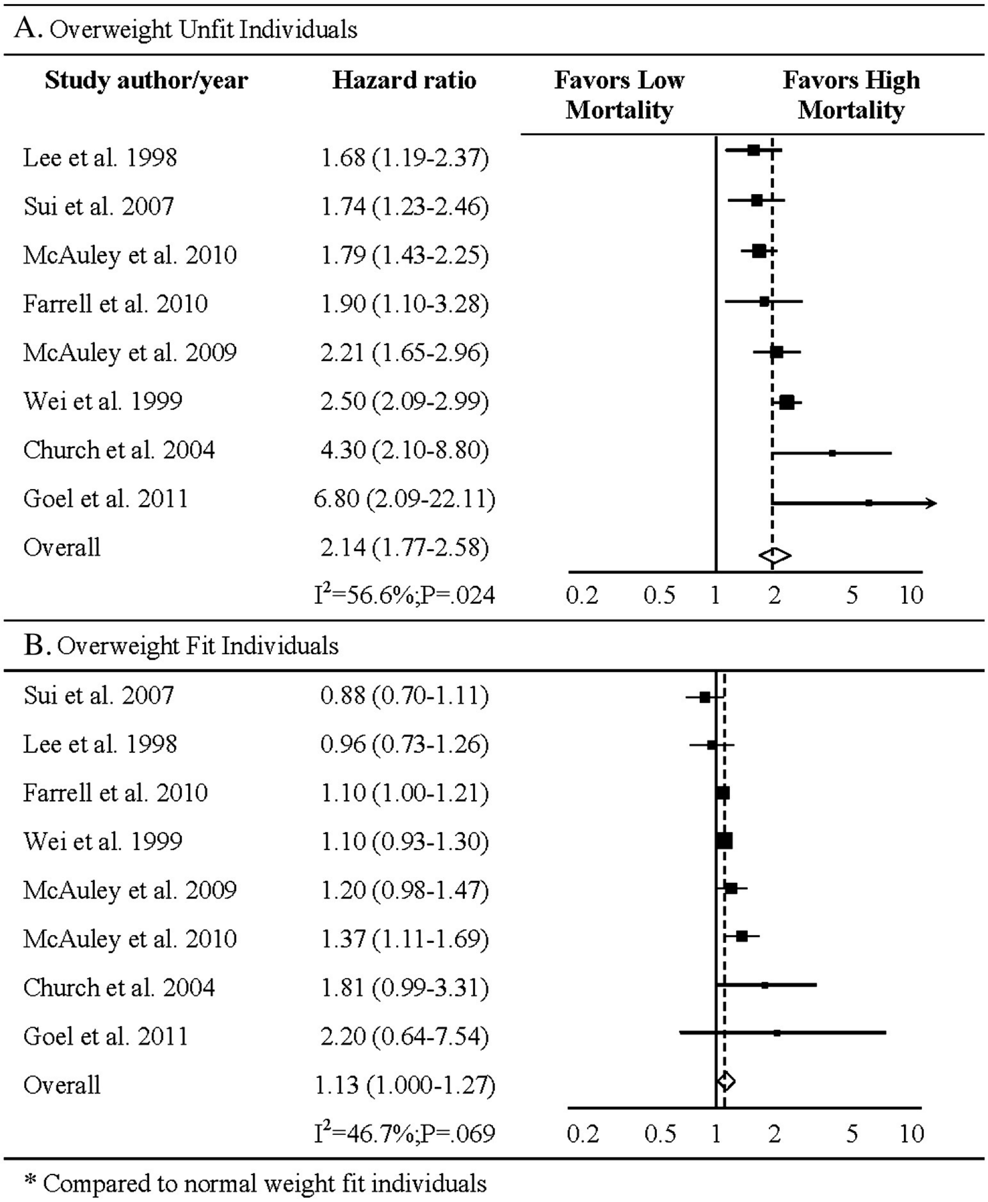


Fig. 3 – Meta-analysis of all-cause mortality on overweight individuals.

individuals with poor CRF.[18] Although both review articles concluded that CRF was a better predictor of all-cause mortality than BMI, the present review applies quantitative analyses to this relationship.

When assessing all individuals who were unfit, it is interesting to note that those who were overweight had the lowest risk of death while normal weight and obese individuals had higher risk scores. This outcome is indicative of the obesity paradox portrayed in a recent systematic review and meta-analysis of 2.88 million individuals on all-cause mortality.[52] In this analysis Flegal et al. showed a significant mortality risk reduction (i.e. hazard ratio, 95% CI: 0.94, 0.91–0.96) in overweight individuals when compared to those who were normal weight. However, this relationship may not be significant when individuals are fit. Although one included article in the current analysis did show significant mortality risk reduction in the overweight fit population,[39] the current overall outcome suggests that the obesity paradox does not apply to fit individuals.

In further examining the obesity paradox between unfit and fit individuals, the age moderator was only significant in unfit normal weight and obese individuals. In unfit normal weight individuals, participants over the age of 50 had a greater risk of death compared to the younger, unfit, and normal weight population. While this seems intuitive, obese unfit older adults had lower mortality risk when compared to the younger, unfit, and obese individuals. This suggests that either 1) obesity provides protection against mortality in unfit older populations compared to their younger counterparts or 2) a survival bias has occurred, where many of the younger,

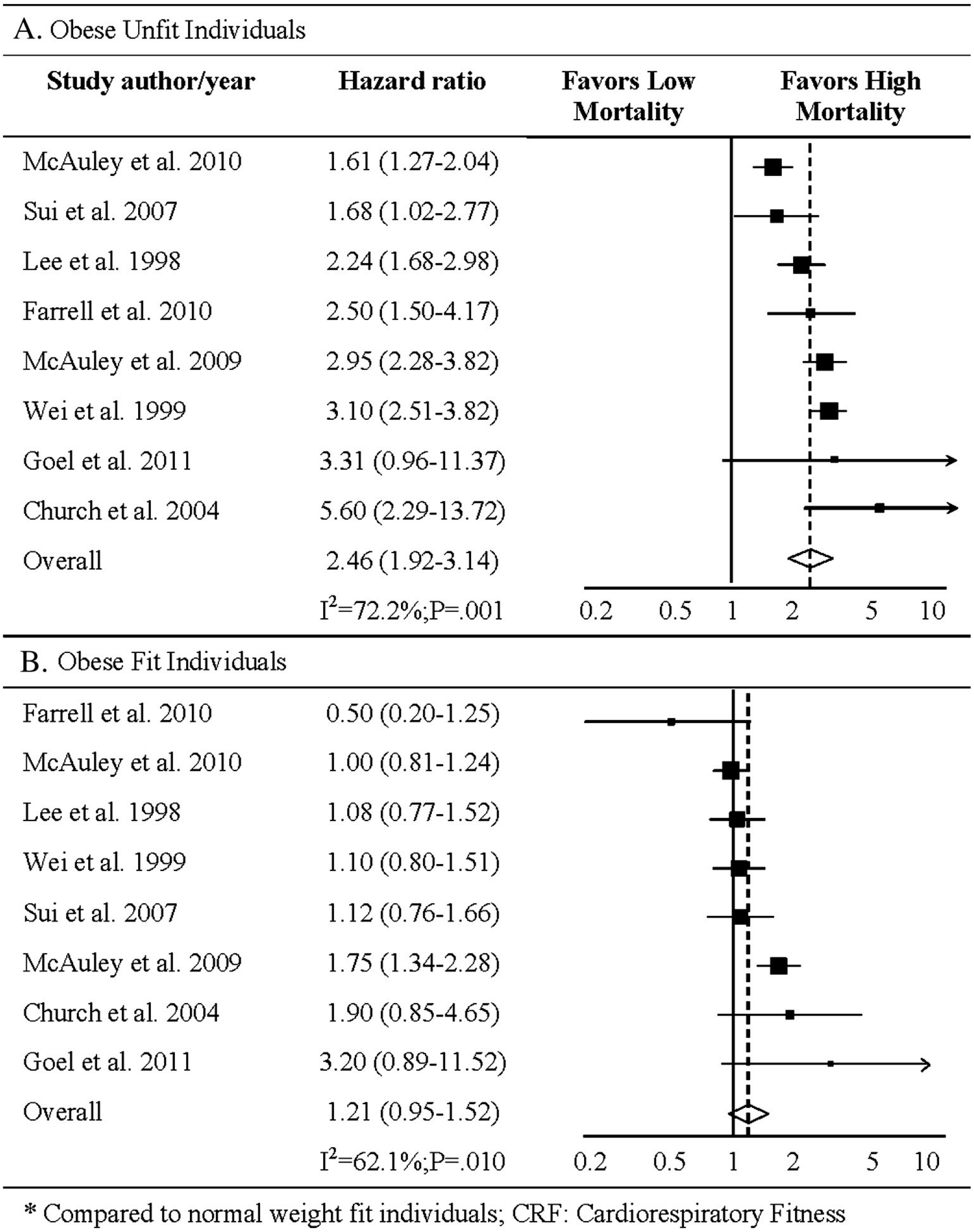


Fig. 4 – Meta-analysis of all-cause mortality on obese individuals.

unfit and obese individuals have died while the older, unfit, and obese individuals were selected survivors, reducing the hazard ratio in older adults. When participants were considered fit, age was not a significant moderator in any of the BMI categories, again suggesting that fit individuals may not be influenced by the obesity paradox.

There are significant limitations to this analytical review. First, only ten articles were included in the analysis. However, many of these articles had thousands of participants. Second, data for this analysis were from three independent sources and overlapping of some participants occurred between studies in the main analysis. We accounted for this by duplicating the main outcome using four studies (i.e. male and female studies form the ACLS dataset). After completing this adjustment, the risk of death increased in overweight and unfit individual only. A third limitation to this analysis is the quality of the included articles as there were significant differences in unfit individuals' mortality risk in two BMI categories (i.e. overweight and obese) after assessing article quality. This may have occurred for two reasons: 1) the rigor applied to the studies when assessing article quality and 2) when performing the moderator analysis the binary variable chosen was the approximate mean of the included studies. To improve the understanding of this relationship, particularly in disadvantaged populations, additional databases and high quality research articles are needed.

The findings from this meta-analysis have important public health implications, as it is concluded that unfit individuals have twice the risk of death regardless of BMI, while fit and overweight and obese individuals have similar mortality risk as their normal weight counterparts. Researchers, clinicians, and public health officials should focus on PA-based interventions rather than weight loss driven approaches to reduce mortality risk. Much more attention should be given to promoting PA and CRF as a means to reduce risk for disease and death. The amount of PA needed to develop a moderate level of CRF can be obtained with the DHHS 2008 Physical Activity Guidelines, 150 minutes of moderate intensity PA per week, which can be accumulated in doses of 10 minutes or more.[50] This amount of PA should not be intimidating and is achievable by most unfit individuals. A number of evidence-based programs for promoting PA using several approaches, channels, and settings exist resulting in meaningful short-term increases in PA.[53,54] However continued work is needed, particularly in how to successfully translate and disseminate these programs for broader reach and impact among all populations.

Statement of Conflict of Interest

All authors declare that there are no conflicts of interest.

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