



**ASSOCIATIONS OF FATNESS, FITNESS AND PHYSICAL
ACTIVITY WITH MORTALITY IN OLDER ADULTS:
SYSTEMATIC REVIEW OF OBSERVATIONAL STUDIES**

Journal:	<i>Obesity</i>
Manuscript ID:	15-0087-Rev.R2
Manuscript Type:	Review
Date Submitted by the Author:	12-May-2015
Complete List of Authors:	Yerrakalva, Dharani; Cambridge University, Primary Care and Public Health Mullis, Ricky; Cambridge University, Primary Care And Public Health Mant, Jonathan; Cambridge University, Primary Care And Public Health
Keywords:	Obesity, Body-Mass Index, BMI, Physical Activity, Physical Fitness, Elderly

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Dear Dr Allison,

Thank you very much for your consideration and acceptance of our manuscript.

In response to your comment "Page 10, line 25, include the Beavers reference in place of REF", we have added in the missing reference on page 10.

Once again, thank you for your time in consideration of our paper. We are happy to receive any further comments.

Yours sincerely,

Dr Dharani Yerrakalva

Title:

The Associations of 'Fatness', 'Fitness' and Physical Activity With All-Cause Mortality in Older Adults: A Systematic Review Of Observational Studies.

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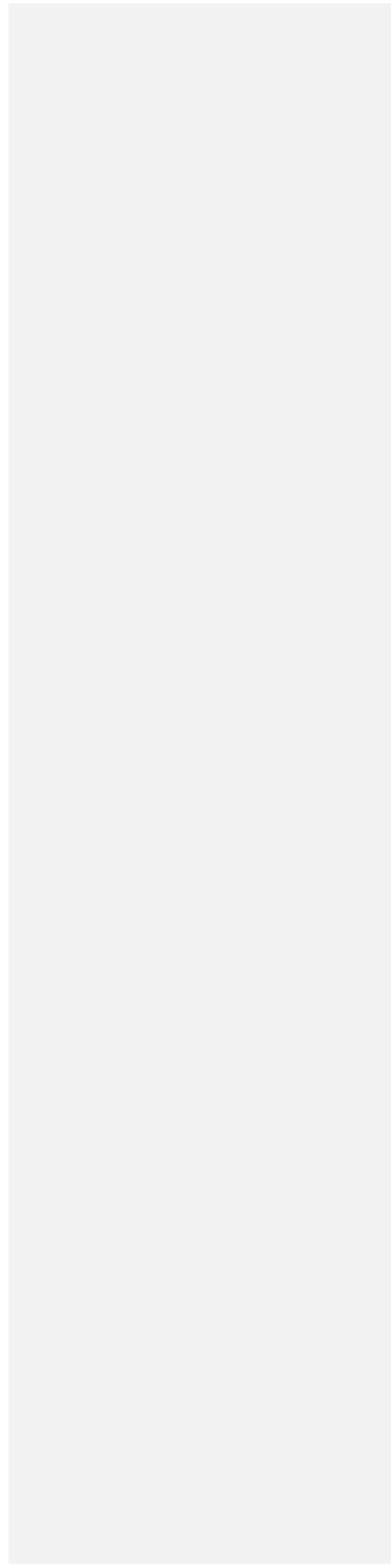
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Key Words: Obesity, cardiovascular fitness, physical activity, older adults, elderly

Running Title: The Associations of ‘Fatness’, ‘Fitness’ and Physical Activity in Older Adults.

Word Count: [4186](#)

Potential Conflicts of Interest: None declared



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7 **What is already known on this subject?**

- 8
- 9 • There is a growing body of evidence from prospective longitudinal studies of an inverse relationship
10 between excess adiposity, predominantly defined by body mass index, and mortality in older adults.
11 This is commonly referred to as the obesity paradox: i.e. being overweight is associated with longer
12 rather than shorter survival.
 - 13 • Though a number of theories have been put forward to explain this, but convincing evidence to support
14 any one theory is yet to emerge.
 - 15 • One largely neglected explanation for the obesity paradox is that cardiorespiratory fitness or physical
16 activity may act either as confounders (i.e. older adults who are physically fit may weigh more than
17 people who are unfit) or effect modifiers (the impact of being overweight may be different in people
18 who are physically fit compared to those who are unfit).
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26 **What does this review add?**

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- 28 • This review is the first in older adults to examine whether cardiorespiratory fitness or physical activity
29 influence the observed association of excess adiposity with all-cause mortality .
 - 30 • All but one of the included studies demonstrated a paradox which persisted after adjustment for
31 physical activity or cardiorespiratory fitness, suggesting that confounding by physical fitness is not an
32 explanation. However, subjective and unvalidated physical activity measures were used in many of
33 these studies, so it is plausible that there is residual confounding.
 - 34 • Two studies that stratified the impact of BMI by physical fitness did not demonstrate any significant
35 interaction between these factors, but did observe lower mortality in the groups with higher fitness.
36 Overweight people who were physically fit had lower mortality than people of normal weight who
37 were unfit.
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ABSTRACT

Objectives: This review explored whether cardiorespiratory fitness or physical activity act as either confounders or effect modifiers of the relationship between adiposity markers and all-cause mortality in older adults.

Methods: Systematic searches were carried out to identify observational studies that examined the association of adiposity markers (body mass index, waist circumference and waist-hip ratio) with all-cause mortality in adults aged ≥ 60 which took into account cardiorespiratory fitness or physical activity. Data from each included study was analysed to produce a graphical representation of this relationship.

Results: 14 of the 15 identified studies found that increasing BMI had a non-positive association with all-cause mortality, with persistence of the obesity paradox despite adjustment for physical activity or cardiorespiratory fitness. Physical activity measurement methods were all subjective and often unvalidated. The two studies stratifying for cardiorespiratory fitness did not find that fitness had a significant impact on the relationship between excess adiposity and mortality, but found that overweight and fit people had better survival than normal weight unfit people,

Conclusions: The predominant use of poor physical activity measurement suggests that studies are currently not adequately accounting for possible physical activity confounding. More studies are needed addressing the modification of the relationship between adiposity markers and mortality by cardiorespiratory fitness.

INTRODUCTION

In the general adult population excess adiposity is associated with increased risks of cardiovascular and all-cause mortality (1–3). However, in older adults there is evidence that excess adiposity is associated with reduced mortality. This is commonly referred to as the obesity paradox, (4–6). The term was first used when this association was seen in chronic disease populations such as patients with heart failure and renal failure (7–12), although even in the general adult population, it is increasingly being demonstrated that a BMI of 25–35 is associated with reduced mortality compared to people with lower BMIs (13–15).

There is considerable scepticism about the validity of the obesity paradox and a number of explanations have been put forward as to what might account for it. It may be a consequence of using BMI (8,16) which is a poor marker of adiposity in older adults (6,8,17,18) Another possible explanation is reverse causality, though this can be minimised by excluding patients who die in the first few years of follow-up. Confounding by chronic diseases, smoking and alcohol consumption (though adjustment for these variables does not appear to attenuate the paradox) and ‘selective survivor effect’ (those with the worst obesity having died already and those with ‘healthy obesity phenotype’ survive) are alternative explanations, though little convincing evidence to support any one theory is yet to emerge.

One largely neglected explanation for the obesity paradox is that cardiorespiratory fitness or physical activity may act as either confounders or effect modifiers of the relationship between adiposity markers and all-cause mortality, as until recently studies rarely adjusted or stratified for these factors. (19). If physical activity or cardiorespiratory fitness are confounders of this relationship, then adjustment for these factors in the analysis will attenuate the association. If they are effect modifiers of the association, then different effects of increasing weight will be observed in fit/active individuals compared to unfit/inactive individuals.

Few studies and no reviews have explored this in older adults. Cardiorespiratory fitness and physical activity are distinct but related concepts (20,21) that appear to be independent dose-response risk predictors of mortality independent of BMI in older adults (22–26), and have been suggested separately as modifiers of the obesity paradox. Steele et al. (27) defines physical activity as any bodily movement produced by skeletal muscle that results in energy expenditure, usually expressed in metabolic equivalents (METs) whereas cardiorespiratory

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7 fitness (28) can be defined as the ability of the circulatory, respiratory, and muscular systems to supply oxygen
8 during sustained physical activity and is often expressed in terms of maximal oxygen uptake (VO_2 max).
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11 Reviews by Lavie et al. (29) and McAuley et al. (30) in patients with heart disease and a recent meta-analysis by
12 Barry et al. (31) in the general adult population suggest that effect modification between adiposity and fitness on
13 mortality might have masked true associations of adiposity with mortality. Studies which have used
14 stratification have found associations of adiposity with mortality vary with stratification for cardiorespiratory
15 fitness (23,32–36). Studies of the joint associations of cardiovascular fitness and adiposity measures with
16 mortality in the general adult population suggest that higher levels of fitness attenuate the increased risk of
17 mortality associated with increased adiposity (16,20,32,37). A recent meta-analysis of 10 studies in the general
18 adult population examining the joint association of cardiorespiratory fitness and BMI on all-cause mortality
19 concluded that unfit individuals have an increased mortality regardless of BMI, while fit and overweight and
20 obese individuals have similar mortality risk as their normal weight counterparts (31). The ‘fat but fit’ theory,
21 the idea that it is ‘better to be fat and fit than thin and unfit’, has a growing evidence base in the general adult
22 population (32–35) and may also be true for older adults. It is suggested that individuals who are overweight or
23 obese are surviving longer than their normal-weight counterparts because in those that are “fat and fit” their
24 higher fitness or activity levels are somehow modifying the malignant mechanisms of adiposity.
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35 Understanding how physical activity and cardiorespiratory fitness influence the association of adiposity with
36 mortality may further our understanding of the obesity paradox and inform guidance on optimal weight, fitness
37 and activity levels in older adults. This review sought to investigate whether cardiorespiratory fitness and
38 physical activity could underlie the obesity paradox in older adults. It examines the association of BMI and
39 other adiposity markers with all-cause mortality in people aged 60 or over and whether cardiorespiratory fitness
40 or physical activity affects this relationship.
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46 METHODS

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50 This systematic review sought to identify papers examining the relationship between adiposity measures and all-
51 cause mortality that either adjusted or stratified for cardiorespiratory fitness or physical activity measures.
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53 Inclusion criteria included study design of prospective cohorts or randomised control trials, presence of at least
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7 one adiposity measure and presence of either a cardiorespiratory fitness or physical activity measure, and
8 outcome measure of all-cause mortality. Studies had to include at least one group of ≥ 1000 individuals aged 60
9 or older and have a minimum of two years follow-up. The age of 60 was used in concordance with the United
10 Nations agreed cut-off for older adults (38). Studies that included subjects aged over 60 but did not include
11 separate analysis for a group of subjects over aged 60 were excluded. A total of 15 papers met these criteria.
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14 15 16 Data Sources & Search Strategy

17 Systematic computerised searches of Medline (through OVID, 1946-2013), EMBASE (through OVID, 1974-
18 2013), the Cochrane Library (1990-2013) and Web of Science (1900-2013) were carried out between January
19 2014- January 2015. Key search terms used included fit*, exercise, physical activity, treadmill, walking,
20 exercise capacity, BMI, body mass index, adiposity, anthro*, waist*, obesity, weight, fat*, risk, morbidity,
21 mortality, and death.
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27 The titles and abstracts of 14731 references were examined to see if they met inclusion criteria. The full text of
28 596 of these papers was then further examined for inclusion. Snowballing from references of important papers,
29 grey literature searches and previous literature reviews were also used to yield a further 156 papers (figure 1).
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34 **INSERT FIGURE 1**
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37 Data extraction & Quality assessment

38 Data was extracted by DY (Dharani Yerrakalva) and RM (Ricky Mullis), and included study characteristics
39 (sample size, recruitment method, setting, trial design, follow-up length), patient characteristics (age range,
40 gender, ethnicity and concurrent diagnoses) and exposure and outcome details (definitions and methods of
41 recording), methods of analyses and summary estimates (relative risks or hazard ratios and their respective
42 confidence intervals). Quality assessment was done with modified versions of SIGN (39) and CASP checklists
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49 Data synthesis 50 51 52 53 54 55 56 57 58 59 60

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7 Due to heterogeneity between studies (especially methods of measuring physical activity and cardiorespiratory
8 fitness, variety of adiposity measure categories and different reference categories which are further discussed in
9 the discussion section and are outlined in tables 1-3) data synthesis by meta-analysis was not attempted.

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13 In order to allow easier comparison of studies, data from each included study was used to produce a graphical
14 representation of the relationship of adiposity markers with all-cause mortality. Separate figures were produced
15 for studies using BMI (figure 2-3), waist circumference (figure 4) and waist-hip ratio (figure 5). Additionally,
16 figures were produced separately for studies stratifying for cardiorespiratory fitness (figure 3) and those
17 adjusting for either cardiorespiratory fitness or physical activity (figure 2).

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22 The data needed to create these graphs was not obtainable from some of the included studies as findings were
23 presented in figures with only key summary estimates within the text of the article. Authors were contacted to
24 gain the additional data. Studies for which the data were not available are referred to in the text of the results
25 section, but not represented in the figures.

26 27 28 29 30 **RESULTS:**

31 32 33 **Characteristics of Included Studies**

34 35 36 **INSERT TABLE 1**

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40 A total of 15 studies met the inclusion criteria (*Table 1*). All studies examined the association of adiposity with
41 all-cause mortality, with three studies adjusting for measures of cardiorespiratory fitness (41–43) and 14 studies
42 adjusting for measures of physical activity. Two studies stratified for cardiorespiratory fitness (41,42) and none
43 stratified for physical activity.

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48 All included studies used BMI, and in nine studies this was the sole adiposity measure. BMI was measured by a
49 health professional in ten studies, and five studies used self-report. Six studies also used a central adiposity
50 measure. Four studies used waist circumference and three studies used waist-hip ratio (all measured by health
51 care professional).

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8 Three studies included cardiovascular fitness measures, all obtained by a medical professional. 14 studies used
9 physical activity measures, all with self-report questionnaires. Only two of these were validated physical
10 activity questionnaires. Ten studies only asked one question with regards to physical activity.
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14 All the studies adjusted for potential confounders, with most frequent being for age, smoking and alcohol (*Table*
15 2).
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22 All studies included both sexes. Nine studies were in Caucasian populations, with six studies in Asian
23 populations. Two studies (44,45) stratified participants into groups depending on the number of co-morbidities.
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27 Further heterogeneity was noted with regards to sampling methods, sample exclusions and response rates (*Table*
28 3).
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32 **INSERT TABLE 3**
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35 **Relationship Between BMI and All-Cause Mortality with Adjustment for Physical Activity or**
36 **Cardiorespiratory fitness**
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39 All but one of the included studies found that increasing adiposity either had no association or a negative
40 relationship with all-cause mortality (the obesity paradox) after adjustment for physical activity or
41 cardiorespiratory fitness (Figure 2 shows these relationships after adjustment in those studies where individual
42 data was available). Not all the studies documented pre-adjustment relative risks or hazard ratios. Hwang et al.
43 (46) was the only study to find a positive association between adiposity and all-cause mortality, but the highest
44 BMI group was BMI>25 and this was in an Asian population where BMI ranges are lower (BMI>23 is classed
45 as overweight).
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8 A BMI of less than 18.5 was consistently associated with the highest risk of death in the six studies which
9 included such a BMI group (*Figure 2*). Overall, being overweight conferred no survival disadvantage compared
10 to normal weight. Seven studies found no increased all-cause mortality risk with being 'overweight' (BMI 25-
11 30) compared to being 'normal BMI' (BMI 18.5-25) (41,45,47-51) and five studies found a survival advantage
12 to being 'overweight' compared to 'normal BMI' (44,52-55).
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16 11 studies included a BMI group of 'obese' individuals (BMI>30). The highest BMI classification for three of
17 the included studies contained a mixture of individuals that would be classified as overweight or obese
18 (42,45,52). There was no consistent disadvantage to being 'obese' compared to 'normal-weight'. Four studies
19 found obese individuals had better survival than normal-weight individuals (43,44,53,54), two that obese
20 individuals did slightly worse than normal-weight individuals (48,49) and three that there was no difference
21 (47,50,51).
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27 **Relationship between BMI and All-Cause Mortality with Stratification for Fitness**

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30 Both studies which stratified for cardiorespiratory fitness performed cross-product interactions tests which were
31 not statistically significant in the analyses of each adiposity-fitness combination (*Figure 3*). Both found that
32 BMI and central adiposity measures were highly inversely correlated with fitness measures and therefore there
33 were fewer higher adiposity individuals in the fittest groups (few 'fat but fit').
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37 Woo et al. (42) included an underweight group (BMI<18.5) that had significantly higher risk than any other
38 BMI group, with this risk highest in the unfit. Excluding this group, there was no clear association between
39 increasing BMI and increased mortality in any of the fitness strata. Similarly, Sui et al (41) found no clear
40 association between increasing BMI and mortality in either fitness strata.
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45 Both studies stratifying for cardiorespiratory fitness (41,42) found a greater survival benefit in being overweight
46 and fit compared to normal weight and unfit (*figure 3*).
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7 **Relationship between Waist Circumference and All-Cause Mortality with Adjustment for Physical**
8 **Activity or Cardiorespiratory Fitness**
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11 Four studies included waist circumference (*Figure 4*). Two studies found no clear association between waist
12 circumference and all-cause mortality (41,53) one (44) a positive relationship (strengthening after adjustment
13 for BMI) and one (49) a U-shaped distribution with highest mortality risk associated with the lowest (less than
14 73cm) and highest (more than 105cm) waist circumferences.
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19 **INSERT FIGURE 4**
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22 **Relationship between Waist-Hip Ratio and All-Cause Mortality with Adjustment for Physical Activity or**
23 **Cardiorespiratory Fitness**
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27 Lahmann et al. (52) found a U-shaped association between waist-hip ratio and all-cause mortality (*Figure 5*).
28 Price et al. (53) found the same for men but that waist-hip ratio was weakly positively associated with all-cause
29 mortality in women (with increased risk for waist-hip ratio 0.9-1.13). Conversely, Woo et al. (42) found
30 increased mortality risk with waist-hip ratio < 0.88.
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35 **INSERT FIGURE 5**
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38 **Health Stratification**
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41 Two studies (44,45) stratified participants into groups depending on how many comorbidities they had.
42 Guallar-Castillon (44) found that BMI correlated with survival most strongly in those with poor health status.
43 Schooling et al. (45) similarly found BMI > 25 was most strongly associated with survival with those with most
44 morbidity and least strongly associated with survival in the healthy group with no morbidity.
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DISCUSSION:

The observed relationships in the included studies suggest that in people aged 60 or over, increasing BMI was not consistently associated with increased mortality, before or after adjustment for physical activity or cardiorespiratory fitness. However, given that the adjustment for physical activity was predominantly based on subjective, unvalidated physical activity measures, adjustment for physical activity may be inadequate. Therefore, it is plausible that poor measurement of physical activity may contribute to the obesity paradox. Though all measures of cardiorespiratory fitness were objective, only three studies adjusted for this.

While the two studies which stratified for cardiorespiratory fitness (41,42) did not find that fitness had a significant impact on the relationship between excess adiposity and mortality, they did find that overweight and fit people had better survival than normal weight unfit people, suggesting that physical fitness may be a more important determinant of survival than being overweight in this age group. . In the two studies that stratified by health status, being overweight had a much stronger association with improved survival in people with the most morbidity.

Relationship between ‘fatness’ and ‘fitness’

The popularly conceptualised ‘fat but fit’ theory suggests that despite being obese, people with good levels of fitness may survive longer than their thin, unfit counterparts (21,33,34,56).

It has been hypothesised that increased cardiorespiratory fitness might switch on mechanisms of ‘healthy obesity’ (57,58) which is defined as absence of six cardiometabolic risk factors; elevated blood pressure, elevated triglyceride level, decreased HDL-C level (high density lipoprotein C), elevated glucose level, insulin resistance and systemic inflammation. Wildman et al. (59) estimates those with ‘healthy obesity’ form up to 35% in US populations.

Cardiorespiratory fitness leads to lower blood lipid levels which are usually higher in obesity (60–62). In a small study of 19 participants, Johnson et al. (63) found a 21% reduction in hepatic lipid concentration after four weeks of aerobic exercise training without any change in body weight or abdominal adipose tissue. Further, animal models suggest that healthy obese subjects have lower liver triglycerides levels and greater storage of triglycerides in adipose tissue improving insulin sensitivity (64,65). Further, in the fit and ‘healthy obese’,

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excess adipose tissue is thought to have some role in cardioprotective mechanisms (66) with larger coronary arteries seen in these subjects (67) and reduced systemic inflammation (68) through production of TNF-alpha (tumour necrosis factor-alpha) receptors which neutralise the harmful effects of TNF-alpha.

Other Explanations of the Obesity Paradox

As outlined in the introduction, multiple explanations have been suggested for the obesity paradox (5,8,16,69,70).

Though BMI has been widely criticised, it is still the most commonly used adiposity marker. Few studies used central adiposity measures, but when these were used, no consistent pattern emerged of association between increasing adiposity and mortality in this age group. . Only three of the studies in this review excluded patients who self-report recent weight loss at baseline or those who died in the first few years of follow-up in order to minimise the risk of reverse causality(51,53,71), but this had little impact on their results.

Although confounding by chronic diseases, smoking and alcohol is consistently cited as a possible contributor to the obesity paradox, included studies varied widely with how they dealt with comorbidities in attempts to limit confounding (table 3). Three studies documented no adjustment for comorbid disease (42,46,49). Only Stevens et al. (47) chose to exclude comorbidities such as cardiovascular disease, hypertension, and hypercholesterolaemia (intermediaries on causal pathway) and cancer at baseline thus making this a healthier sample. Some studies only showed analyses after adjustment for these diseases (41,51). However, with some of these diseases being on the causal pathway, this may have masked true associations. Most commonly studies showed analyses with and without adjustment for these diseases (43–45,48,52–54).

It is possible that co-morbidity plays an important role. Guallar-Castillon (44) suggests that healthy BMI may be a marker of adverse effects of adiposity, and in those with morbidity BMI largely reflects lean mass and therefore is a marker of nutritional status. Therefore, it may be better to consider distinct subsets of older adults categorised by health status (healthy , frail , and dying). If it were possible to divide the populations in this way,

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7 then it may be that the obesity paradox is only apparent in people with more disease – the findings of the two
8 studies that stratified for co-morbidity in this review support this hypothesis.
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10 11 12 13 **Quality Of Included Studies**

14 ***Representability of samples:*** Only eight studies were reported as population-based (43,44,46,48–50,52,53), only
15 four of these explicitly mention randomisation techniques, and these had variable response rates (40% to 71%)
16 (44,52). The remaining seven studies were volunteer-based convenience samples, half from cohorts of members
17 in receipt of particular health insurance (five of these ten studies).
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19 As a result, study participants were in general more highly educated, of higher socioeconomic status and
20 Caucasian (see Table 3) than the general population, so were under-representing the ‘frail’ older adults.
21 However, if attention is restricted to the population-based studies, there is still no consistent relationship
22 between BMI and mortality. Three studies reported an inverse relationship (44,48,53), four a U-shaped
23 relationship (41,49,50,52) and one a positive relationship (46). The two studies with the highest response rates
24 (over 70%) (44,49) found inverse and U-shaped relationships.
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32 ***Heterogeneity of samples across studies:*** Table 3 outlines the exclusions which were used in the included
33 studies. Some but not all the studies excluded those of BMI<18.5 and those with poorer mobility or who were
34 institutionalised, thus further excluding the ‘frailer older adults’.
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36 Further, the age range of the participants within the studies varied considerably. Very rarely are older adults
37 stratified for age given the often very small numbers of participants in the furthest extremes of age. This often
38 means that ‘older adults’, which could include someone of 60 or someone of 100, are put into one group to
39 maximise statistical power. It has been suggested that it would be more useful to stratify older adults by age
40 given the possible physiological differences under the bracket of older adults. In the studies included in this
41 review, all participants in the study by Price et al. (53) were over age 75 whereas Hwang et al. (46) excluded
42 people aged over 75. An arbitrary age cut-off to define older adults will never be globally satisfactory. A cut-
43 off of 60 is arguably too low for Western and Asian nations and too high for African nations. . However, 11 out
44 of the 15 studies had populations aged over 65 and there was no difference in observed relationships between
45 studies with populations aged over 60 and those over 65.
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7 Further sources of heterogeneity included race (Asian versus Caucasian populations), follow-up length and
8 variation in adjustments applied. Given the fact that Asian populations have different optimal BMI ranges and
9 classification of 'overweight' and 'obese' are different in these populations, this could have affected results.
10 Most studies had predominantly Caucasian populations (9 of those included). Only six included studies were in
11 Asian populations (2 Japan, 2 China, 2 Taiwan) but they did not give consistent results with regard to the pattern
12 of association.
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18 **Adiposity Measurement Quality:** Another problem relates to the quality of the adiposity measures. Self-report
19 adiposity measurement is much more common (more than half of included studies) than measurement by a
20 health care professional due to cost and time. This is likely to lead to misclassification of BMI and waist
21 circumference. However, studies using self-report measures gave similar overall results to those with
22 professionally obtained measures. Furthermore, in most studies these data were only collected at baseline, so
23 there is scope for considerable residual confounding due to misclassification over time. It has been speculated
24 that it is the change in weight with ageing that is crucial to mortality risk rather than the stand-alone
25 measurements of adiposity (6).
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32 In addition to the problems in measuring adiposity and physical activity outlined above, another issue is that the
33 studies used different BMI class ranges mixing overweight and obese, and normal weight with underweight, in
34 order to increase power. There was also often exclusion of underweight or obese groups due to small numbers;
35 these most important groups were therefore often the most under-represented.
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40 **Physical Activity Measurement Quality:** Further possible explanations for the findings here relate to the quality
41 of assessment of physical activity in included studies. Only two out of the 13 included studies which included
42 physical activity measures used validated questionnaires (52,54) and nine studies only asked one question with
43 regards to physical activity in their 'self-report questionnaires'. However, the three studies that did use
44 validated fitness measures (41–43) and two studies using validated physical activity questionnaires still found
45 that the obesity paradox persisted.
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51 **Overall Assessment of Study Quality:** All the studies included large cohorts of more than 1000 participants and
52 more than two years follow-up. Despite this, the quality of included studies varied considerably (Tables 1-3),
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6 therefore limiting the comparability of studies and decreasing the certainty of associations observed. The main
7 impact of this was it would have been unhelpful to perform a meta-analysis. Overall, the poor quality of
8 physical activity measures used (subjective and often unvalidated measures) makes it difficult to conclude with
9 certainty that physical activity is not affecting the relationship between adiposity markers and all-cause
10 mortality. Therefore, there is a need for further studies using validated measures. Further multiple
11 methodological issues are highlighted above which suggest that other explanations of the obesity paradox are
12 still not being adequately accounted for.
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19 **CONCLUSIONS**

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23 *Is this a true paradox and what is the contribution of cardiorespiratory fitness and physical activity?* This
24 systematic review is novel in that it is the first in older adults to examine the association of adiposity markers
25 with all-cause mortality when cardiorespiratory fitness or physical activity is taken into account. This review
26 found a limited number of studies reporting on the association of adiposity markers with all-cause mortality
27 which took into account measures of cardiorespiratory fitness or physical activity, and even fewer which used
28 validated measures. We still do not know if this is a true obesity paradox and what the optimal adiposity level is
29 in older adults. All but one of the included studies demonstrated a paradox, and there is a good body of
30 evidence in the literature in agreement with the existence of the paradox, but the general tone of commentary in
31 the literature is of scepticism due to methodological concerns and lack of clarity over possible mechanisms.
32 This review confirms that these methodological concerns have yet to be completely addressed, and highlights
33 the inadequate measurement of (and therefore adjustment for) physical activity as an additional problem.
34 However, this review also highlights the potential of cardiorespiratory fitness to be contributing to the obesity
35 paradox, as well as the need for increased and better quality work in this area given the quality and number of
36 included studies. Specifically, there are currently no studies examining the association between adiposity and
37 all-cause mortality with stratification for physical activity, and only two stratifying for cardiorespiratory fitness.
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49 *What should those designing future studies in this area consider?* Particular attention should be paid to
50 increasing the quality of studies in this area. Many of the design problems could be addressed by using
51 emerging datasets with higher quality measures of physical activity, cardiorespiratory fitness and adiposity. In
52 particular, the use of objective verifiable measures of physical activity should now be possible. Further,
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7 consideration of stratification for different types of older adults or studies in particular subsets of older adults
8 may be useful given the diverse nature of someone that is 'old' (e.g. health stratification for healthy and frail,
9 and stratification for age). Finally, future stratification studies should consider risk reduction analysis according
10 to levels of fitness within BMI subgroups to investigate whether fitness confers greater risk-reduction benefit in
11 those who are overweight or obese compared to normal-weight counterparts.
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16 **Public health message going forward:** It is currently not possible to draw any conclusions as to what might be
17 an optimal weight in older people. However, physical activity and fitness (22,23,25) alter cardiovascular
18 intermediaries on the causal pathway between adiposity and mortality (72–74), are associated with better
19 survival, health status and functional capacity in older people (21). Therefore as the public health message on
20 obesity in older people remains unclear, the emphasis on increasing physical activity and cardiorespiratory
21 fitness in spite of weight change may be more important.
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LIST OF TABLES

Table 1: Major Characteristics of Included Studies.

LEGEND: Table 1 shows the major characteristics of included studies. This table highlights pertinent information regarding included studies including age ranges, follow-up length, sex, adiposity measures, physical activity measures and cardiorespiratory fitness measures.

Table 2: A Table to Show the Confounding Variables that were Adjusted for in the Individual Studies

LEGEND: This table shows model adjustments used in analyses within each studies where numerical data was tabulated. The adjustments used in models with and without physical activity or cardiorespiratory fitness are documented. These models correspond to those used in Figures 2-5. Physical activity or cardiorespiratory fitness adjustment is indicated in capital letters and the method in brackets.

Table 3: Characteristics of Study Populations

LEGEND: Table 3 shows the major characteristics of study populations of included studies.

LIST OF FIGURES

Figure 1: Figure Showing Search Strategy Methodology

Figure 2: Figure showing the relationship between all-cause mortality and BMI adjusted for physical activity or cardiorespiratory fitness.

LEGEND: Figure 2 shows the relationship between BMI and all-cause mortality after adjustment for cardiorespiratory fitness (Sui et al. and Woo et al.) or physical activity (all other studies) for included studies with enough extractable data. Data included here is from Sui et al.(41), Woo et al.(42), Guallar-Castillon et al.(44), Schooling et al (45), Kvamme et al (49), Lahmann et al.(52), Nagai et al (50), Snih et al(43), Price et al.(53), Tamakoshi et al. (51), Wu et al. (55), Janssen et al. (54), Corrada et al. (48), Hwang et al (46). Other adjustments used in each individual study can be found in Table 2. Relationship lines in orange denote both sexes, in red denote females and in blue denote males. Dashed relationship lines denote pre-adjustment, and solid lines denote post-adjustment. Some studies did not provide combined sex data or pre-adjustment data.

Figure 3: Figure of Studies Demonstrating the Relationship between BMI and All-Cause Mortality with Stratification for Fitness.

LEGEND: Figure 3 is a graphical representation of the findings of the only two studies (41,42) that stratified for cardiorespiratory fitness. The first graph shows data from Sui et al. (43), cohort from the Aerobics Center Longitudinal Study. Hazard ratios for fit groups are in green and unfit groups in red with vertical lines representing 95% confidence intervals The second graph is data from Woo et al.(42), a Hong Kong community cohort using 6-metre walking speed as a cardiorespiratory fitness surrogate measure. Hazard ratios for high fitness groups are in green, moderate fitness in yellow and low fitness in red with vertical lines representing 95% confidence interval. Other adjustments used in individual studies can be found in Table 2.

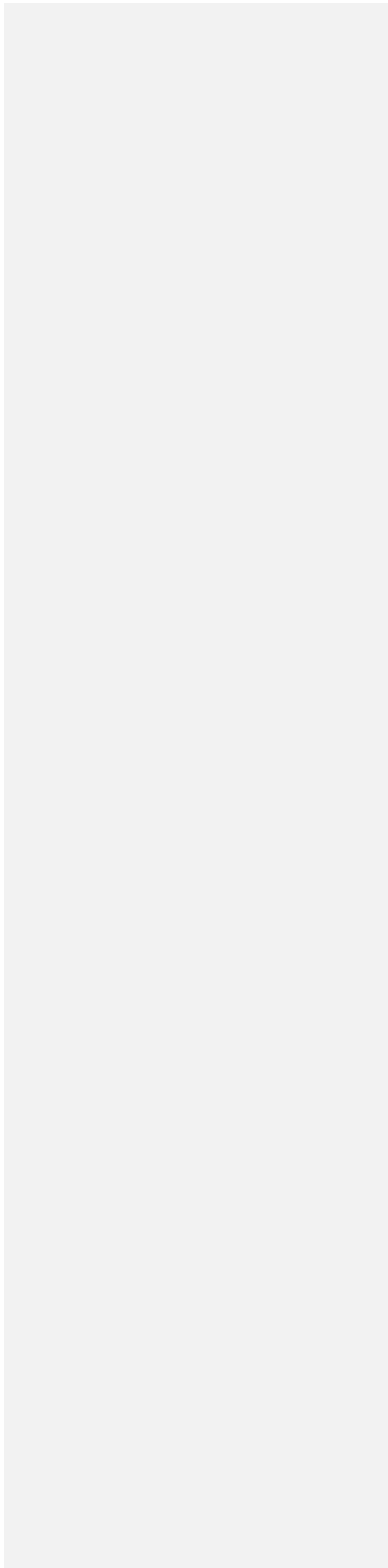
Figure 4: Figure of Studies Demonstrating the Relationship between Waist Circumference and All-Cause Mortality after Adjustment for Cardiorespiratory Fitness or Physical Activity.

LEGEND: Data included here is from Sui et al. (41), Guallar-Castillon et al.(44), Kvamme et al (49), Price et al.(53). Other adjustments used for individual studies can be found in Table 2. Relationship lines in orange denote both sexes, in red denote females and in blue denote males. Dashed relationship lines denote pre-adjustment, and solid lines denote post-adjustment. Some studies did not provide combined sex data or pre-adjustment data.

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Figure 5: Figure of Studies Demonstrating the Relationship between Waist-Hip Ratio and All-Cause Mortality after Adjustment for CRF or Physical Activity.

LEGEND: Data included here is from Price et al.(53), Woo et al.(42), Lahmann et al.(52), Other adjustments used in Individual studies can be found in Table 2. Relationship lines in orange denote both sexes, in red denote females and in blue denote males. Dashed relationship lines denote pre-adjustment, and solid lines denote post-adjustment. Some studies did not provide combined sex data or pre-adjustment data.



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TABLE 1: Major Characteristics of Included Studies.

First Author	Year of publication	Cohort (Population-based or Volunteer based)	Average Follow-up (years)	Country	Sample Size & Age Range	Adiposity Measures	Physical Activity/Cardiorespiratory Fitness Measure
Corrada (48)	2005	Leisure World Cohort Survey (population)	13	USA	n=13978 (aged>65)	BMI	Questionnaire
Guallar-Castillon(44)	2009	Multistage Cluster Census in Spain (population-based)	5.7	Spain	n=3536 (aged>60)	BMI, WC	Questionnaire
Hwang (46)	2009	Six-Community Hypertension Intervention Project Study (population-based)	23	Taiwan	n=1568 (aged>60)	BMI	Questionnaire
Janssen (54)	2007	Cardiovascular Health Study (population)	9	USA	n=4968 (aged >65)	BMI	Questionnaire
Kvamme (49)	2011	Norway-wide survey (population-based)	9.3	Norway	n=16711 (aged >65)	BMI, WC	Questionnaire
Lahmann (52)	2002	Malmö Diet and Cancer Study, Sweden (population-based)	5.7	Sweden	n=12107 (aged>60)	BMI, WHr	Questionnaire
Nagai (50)	2010	Ohsaki National Health Insurance Beneficiaries (population-based)	12	Japan	n=15746 (aged>65)	BMI	Questionnaire
Price (53)	2006	Health and social assessment of older persons, 106 GP practices UK (population-based)	5.9	UK	n=14833 (aged >75)	BMI, WHr , WC	Questionnaire
Schooling (45)	2006	Chinese Elderly Health Centres (volunteer)	4.1	China	n=56167 (aged>65)	BMI	Questionnaire
Snih (43)	2002	Hispanic Established Population for the Epidemiological Study of the Elderly (population-based)	5	USA	n=3050 (aged>65)	BMI	Timed walk
Stevens (47)	2002	American Cancer Society Cancer Prevention Study (volunteer)	12	USA	n=7917(aged 65-74) n=1771(aged75-84) n=128 (aged >85)	BMI	Questionnaire
Sui (41)	2007	Aerobics Center Longitudinal Study (volunteer)	12	USA	n=2603 (aged>60)	BMI, WC	Maximal treadmill test
Tamakoshi (51)	2009	Japan Collaborative Cohort Study (volunteer)	11.2	Japan	n=26747 (aged >65)	BMI	Questionnaire
Woo (42)	2012	Hong Kong Community Cohort (volunteer)	7	China	n=4000 (aged>65)	BMI, WHr	Walking speed test
Wu (55)	2014	Taipei Geriatric Health Examination Database Volunteers (volunteer)	3.3	Taiwan	n=77541 (aged>65)	BMI	Questionnaire

Table 2: A Table to Show the Confounding Variables that were Adjusted for in the Individual Studies

First Author	Adjustments in Analyses	
	Model without physical activity or cardiorespiratory fitness adjustment	Model with physical activity or cardiorespiratory fitness adjustment
Corrada (48)	<i>Model 1:</i> Age, sex, smoking	<i>Model 2:</i> Age, sex, smoking and PHYSICAL ACTIVITY (1 self-report question)
Guallar-Castillon (44)		Age, sex, education, smoking, alcohol, COPD, cancer, untreated cataracts, depression, dementia and PHYSICAL ACTIVITY (1 self-report question).
Hwang (46)		Age, education, alcohol, smoking status and PHYSICAL ACTIVITY (questionnaire)
Jannsen (54)	<i>Model 1:</i> Age, sex, race	<i>Model 2:</i> Age, sex, race, socioeconomic status, smoking and PHYSICAL ACTIVITY (validated questionnaire)
Kvamme (49)		Age, study site, smoking, education, marital status and PHYSICAL ACTIVITY (1 self-report question)
Lahmann (52)		Age, height, smoking and PHYSICAL ACTIVITY (validated questionnaire)
Nagai (50)	<i>Model 'Age-smoking adjusted':</i> Age, smoking	<i>Model 'multivariate HRs 1':</i> Age, weight change since age 20, education, marital status, smoking, alcohol, kidney disease, liver disease and PHYSICAL ACTIVITY (2 self-report questions)
Price (53)	<i>Model 2:</i> Age, height, serious illness, depression, cognitive impairment, unexplained weight loss >3.2kg, housing type, smoking, alcohol	<i>Model 3:</i> Age, height, serious illness, depression, cognitive impairment, unexplained weight loss >3.2kg, housing type, smoking, alcohol, falls in past 6 months, previously diagnosed cancer, diabetes, cardiovascular or respiratory diseases, respiratory or angina symptoms, sitting systolic blood pressure, number of ADLs unable to do and PHYSICAL ACTIVITY (1 self-report question)
Schooling (45)		Age, sex, education, ever drinking alcohol, ever smoking, monthly personal expenditure, housing and PHYSICAL ACTIVITY (questionnaire)
Snih (43)		Age, sociodemographic variables, functional disability, smoking, medical conditions and CARDIORESPIRATORY FITNESS (timed walk)
Stevens (47)		Age, education, alcohol consumption and PHYSICAL ACTIVITY (1 self-report question)
Sui (41)	Model 1: Age, sex, smoking, hypercholesterolaemia, hypertension, diabetes, cardiovascular disease, abnormal ECG, family history of cardiovascular disease/cancer	Model 2: Age, sex, smoking, hypercholesterolaemia, hypertension, diabetes, cardiovascular disease, abnormal ECG, family history of cardiovascular disease/cancer and CARDIORESPIRATORY FITNESS (treadmill test)
Tamakoshi (51)	Model 'age-adjusted': Age	Model 'multivariate-adjusted': Age, smoking, alcohol, sleep duration, stress, education, marital status, green vegetables, stroke, MI, cancer and PHYSICAL ACTIVITY (1 self-report question)
Woo (42)	Model 1: Age, sex, medical history (diabetes, stroke, hypertension, myocardial infarction, angina, chronic heart failure), smoking, cardiovascular medication	Model 2: Age, sex, medical history (diabetes, stroke, hypertension, Myocardial infarction, angina, chronic heart failure), smoking, cardiovascular medication and CARDIORESPIRATORY FITNESS (walking speed)
Wu (55)		Age, sex, marital status, education level, smoking, alcohol consumption, PHYSICAL ACTIVITY (1 question)

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TABLE 3: Characteristics of Study Populations
(ND=not documented)

First Author	Sample Exclusions	Sampling Methods	Reported Overrepresented in population	Baseline year	Response rate
Corrada (48)	Died in 1st 5 years of follow-up	Respondents to questionnaire sent to all residents in retirement community (Leisure World Laguna Hills)	Caucasian, educated, upper-middle class	1983-1985	61%
Guallar-Castillon (44)	BMI<18.5	Probabilistic sampling by multistage clusters (census sections were chosen at random within each cluster)	ND	2000-2001	71%
Hwang (46)	Age>75, bedridden, died in 1st 3 years of follow-up, cancer	Stratified systematic clustering sampling, nationwide, population -based survey across 6 communities in Taiwan	ND	1982	ND
Janssen (54)	BMI<18, institutionalised, required proxy questionnaire	Washington and Pittsburgh only, population-based study, sampled from Medicare eligibility lists	Caucasian	1989-1990	ND
Kvamme (49)	Too frail to get to centre, follow-up<1 year	All aged >65 in two areas in Norway (Tromso and North- Trøndelag) sent questionnaire	ND	1994-1997	70%
Lahmann (52)	Nil	Selected randomly from municipal register of city of Malmo (Sweden), sent questionnaire	ND	ND	40%
Nagai (50)	Cancer/MI/Stroke	Questionnaire to all NHI health insurance beneficiaries in Ohsaki Public Health Centre catchment area	ND	1994	95%
Price (53)	Institutionalised, terminally ill, cancer diagnosis	One randomized arm of 'trial of health and social assessment of older persons,' study across 53 General Practices in UK, random assignment	ND	ND	ND
Schooling (45)	Nil	Elderly health centres self-referral	ND	1998-2000	96%
Snih (43)	Nil	Area probability sampling procedures, door-to-door screening of Mexican-Americans in Texas/Colorado/New Mexico/Arizona	ND	1993-1994	83%
Stevens (47)	Smokers, Afro-Caribbean, weight loss at baseline, cardiovascular disease, stroke, cancer	"Convenience sample", volunteers recruited into American Cancer Society Cancer Prevention Study	Caucasian middle-class	1959-1960	ND
Sui (41)	BMI<18.5, maximal treadmill<85% of predicted	Volunteers referred from employers/physician/self into Aerobics Center Longitudinal Study	Men, Caucasian, well-educated	1979-2001	ND
Tamakoshi (51)	Nil	Multicentre, collaborative study in which 24 institutions voluntarily participated with self-administered questionnaire	ND	1988-1990	ND
Woo (42)	Can't walk independently, bilateral hip replacements, medical condition with unlikely survival >4 years	Self-recruitment from notices in care home/social centres in Hong Kong	Higher educational level than normal.	2001-2003	ND
Wu (55)	Nil	Volunteer recruitment from elderly residents of Taipei attending for standard annular physical examination program run by local government	ND	2006-2010	ND

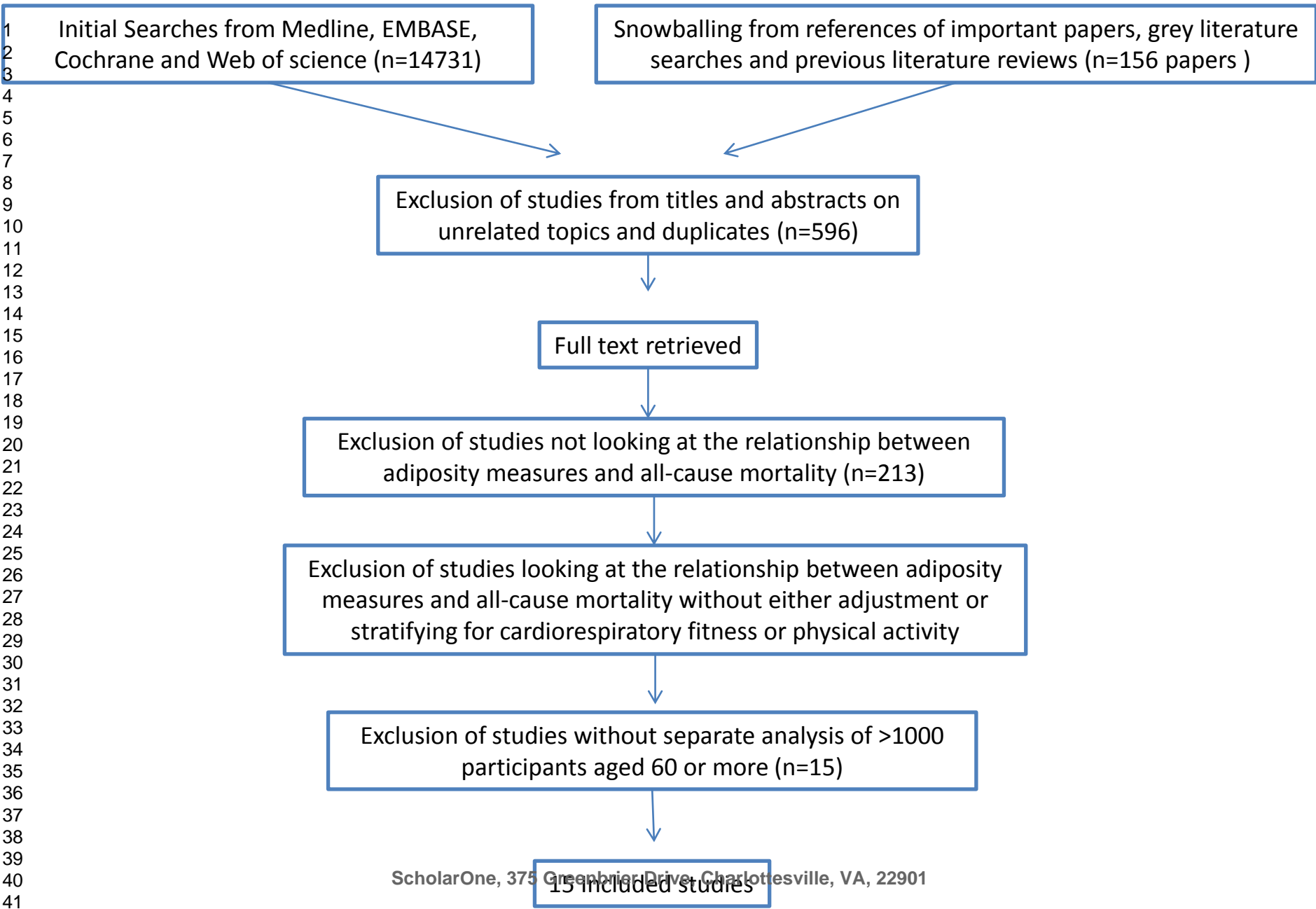


FIGURE 2: Figure showing the relationship between all-cause mortality and BMI adjusted for physical activity or cardiorespiratory fitness.

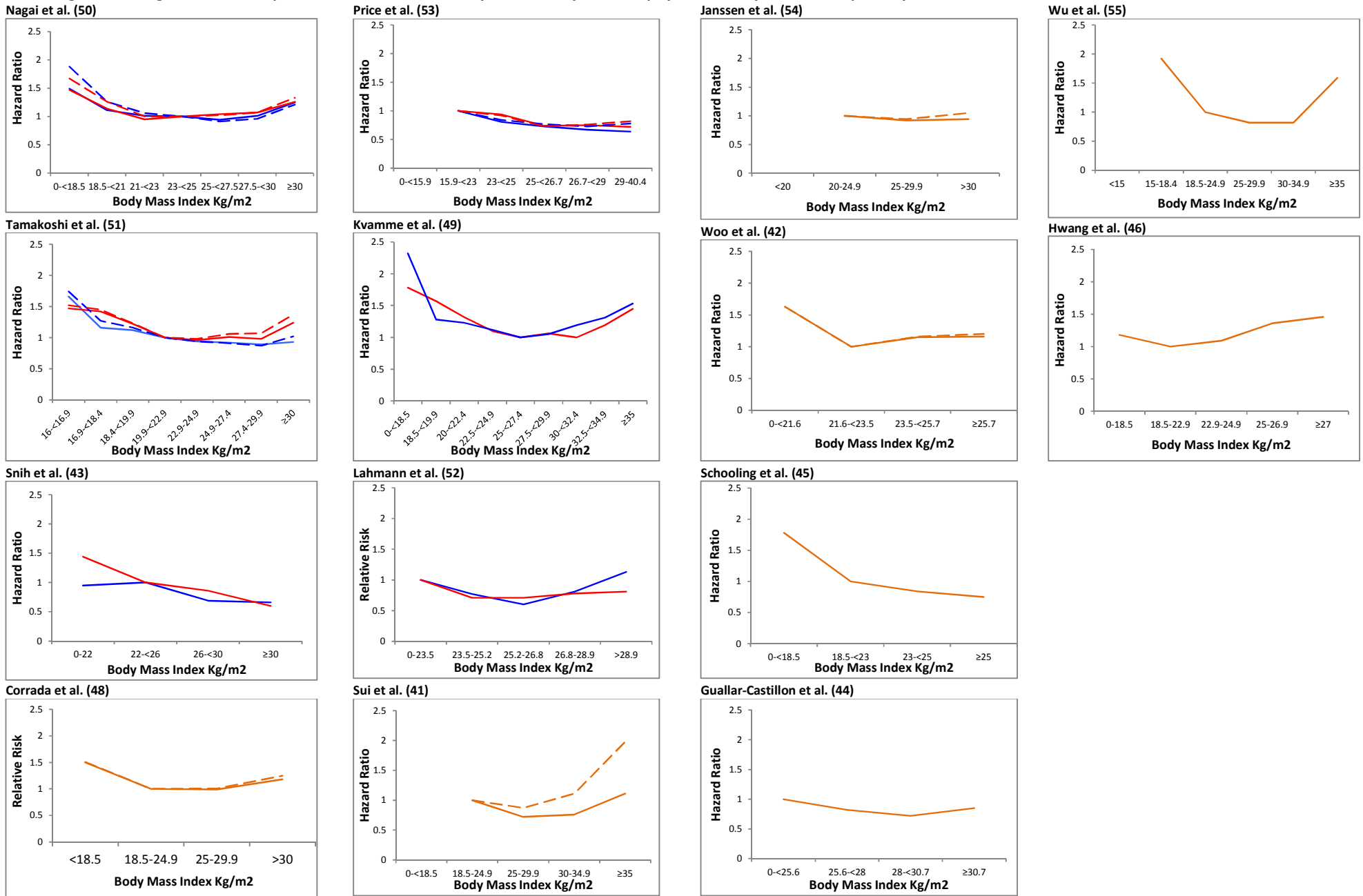
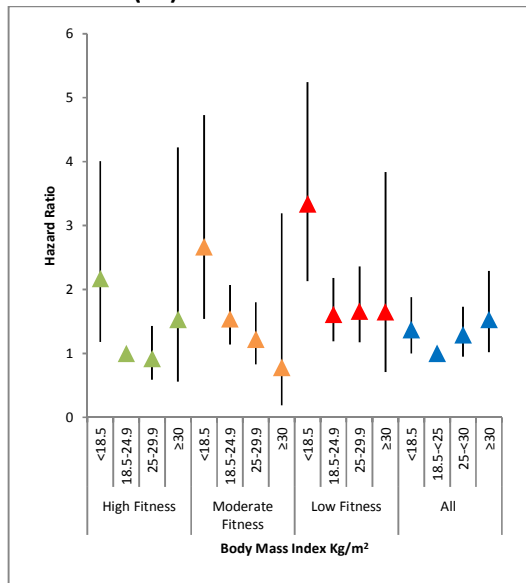


Figure 3: Figure of Studies Demonstrating the Relationship between BMI and All-Cause Mortality with Stratification for Fitness.

Woo et al. (42)



Sui et al. (41)

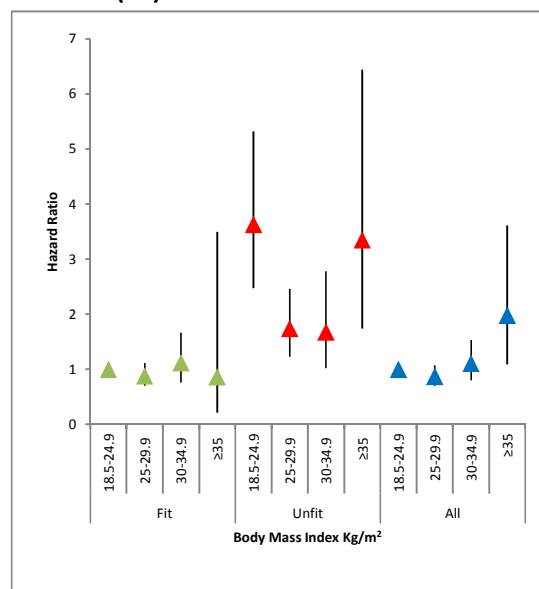
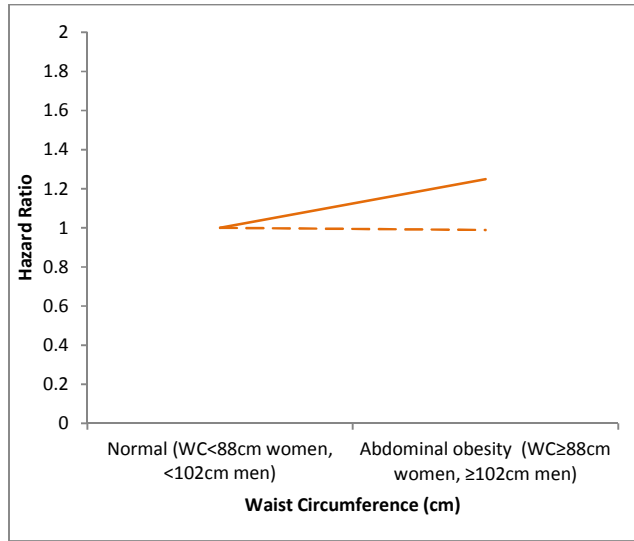
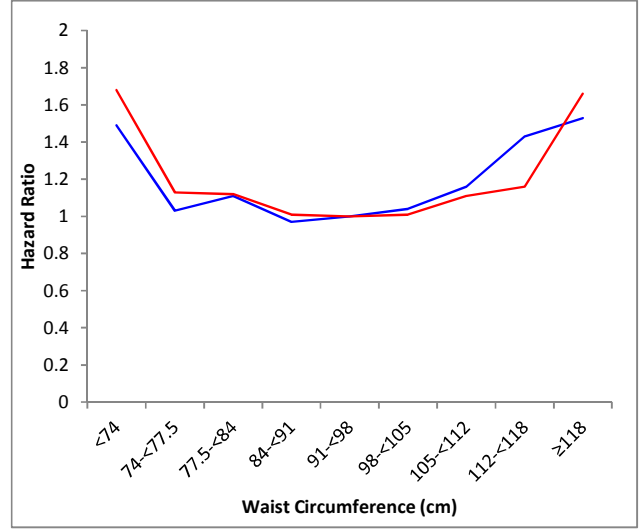


Figure 4: Figure of Studies Demonstrating the Relationship between Waist Circumference and All-Cause Mortality after Adjustment for Cardiorespiratory Fitness or Physical Activity.

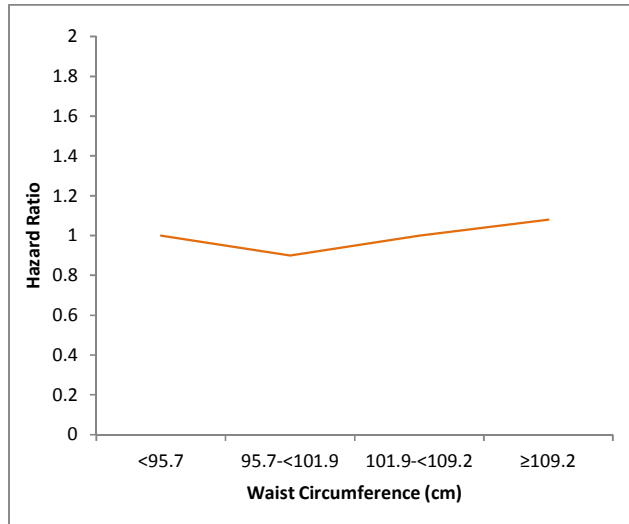
Sui et al. (41)



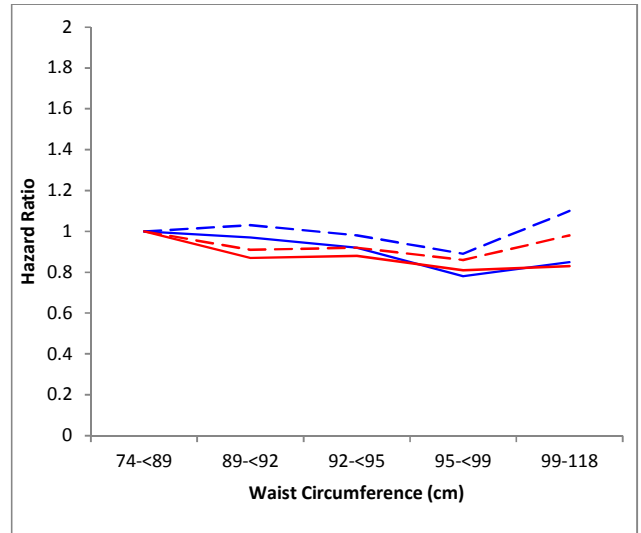
Kvamme et al. (49)



Guallar-Castillon et al. (44)



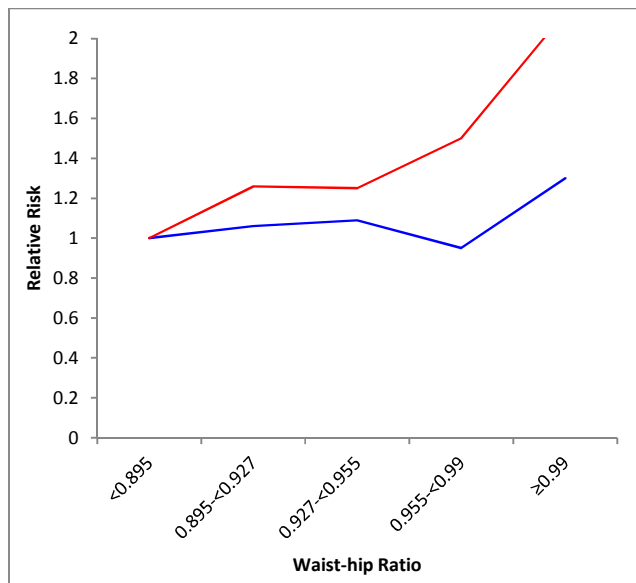
Price et al. (53)



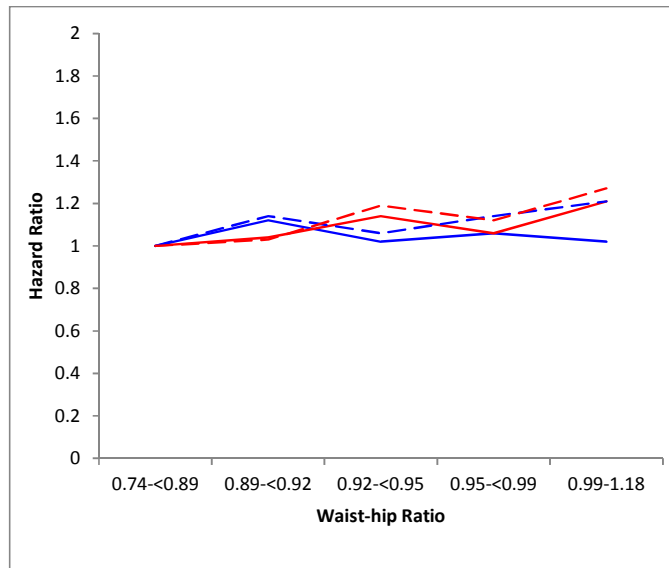
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Figure 5: Figure of Studies Demonstrating the Relationship between Waist-Hip Ratio and All-Cause Mortality after Adjustment for Cardiorespiratory Fitness or Physical Activity.

Lahmann et al. (52)



Price et al. (53)



Woo et al. (42)

