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The Association between Body Mass Index and All-Cause Mortality: A Meta-Analysis

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***Abstract*---**Associations between body mass index (BMI) and mortality can help to estimate the public health impact, including mortality by all-cause. However, the association between BMI and all-cause mortality is still unclear. This study aimed to review the association between body mass index with all-cause mortality. Articles that reported hazard ratio (HR) for all-cause mortality using standard BMI categories of general populations of adults were selected from the following databases including PubMed, ProQuest, Springer link, Science direct, and Google scholar for English language articles published from 2000 until 2021. Twelve studies were included in this study. Random-effects summary all-cause mortality HRs were 1.83 (95% CI, 1.60-2.10) for underweight, 0.81 (95% CI 0.74-0.88) for overweight, and 1.09 (95% CI, 0.89-1.34) for obesity. Being overweight may decrease the risk for all-cause mortality while being underweight suggests increased risk. There is no association between obesity and the risk of all-cause mortality.

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***Keywords*---**all-cause mortality, body mass index, cohort, meta-analysis.

Introduction

The worldwide prevalence of overweight and obesity is high and is increasing [1, 2]. WHO estimates that more than 1.3 billion adults worldwide are overweight, defined by WHO as a body-mass index (BMI) of 25–<30 kg/m^2, and a further 600 million are obese (BMI ≥30 kg/m^2) [3]. Many general population cohort studies over the past century have reported that excess adiposity (usually estimated with BMI is associated with an increased risk for all-cause death [4–6]. Overweight and obesity are clustered with many metabolic abnormalities, and the prevalence of morbid obesity is increasing in the general population worldwide [7]. It is well established that obese people defined as having a body-mass index (BMI) (the weight in kilograms divided by the square of the height in meters) of 30.0 or more — have increased death rates from heart disease, stroke, and many specific cancers [6], the strength of the relationship between a high BMI and all-cause mortality remains uncertain, as does the optimal BMI concerning mortality [5]. A recent systematic review has indicated that being overweight may modestly decrease the risk of death, and that grade I obesity (BMI of 30–34.9) may not increase the risk of death [8]. However, some studies stated that obesity is a well-known risk factor for the development of cardiovascular disease (CVD) and adversely affects cardiovascular hemodynamics, structure, and function [9].

The appearance of controversy may arise in part because studies of body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) and mortality have used a wide variety of BMI categories and varying reference categories, which can make findings appear more variable than when standard categories are used and also can make it difficult to compare and synthesize studies [8]. In this study, we used the National Heart, Lung, and Blood Institute's terminology with categories of underweight (BMI of <18.5), normal weight (BMI of 18.5–<25), overweight (BMI of 25–<30), and obesity (BMI of ≥30).

Appropriate analyses of large-scale studies with prolonged follow-up generally indicate that both overweight and obesity are associated with increased mortality, as is underweight. Therefore, this meta-analysis aimed to investigate the association between body mass index and all-cause mortality.

Methods

This was a meta-analysis of cohort studies that examines the association between BMI categories and all-cause mortality. The BMI categories used were underweight, overweight, and obesity compared to normal BMI. Article searches for this meta-analysis were using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline [10].

Searching Strategy

A comprehensive search was conducted to find relevant articles from electronic databases and grey literature published between 2000 and 2021 in English language articles. Electronic databases PubMed, ProQuest, Springer link, Science direct, and Google scholar were utilized for searching relevant articles. Literature searches were carried out to identify studies investigating the association between body mass index and all-cause mortality. An initial search was performed based on the framework of PICO (participants, comparison, intervention, and outcomes) and key terms. The following key terms were used, including "body mass index"[Mesh] OR “body mass index”[tiab] AND "body mass index "[tw] OR "BMI"[tw] AND "all-cause mortality"[Mesh] AND "all-cause mortality"[tiab] AND “all-cause mortality”[tw] AND “cohort” [Mesh] OR “cohort”[tw] AND "cohort"[tiab].

Inclusion and Exclusion Criteria

The inclusion criteria for this meta-analysis were, articles that reported HRs for all-cause mortality using standard body mass index (BMI) categories of general populations of adults. Articles will be excluded if not cohort, do not contain a hazard ratio, the cause of death was specific.

The Selection of Study

A screening process was conducted by two authors independently. In the first stage, reviewers independently extracted information from potentially relevant titles and abstracts in the studies. The screened studies were then included in the second stage for a review of the full text. Again, independently, two authors read and evaluated the full-text articles based on predefined exclusion and inclusion criteria. Finally, two authors compared the results, and any differences were resolved by reaching a consensus. Through this process, articles qualifying for meta-analysis were included.

Extraction of Data

Two authors independently extracted data from included articles into the structured table. The extracted data consisted of the first author, year of publication, study design, settings, country, mean participant age, sample size, year of follow-up, BMI categories, hazard ratio with CI 95%, and adjusted factors within the study.

Bias and Quality Assessment

This study used Cochrane Collaboration’s Risk of Bias tool in Non-Randomized Studies-of Interventions (ROBINS-I) to evaluate the risk of bias in the included studies by two authors independently. The risk of bias was examined in the Cochrane Risk of Bias tool following these criteria: Bias due to confounding, Bias in the selection of participants into the study, Bias in the classification of interventions, Bias due to deviations from intended interventions, Bias due to missing data, Bias in the measurement of the outcome, and Bias in a selection of the reported result or bias publication [11]. In addition, the risk of bias for each domain could be rated in three categories: high risk, low risk, and unclear.

Statistical Analysis

By utilizing Review Manager (REVMAN) 5, statistical analysis was performed to inspect the effect of BMI on mortality rate. Extracted data, including the hazard ratio and CI 95% were entered into REVMAN. The effect size was calculated as a hazard ratio with a confidence interval of 95% and a two-sided p-value less than 0.05, signifying a statistical significance difference between groups. The pooled hazard ratio was utilized to estimate the effect of BMI on mortality rate. To provide more detailed results, the authors performed subgroup analyses based on the studies' characteristics. The following subgroup was included sample size divided into general, male and female populations. The heterogeneity between studies was measured statistically by using the intuitive index (I^2). An intuitive index is a total variation across studies that describe the percentage because of heterogeneity instead of the error of the sample [12]. An I^2 value of more than 50% indicates a substantial heterogeneity level [13]. Random effect analysis models are used if heterogeneity is detected by more than 50%[14]. Publication bias was assessed by funnel plot asymmetry test. The symmetrically distributed shape of funnel plots indicates no potential publication bias; otherwise, the asymmetrical shape of funnel plots signifies potential publication bias [15].

Results

A total of 1435 published articles were collected from online databases, including PubMed, ProQuest, Science Direct, Springer Link, and Google scholar. All articles had published from 2000 to 2021. After deleting the identical ones, 649 abstracts were obtained. After the review of the abstract, 19 articles were chosen for review of the full text. Besides, 7 articles were excluded for several reasons, e.g., not containing hazard ratio, all BMI variables were measured with non-standart WHO categories. Twelve articles were selected for qualitative synthesis. Finally, 12 articles were eligible for inclusion criteria. Figure 1 reveals the PRISMA flowchart of the article selecting process.

Included Studies Characteristics

The included studies' characteristics can be found in Table 1. The study's characteristics consisted of the author, years of publication, country, study design, sample size, duration of follow-up, hazard ratio with CI 95%, and adjusted factors. Five studies were carried out in Korea, two in China, one in Canada, one in China-Taipei, one in Austria, one in Taiwan, and one in Denmark. Overall, 1,560,948 respondents were included in this study from all articles. The longest year of followed up was 20 years. Meanwhile, the shortest was 1 year.

The Association between BMI and All-cause Mortality

Table 1 displays the effect size and 95%CI of the included Studies. The association between BMI and all-cause mortality was evaluated in 12 studies. Due to significant heterogeneity, a random effect model was employed to evaluate the differences in effect BMI on all-cause mortality between the control (BMI normal) and intervention group. The denominator for BMI was underweight (BMI of <18.5), overweight or pre-obesity (BMI of 25–<30), and obesity (BMI of >30) were calculated then compared to normal weight (BMI of 18.5–<25). We performed the subgroup analysis based on gender (mix/ general (male and female), female only, and male-only). The pooled effect size of the hazard ratio of the underweight category was 1.83 (95% CI 1.60-2.10), and it was statistically significant (p<0.00001), favoring the control group. There was high heterogeneity between studies, and it was statistically significant (I^2= 95%; p<0.00001) (figure 2). The results of the publication bias assessment showed a symmetrical funnel plot indicating there is no publication bias existed (figure 3).

The pooled effect size of the hazard ratio of overweight was 0.81 (95% CI 0.74-0.88), and it was statistically significant (p= 0.<00001), favoring the overweight group. There was high heterogeneity between studies, and it was statistically significant (I^2 = 92%; p<0.00001) (figure 4). The results of the publication bias assessment showed a symmetrical funnel plot indicating there is no publication bias existed (figure 5).

The pooled effect size of the hazard ratio of obesity was 1.09 (95% CI 0.89-1.34), and it was statistically not significant (p= 0.42), favoring slightly the obesity group. There was high heterogeneity between studies, and it was statistically significant (I^2 = 68%; p= 0.008) (figure 6). The results of the publication bias assessment could not be determined because of the odd of number studies or articles (figure 7).

Discussion

In this study, we analyzed the association between three categories of body mass index including underweight, overweight, and obesity with all-cause mortality. Our meta-analysis results showed that being overweight can reduce all-cause mortality. There is a meta-analysis study with a population of older nursing home residents which suggests the same result, a meta-analysis by Veronese (2015) stated that compared with normal weight, all-cause mortality HRs were 0.85 lower in overweight [16]. Orpana et al., (2010) also confirming that being underweight is a clear risk factor for mortality, and showing that when compared to the acceptable or normal BMI category, overweight appears to be protective against mortality. In obesity class, I was not associated with an increased risk of mortality

This meta-analysis stated that being underweight can increase the risk of all-cause mortality. A study by Corrada (2006) also stated similarly that relative to normal weight, being underweight (relative risk (RR) = 1.51) was associated with increased mortality [17]. The "low-normal weight, decreasing" subgroup had the highest mortality risk, followed by the "mid-normal weight, decreasing," the "high-normal weight, decreasing," and the "overweight, stable" subgroups. This is also consistent with prior observations showing that weight loss in underweight individuals is associated with an increased mortality risk than in normal-weight or overweight/obese individuals [18,19]. The reason for increased mortality among the underweight maybe include being lean (nutrient deficiency, frailness, and reduced functional status), illness, older age, and being smokers [20]. The association between lowest BMI categories and all-cause mortality seem to be partly explained by undiagnosed pre-existing diseases and residual bias due to smoking, though it cannot explain the complete pattern yet. There is a debate if the increased risks among the leanest persons may be due to reverse causation generated by underlying diseases or misclassification of smoking status. Both pre-existing diseases and smoking can lead to a reduction in body weight and both are positively associated with mortality [21, 22, 23].

As for obesity, our results suggest there is no association between BMI and all-cause mortality. This result is different from the conclusion of both meta-analysis study by Flegal and The Global BMI Mortality Collaboration [21, 24], which stated that relative to normal weight, both obesity (all grades) were associated with significantly higher all-cause mortality. Our result could be compromised by the low number of studies or articles included in meta-analysis. A recent studies suggest that the effect of obesity on the mortality rate is reduced in the elderly population, with a higher mortality in those with a low BMI (Flegal *et al.*, 2007; Murayama *et al.*, 2015; The Global BMI Mortality Collaboration *et al.*, 2016). Meta-analysis by The Global BMI Mortality Collaboration *et al.*, (2016) suggest that the associations of both overweight and obesity with higher all-cause mortality were broadly consistent in four continents (Asia, Australia and New Zealand, Europe, and North America).

According to Jee *et al.*, (2006) underweight, overweight, and obese men and women had higher rates of death than men and women of normal weight. The association of BMI with death varied according to the cause of death and was modified by age, sex, and smoking history. A study by Janssen and Mark (2007) also concluded that BMI in the overweight range is not associated with a significantly increased risk of mortality in the elderly, while a BMI in the moderately obese range is only associated with a modest increase in mortality risk. Excess body weight increases the risk of death from any cause and cardiovascular disease in adults between 30 and 74 years of age. The relative risk associated with greater body weight is higher among younger subjects [20].

The influence of age on the relation between BMI and mortality has not been widely studied, especially in the elderly. The few available studies suggest that the association between increased weight and higher mortality is primarily relevant for the younger elderly. A study with over 12 years of follow-up [20] found that greater BMI was associated with higher mortality only up to 75 years of age. Beyond age 75, increased BMI was associated with increased mortality only among men, and above age 85, low BMI was associated with higher mortality only among women. Another study with 14 years of follow-up found an association between high BMI and increased mortality at all ages, while low BMI was associated with mortality only among persons aged 75 years or more [28].

Although overweight and obesity have been associated with morbid conditions like heart disease, hypertension, and type 2 diabetes [29]. The threshold for morbidity may differ from the threshold for mortality, indicating the need for the use of summary measures of population health that incorporate both mortality and morbidity consequences of excess weight. Further research and more concern should be given to people with low BMI, because low BMI may increase all-cause mortality, or underweight individuals may have unidentified underlying conditions that could lead to death [30].

Strength

This study has several strengths. Firstly, the PRISMA method was used to do a meta-analysis and systematic review. Secondly, a broad searching strategy was employed to collect all relevant articles. Thirdly, the process of reviewing this study was done thoroughly by two independent reviewers. Fourthly, subgroup analysis based on the study characteristics was conducted to find essential findings.

Limitation

There are several limitations in this review. First, this study was limited to only English language articles, so the researchers considered publication bias's potential despite statistical analysis did not detect publication bias. Also, the researchers were not aware of any unpublished articles that fulfilled this study's criteria. Third, performed subgroup analysis was limited to only one characteristic, whereas more characteristics can be explored such as physical activity, age, other health conditions. Finally, there are a limited number of studies on the association of BMI with all-cause mortality, so further study is needed for more evidence.

Conclusion

In conclusion, being overweight might reduce all-cause mortality in all populations, including males and females, while being underweight suggests increased risk in the general population. As for being obese both in the male and female populations, this study suggests there is no association between being obese and all-cause mortality.

The government through healthcare providers should design compact educational programs. It can use social media with flyers and posters, or it can be like study sessions in smaller sizes, shorter duration of the class, weekly meetings, and closer group sessions with peer support involvement to give more information about body mass index, the effect on human health and how maintaining normal BMI.

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Table 1 Characteristics of the included studies

No	Author	Method	Country	Sample Size	Year Follow Up	Hazard Ratio (CI 95%)	Adjusted
1.	[31]	Cohort	Denmark	74,589	1-10	U= na O= 0.79 (0.77-0.81) OB= na	Age, marital status, Barthel Index, CCI, number of different medications purchased in the 120 days before index date, number of hospital admissions during 1 year before baseline, and period of index admission.
2.	[32]	Cohort	Canada	10,522	13.9	Male O= 0.99 (0.83-1.18) Female O= 1.16 (0.92-1.46)	Age, sex, exam year, smoking status, alcohol consumption and education
3.	[33]	Cohort	Korea	153,484	9	U= 2.31 (2.02-2.63) O= na OB= na	Age, sex, smoking status, alcohol intake, physical activity, socioeconomic status, and body weight change.
4.	[34]	Cohort	Austria	184,697	15.1	Male U= 2.57 (2.17–3.05) Female U= 1.40 (1.21–1.62)	Age, smoking status.
5.	[35]	Cohort	Korea	415,796	4-11	Male OB=1.24 (1.04-1.48) Female OB= 1.38 (1.16-1.64)	Age, behavior, income, and family history of cardiovascular disease.
6.	[36]	Cohort	Korea	75,856	1	U= 2.58 (2.24-2.97) OB=1.12 (0.85-1.47)	Age, sex, smoking status, drinking status, exercise level, SES, and waist circumference.
7.	[37]	Cohort	Taiwan	81,221	5	U= 1.95 (1.79-2.12) O= na OB= na	Age, smoking status, and sex.
8.	[38]	Cohort	Korea	125,391	7	U= 1.65 (1.40–1.95) O= 0.68 (0.61–0.75)	Age, sex, smoking status, alcohol consumption, physical activity, household income level, hypertension, diabetes mellitus, and dyslipidemia.

						OB= 0.77 (0.59–1.01)	
9.	[39]	Cohort	Korea	351,735	11.5	U= 1.86 (1.72-2.00) O= 0.96 (0.92-1.01) OB= na	Age, sex, income, smoking status, drinking, exercise, and Charlson Comorbidity Index score
10.	(Wang et al., 2017)	Cohort	China	8,026	12-13	U= 1.16 (1.08-1.23) O= na OB= na	Age, gender, residence, education, smoking, alcohol drinking, physical activity, intake of fruit, vegetable, meat, fish , and tea.
11.	[41]	Cohort	China	2,090	20	U= 1.39 (1.16-1.65) O= 0.76 ((0.66-0.88) OB= na	Age, gender, smoking status drinking status, pre-existing disease like hypertension, coronary heart disease, rheumatic heart disease and COPD.
12.	[42]	Cohort	China-Taipei	77,541	4	U= 1.92 (1.71–2.15) O= 0.82 (0.76–0.88) OB= na	Age, sex, marital status, education level, smoking, alcohol consumption, and exercise status.

U= underweight; O= overweight; OB= obesity; na= not included because the difference of standart categories

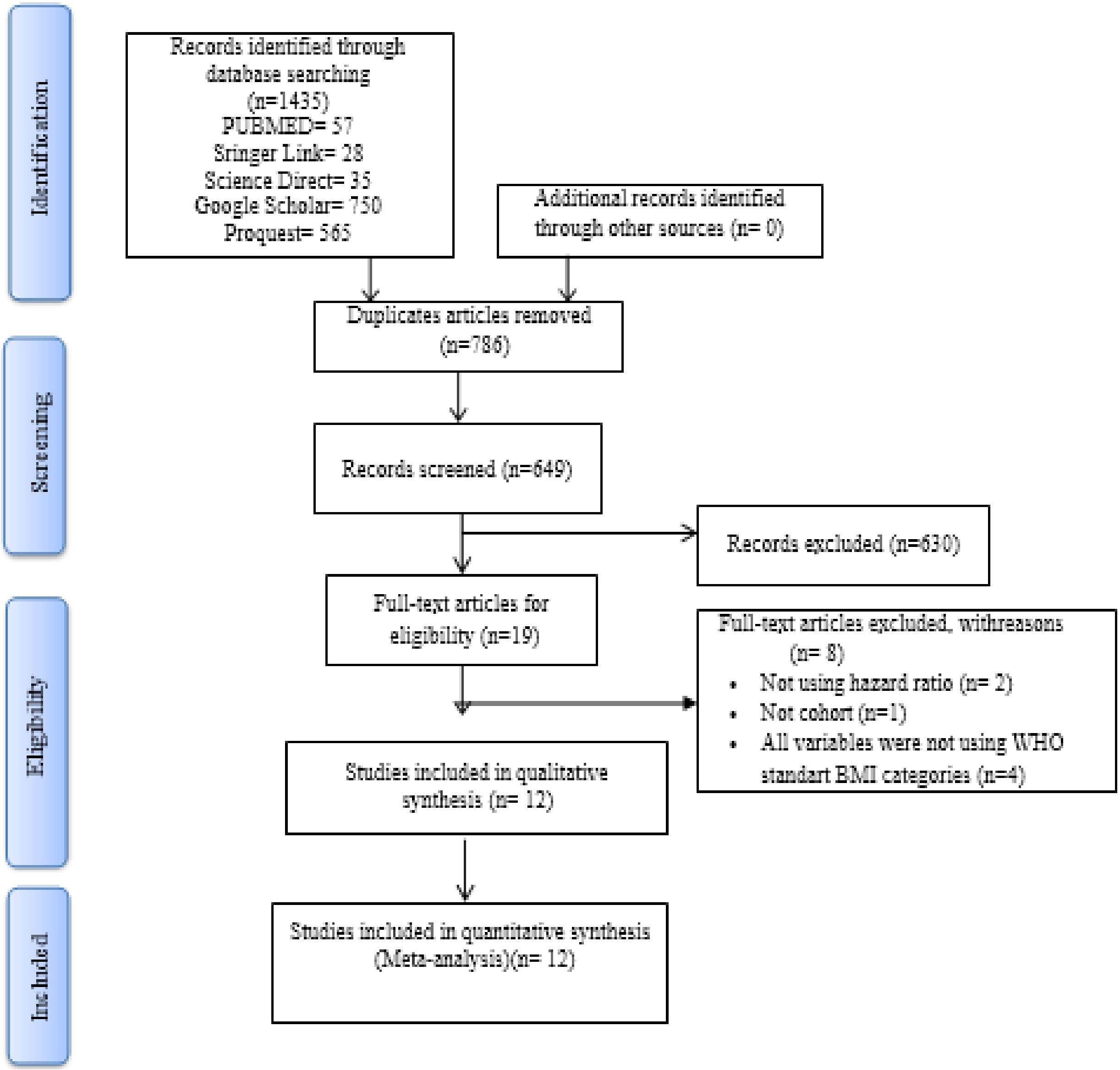

Figure 1 PRISMA Flowchart

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
1.2.1 General				
Kim (2015)	0.8372	0.0684	5.2%	2.31 [2.02, 2.64]
Lee (2018)	0.9478	0.0721	5.2%	2.58 [2.24, 2.97]
Lin (2020)	0.6678	0.0437	5.4%	1.95 [1.79, 2.12]
Nam (2019)	0.5008	0.0838	5.1%	1.65 [1.40, 1.94]
Park (2018)	0.6206	0.0399	5.4%	1.86 [1.72, 2.01]
Wang a (2017)	0.1484	0.0365	5.4%	1.16 [1.08, 1.25]
Wang b (2017)	0.3293	0.0923	5.0%	1.39 [1.16, 1.67]
Wu (2014)	0.6523	0.0591	5.3%	1.92 [1.71, 2.16]
Subtotal (95% CI)			**41.9%**	**1.80 [1.48, 2.19]**
Heterogeneity: Tau² = 0.08; Chi² = 187.28, df = 7 (P < 0.00001); I² = 96%				
Test for overall effect: Z = 5.85 (P < 0.00001)				
1.2.2 Female				
Kim (2015)	0.7747	0.1245	4.7%	2.17 [1.70, 2.77]
Klenk (2009)	0.3365	0.0744	5.2%	1.40 [1.21, 1.62]
Lee (2018)	0.8242	0.1066	4.9%	2.28 [1.85, 2.81]
Nam (2019)	0.4447	0.16	4.3%	1.56 [1.14, 2.13]
Wang a (2017)	0.2624	0.1339	4.6%	1.30 [1.00, 1.69]
Wang b (2017)	0.157	0.0361	5.4%	1.17 [1.09, 1.26]
Subtotal (95% CI)			**28.9%**	**1.58 [1.25, 2.01]**
Heterogeneity: Tau² = 0.08; Chi² = 55.11, df = 5 (P < 0.00001); I² = 91%				
Test for overall effect: Z = 3.79 (P = 0.0002)				
1.2.3 Male				
Kim (2015)	0.8629	0.1461	4.4%	2.37 [1.78, 3.16]
Klenk (2009)	0.9439	0.0863	5.1%	2.57 [2.17, 3.04]
Lee (2018)	1.0152	0.0997	4.9%	2.76 [2.27, 3.36]
Nam (2019)	0.5365	0.0984	4.9%	1.71 [1.41, 2.07]
Wang a (2017)	0.3221	0.1204	4.7%	1.38 [1.09, 1.75]
Wang b (2017)	0.9439	0.0863	5.1%	2.57 [2.17, 3.04]
Subtotal (95% CI)			**29.1%**	**2.17 [1.76, 2.68]**
Heterogeneity: Tau² = 0.06; Chi² = 33.32, df = 5 (P < 0.00001); I² = 85%				
Test for overall effect: Z = 7.16 (P < 0.00001)				
Total (95% CI)			**100.0%**	**1.83 [1.60, 2.10]**
Heterogeneity: Tau² = 0.09; Chi² = 390.21, df = 19 (P < 0.00001); I² = 95%				
Test for overall effect: Z = 8.67 (P < 0.00001)				
Test for subgroup differences: Chi² = 3.93, df = 2 (P = 0.14), I² = 49.1%				

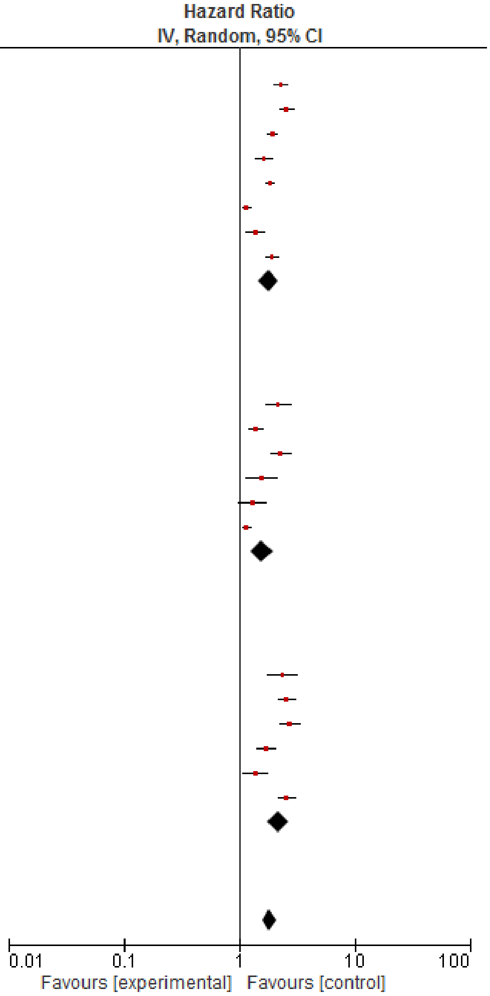

Figure 2 Forest plot of the underweight in general

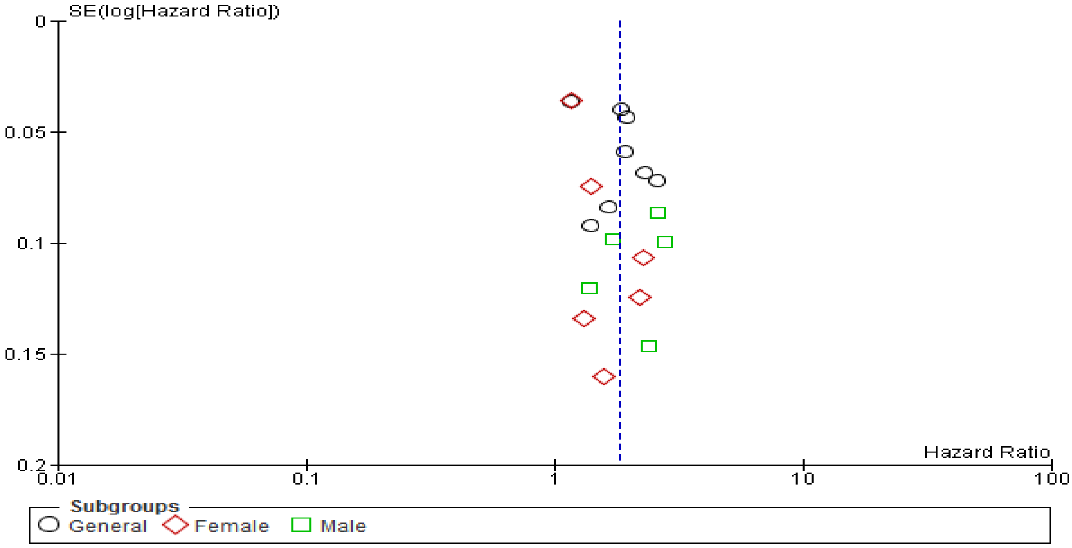

Figure 3 Forest plot of the underweight

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
1.3.1 General				
Nam (2019)	-0.3857	0.0554	10.3%	0.68 [0.61, 0.76]
Park (2018)	-0.0408	0.0217	12.0%	0.96 [0.92, 1.00]
Wang b (2017)	-0.2744	0.072	9.3%	0.76 [0.66, 0.88]
Wu (2014)	-0.1985	0.0388	11.3%	0.82 [0.76, 0.88]
Subtotal (95% CI)			**42.9%**	**0.80 [0.69, 0.94]**
Heterogeneity: Tau² = 0.02; Chi² = 45.01, df = 3 (P < 0.00001); I² = 93%				
Test for overall effect: Z = 2.70 (P = 0.007)				
1.3.2 Female				
Jesper (2021)	-0.2485	0.02	12.1%	0.78 [0.75, 0.81]
Katzmarzyk (2012)	0.1484	0.1183	6.5%	1.16 [0.92, 1.46]
Nam (2019)	-0.2877	0.089	8.2%	0.75 [0.63, 0.89]
Subtotal (95% CI)			**26.8%**	**0.86 [0.70, 1.05]**
Heterogeneity: Tau² = 0.02; Chi² = 11.25, df = 2 (P = 0.004); I² = 82%				
Test for overall effect: Z = 1.51 (P = 0.13)				
1.3.3 Male				
Jesper (2021)	-0.2744	0.0205	12.0%	0.76 [0.73, 0.79]
Katzmarzyk (2012)	-0.0101	0.0899	8.2%	0.99 [0.83, 1.18]
Nam (2019)	-0.4463	0.0591	10.1%	0.64 [0.57, 0.72]
Subtotal (95% CI)			**30.3%**	**0.77 [0.65, 0.92]**
Heterogeneity: Tau² = 0.02; Chi² = 17.01, df = 2 (P = 0.0002); I² = 88%				
Test for overall effect: Z = 2.86 (P = 0.004)				
Total (95% CI)			**100.0%**	**0.81 [0.74, 0.88]**
Heterogeneity: Tau² = 0.02; Chi² = 116.14, df = 9 (P < 0.00001); I² = 92%				
Test for overall effect: Z = 4.90 (P < 0.00001)				
Test for subgroup differences: Chi² = 0.58, df = 2 (P = 0.75), I² = 0%				

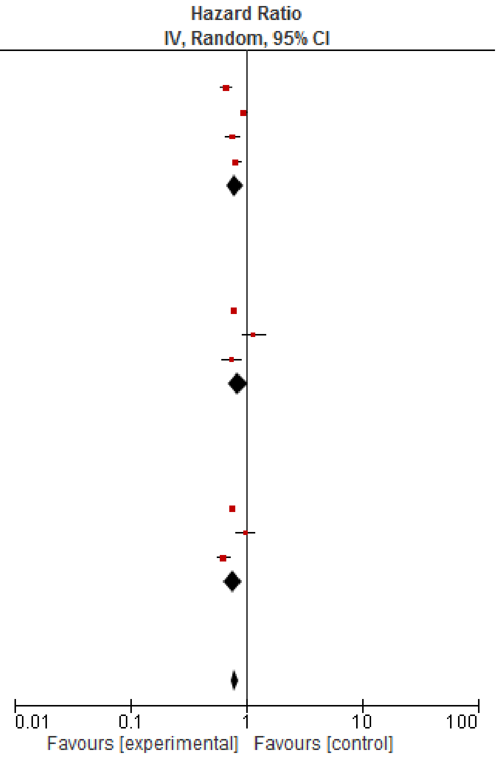

Figure 4 Forest plot of the overweight

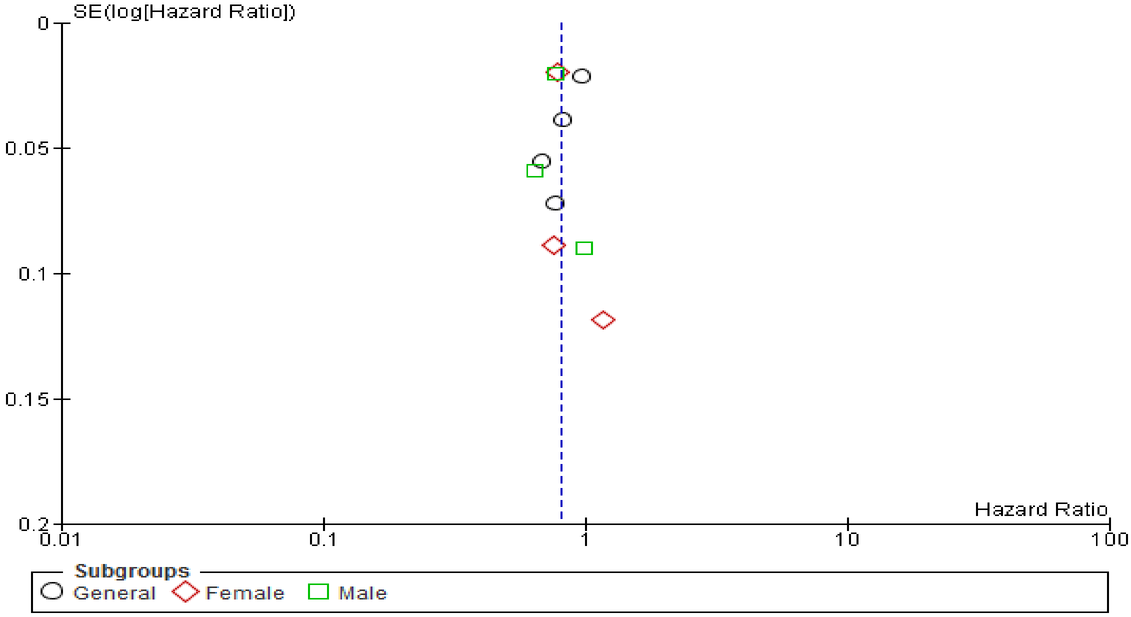

Figure 5 Funnel plot of the overweight

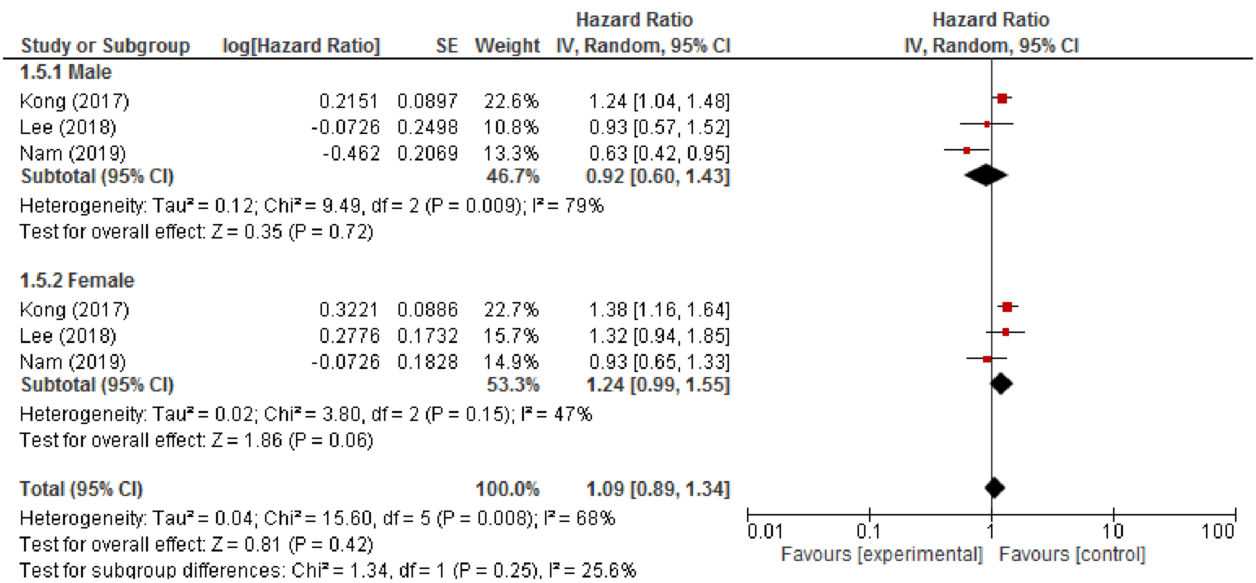

Figure 6 Forest plot of obesity

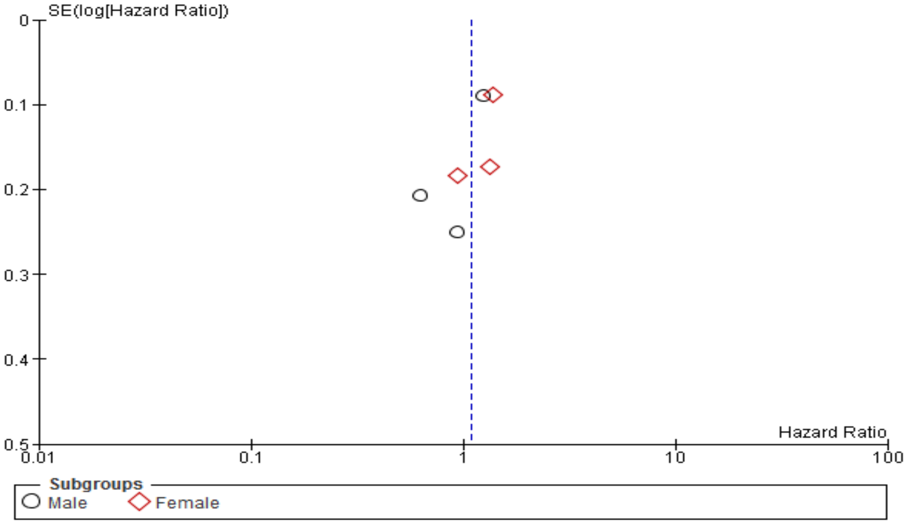

Figure 7 Funnel plot of obesity