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The Association between Body Mass Index and Cardiovascular-Related Mortality: A Systematic Review and Meta-Analysis

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***Abstract*---**The relationship between body mass index (BMI) and cardiovascular (CVD) related mortality has been extensively investigated in the general population. However, the research on this matter is relatively limited, and the conclusions from these studies are inconsistent. This study aimed to review the association between body mass index with CVD related 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, and Science direct for English language articles published until 2022. Ten studies

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were included in this study. Random and Fixed-effects summary of CVD-related mortality HRs were 1.72 (95% CI, 1.51-1.97) for underweight, 1.40 (95% CI, 1.15-1.69), and 1.33 (95% CI, 1.17-1.52) for obesity. Being underweight and obese might increase CVD related mortality in all populations, including males and females.

***Keywords*---**cardiovascular-related mortality, body mass index, cohort, meta-analysis.

Introduction

Cardiovascular disease, chronic respiratory disease, and cancer are leading causes of death worldwide (World Health Organization (WHO), 2014). Between 1990 and 2020, the increase in death from coronary heart disease (CHD) is expected to be 120% in women and 137% in men in low and middle income countries, and 29% and 48%, respectively, among high income countries (Chen *et al.*, 2013). In 2011, the United Nations formally recognized noncommunicable diseases, including CVD, as a major global health concern and announced a worldwide action plan against these diseases (UN, 2011). The Sustainable Development Goals (SDGs), released by the United Nations General Assembly in 2015, include the target of a reduction in premature mortality owing to noncommunicable diseases by one-third by 2030 (UN, 2015).

A large number of epidemiologic studies have evaluated the associations between body weight and, more often, the body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) and a wide range of health outcomes. Obesity is associated with multiple chronic diseases, including type 2 diabetes, hypertension, coronary heart disease, stroke, and several cancers (Haslam and James, 2005).

The WHO listed overweight and obesity as the fifth leading risk factor for death globally in 2008. At least 2·8 million adults die each year as a result of being overweight or obese. Most of the large prospective observational studies that evaluated the relationships between BMI and risks of all-cause and cause-specific mortality were carried out in European, America and a few Asian countries (Zheng *et al.*, 2011; Flegal *et al.*, 2013). The association between BMI and mortality could depend on ethnicity. In contrast to conventional beliefs that obesity and overweight status are associated with increased mortality, a previous study showed that overweight status could decrease all-cause mortality (Feigin *et al.*, 2005).

There is a controversy arise between the relation of weight categories and mortality 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. A report2 in 1997 from the World Health Organization Consultation on Obesity defined BMI-based categories of underweight, normal weight, preobesity, and obesity. The same

cutoff BMI values were adopted by the National Heart, Lung, and Blood Institute in 1998 ('Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: executive summary. Expert Panel on the Identification, Evaluation, and Treatment of Overweight in Adults.', 1998; Obesity: preventing and managing the global epidemic. Report of a WHO consultation., 2000).

Although a high BMI is generally accepted as an indicator of obesity, the relationships between BMI and cardiovascular mortality remain controversial.Therefore this study aimed to investigate the association between BMI and CVD-related mortality.

Method

This was a systematic review and meta-analysis of cohort studies that examines the association between BMI categories and CVD-related mortality. The BMI categories used were underweight, overweight, and obesity compared to normal BMI. Article searches for this study were using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline (Page *et al.*, 2021).

Searching Strategy

A comprehensive search was conducted to find relevant articles from electronic databases and grey literature published until 2022 in English language articles. Electronic databases PubMed, ProQuest, Springer link, and Science direct 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 "cardiovascular mortality"[Mesh] AND "cardiovascular mortality"[tiab] AND "cardiovascular"[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 CVD-related mortality using standard body mass index (BMI) categories of general populations of adults. Articles will be excluded if did not contain CVD-related of death.

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 (Sterne JAC, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, 2016). 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 (Deeks JJ, Higgins JPT, 2019). An I^2 value of more than 50% indicates a substantial heterogeneity level (JPT, 2003). Random effect analysis models are used if heterogeneity is detected by more than 50%(OM, 2018). 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 (Godavitarne *et al.*, 2018).

Results

A total of 817 published articles were collected from online databases, including PubMed, ProQuest, Science Direct, and Springer Link. All articles had published until 2022. After deleting the identical ones, 50 abstracts were obtained. After the review of the abstract, Ten articles were chosen for review of the

full text and were eligible for inclusion criteria. Eight articles were selected for qualitative synthesis and only 8 articles were included in quantitative synthesis because of the unmatched BMI denominator. 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. Four studies were carried out in Korea, one in Canada, one in Japan, one in Malaysia, one in Taiwan, and two in the USA. Overall, 1,094,624 respondents were included in this study from all articles. The longest year of followed up was 51 years. Meanwhile, the shortest was 2 years.

The Association between BMI and CVD Related Mortality

Table 1 displays the effect size and 95%CI of the included Studies. The association between BMI and CVD-related mortality was evaluated in 6 studies. Due to variant heterogenity, a fixed and random effect model was employed to evaluate the differences in effect BMI on CVD-related 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 1.40 (95% CI, 1.15-1.69), and it was statistically significant ($p<0.0006$), favoring the control group (normal BMI). There was low heterogeneity between studies, and it was statistically significant ($I^2= 54\%$; $p<0.01$) (figure 2). The results of the publication bias assessment showed an asymmetrical funnel plot leaning towards the left side indicating there is publication bias existed. It also described that the result was slightly underestimated (figure 3).

The pooled effect size of the hazard ratio of overweight was 1.23 (95% CI 1.17-1.52), and it was statistically significant ($p= 0.001$), favoring the control group. There was also low heterogeneity between studies, and it was statistically not significant ($I^2 = 47\%$; $p= 0.13$) (figure 4). The results of the publication bias assessment showed a symmetrical funnel plot indicating there is no publication bias existed (figure 5). We did perform the analysis of overweight, but we also wanted to describe the review to strengthen the determination of the relationship between overweight and CVD-related mortality. Hong *et al.*, (2015), Katzmarzyk *et al.*, (2012), and Kong *et al.*, (2017) suggested based on the result of their study that there is a different result between men and women regarding the relation between BMI overweight and CVD-related mortality, which men favor the overweight for increasing the mortality, vise versa women favor overweight for decreasing the mortality compare to normal BMI. Kim *et al.*, (2015) and Luijckx *et al.*, (2019) describe otherwise, overweight women had a higher risk of CVD-related mortality than men or all participants combined.

Lin *et al.*, (2021) stated in their study that overweight people had a lower risk of CVD-related mortality. Kee *et al.*, (2017) and Lee *et al.*, (2018) suggested there was no difference between the overweight and normal category in their association with CVD-related mortality

The pooled effect size of the hazard ratio of obesity was 1.33 (95% CI 1.17-1.52), and it was statistically significant ($p< 0.0001$), favoring the control group. There was also low heterogeneity between studies, and it was statistically not significant ($I^2 = 0\%$; $p= 0.55$) (figure 6). The results of the publication bias assessment showed an asymmetrical funnel plot leaning towards the left side indicating there is publication bias existed. It also described that the result was slightly underestimated (figure 7).

Discussion

Our study result suggested there is an association between all BMI categories and CVD-related mortality. Being underweight, overweight, or obese had higher risk of CVD-related mortality. A result of study by Kim *et al.*, (2021) support this results stated that A BMI increase was associated with higher risks of coronary heart disease, heart failure, atrial fibrillation, all-cause stroke, haemorrhagic stroke, ischaemic stroke, hypertension, aortic valve stenosis, pulmonary embolism, and venous thrombo-embolism.

We found one unique fact through our review and sub-group analysis that men is more prone to CVD-related mortality. This fact was similar with the result of study that stated obese men were more prone to unfavourable CVD outcomes than obese women, although the difference was not statistically significant (Kim *et al.*, 2021).

We could assume safely that there is no problem regarding of age distribution between respodents in all articles included in this study because of the adjusted factors included in all studies was age. In younger or older people, being more than normal weight could risk to all kinds of disease including CVD. Studies by Bender *et al.*, (1999), Baker, Olsen and Sørensen, (2007), and Tirosh *et al.*, (2011) supported this thesis explaining that there is increasing evidence for the link between adolescent overweight and obesity and cardiovascular and all-cause mortality.

Study by Matsunaga *et al.*, (2017) suggested that being underweight increase risk of Coronary heart disease. The underweight population had a 19.7% greater risk of CVD than did the normal-weight, and the overweight and obese population had a 50% and 96% increased risk, respectively. When adjusted with covariates, the relative risk for CVD elevated in underweight population (adjusted RR 1.34 [95% confidence interval (CI) 1.335–1.348]) (Park, Lee and Han, 2017). This unexpected result of the increased CVD risk in underweight group can be associated with various clinical factors, such as aging, sarcopenia, and poor nutritional status in underweight population. The CVD risk of underweight was more prominent in the younger population below 40 years old. Considering previous studies that low body muscle mass may be a risk factor for CVD, his may be due to the fact that the underweight of this population may have a relatively large decline in body

muscle mass than the older population, because the body muscle mass tends to occupy a relatively large portion of body weight in the younger population (Mora *et al.*, 2005; Sahin *et al.*, 2014).

Overweight and obesity is a multifactorial disease that results from interactions between genetics and lifestyle. The heritability for obesity is known to be around 40%,while the remainder can be explained by lifestyle factors, which suggests that being overweight and obese is a modifiable risk factor. In this context, the causal effect of overweight and obesity on nearly all specific cardiovascular outcomes provides an enthusiastic prospect in which lifestyle modification to reduce adiposity can result in the overall reduction of cardiovascular health problems and substantial health-economic burden (Eckel and Krauss, 1998; Day and Loos, 2011; van Vliet-Ostaptchouk, Snieder and Lagou, 2012; Jääskeläinen *et al.*, 2013). Significant improvement in CVD morbidity and mortality may be achieved with improved monitoring and management of CVD risk factors, as recommended by WHO treatment guidelines (World Health Organization, 2016).

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, and other health conditions. Finally, there are a limited number of studies on the association of BMI with CVD mortality, so further study is needed for more evidence.

Conclusion

In conclusion, being underweight and obese might increase CVD-related mortality in all populations, including males and females. This study adds important new information on the risks associated with being other than the normal category of BMI. We suggest more concern should be given to people with low and High BMI, because it may increase CVD-related mortality.

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Table 1 Characteristics of the included studies

No	Author	Method	Country	Sample Size	Years Follow Up	BMI Denominator and Hazard Ratio (CI 95%)	Outcome	Adjusted
1.	Hong *et al.*, (2015)	Cohort	Korea	6166 (≥ 55 years)	1985-2008	Men 25-27.5 1.29 (0.90-1.85) Women 25-27.5 0.78 (0.58-1.03)	Lower BMI increased deaths from vascular diseases.	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.	Katzmarzyk et al., (2012)	Cohort	Canada	10,522 (18-74 years)	1986-1995	Men 25-29.9 1.61 (1.17-2.22) ≥30-34.9 1.71 (1.16-2.51) ≥35 2.16 (1.14-4.18) Women 25-29.9 1.44 (0.95-2.16) ≥30-34.9 1.78 (1.10-2.88) ≥35 1.86 (1.02-3.39)	The increased risk of CVD mortality associated with an elevated BMI was significant at levels above 30 kg/m.	Age, sex, exam year, smoking status, alcohol consumption and education.
3.	Kee *et al.*, (2017)	Cohort	Malaysia	32,839 (≥ 18 years)	2006-2010	All Participants <18.5 1.35 (0.81-2.23) 25-29.9 1.03 (0.72-1.48) ≥30-34.9 1.40 (0.88-2.23) ≥35 2.15 (1.11-4.15)	Obesity with increased risk of CVD mortality.	Age group (18–39, 40–59 and ≥60 years), gender (male and female) and ethnicity (Malays, Chinese, Indian and Others).
4.	Khan *et al.*, (2018)	Cohort	USA	190,672 (20-89 years)	1964-2015	Man <18.5 0.54 (0.07-3.87) 25-29.9 1.23 (1.01-1.51) Women <18.5 0.87 (0.41-1.86) 25-29.9 1.04 (0.84-1.27)	Overweight and obesity were associated with significantly increased risk for CVD mortality.	Age, race/ethnicity, and smoking status.
5.	Kim et al., (2015)	Cohort	Korea	153,484 (≥ 30 years)	2002-2010	All Participants <18.5 1.38 (0.92-2.08) Men <18.5 0.94 (0.41-2.11) Women <18.5 2.36 (1.31-4.26)	A positive association between severe obesity and mortality risk was prominent for cases of CVD mortality	Age, sex, smoking status, alcohol intake, physical activity, socioeconomic status, and body weight change.
6.	Kong et al., (2017)	Cohort	Korea	415,796 (≥ 30 years)	2002-2012	Men 27.5-30 1.20 (0.89-1.62) ≥30 1.01 (0.59-1.74) Women 27.5-30 0.86 (0.60-1.23) ≥30 1.50 (1.00-2.26)	Men with a BMI < 22.5 kg/m2 and women with a BMI < 20 kg/m2 displayed an increased risk of cardiovascular	Age, behavior, income, and family history of cardiovascular disease.

							mortality.	
7.	Lee et al., (2018)	Cohort	Korea	75,856 (≥ 65 years)	2009-2013	All Participants <18.5 2.19 (1.59-3.02) 25-27.5 1.02 (0.80-1.31) 27.5-30 0.95 (0.65-1.38) ≥30 0.80 (0.41-1.56)	Cardiovascular-related mortality had the lowest HR in the slightly obese group (27.5 - BMI < 30 kg/m2), but this was not statistically significant.	Age, sex, smoking status, drinking status, exercise level, SES, and waist circumference.
8.	Lin et al., (2021)	Cohort	Taiwan	81,221 (≥ 65 years)	2006-2011	All Participants <18.5 1.98 (1.67-2.35)	The BMI of lowest cause-specific mortality was between 28 kg/m2 and 29 kg/m2 in circulation mortality.	Age, smoking status, and sex.
9.	Luijckx *et al.*, (2019)	Cohort	USA	17,483 (≥18 years)	1988-2011	All Participants <18.5 1.26 (0.67–2.39) ≥30 1.37 (1.12–1.70) Men <18.5 1 (0.55–1.82) ≥30 1.31 (0.96–1.80) Women <18.5 1.42 (0.60–3.35) ≥30 1.45 (1.07–1.95)	CVD mortality risk was the highest among obese current smokers (3.33 [2.98–5.33])	Age, alcohol, race, marital status, education, activity.
10.	Matsunaga *et al.*, (2021)	Cohort	Japan	110,585 (40-79 years)	1988-1990	Men <18.5 1.51 (1.13–2.02) 25-27.4 1.42 (1.17–1.74) Women <18.5 1.18 (0.95–1.45) 25-27.4 1.13 (0.92–1.39)	A BMI more than 25 kg/m2 is associated with an increased risk CVD in male or female.	Age, education level, area of residence, smoking status, alcohol drinking, physical activity, and history of liver disease and blood transfusion.

<18.5 = underweight; 25-27.5, 27.5-30 and 25-29.9 = overweight; ≥30 and ≥35 = obesity

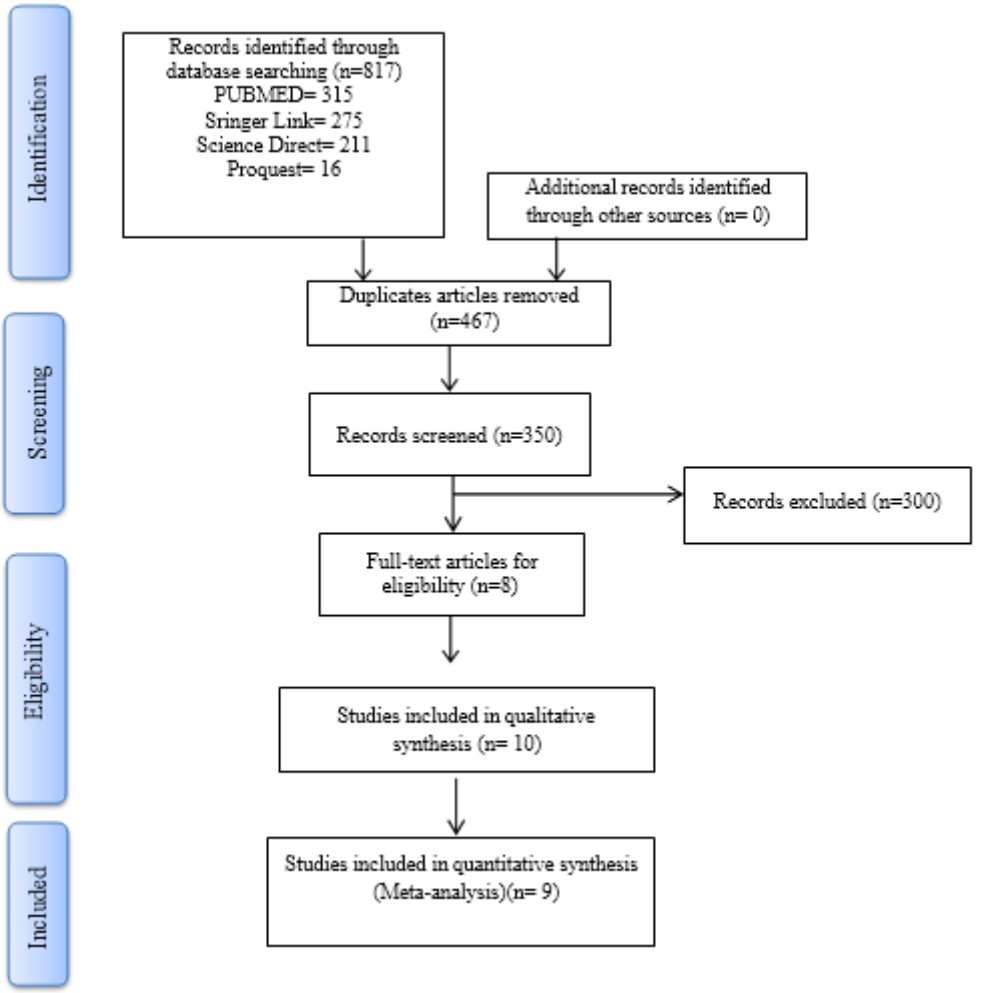


Figure 1 PRISMA Flowchart

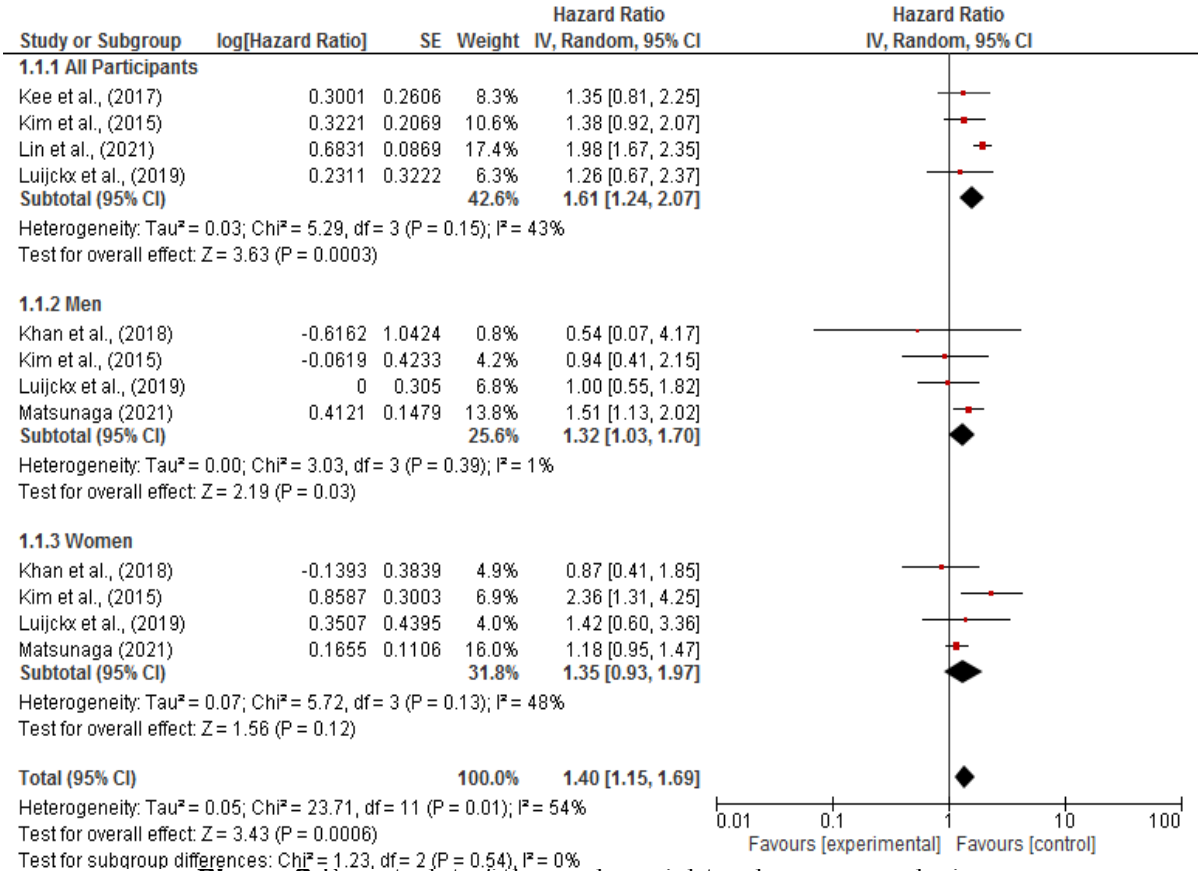
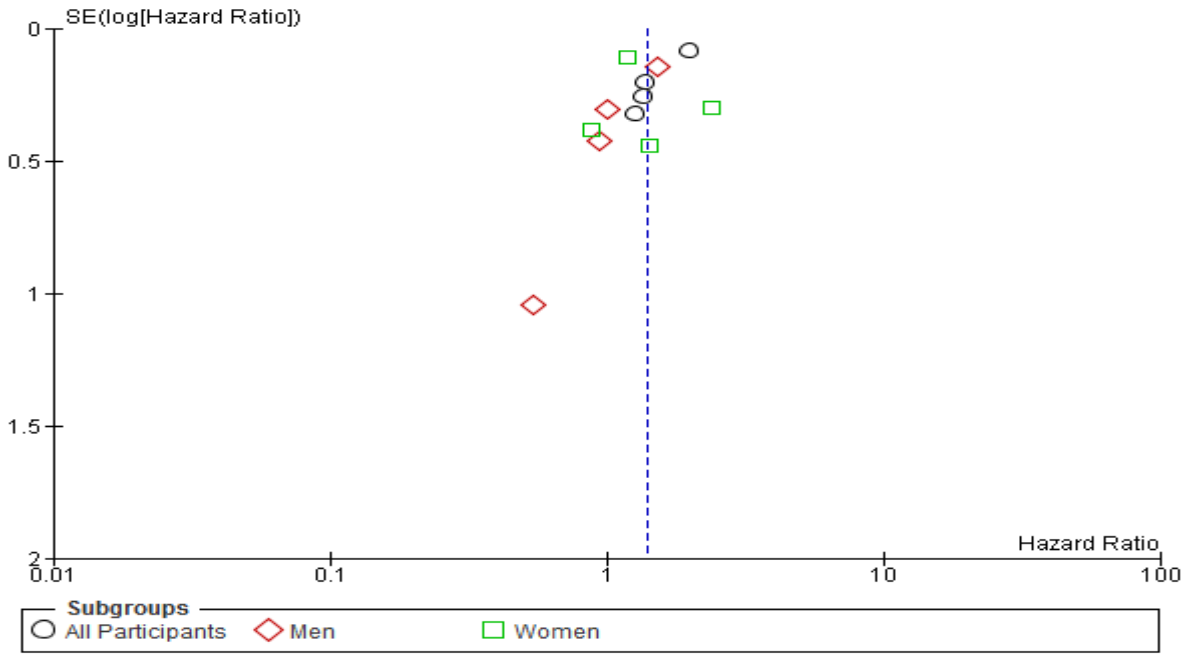


Figure 2 Forest plot of the underweight sub-group analysis



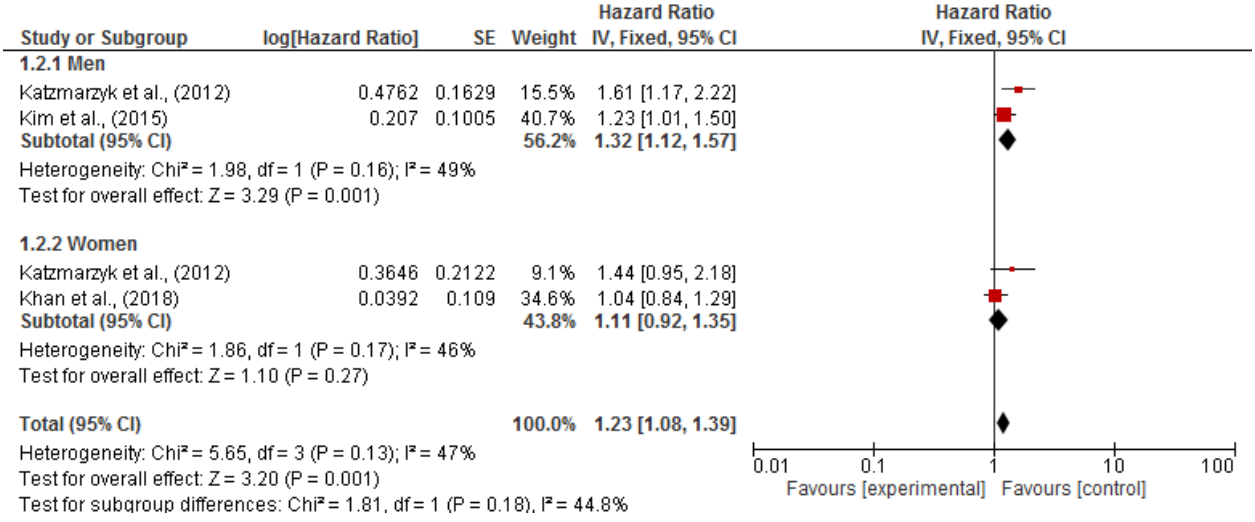


Figure 4 Forest plot of the overweight sub-group analysis

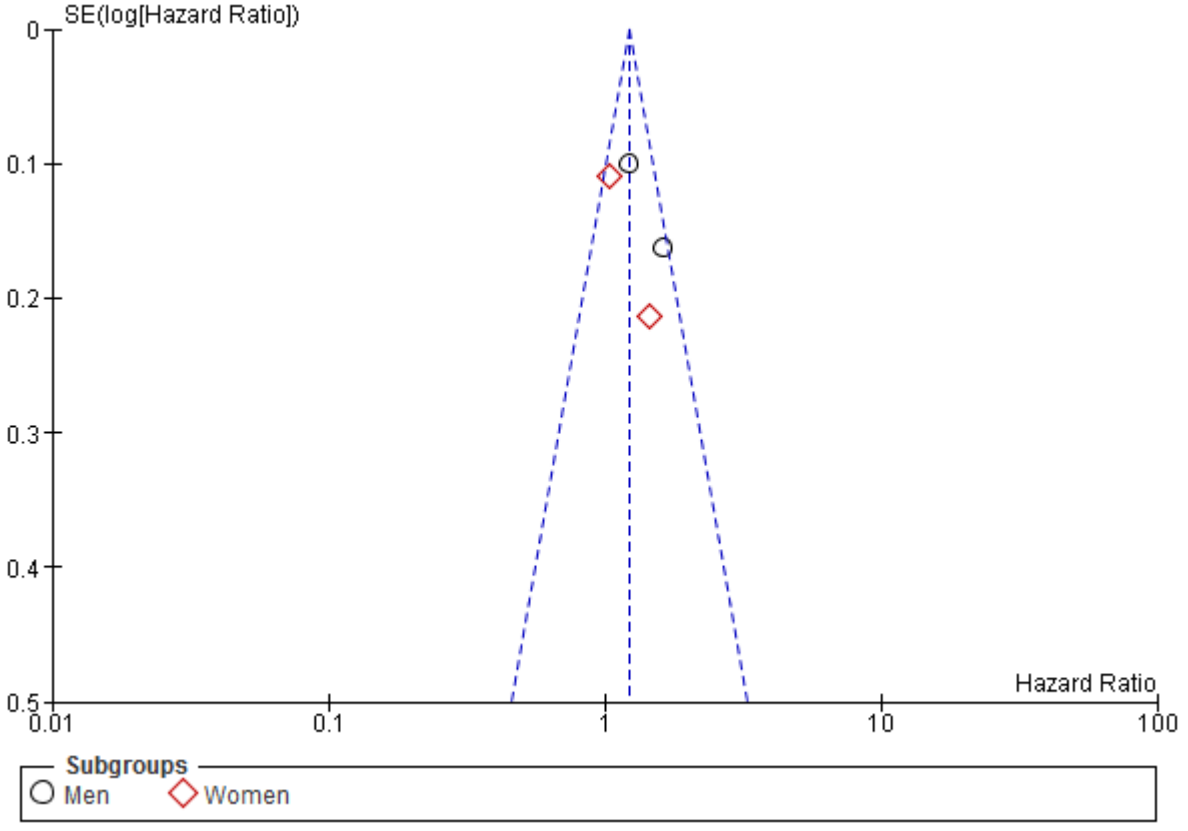


Figure 5 Funnel plot of the overweight

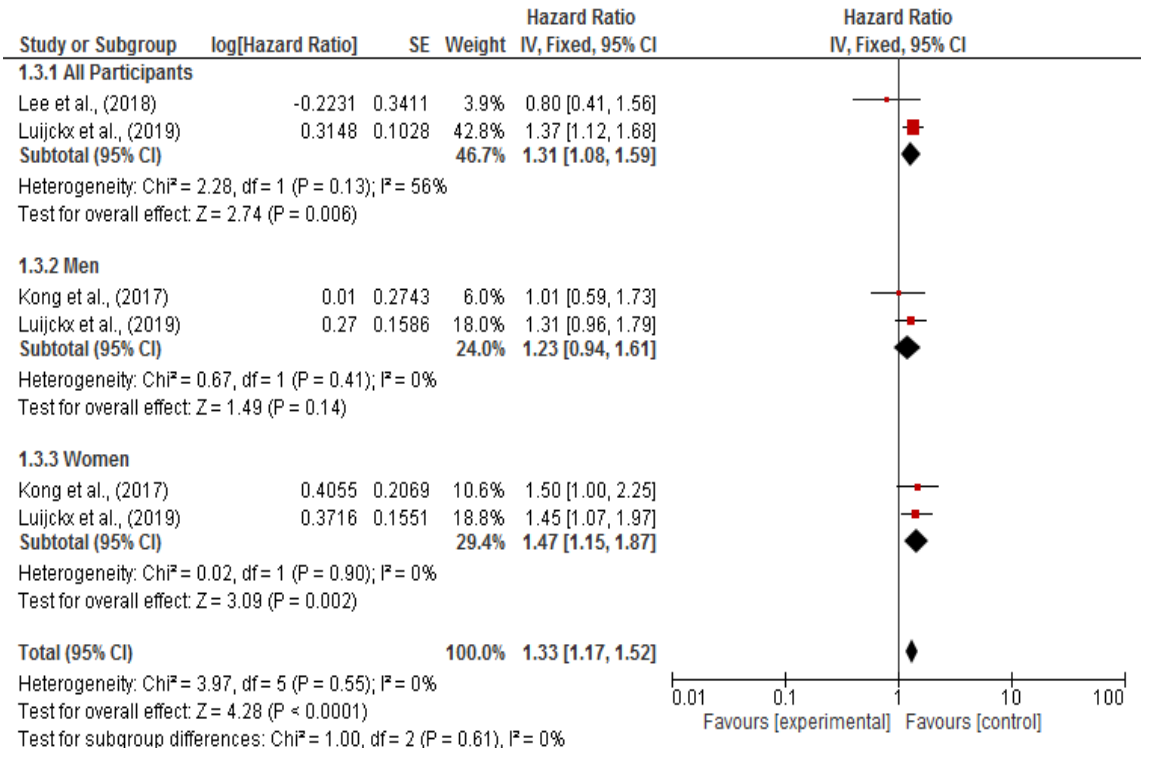


Figure 6 Forest plot of obesity sub-group analysis

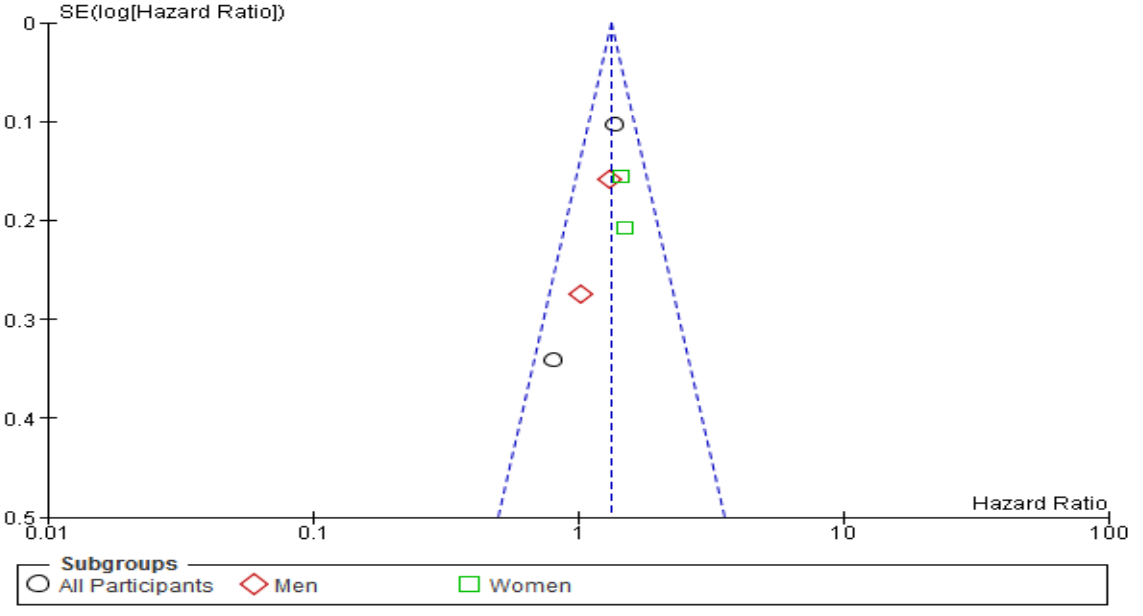


Figure 7 Funnel plot of obesity