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Effects of resveratrol supplementation on liver enzymes: A systematic review and meta-analysis of randomized controlled trials

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The authors report no conflict of interest.

Abstract

Background: The available evidence regarding the possible effects of resveratrol on liver function is inconsistent. Therefore, the present meta-analysis was performed to investigate the overall effects of resveratrol supplementation on liver enzymes in adults.

Methods: A systematic and comprehensive search of the online medical databases including PubMed, Scupos, Web of Science and Cochran Library was performed up to February 2020. All RCTs using resveratrol supplements in adults were included in this systematic review and meta-analysis. The overall effect was presented as weighted mean difference (WMD) and 95% confidence interval (CI) in a random-effects meta-analysis model.

Results: Finally, 15 randomized trials including 714 participants were selected for the present meta-analysis. Pooled analysis did not show any significant changes in alanine aminotransferase (ALT) (WMD: 0 IU/L, 95% CI: -3.17 to 3.17, p = 0.99; I^2 = 74.2%), aspartate aminotransferase (AST) (WMD: -2.40 IU/L, 95% CI: -5.45 to 0.65, p = 0.11; I^2 = 82.9%), gamma-glutamyl transferase (GGT) (WMD: -1.26 IU/L, 95% CI: -4.64 to 2.13, p = 0.64; I^2 = 23.7%), alkaline phosphatase (ALP) (WMD: 3.80 IU/L, 95% CI: -4.65 to 12.25, p = 0.37; I^2 = 29.9%) and bilirubin (WMD: 0.13 IU/L, 95% CI: -0.43 to 0.17, p = 0.39; I^2 = 8.9%) after supplementation with resveratrol.

Conclusion: Overall in our study resveratrol does not effect on liver enzyme levels significantly, but subgroup analysis indicates that these results may be influenced by resveratrol dose, duration of the study and population status, so future high-quality studies are necessary to get definitive results.

Keywords: Resveratrol, Alanine aminotransferase, Aspartate aminotransferase, Liver enzyme, Systematic review, Meta-analysis

What's already known about this topic?

• Some previous studies showed the beneficial effects of resveratrol.

• There have been no meta-analysis to summarize the effect of resveratrol on liver enzymes in adults.

What does this article add?

• This study is the first systematic review and meta-analysis that was designed to evaluate the effect of resveratrol on liver enzymes in adults.

• The present study suggests that resveratrol supplementation does not effect on liver enzyme levels significantly.

• However, subgroup analysis indicates that these results may be influenced by resveratrol dose, duration of the study and population status.

Introduction

Over the last several decades, liver diseases have rapidly risen to become one of the global public health problems [1]. In 2010, rather than 2 million deaths happened due to the chief liver disorders including acute hepatitis, cirrhosis, and liver cancer, which were responsible for about 4% of all of global mortality [2]. Therefore increasing the prevalence of liver diseases in the world increases the overall cost of health care systems and decreases the quality of life [3] . The pathogenesis of the liver disease is complex, causes of liver disease include genetic and environmental factors such as viral infections, excessive alcohol consumption, and obesity [4]. There are various drug therapies available for the treatment of liver disease [5], but in recent years, along with these pharmacologic strategies, the use of herbal remedies [6] and medicine has become more prosperous due to fewer side effects and lower costs than chemical drugs [7]. Resveratrol (3,5,4′-trihydroxystilbene) is one of the most favourite acetylbene-derived phytochemicals belonging to the polyphenol strain. Rich dietary sources of resveratrol include peanuts, cocoa, red grapes, red and white wine, and various berries [8]. Numerous experimental studies have shown the protective effects of resveratrol in the prevention and treatment of various diseases including cancer [9], Alzheimer [10], viral infections [11], cardiovascular [12] and inflammatory disease [13]. The major mechanisms of the protective effects of resveratrol are due to its antioxidant [14], anti-inflammatory [15], anti-apoptotic [16] and immune-activities [17]. Recently, several studies have reported the beneficial effects of resveratrol in prevention of fat accumulation [18], reduction of liver enzymes [19], lipid peroxidation and oxidative stress in hepatocytes [20], but in another study resveratrol had no significant effect on liver enzymes [21]. Due to the increasing prevalence of liver disease in communities and inconclusive evidence of the efficacy of resveratrol in the treatment of liver dysfunction, we conducted a systematic review and meta-analysis of all available randomized controlled trials (RCTs) to investigate the influence of resveratrol on liver function.

Methods

This systematic review and meta-analysis was performed in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement guidelines [22] and the PICOS model for the definition of the inclusion criteria: P (Population): “adults”, I (Intervention): “impact of the of resveratrol supplementation”, C (Comparators): “same conditions with control or placebo”, O (Outcome): “liver enzymes”, and S (study design): “randomized controlled trials”

Search strategy

A systematic and comprehensive search of the online medical databases including PubMed, Scupos, Web of Science and Cochran Library was performed up to February 2020, using the following search terms in titles and abstracts to identify the potential interest articles: (“Resveratrol” OR “Vitis vinifera") AND "("Intervention Studies" OR "Intervention" OR "Controlled trial" OR "Randomized" OR "Randomised" OR "Random" OR "Randomly" OR "Placebo" OR "Assignment"). The search was conducted with no restriction on articles' language or time of publication. In addition, since that several studies examined the effect of resveratrol supplementation on liver function test as the secondary outcome, we did not use liver function test keywords. The complete search method is shown in supplementary **Table 1.** All reference lists of retrieved eligible papers and related reviews were also checked manually to avoid missing any relevant studies.

Study selection

First, electronic and manual search results were exported to End-Note software, version X8 (Thomson Reuters) and duplicate publications were removed. Then, two investigators (M.D and A.GH) selected eligible articles, independently, by reading the title, abstract, and, where required, the full-text version of remaining publications. Finally, all human RCTs (either parallel or cross-over designs) that examined the effects of resveratrol supplementation on liver function in adults (age ≥18 years old) were included.

Studies were excluded if they (i) supplemented resveratrol in combination with any other drugs, minerals, or botanicals (unless a separate arm controlled the effect of the mixed substance); (ii) were publications with duplicate data; (iii) contained trials with follow up duration less than 4 weeks; (iv) used red wine instead of resveratrol supplements; (v) did not have control group and (vi) were publications that did not report outcome measures at study baseline and end of intervention (or changes in outcome measures) or which examined the effects of resveratrol. Disagreements regarding the study selection process were resolved by discussion with a third researcher (E.K).

Data extraction

The following data were extracted from the full-text of included studies using a predesigned abstraction form as follows: first author's last name, publication year, location of the study, study design, target population, body mass index (BMI of participants), mean age, gender, total sample size, study duration, type of resveratrol, dose of resveratrol supplementation, and main results. When the data were reported at multiple measurements, only the outcomes at the end of the intervention were included in the analysis. Data extraction was conducted by two authors, independently (M. D and A.GH). Subsequently, full texts studies were assessed, and discrepancies were resolved through discussion with a third, independent researcher. In the case of multiple publications with duplicate/overlapped data for the same trial, we selected the publication with comprehensive and complete data.

Quality assessment of studies

We appraised the quality of relevant trials based on the Cochrane criteria [23], which is composed of the following ones: sequence generation sufficiency, allocation concealment, blinding, clarification of failures (imperfect outcome data) and selective outcome reporting. According to the Cochrane's Handbook, studies were ranked as low (L), or high risk of bias (H) or unclear (U) regarding each field.

Statistical analysis

All analyses were performed using STATA software version 12 (STATA corp, College Station, TX, USA). The mean difference (WMD) and the standard deviation (SD) of the alanine aminotransferase (ALT), aspartate aminotransferase (AST), Gamma-glutamyl transferase (GGT), alkaline phosphatase (AL) and bilirubin between the intervention and control groups were applied to calculate overall effect size. The SD of the mean difference for not reported studies was calculated by the following formula: SD = square root [(SD pre-treatment) ^{2} + (SD post-treatment) ^{2} – (2 × R × SD pretreatment × SD post-treatment)], where correlation coefficient (R) was considered as 0.5 [24]. To make sure that our meta-analysis is not sensitive to the selected correlation coefficient (R = 0.5), we used correlation coefficients (R) 0.2 and 0.8 for reporting all the analyses of body indices. Random-effects models were used to conduct all meta-analyses. The heterogeneity between studies was examined by the I-squared (I^2) index. We carried out subgroup analysis based on dosage of resveratrol (≥ 1000 mg/day and < 1000 mg/day), study duration (> 12 weeks and ≤ 12 weeks), study population (healthy and unhealthy), baseline BMI (≥ 30 and < 30), gender (men and both) and (≥ 48y and < 48y) to assess the impact of this variable on outcomes.

Rather, sensitivity analyses were performed to explore the extent to which inferences might depend on a particular study or group of studies. We also evaluated publication bias by two formal tests, the Begg-adjusted rank correlation test and the Egger's regression asymmetry test.

Results

Search results and study selection

Briefly, the initial literature search provided 3560 articles from all the electronic reference databases, we removed 2204 duplicate articles. After screening the titles and abstracts of these articles 1320 abstracts were deemed to be potentially irrelevant for the meta-analysis. In the next step, full-text articles were carefully appraised, then twenty-one papers were excluded based on the full-text review. These exclusions were because of the following reasons: administered resveratrol in combination with other (n = 5), duplicate dataset (n = 6), not having placebo group (n = 3), studies that did not provide sufficient data for outcomes (n = 7). Finally, fifteen trials [25-39] were included in this meta-analysis. Of these, all trials [25-39] reported the effect of resveratrol on ALT, twelve articles [25-30,32,33,36-39] on AST, seven articles [25,29,30,32,33,37,39] on GGT, four trials on ALP [26,32,37,39] and five trials [26,28,30,32,36] on bilirubin. The process of study identification is presented in **Figure 1**.

Characteristics of the included studies

The main characteristics of eligible trials, which were performed in 2013 and 2018, are summarized in **Table 1**. These trials used parallel designs. Out of fifteen included studies, six studies performed in Europe [32-36,39], two in America [25,26], six studies in Asia [27,29-31,37,38] and one study in Australia [28]. Participant's age ranged from 21 to 73 years. Six studies [25,28,31,34,35,39] were conducted exclusively on males, and nine [26,27,29,30,32,33,36-38] were performed on both genders. Resveratrol dose ranged from 100 to 3000 g/day, and intervention duration ranged from 4 to 52 weeks. Included studies were carried-out in subjects with overweight and obese adults [26,33,35], T2DM [31,37-39], metabolic syndrome [34], non-alcoholic fatty liver (NAFLD) [27-30,32] and healthy volunteers [25,36]. Also in two studies, the unit of measurement of the enzymes was mg / dl which was different from the other (IU/L), so we excluded them. In both studies, resveratrol significantly reduced the levels of some liver enzymes [40,41].

Risk of bias assessment

Table 2 presents a quality assessment of included studies based on the Cochrane collaboration's risk of bias assessment tool [23]. According to a random sequence generation, six studies were characterized by lack of information [26,32-34,38,39] and one study showed high risk of bias [25]. Also, all studies provided sufficient data on allocation concealment and showed low risk of bias regarding blinding of participants and personnel, nonetheless most studies showed unclear risk of bias based on blinding of outcome assessment. However, all included studies showed low risk of bias according to incomplete outcome data except two studies [25,34].

Effect of resveratrol supplementation on ALT

Overall, fifteen eligible studies [25-39], including a total of 714 participants (327 intervention, 342 placebo), examined the effect of resveratrol supplementation on ALT. Combining their findings, based on the random effects model, we found that ALT was not affected by resveratrol supplementation (WMD: 0 IU/L, 95% CI: -3.17 to 3.17, p = 0.99), with a significant between-study heterogeneity (I^2 = 74.2%, p < .001; **Figure 2**). Subgroup analysis based on dosage (< 1000 mg/day vs ≥ 1000 mg/day), (duration > 12-week vs duration ≤ 12 week), (baseline BMI < 30 vs baseline BMI ≥ 30), gender (Men and both), (age < 48y vs age ≥ 48y) Could not explain the source of heterogeneity, although supplementation of resveratrol with longer duration (> 12 week) (WMD: -2.96 IU/L, 95% CI: -12.68 to 6.76), and in subjects younger than 48 years (WMD: -3.66 IU/L, 95% CI: -8.42 to 1.10), had a greater effect size then overall **(Table 3)**.

Effect of resveratrol supplementation on AST

Twelve articles [25-30,32,33,36-39], including a total of 614 subjects (313 intervention, 301 placebo), reported the effect of resveratrol consumption on AST. Pooled effect size did not show any significant effect of resveratrol supplementation on AST (WMD: -2.40 IU/L, 95% CI: -5.45 to 0.65, p = 0.11), with a significant between-study heterogeneity (I^2 = 82.9%, p < .001) **(Figure 3**). Subgroup analysis based on dosage (< 1000 mg/day ≥ 1000 mg/day), (duration > 12 week, duration ≤ 12 week), (baseline BMI < 30, baseline BMI ≥ 30), gender (Men, both) could not eliminate heterogeneity, although subgroup analysis based on age showed significant effects of resveratrol on AST in younger subjects (age < 48y) (WMD: -5.91 IU/L, 95% CI: -10 to -1.83), also the results revealed that resveratrol supplementation was more effective in longer periods (> 12 week) (WMD: -11.78 IU/L, 95% CI: -42.75 to 19.19) and in non-obese individuals (WMD: -2.76 IU/L, 95% CI: -6.22 to 0.70) **(Table 3)**.

Effect of resveratrol supplementation on GGT

Seven articles [25,29,30,32,33,37,39], including a total of 394 subjects (198 intervention, 196 placebo), reported the effect of resveratrol consumption on GGT. Pooled effect size did not show any significant effect of resveratrol supplementation on GGT (WMD: -1.26 IU/L, 95% CI: -4.64 to 2.13, p = 0.64) (**Figure 4**). Also between-study heterogeneity was not significant (I^2 = 23.7%, ***p*** = 0.248). Subgroup analysis based on duration and dosage showed a significant reduction of GGT in the subset of studies with ≤ 12 weeks' duration (WMD: WMD: -2.64 IU/L, 95% CI: -4.08 to -1.19) and dosage of < 1000 mg/day (WMD: -2.73 IU/L, 95% CI: -4.17 to -1.28). Also, additional subgroup analysis showed a significant decrease in GGT in younger subjects (age < 48y) (WMD: -2.78 IU/L, 95% CI: -4.25 to -1.32) with baseline BMI< 30 (WMD: -2.64 IU/L, 95% CI: -4.08 to -1.19) **(Table 3)**.

Effect of resveratrol supplementation on ALP

Overall, four clinical trials [26,32,37,39], including a total of 148 subjects (81 intervention and 67 placebo), reported the effect of resveratrol consumption on ALP. Pooled effect size did not show any significant effect of resveratrol supplementation on ALP (WMD: 3.80 IU/L, 95% CI: -4.65 to 12.25, p = 0.37) (**Figure 5**). Also between-study heterogeneity was not significant (I^2 = 29.9%, p =0.22). We could not perform subgroup analysis due to a lack of eligible studies. The sensitivity analysis showed that overall estimates were not affected by elimination of any individual study.

Effect of resveratrol supplementation on bilirubin

Five clinical trials [26,28,30,32,36], including a total of 208 subjects (120 intervention and 88 placebo), reported the effect of resveratrol consumption on bilirubin. Pooled effect size did not show any significant effect of resveratrol supplementation on bilirubin (WMD: 0.13 IU/L, 95% CI: -0.43 to 0.17, p = 0.39) (**Figure 6**). Also between-study heterogeneity was not significant (I^2 = 8.9%, *p* =0.35). We could not perform subgroup analysis due to lack of eligible studies. The sensitivity analysis showed that overall estimates were not affected by elimination of any individual study.

Sensitivity analysis

The sensitivity analysis suggested that overall estimates for serum ALT, AST, GGT, ALP and bilirubin were not affected by elimination of any individual study.

Publication bias

No evidence of publication bias was found for ALT (p= 0.24, Begg's test and p= 0.06, Egger's test), AST (p= 0.1, Begg's test and p= 0.67, Egger's test), GGT (p=0.055, Begg's test and p=0.66, Egger's test), ALP (p=0.62, Begg's test and p= 0.83, Egger's test) and bilirubin (p=0.34, Begg's test and p= 0.39, Egger's test).

Discussion

Despite the beneficial effects of plant on the health and treatment of numerous diseases, there are currently concerns about their potential useful or harmful effects on liver function. Resveratrol is one of the plants that is currently widely used for its antioxidant, anti-inflammatory and anti-apoptotic effects [14-16] in liver disease. To the best of our knowledge, the present study is the first systematic review and meta-analysis of outcomes from fifteen RCTs on the efficacy of resveratrol supplementation on liver function.

The results of our meta-analysis did not show any significant changes in ALT, AST, GGT, ALP and bilirubin after supplementation with resveratrol, but subgroup analysis illustrate resveratrol had a greater effect size than the overall outcome in the longer term (> 12 week) and younger subjects (age < 48y), but could not explain the source of significant between-study heterogeneity in the effects of resveratrol on ALT and AST.

Resveratrol is a type of natural plant polyphenol specifically present in red grapes, it has anti-aging, anti-inflammatory, and that might be linked to chronic diseases and/or length of life in humans [42-45]. Animal and human studies illustrated resveratrol supplementation has many benefits, including protection against cardiovascular disease and chronic inflammation by reducing LDL oxidation and platelet aggregation [46], improvement of insulin sensitivity [47,48] and dyslipidaemia [49], reduced systolic and diastolic blood pressure [50], promoting brain health and preventing neurological disorders such as Alzheimer's [51], however, the present results did not reveal the beneficial effect of resveratrol use on liver enzymes.

Previous studies regarding the effect of resveratrol supplementation on liver function have shown conflicting results. Similar to our study, two meta-analyzes showed that resveratrol consumption had no effect on ALT and AST levels [52,53]. Heebøll et al. consistently demonstrated that resveratrol treatment had no therapeutic benefit on ALT levels in NAFLD [32]. In contrast,

Faghihzadeh et al. reported that 12 weeks of 500 mg of decreases ALT levels and hepatic steatosis in NAFLD patients [30], and chen et al. demonstrated that 300 mg/d resveratrol significantly decreased AST and ALT levels [29], however, in Chachi et al.'s study, liver enzyme levels elevated after 6 weeks of resveratrol supplementation [28]. In addition, most animal studies have demonstrated that the administration of resveratrol significantly reduced ALT, AST and GGT [54,55].These previous outcomes are antithesis, therefore, further high-quality RCTs should be done for resolve these discrepancy.

The bases for the beneficial effects of resveratrol on liver function are not totally elucidated but the mechanism may involve the following aspects: resveratrol significantly enhanced survival after liver transplantation, diminished fat accumulation, necrosis, and apoptosis which induced by ischemia in rats. It's protects the liver from chemical and alcohol injury[56]. Resveratrol can ameliorate glucose homeostasis and lipid metabolism and lessen liver fibrosis and steatosis, in fact, in addition to its direct antioxidant effects and reduced ROS production, resveratrol increases antioxidant enzymes gene expression and the activity of silent information regulator 2/sirtuin-1 (Sirt-1) and adenosine monophosphate activated protein kinase (AMP-K), two key factors in regulating lipid and glucose metabolism [46]. Upregulation of SIRT1 is associated with suppression of lipogenic genes expression, improved insulin sensitivity, serum lipid profile and reduced steatosis [57]. Resveratrol can also reduce inflammation by inhibiting cellular stress, suppressing inflammatory gene expression, and enhancing peroxisome receptor-proliferative activity[58].

It seems that one of possible reason for the lack of effect of resveratrol on liver enzymes was the length of the supplementation period, so that the results of our subgroup analysis showed that resveratrol supplementation over longer periods improved the liver enzymes especially ALT and AST, so further studies are needed with longer periods in this area. Another possible reason is the age of the participants, so the results of the subgroup analysis showed that resveratrol supplementation in younger people had a greater effect on liver enzyme levels, especially GGT, because older people were considered to be high risk groups. Subgroup analysis also showed that resveratrol at a dose of less than 1000 mg significantly reduced GGT levels. In addition, the included trials were carried out in study populations with various health conditions, therefore the interpretation of the results in this context is complicated.

The present study has a few strengths and limitations. This meta-analysis only includes RCTs and there were no time limitations for the literature search. However, significant statistical

heterogeneity was found among the eligible studies, which may be because of differences in the intervention term, study population, sample size and daily dosages of resveratrol. Furthermore, the trials included participants with different health conditions, therefore prospective studies in people with specific conditions are necessary to achieve definitive results. Also in two studies, the unit of measurement of the enzymes was mg / dl which was different from the other (IU/L), so we excluded them. In the case of bilirubin and ALP, due to a lack of eligible studies, we could not perform subgroup analysis. In addition, we did not register the protocol of the current study on PROSPERO registry system due to the delay in processing the submitted protocols for studies outside the UK. This lack of registration might be a source of bias for this review. However, this review and meta-analysis was designed and performed according to the Cochrane guidelines.

Conclusion

In conclusion, present meta-analysis indicated that resveratrol supplementation had no significant effect on liver function tests such as ALT, AST, GGT, ALP and bilirubin. Further analysis indicated that resveratrol supplementation had a greater effect size than the overall outcome in the longer term (> 12 week)and younger subjects (age < 48y). However, further well designed, large-scale studies are needed in the future.

Conflict of interest

The authors declare no conflict of interest.

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Author Contribution

E.K and A.Gh wrote the concept, design, and carried out drafting of this study. E.K and A.Gh performed searches of the electronic databases, screened the articles and extracted the data. A.H performed the acquisition, analysis, and interpretation of data. E.K and A.Gh critically revised the manuscript. A.H. performed a final revision and proofread of the article. All authors approved the final version of the manuscript. M.D and A.Gh are the guarantors of this study.

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Legends of figures:

Figure 1: Preferred reporting items for systematic reviews and meta-analyses flow diagram of study selection process

Figure 2: Forest plot of the effect of resveratrol supplementation on ALT.

Figure 3: Forest plot of the effect of resveratrol supplementation on AST.

Figure 4: Forest plot of the effect of resveratrol supplementation on GGT.

Figure 5: Forest plot of the effect of resveratrol supplementation on ALP.

Figure 6: Forest plot of the effect of resveratrol supplementation on bilirubin.

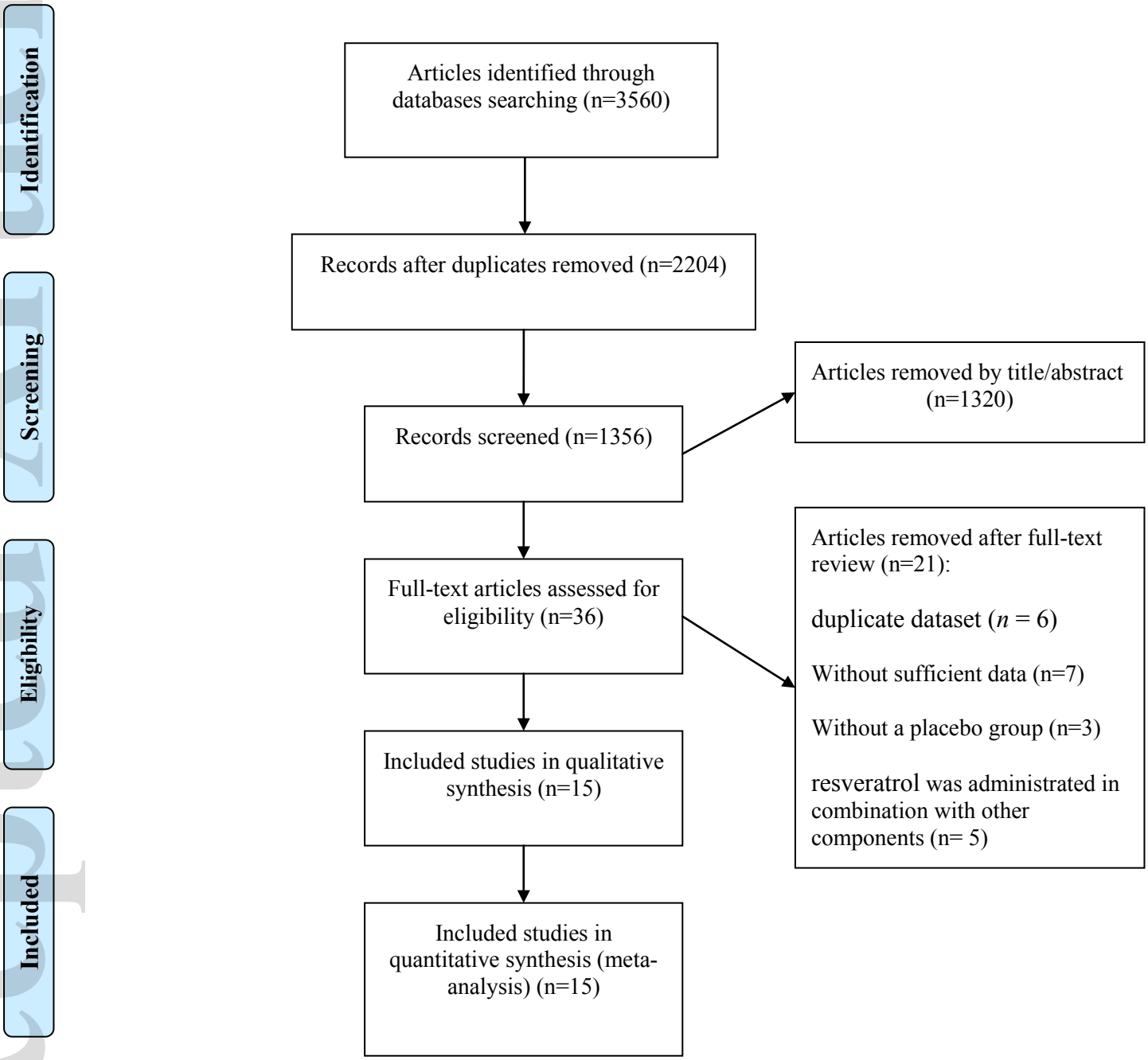

Figure 1

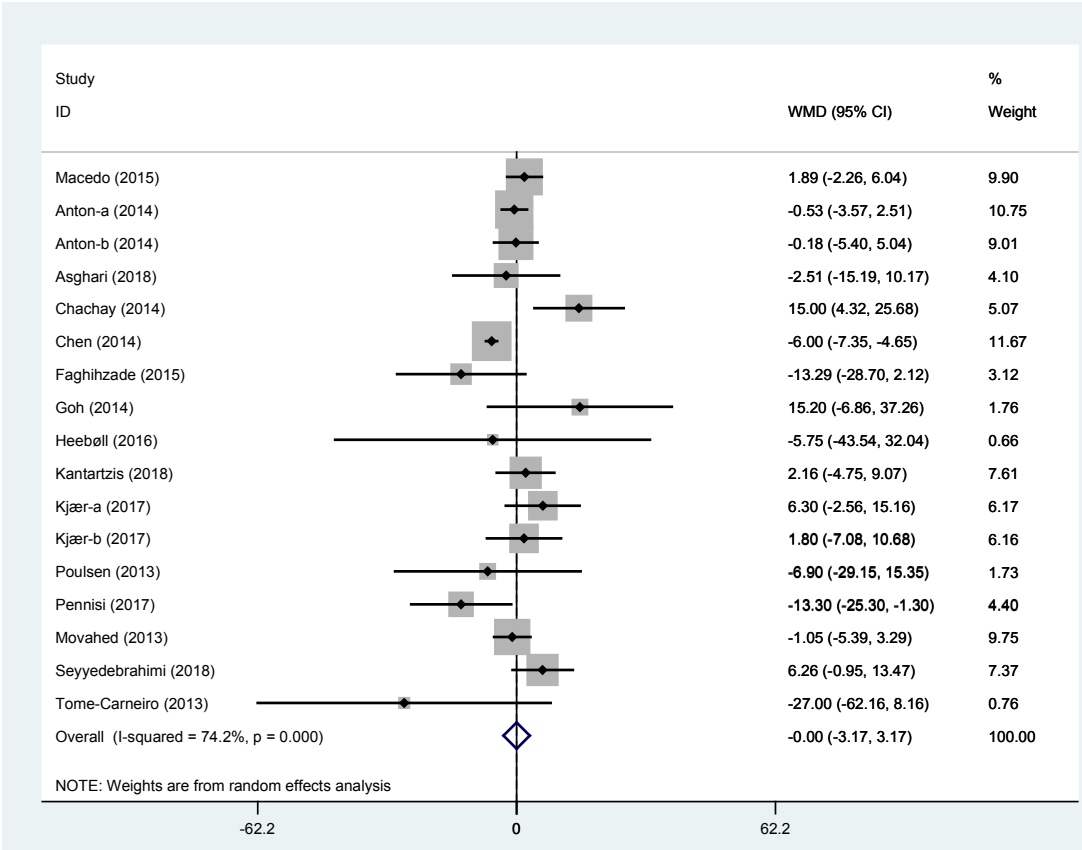

Figure 2

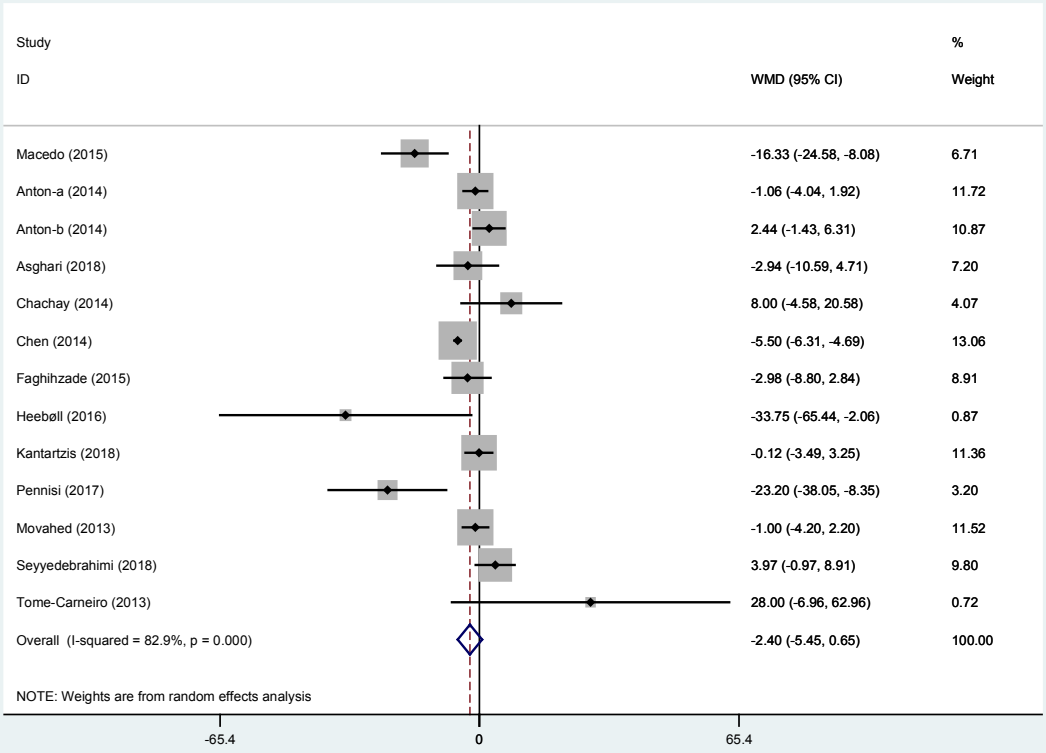

Figure 3

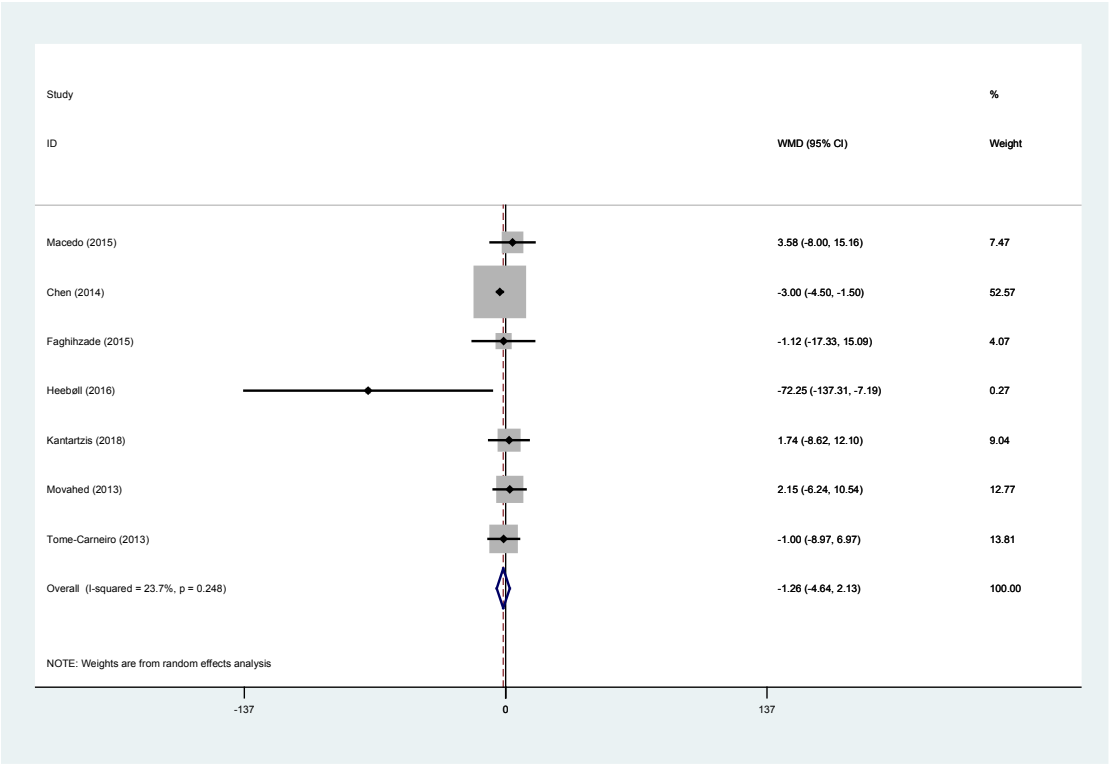

Figure 4

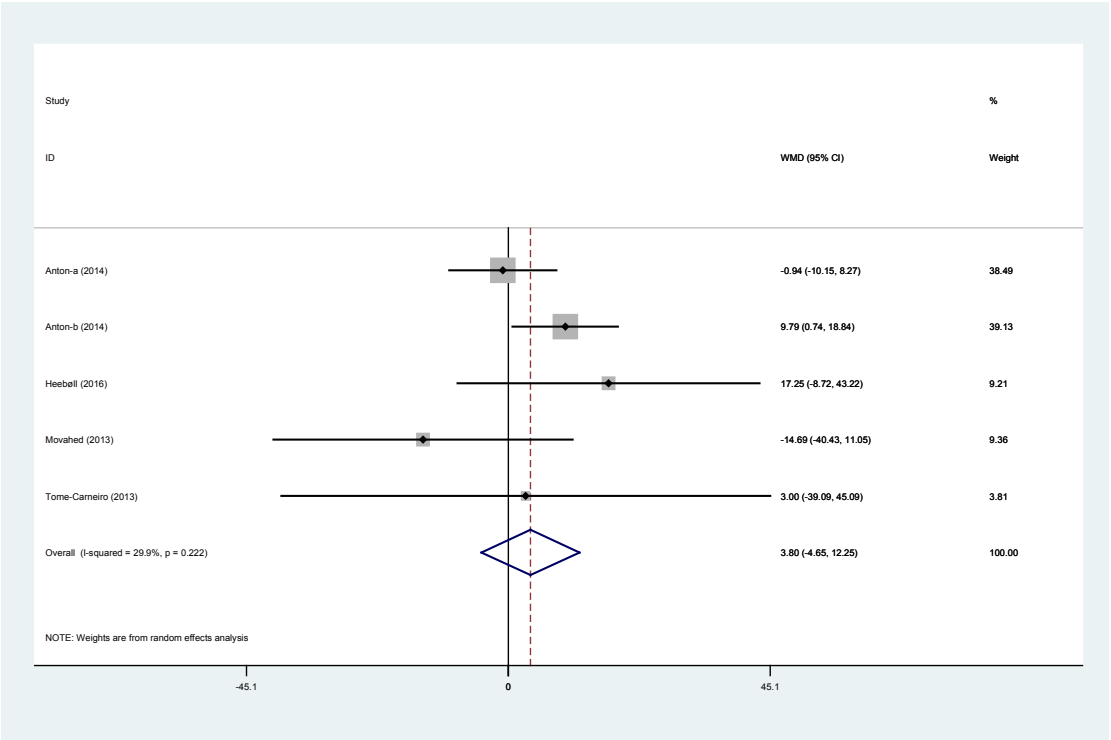

Figure 5

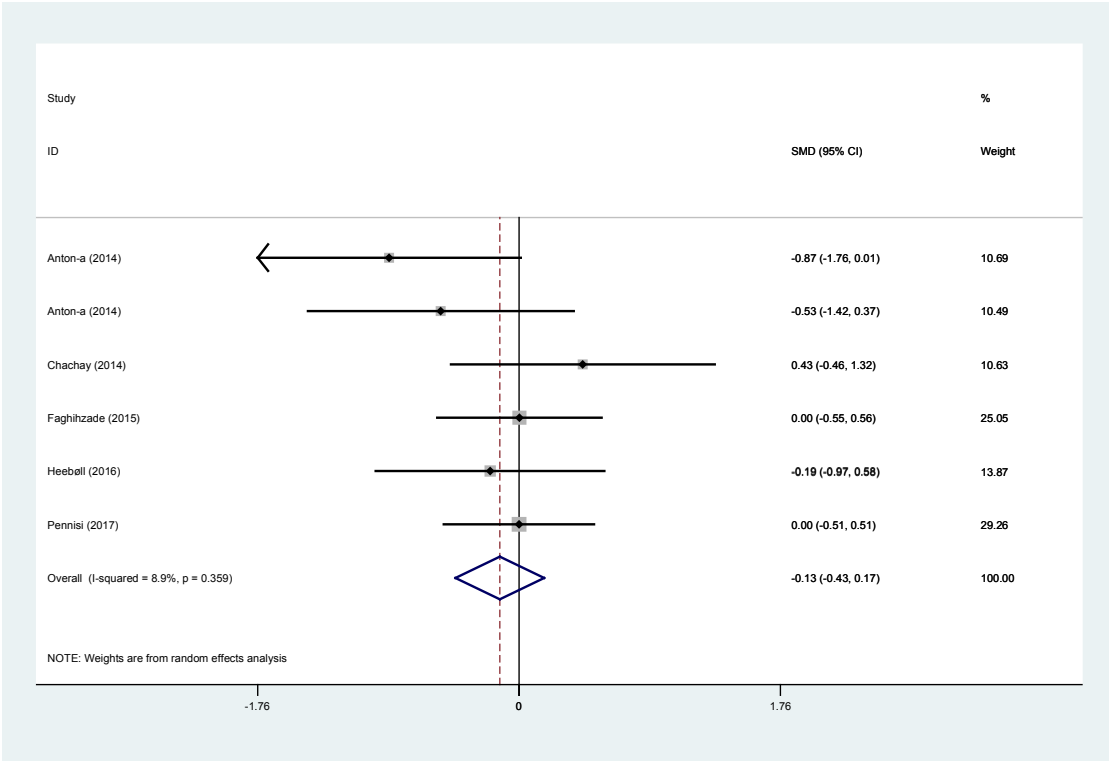

Figure 6