Effect of resveratrol on glucose control and insulin sensitivity: a meta-analysis of 11 randomized controlled trials[1–3]

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ABSTRACT

Background: The results of human clinical trials investigating the effects of resveratrol on glucose control and insulin sensitivity are inconsistent.

Objective: We aimed to quantitatively evaluate the effects of resveratrol on glucose control and insulin sensitivity.

Design: We performed a strategic literature search of PubMed, Embase, MEDLINE, and the Cochrane Library (updated to March 2014) for randomized controlled trials that estimated the effects of resveratrol on glucose control and insulin sensitivity. Study quality was assessed by using the Jadad scale. Weighted mean differences were calculated for net changes in glycemic measures by using fixed-effects or random-effects models. We performed prespecified subgroup and sensitivity analyses to evaluate potential heterogeneity. Meta-regression analyses were conducted to investigate dose effects of resveratrol on fasting glucose and insulin concentrations in nondiabetic subjects.

Results: Eleven studies comprising a total of 388 subjects were included in this meta-analysis. Resveratrol consumption significantly reduced fasting glucose, insulin, glycated hemoglobin, and insulin resistance (measured by using the homeostatic model assessment) levels in participants with diabetes. No significant effect of resveratrol on glycemic measures of nondiabetic participants was found in the meta-analysis. Subgroup and sensitivity analyses indicated that the pooled effects of resveratrol on fasting glucose and insulin concentrations in nondiabetic participants were not affected by body mass index, study design, resveratrol dose, study duration, or Jadad score.

Conclusions: Resveratrol significantly improves glucose control and insulin sensitivity in persons with diabetes but does not affect glycemic measures in nondiabetic persons. Additional high-quality studies are needed to further evaluate the potential benefits of resveratrol in humans. *Am J Clin Nutr* 2014;99:1510–9.

INTRODUCTION

Diabetes mellitus is one of the most important public health burdens, and its prevalence has rapidly increased worldwide over the past decades. Global estimates suggest that the number of people with diabetes mellitus will rise to 552 million by 2030 (1, 2). Moreover, the population of people with impaired glucose tolerance, who are likely to develop type 2 diabetes mellitus (T2DM)[4], is projected to reach 472 million in 2030 (3). Epidemiology data show that the prevalence of diabetes can be attributed to associated lifestyle changes, aging, and urbanization (4). Lifestyle modifications can improve hyperglycemic status, and, in turn, decrease the complications and morbidity of diabetes. Therefore, lifestyle interventions, including nutritional interventions, have been incorporated into guidelines for diabetes prevention (5).

Although a previous meta-analysis (6) found that 3 or more daily servings of a variety of fruit were not associated with a substantial reduction of T2DM risk (7–10), Muraki et al (11) found that greater consumption of grapes was significantly associated with a lower risk of T2DM. Resveratrol, a natural polyphenolic compound that mainly exists in the skin of red grapes, has been reported to improve glucose tolerance and insulin sensitivity at a dose ranging from 2.5 to 400 mg $\cdot$ kg^{-1} $\cdot$ d^{-1} (median: 200 mg $\cdot$ kg^{-1} $\cdot$ d^{-1}) in several animal studies (12–15). In addition, a recent study suggested that 4.9 mg resveratrol $\cdot$ kg^{-1} $\cdot$ d^{-1} can mimic the effect of calorie restriction on insulin-mediated glucose uptake in isolated mouse skeletal muscles (16). Moreover, one study even found that the administration of 1.5 mg resveratrol $\cdot$ kg^{-1} $\cdot$ d^{-1} can stimulate glucose uptake in the absence of insulin in streptozotocin-induced diabetic rats (17). Furthermore, resveratrol can reduce adiposity in the whole organism by decreasing the accumulation of triglycerides in fat cells, which may in turn improve insulin resistance (18). Therefore, we hypothesized that resveratrol may have a favorable effect on the prevention and control of diabetes by regulating glucose metabolism and insulin sensitivity. However, the results of human clinical trials investigating the effect of resveratrol on glucose control and insulin sensitivity have been inconsistent. Thus, we conducted a meta-analysis of all published randomized controlled trials (RCTs) to quantitatively assess the effect of resveratrol on measures of glucose control and insulin sensitivity based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

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[4] Abbreviations: Hb A_{1c}, glycated hemoglobin; RCT, randomized controlled trial; T2DM, type 2 diabetes mellitus.

Received December 16, 2013. Accepted for publication March 13, 2014.
First published online April 2, 2014; doi: 10.3945/ajcn.113.082024.

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METHODS

Search strategy

PubMed (up to March 2014; http://www.ncbi.nlm.nih.gov/pubmed/), Embase (1980 to March 2014; http://www.embase.com/search/advanced/; records from Embase), MEDLINE (up to March 2014; http://embase.com/search/advanced/; records from MEDLINE), and the Cochrane Library (1985 to March 2014; http://www.cochrane.org/) were searched by using the following terms in the title and abstract: resveratrol OR resveratrols. The search was restricted to clinical trials in humans. References in reference lists and reviews were hand-searched to further identify RCTs examining the effects of resveratrol on glucose control and insulin sensitivity in humans.

Study selection

We selected studies for the analysis that met the following criteria: *1*) subjects ingested resveratrol for ≥2 wk; *2*) the study was an RCT in humans with either a parallel or crossover design; *3*) the baseline and endpoint values for fasting glucose, insulin, or glycated hemoglobin (Hb A_{1c}) or HOMA-IR (or their differences) with SDs, SEMs, or 95% CIs were available for each group in the study; *4*) resveratrol was not given as part of a multicomponent supplement, such as grape, grape juice, or wine in the study; *5*) the study used a concurrent control group for the resveratrol intervention group, and the only difference between the control and treatment groups was resveratrol.

Quality assessment

We evaluated the quality of the studies for potential inclusion in the meta-analysis by using the Jadad scoring criteria: *1*) randomization (the study was described as randomized), *2*) double blinding (participant masking and researcher masking), *3*) reporting of the number of dropouts and reasons for withdrawal, *4*) allocation concealment, and *5*) generation of random numbers (by using computer, random numbers table, shuffled cards, or tossed coins). RCTs scored 1 point for each area addressed in the study design for a possible score between 0 and 5 (highest level of quality) (19). A score ≥4 indicated a high-quality study, whereas a score <4 indicated a lower-quality study.

Data extraction

We collected the data with the use of a pilot-tested data extraction form that included the following items: *1*) study characteristics, including authors, publication year, region, sample size, study design, type of intervention, dose, treatment duration, and type of diet; *2*) population information, including age and baseline diabetes status; *3*) mean differences in changes of fasting glucose and insulin concentrations, representing primary outcome measures; and *4*) net changes in Hb A_{1c} and HOMA-IR, representing secondary outcome measures. All values were converted to mg/dL for glucose and to μIU/mL for insulin by using the conversion factors 1 mmol/L = 18 mg/dL for glucose and 1 pmol/L = 6.945 μIU/mL for insulin values. If outcomes were reported multiple times at different stages of the trials, only the final outcome concentrations, at the end of the trial, were included in the meta-analysis.

Statistical analysis

We performed this meta-analysis with the use of the STATA program (version 11; StataCorp). Intervention effects were defined as weighted mean differences and 95% CIs calculated for net changes in glucose and insulin concentrations and Hb A_{1c} and HOMA-IR values. The statistical heterogeneity was estimated by using Cochran's test ($P < 0.1$). The I^2 statistic was calculated, and $I^2 > 50\%$ indicated significant heterogeneity across studies (20). We used a random-effects model (inverse variance heterogeneity) if significant heterogeneity was shown among trials. Otherwise, we used a fixed-effects model (inverse variance).

We excluded percentage changes in mean and SD values when we extracted data for the meta-analysis. SD values were calculated from standard errors, 95% CIs, *P* values, or *t* statistics when they were not directly available. In addition, change-from-baseline SD values were imputed as suggested by Follmann et al (21), assuming a correlation coefficient of 0.5.

We used funnel plots and Egger's regression test to assess publication bias. We also performed prespecified subgroup analyses that included diabetes status, BMI, study design, type of intervention, resveratrol dose, duration, and Jadad score to examine possible sources of heterogeneity within the included studies. In addition, sensitivity analyses were performed according to the Handbook for Systematic Review of Interventions of Cochrane software (version 5.0.2; The Cochrane Collaboration). Furthermore, meta-regression analyses were conducted to investigate the dose-effect relation between resveratrol and fasting glucose and insulin concentrations.

RESULTS

Results of the literature search

The detailed process of the study selection is shown in **Figure 1**. In total, 131 articles were initially identified, and 106 articles

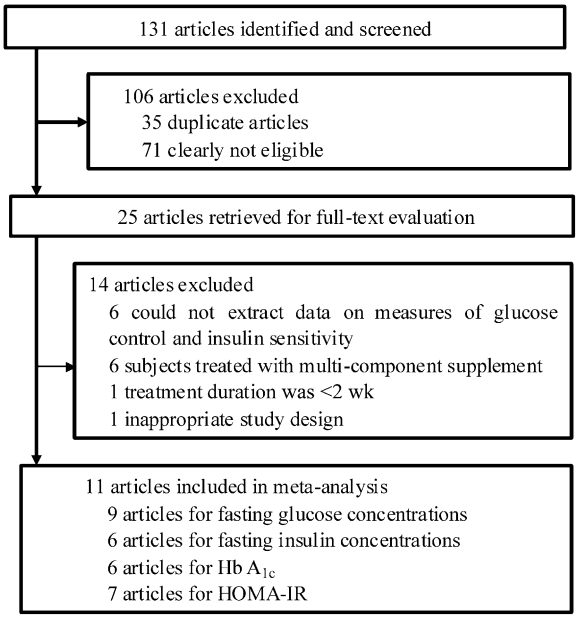

FIGURE 1. Flow diagram of the study selection procedure showing the number of eligible articles included in the meta-analysis. Hb A_{1c}, glycated hemoglobin.

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TABLE 1
Characteristics of the 11 randomized controlled trials included in the analysis[1]

Author, publication year, country (ref), continent	No. of subjects	Study design	Population and age[2]	Duration	Resveratrol group	Control group	BMI	Jadad score	Type of diet[3]
							kg/m^2		
Dash, 2013, Canada (22), North America	8	Crossover	Overweight/obese, 45.8 ± 8.77 y	2 wk	Resveratrol pills (1 g/d for 1 wk, followed by 2 g/d for the second week)	Placebo pills	31.1 ± 4.8	3	Usual diet
Poulsen, 2013, Denmark (23), Europe	24	Parallel	Obese, 44.7 ± 12.1 y	4 wk	Resveratrol tablets (1500 mg)	Placebo tablets	32.5 ± 2.1	5	Usual diet
Movahed, Iran, 2013 (24), Asia	66	Parallel	T2DM, 52.4 ± 6.2 y	45 d	Resveratrol capsules (1 g/d)	Placebo capsules (microcellulose)	27.1 ± 3.1	5	Usual diet, resveratrol-free
Bhatt, 2012, India (25), Asia	57	Parallel	T2DM, 56.7 ± 8.9 y	3 mo	Resveratrol capsules (250 mg/d) with oral hypoglycemic agents	Only oral hypoglycemic agents	24.7 ± 3.6	3	Usual diet
Yoshino, 2012, USA (26), North America	29	Parallel	Healthy, 58.2 ± 4.0 y	12 wk	Resveratrol capsules (75 mg/d)	Placebo capsules	24.2 ± 2.8	3	Usual diet
Tome-Carneiro, 2012, Spain (27), Europe	50	Parallel	CVD, 62.0 ± 9.0 y	6 mo	GE-RES capsules (16 mg)	GE capsules (without resveratrol)	32.0 ± 9.0	5	Usual diet
Tome-Carneiro, 2012, Spain (28), Europe	50	Parallel	CVD, 62.0 ± 9.0 y	6 mo	GE-RES capsules (8 mg)	GE capsules (without resveratrol)	32.1 ± 8.7	4	Usual diet
Magyar, 2012, Hungary (29), Europe	40	Parallel	CVD, 65.3 ± 9.7 y	3 mo	Resveratrol tablets (10 mg/d)	Placebo tablets	29.3 ± 2.1	4	Usual diet
Brasnyo, 2011, Hungary (30), Europe	19	Parallel	T2DM, 57.9 ± 7.9 y	4 wk	Resveratrol capsules (10 mg/d)	Placebo capsules (microcrystalline cellulose)	NR	3	NR
Fujitaka, 2011, Japan (31), Asia	34	Parallel	Metabolic syndrome, 63.0 ± 9.0 y	3 mo	Resveratrol capsules (100 mg/d)	No intervention	27.9 ± 3.8	2	Usual diet
Timmers, 2011, Netherlands (32), Europe	11	Crossover	Obese, 52.5 ± 7.0 y	30 d	Resveratrol capsules (150 mg/d)	Placebo capsules	31.5 ± 2.7	3	Usual diet, resveratrol-free

[1] CVD, cardiovascular disease; GE, grape extract; GE-RES, grape extract containing resveratrol; NR, not reported; ref, reference; T2DM, type 2 diabetes mellitus.
[2] Age is provided as mean ± SD.
[3] The usual diet was similar to a conventional diet.

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were excluded, either because of duplication or because they were deemed irrelevant to this meta-analysis after careful review of the titles and abstracts. In addition, of the 25 trials that remained, an additional 14 articles were excluded for various reasons: 6 articles were excluded because they did not contain data on fasting glucose or insulin concentrations or Hb A_{1c} or HOMA-IR, 6 studies were discarded because resveratrol was given as part of a multicomponent supplement, 1 study was excluded because the duration of resveratrol treatment was <2 wk, and 1 study was excluded because it used an open-label, uncontrolled design. Thus, 11 articles were ultimately selected for inclusion in the meta-analysis (22–32).

Study characteristics

A summary of the study characteristics included in the meta-analysis is presented in **Table 1**. In total, 388 subjects were included in the 11 eligible studies, and the total number of subjects included in each study ranged from 8 to 66 subjects. Resveratrol dosing ranged from 8 to 1500 mg/d (median: 100 mg/d), and the duration of resveratrol intervention varied from 2 wk to 6 mo (median: 12 wk). Three trials selected subjects with T2DM; of the remaining 8 trials, 3 trials were conducted in patients with cardiovascular diseases, 3 trials were conducted in participants with obesity, 1 study included patients with the metabolic syndrome, and 1 study was performed in healthy subjects. Most of the studies (9 of 11) used a parallel design. Eight of the 11 selected RCTs included overweight or obese subjects with a BMI (in kg/m^2) ≥25. Eight of the 11 studies suggested that the subjects maintain a usual diet, 2 studies imposed restrictions on resveratrol intake, and 1 study did not report dietary information.

Data quality

Study quality was assessed by using the Jadad scale, and the results varied. Five of the included trials (23, 24, 27–29) were classified as high quality (Jadad score ≥4), and the remaining 6 trials were classified as lower quality (Jadad score <4). Four of the 5 high-quality trials had adequate allocation concealment (ie, conducted by a third-party or used opaque envelopes) and reported the use of random number generation or a randomization list. Nine of the 11 RCTs used a double-blind design, 1 trial was unclear, and 1 trial used an open-label design. Details related to dropouts were reported in all of the studies, unless there was no dropout.

Effect of resveratrol on glucose control and insulin sensitivity

As shown in **Figures 2–5**, resveratrol did not significantly affect fasting glucose and insulin concentrations or Hb A_{1c} and HOMA-IR values in nondiabetic participants, but significantly reduced these measures in diabetic participants. No significant

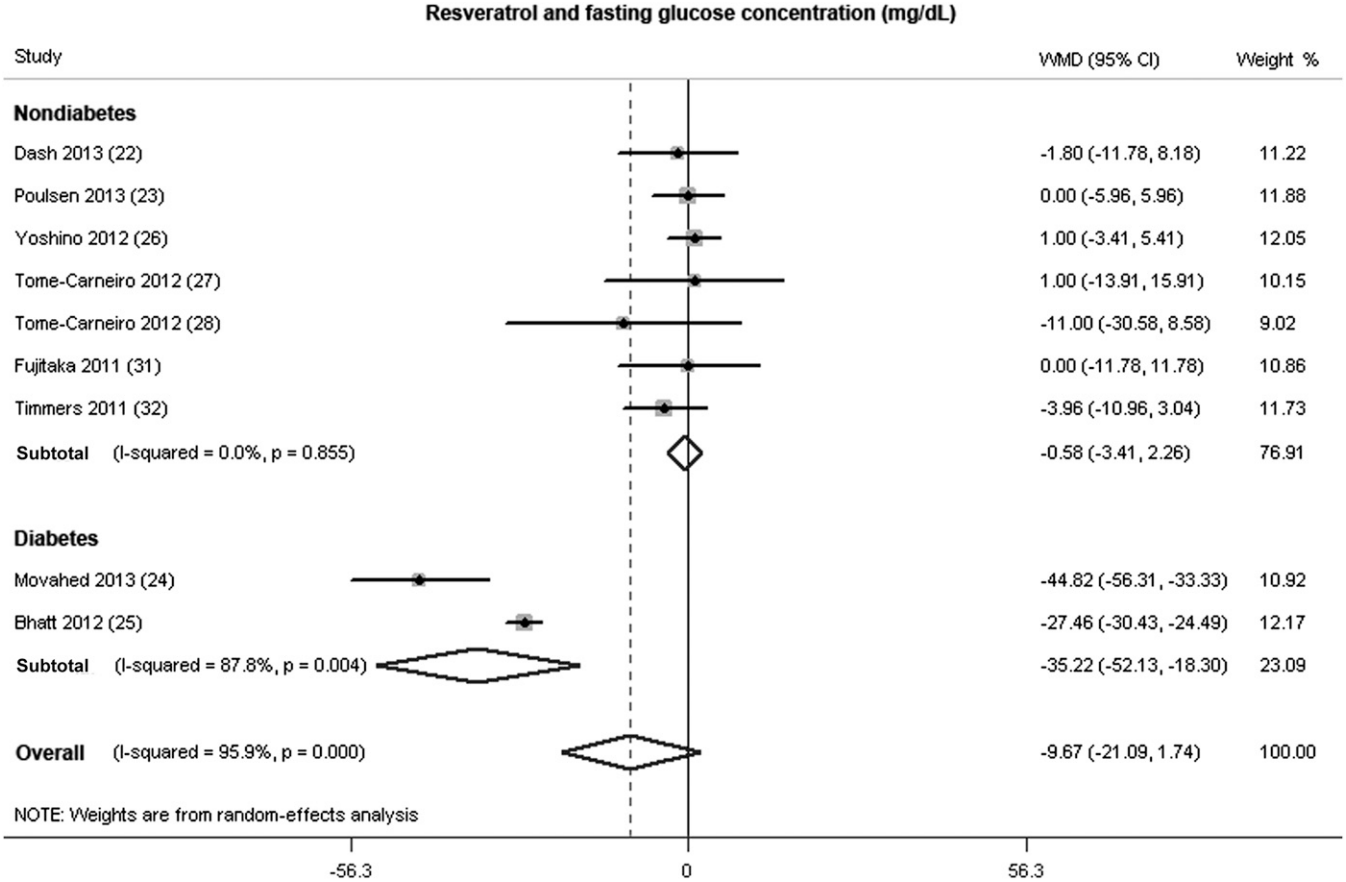

FIGURE 2. Meta-analysis of the effects of resveratrol on fasting glucose concentrations. Weight was assigned by STATA (version 11; StataCorp) using the number of subjects and SD. Sizes of data markers indicate the weight of each study in the analysis. The diamond represents the overall estimated effect, and the result was obtained from a random-effects model. WMD, weighted mean difference.

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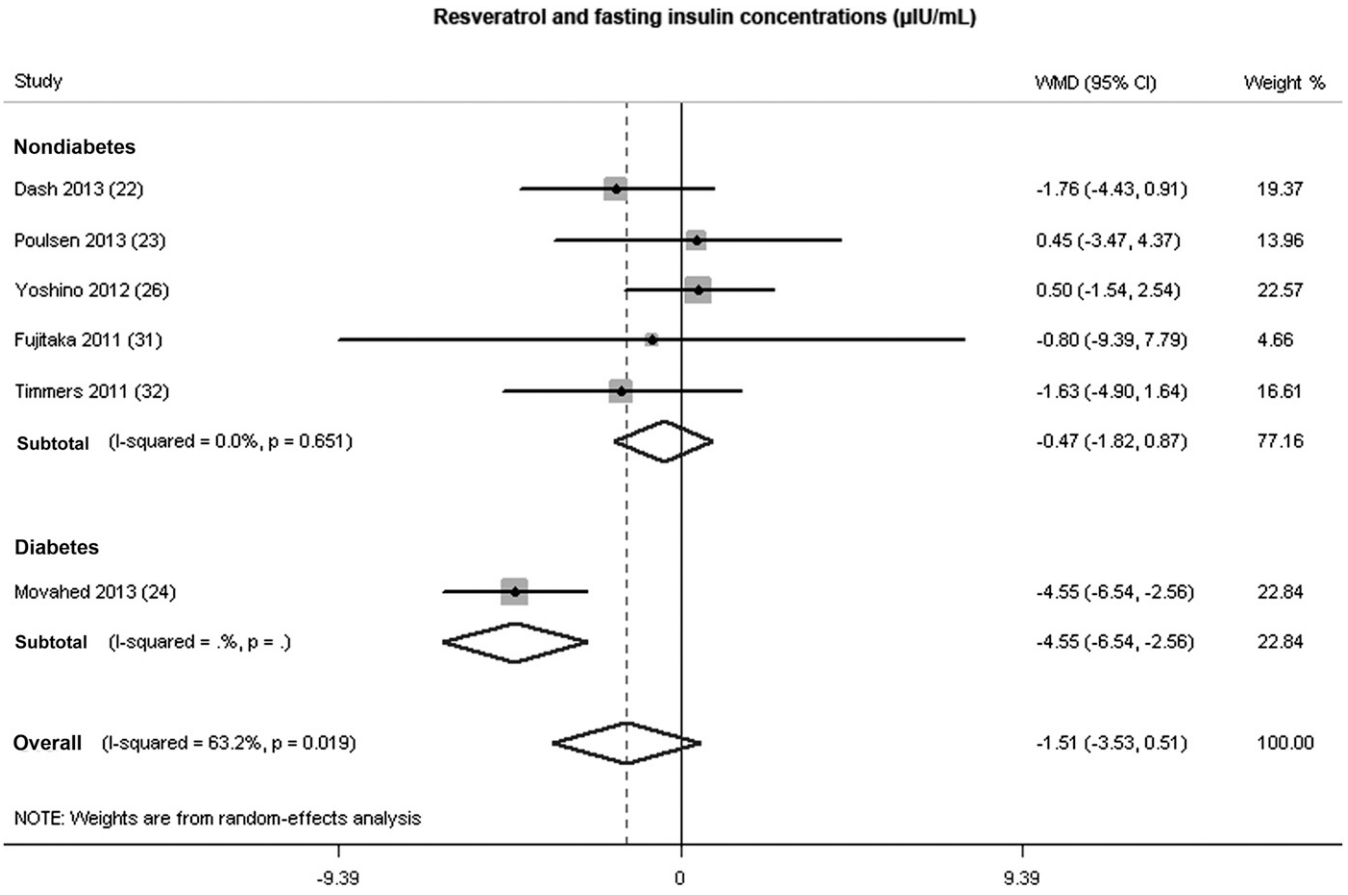

FIGURE 3. Meta-analysis of the effects of resveratrol on fasting insulin concentrations. Weight was assigned by STATA (version 11; StataCorp) using the number of subjects and SD. Sizes of data markers indicate the weight of each study in this analysis. The diamond represents the overall estimated effect, and the result was obtained from a random-effects model. WMD, weighted mean difference.

heterogeneity was found for the outcomes in nondiabetic participants. However, we observed significant between-study heterogeneity in the effects of resveratrol on blood glycemic measures in subjects with T2DM (Figures 2–5). For trials that reported data on fasting glucose concentrations, a significant reduction in fasting glucose concentrations was observed in subjects with diabetes (−35.22 mg/dL; 95% CI: −52.13, −18.30 mg/dL; $P < 0.01$) compared with control subjects. The mean difference in change in fasting insulin concentrations, Hb A_{1c}, and HOMA-IR was also found to be significantly different in participants with diabetes: −4.55 μIU/mL (95% CI: −6.54, −2.56 μIU/mL; $P < 0.01$), −0.79% (95% CI: −1.48, −0.11%; $P = 0.02$), and −2.25 (95% CI: −3.58, −0.93; $P < 0.01$).

Subgroup and sensitivity analyses

We conducted subgroup analyses (**Table 2**) to explore the effect of BMI, study design, resveratrol dose, treatment duration, and study quality on the overall effects of resveratrol on nondiabetic participants. The resveratrol dose was categorized as either a high dose (≥100 mg/d) or a low dose (<100 mg/d). An additional subgroup analysis was conducted by dividing the treatment duration into a longer-term subgroup (≥12 wk) and a shorter-term subgroup (<12 wk). Subgroup analyses indicated that the pooled effects of resveratrol on fasting glucose and insulin concentrations (Table 2) as well as Hb A_{1c} and HOMA-IR values (data not shown) in nondiabetic participants were not influenced by BMI, study design, type of intervention, study duration, or Jadad score. Meta-regression analyses did not indicate dose effects of resveratrol on fasting glucose and insulin concentrations in nondiabetic subjects. The sensitivity analysis showed that the pooled effects of resveratrol on fasting glucose and insulin concentrations did not change after imputation using a correlation coefficient of 0.5. Finally, systematic removal of each trial during sensitivity analyses did not significantly change the overall effects of resveratrol on fasting glucose and insulin concentrations.

Publication bias

The funnel plots were symmetrical and Egger's tests showed no significant publication bias in the current meta-analysis of fasting glucose, fasting insulin, Hb A_{1c}, and HOMA-IR (Egger's test: $P = 0.35$, 0.65, 0.33, and 0.26, respectively).

DISCUSSION

Our meta-analysis showed that resveratrol intervention significantly reduced fasting glucose (2 studies) and insulin (1 study) concentrations and decreased Hb A_{1c} (2 studies) and HOMA-IR (2 studies) values in subjects with T2DM. However, resveratrol did not significantly affect measures of glucose control and insulin sensitivity in nondiabetic participants. Subgroup analyses

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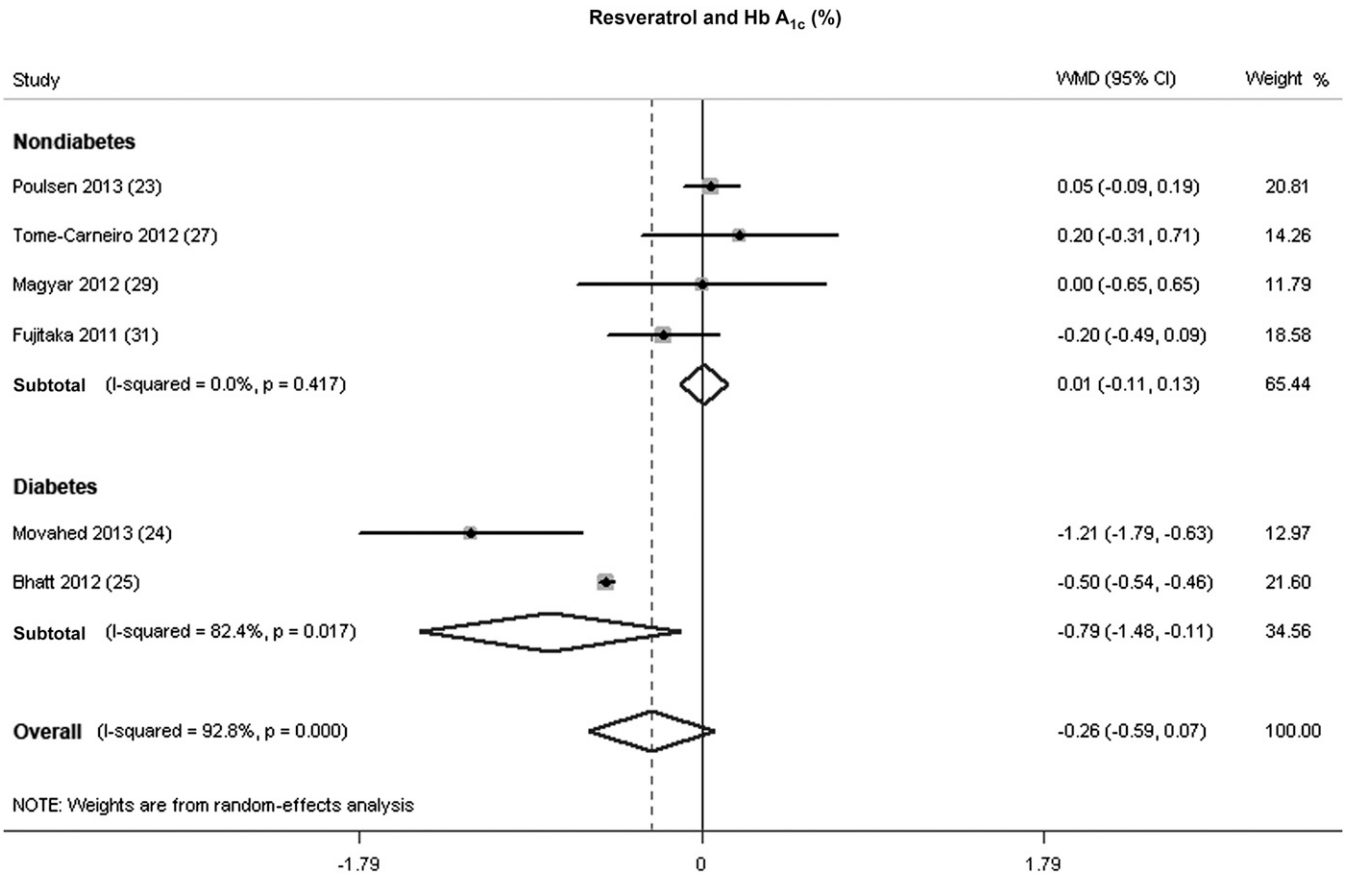

FIGURE 4. Meta-analysis of the effects of resveratrol on Hb A_{1c}. Weight was assigned by STATA (version 11; StataCorp) using the number of subjects and SD. Sizes of data markers indicate the weight of each study in this analysis. The diamond represents the overall estimated effect, and the result was obtained from a random-effects model. Hb A_{1c}, glycated hemoglobin; WMD, weighted mean difference.

showed that the pooled effects of resveratrol on fasting glucose and insulin concentrations were not influenced by BMI, study design, resveratrol dose, study duration, or study quality in nondiabetic participants.

The current study suggests that the consumption of resveratrol had a favorable effect on glucose control and insulin sensitivity in participants with diabetes. Consistent with our results, several studies have shown that resveratrol supplementation significantly improved hyperglycemia status in diabetic rats (17, 33). In addition, recent animal studies have indicated that the administration of resveratrol to diabetic rats can also reduce Hb A_{1c} concentrations, which reflects the prolonged decrease of glycemia (33, 34). The mechanism underlying the beneficial effect of resveratrol on glucose control may involve the following aspects:

1) Resveratrol can activate the in vivo expression of sirtuin 1 (13, 32), which acts downstream of energy restriction and provides a beneficial effect on glucose control (35).

2) Resveratrol can stimulate glucose uptake by increasing the expression of GLUT4, which is the insulin-dependent glucose transporter (36, 37).

3) Resveratrol is able to activate glucose uptake in the absence of insulin (17).

Previous studies have found that resveratrol effectively reduces the plasma insulin concentration and increases insulin sensitivity in diet-induced diabetic mice (15, 38). Several possible explanations for these results are as follows:

1) Resveratrol is able to inhibit insulin secretion from freshly isolated animal pancreatic islets (39–41) and may attenuate β cell degradation induced by chronic overstimulation through inhibition of insulin secretion. This beneficial effect of resveratrol on the endocrine pancreas may result from resveratrol-mediated inhibition of cytokine action through decreased DNA binding of nuclear transcription factor κB, production of nitrous oxide, and expression of inducible nitrous oxide synthesis (42).

2) Resveratrol can activate Akt expression, which is known to be a modulator of insulin-signaling pathways (43).

3) Resveratrol can also prevent inflammation by improving cellular stress, inhibiting inflammatory gene expression, and increasing peroxisome proliferator–induced receptor-γ activity (44).

4) Resveratrol administration may improve insulin resistance by reducing the inflammatory response in diabetic rats (33).

In contrast with the results in participants with diabetes, resveratrol consumption did not significantly affect plasma measures of glucose control and insulin sensitivity in nondiabetic participants. Subgroup analyses according to BMI, study design, resveratrol dose, treatment duration, or Jadad score consistently showed similar results. Consistent with our study, animal studies have shown that the administration of resveratrol does not significantly affect insulin sensitivity, glucose tolerance, and plasma lipid profile in normal rodents (45, 46). However, the mechanisms of how resveratrol influences glucose control and insulin sensitivity in nondiabetic participants are unclear. One possible

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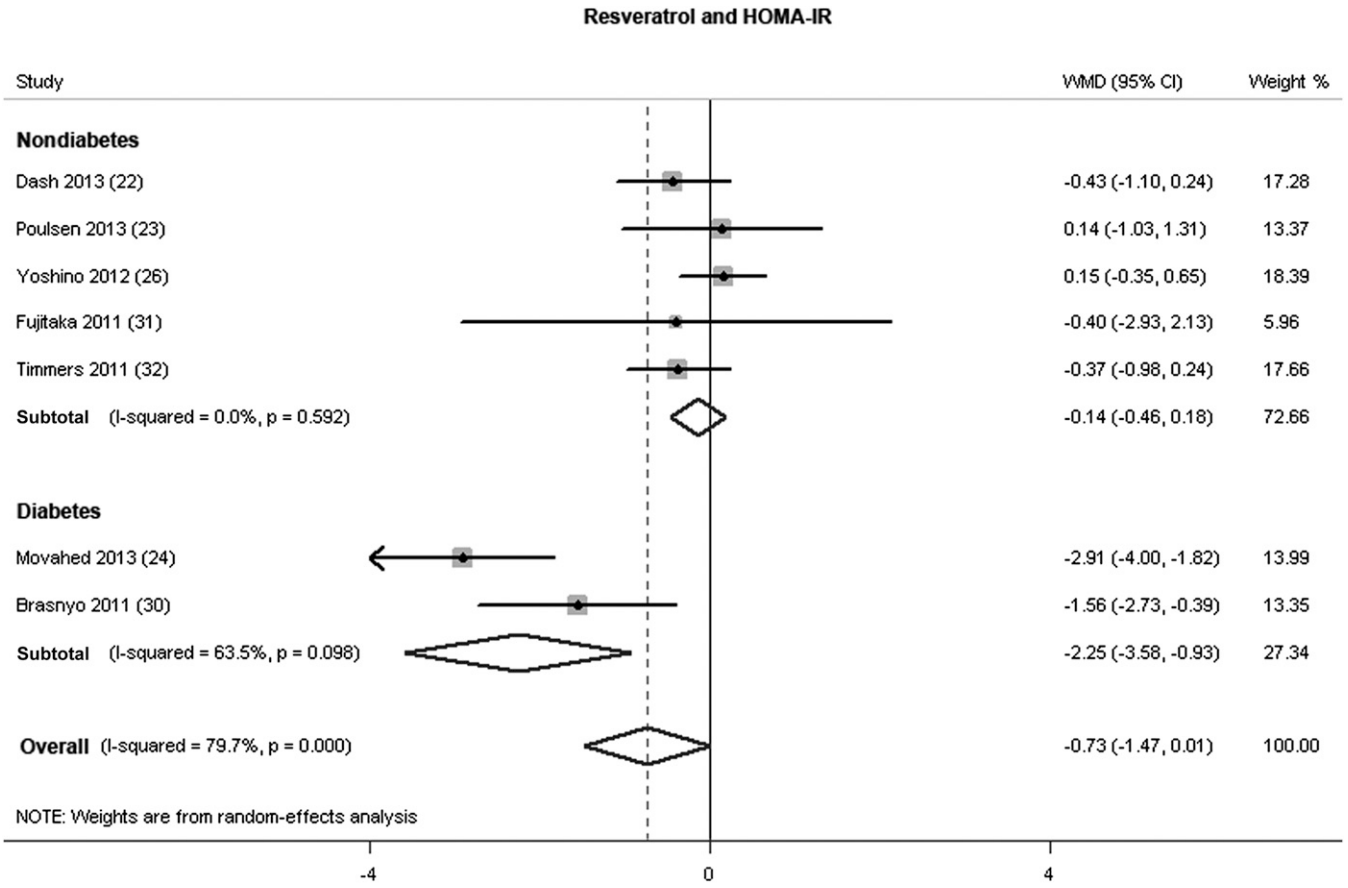

FIGURE 5. Meta-analysis of the effects of resveratrol on HOMA-IR. Weight was assigned by STATA (version 11; StataCorp) using the number of subjects and SD. Sizes of data markers indicate the weight of each study in this analysis. The diamond represents the overall estimated effect, and the result was obtained from a random-effect model. WMD, weighted mean difference.

explanation is that nondiabetic participants have normal baseline glucose concentrations, which fluctuate in a certain range under normal physical conditions (47), and resveratrol treatments may not affect the physiologic regulation of plasma glucose and insulin concentrations in these subjects. This potential effect needs to be evaluated by more high-quality RCTs.

Although the relatively larger number of pooled participants provides stronger statistical power to evaluate the intervention effect, this meta-analysis had several inevitable limitations. First, our assessment of the effects of resveratrol on glycemic measures in T2DM subjects was limited because of the small number of trials available for subgroup analyses. For the same reason, it was difficult to evaluate the optimal dose and duration for resveratrol intervention aimed at improving hyperglycemic status in subjects with T2DM.

Second, the intervention durations were shorter than 3 mo in one-half of the included studies. According to a statement from the American Diabetes Association, Hb A_{1c} has several advantages over fasting plasma glucose and the oral-glucose-tolerance test, including greater convenience, greater preanalytical stability, and less day-to-day perturbations (48). In addition, it is suggested to monitor Hb A_{1c} changes every 2–3 mo when evaluating the progression of diabetes (48). Therefore, intervention durations >3 mo might be more appropriate for RCTs that assess the effects of resveratrol on glycemic control.

Third, the age of the participants in the included studies ranged from 18 to 80 y, but we could not perform an advanced analysis for the effect of age on clinical heterogeneity across the selected RCTs. In addition, we could not analyze the treatment interaction between resveratrol administration and medicine use because of incomplete information in the included trials. Of the 2 studies that included subjects with T2DM, 1 study (24) allowed all patients to continue their existing antidiabetic medications during the study period. Oral hypoglycemic agents and insulin were not modified during the course of the study. Another study reported (25) that patients in the intervention group received resveratrol supplementation along with oral hypoglycemic agents such as glibenclamide and/or metformin, whereas patients in the control group received only oral hypoglycemic agents. Therefore, the results of this meta-analysis might be partly limited because of the unbalanced control of insulin use, oral hypoglycemic agent types, and medicine doses between the intervention and control groups in these 2 studies.

Fourth, the quality of the included studies varied from low to high, and only 5 studies were found to be of high quality. The 2010 Consolidated Standard of Reporting Trials is used worldwide to improve the reporting of RCTs and also provides professional guidance on study design and conduct (49). To improve the quality of studies, future RCTs should be conducted in accordance with the 2010 Consolidated Standard of Reporting Trials statement; in particular, they should provide enough

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TABLE 2
Subgroup analyses of fasting glucose and insulin concentrations in nondiabetic subjects stratified by previously defined study characteristics

	Fasting glucose					Fasting insulin				
Variables	No. of trials	Net change (95% CI)	Test of heterogeneity[1]		P^2	No. of trials	Net change (95% CI)	Test of heterogeneity[1]		P^2
			P	I^2				P	I^2	
		mg/dL		%			*μIU/mL*		%	
BMI										
<25 kg/m^2	1	1.00 (−3.41, 5.41)	—	—	0.66	1	0.50 (−1.54, 2.54)	—	—	0.63
≥25 kg/m^2	6	−1.69 (−5.39, 2.02)	0.88	0.001	0.37	4	−1.22 (−3.01, 0.57)	0.82	0.001	0.18
Study design										
Parallel	5	0.29 (−2.98, 3.55)	0.85	0.001	0.86	3	−0.44 (−1.34, 2.21)	0.96	0.001	0.63
Crossover	2	−3.25 (−8.98, 2.48)	0.73	0.001	0.27	2	−1.71 (−3.78, 0.36)	0.95	0.001	0.11
Resveratrol dose										
<100 mg/d (lower than median)	3	0.46 (−3.67, 4.60)	0.50	0.001	0.83	1	0.50 (−1.54, 2.54)	—	—	0.63
≥100 mg/d (higher than median)	4	−1.50 (−5.40, 2.40)	0.85	0.001	0.45	4	−1.22 (−3.01, 0.57)	0.82	0.001	0.18
Duration										
<12 wk (lower than median)	3	−1.69 (−5.82, 2.44)	0.70	0.001	0.42	3	−1.24 (−3.07, 0.59)	0.63	0.001	0.19
≥12 wk (higher than median)	4	0.41 (−3.49, 4.32)	0.71	0.001	0.84	2	0.43 (−1.55, 2.42)	0.77	0.001	0.67
Jadad score										
Low (<4)	4	0.52 (−3.18, 4.22)	0.97	0.001	0.78	3	−1.66 (−3.67, 0.35)	0.98	0.001	0.11
High (≥4)	3	−2.14 (−6.56, 2.28)	0.46	0.001	0.34	2	0.49 (−1.32, 2.30)	0.92	0.001	0.23

[1] *P*-heterogeneity: heterogeneity was assessed by using Cochran's test, and $P < 0.1$ was considered to indicate significant heterogeneity across studies. I^2 for heterogeneity was also calculated by using Cochran's test, and $I^2 > 50\%$ was considered to indicate significant heterogeneity across studies.

[2] *P* for meta-analysis. $P < 0.05$ was considered to indicate a significant effect of resveratrol on fasting glucose and insulin concentrations by using a fixed-effects or random-effects model.

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information on the 5 items of the Jadad scoring criterion, which are essential for subsequent quality evaluation in the meta-analysis (19). On the other hand, most of the selected studies (9 of 11) did not report information on sample size calculation. We could not directly evaluate the rationality of sample sizes in these studies, because the appropriate sample size for the RCT is based on the power calculation, α value, SD value, and expected difference according to the specific study design. The investigators should properly calculate sample sizes before starting the future RCTs and report the details in the publication.

In conclusion, resveratrol consumption significantly improved glucose control and insulin sensitivity in patients with T2DM but did not show a similar effect on nondiabetic participants. More high-quality RCTs with durations longer than 3 mo are needed to further confirm the effects of resveratrol on glucose control and insulin sensitivity. In addition, these effects will be more convincing if studies can effectively rule out the potential confounding effect of medicine use.

The authors' responsibilities were as follows—KL and M-TM: conceived the research idea and drafted the protocol; KL, BW, M-TM, and RZ: selected and screened the trials included in the analysis; and KL, BW, and RZ: extracted data, conducted the analyses, and contributed to updating the review. All of the authors contributed to the writing and the revision of the manuscript. None of the authors declared a conflict of interest.

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