

Gene-diet interaction of *FTO*-rs9939609 gene variant and hypocaloric diet on glycemic control in overweight and obese adults: a systematic review and meta-analysis of clinical trials

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Abstract

Background: The hypocaloric diets improve glycemic status in obese individuals, but the response to hypocaloric diets in fat mass and obesity-associated gene (*FTO*)-rs9939609 gene variant is unknown. This systematic review and meta-analysis aimed to assess the gene-diet interaction of *FTO*-rs9939609 gene variant and hypocaloric diets on glycemic control in overweight and obese adults.

Methods: Cochrane Central Register of Controlled Trials, PubMed, ISI Web of Science, Embase, Scopus, and Google scholar were searched up to December 2018, for relevant clinical trials. Mean changes in fasting blood sugar (FBS), serum insulin, and homeostasis model assessment of insulin resistance (HOMA-IR) were extracted.

Results: The pooled analysis of nine studies showed that there was no significant difference between AA/AT and TT genotypes in FBS (weighted mean difference [WMD] = 0.01, 95% confidence interval [CI]: -1.08, 1.10, $P = 0.984$) and serum insulin (WMD = 0.20, 95% CI: -0.85, 1.26; $P = 0.707$) after intervention hypocaloric diets. The overweight/obese participants in AA/AT group showed the greatest reduction in HOMA-IR compared with TT genotype following intervention, and this difference was not statistically significant (WMD = -0.38, 95% CI: -0.94, 0.16, $P = 0.167$).

Conclusion: This meta-analysis suggests that there was no significant difference between AA/AT and TT genotypes of *FTO*-rs9939609 on FBS, serum insulin level, and insulin resistance in response to hypocaloric diets.

Keywords: Low-caloric diet; Obesity-associated gene; RS9939609 gene variant; Insulin resistance; Fasting blood sugar

Introduction

There is a significant relationship between overweight/obesity and glycemic status, so that weight loss can improve fasting glucose.^[1] The hypocaloric diet regardless of its severity and macronutrient distribution through weight loss can improve insulin resistance and glycemic status.^[2,3] However, insulin resistance has multiple causes and is determined by the interaction between genetic and environmental factors. The individual responses to diet therapy can be influenced by individual genetic background.^[4]

Common polymorphisms of the fat mass and obesity-associated gene (*FTO*) have been linked obesity and glycemic traits.^[5] In addition, replicable evidence has shown that genetic variants of *FTO* may interact with effective low-calorie dietary interventions on glycemic status.^[6] Mainly, studies' results indicated that overweight

and obese individuals with TA/AA genotype of *FTO* have greater improvement in response to diet/lifestyle interventions.^[7]

To the best of our knowledge, few studies have been published trying to summarize the gene-diet interaction of *FTO* gene on glycemic status. Therefore, in the present study, we conducted this systematic review and meta-analysis to investigate the gene-diet interaction of *FTO*-rs9939609 gene variant and hypocaloric diets on insulin resistance and glycemic control.

Methods

This research was conducted following the guidelines and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting systematic reviews and meta-analysis. Due to the study type, ethical approval was not necessary according to local legislation.

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Search strategy

Two independent reviewers (HR and AAR) searched databases including the Cochrane Central Register of Controlled Trials, PubMed, Scopus, ISI Web of Science, and Google scholar for clinical trials that investigated the gene-diet interaction of *FTO*-rs9939609 gene variant and hypocaloric diet on glycemic control in overweight and obese adults. The search included all studies published as original full-text articles covering a period up to December 2018. The literature search was conducted using the following keywords and medical subject heading (MeSH) terms in any possible combination: *FTO*, obesity-associated gene, obesity-risk allele, fasting blood glucose, fasting blood sugar (FBS), glucose, sugar, insulin, homeostasis model assessment (HOMA), glucose intolerance, diabetes, hemoglobin A1c, type 2 diabetes mellitus, glycemic control, and clinical trial. No restriction was applied to publication year, and all studies published in English were included. The reference lists of included studies were investigated to identify any additional relevant studies. The papers were selected by title and abstract, then full texts of all potentially relevant studies were retrieved by two reviewers separately, and potentially relevant studies were identified.

Study selection

After the relevance of a study was confirmed, publication's full texts were reviewed, and those that fulfilled the eligibility criteria were included. The following eligibility criteria were applied: (1) published in English; (2) using hypocaloric diets; and (3) reporting FBS, insulin and HOMA of insulin resistance (HOMA-IR) as the outcome of the study. Following studies were excluded: (1) articles without full-text availability, non-English, ecological study, qualitative study, opinion pieces, conference abstracts, review articles, and editorials; and (2) reporting unrelated data.

Data extraction

The data were extracted independently by two reviewers (HR and AAR), and in the event of disagreement, a decision being made after HT cross-examined doubtful data. Studies characteristics including first author's name, publication year, country, study design, quality score, sample size, type of diet, study duration, participant's gender, age, and health status were extracted.

Assessment of risk of bias

The quality of the studies was evaluated by two separate reviewers according to the Jadad score.^[8] The Jadad score considers randomization, blinding, description of withdrawals and dropouts. Each study was scored between 0 and 5; higher numbers represent better quality.

Statistical analysis

The effect size, estimated as the mean difference (MD), was used to perform the fixed method meta-analysis. In case of significant heterogeneity between studies, a random-effects

meta-analysis was carried out.^[9] Heterogeneity was evaluated using the I^2 index and Cochrane's Q test. Heterogeneity was considered low if $I^2 < 30\%$, moderate if $I^2 = 30\%$ to 75% , and high if $I^2 > 75\%$.^[10] Subgroup analyses were performed according to study quality (low or high), and randomization (yes or no) to identify the potential sources of heterogeneity. In addition, sensitivity analysis and meta-regression were performed to further investigation on heterogeneity sources. Begg's rank correlation, Egger's linear regression, and funnel plots were used to examine for the presence of publication bias. All analyses were carried out using Stata, version 14 SE (Stata Crop, College Station, TX, USA). P -values < 0.05 were considered statistically significant.

Results

Characteristics of the studies

As shown in Figure 1, the early electronic search resulted in 1434 studies, after duplicate removal. Following the title and abstract screen, 1381 studies were excluded due to reporting unrelated data, being review articles, and not being written in English. Overall, 53 studies were evaluated for eligibility, and 44 studies were excluded for the following reasons: did not report FBS, serum insulin or HOMA-IR as study outcomes, did not provide enough data, was not conducted in clinical trial design, or was published as study protocol. Nine studies met the inclusion criteria for the meta-analysis.^[3,11-18] Table 1 summarizes the characteristics of all studies that were included in the systematic review. Studies were conducted in Spain,^[3,12,14,16,18] Japan,^[13,15] and the United States.^[17] Also one of the trials was a multi-center study including eight clinical centers in seven European countries (Sweden, Denmark, United Kingdom, The Netherlands, Czech Republic, France, and Spain).^[11] Most of the studies recruited both male and female genders, while two studies were conducted only in females.^[13,15] Duration of the intervention ranged from 12 to 104 weeks. All studies recruited overweight or obese subjects into the study. According to Jadad scores, only one study was classified as high-quality papers (score ≥ 3)^[11] and the other studies were classified as low quality due to issues regarding blinding in prescribing diets.

Meta-analysis of the FBS

Overall, nine studies provided 13 effect sizes, including 1799 subjects with AA/AT genotype and 921 subjects with TT genotype, regarding the effect of hypocaloric diet on the FBS.^[3,11-18] According to the meta-analysis, there is no difference between AA/AT and TT genotypes in the effect of hypocaloric diet on FBS (weighted MD [WMD] = 0.01, 95% confidence interval [CI]: -1.08, 1.10; $P = 0.984$) [Figure 2]. A moderate level of heterogeneity was observed among the studies ($I^2 = 42.3\%$, $P = 0.054$). The subgroup analysis showed no heterogeneity among studies with randomization ($n = 7$, $I^2 = 0.0\%$, $P = 0.637$); however, in studies without randomization there was a moderate heterogeneity ($n = 6$, $I^2 = 47.8\%$, $P = 0.088$). Subgroup analysis did not suggest study quality as a source of heterogeneity [Table 2]. Sensitivity analysis did not

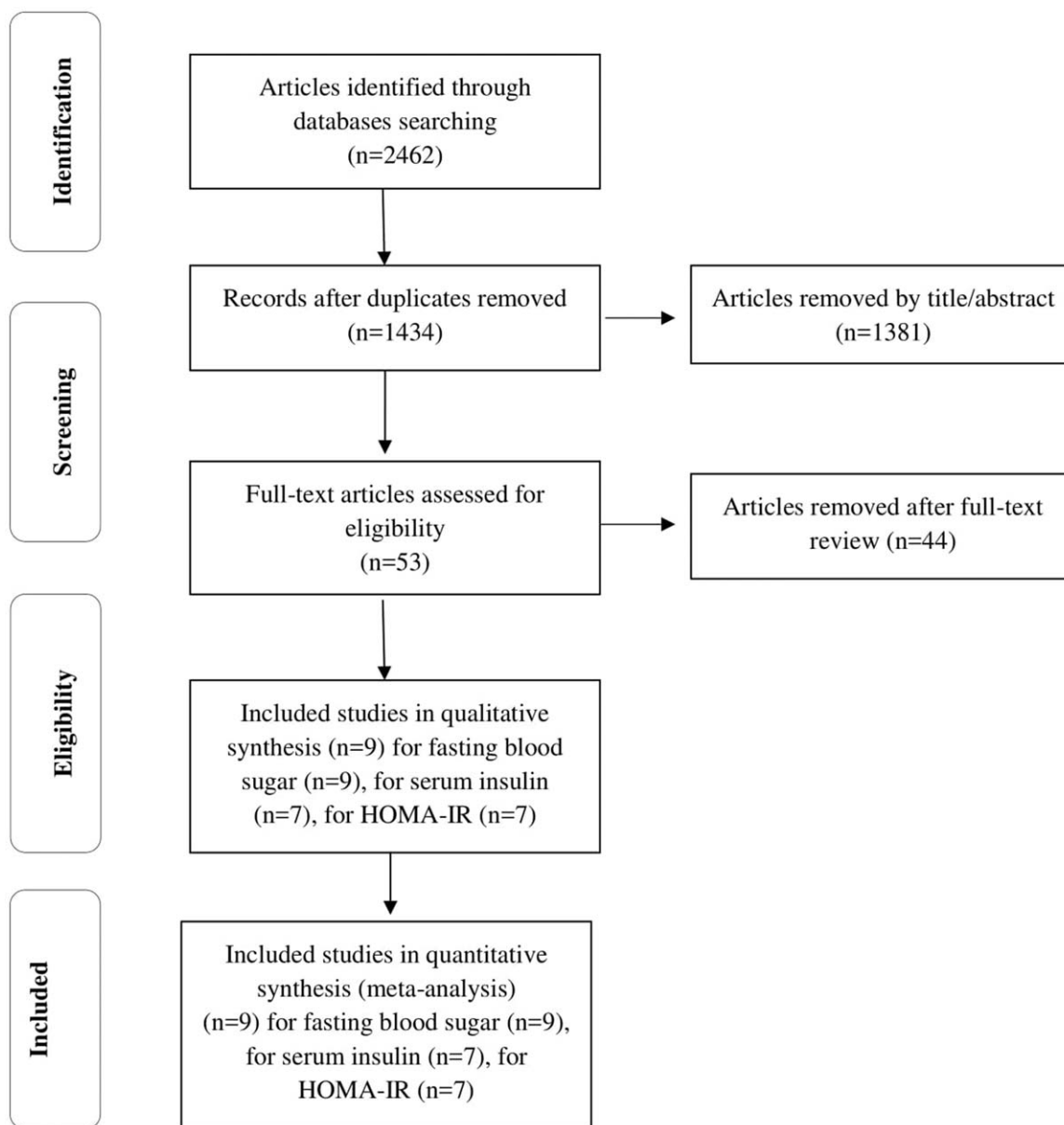


Figure 1: Flow chart the study selection to investigate gene-diet interaction of *FTO*-rs9939609 gene variant and hypocaloric diets on insulin resistance and glycemetic control. HOMA-IR: Homeostasis model assessment of insulin resistance.

provide further information. According to meta-regression, randomization, study duration, participants' age, and study quality were not found to be associated with the relationship between A/T genotype and FBS following a hypocaloric diet [Table 3]. Visual inspection of the funnel plot [Figure 3A] demonstrated no publication bias of trials that investigate the effect of hypocaloric diet on the FBS according to the rs9939609 genotype (Egger's test, $P = 0.073$; Begg's test, $P = 0.127$).

Meta-analysis of the serum insulin

A total of 11 effect sizes ($n = 699$ AA/AT and 299 TT) were reported considering the effect of the rs9939609 genotype on serum levels of insulin following hypocaloric diet. As shown in Figure 4, there was no significant difference

between AA/AT and TT genotype in serum insulin after intervention (WMD = 0.20, 95% CI: -0.86, 1.26; $P = 0.707$) [Figure 4]. Moderate level of heterogeneity was observed among the studies ($I^2 = 71.7\%$, $P < 0.001$). The subgroup analysis according to the study quality failed to identify source of heterogeneity. The subgroup analysis of randomization (yes or no) suggested that heterogeneity is significant in trials that performed randomization ($n = 7$, $I^2 = 67.8\%$, $P = 0.005$). Also, after hypocaloric diet, there was a significant increase in serum insulin in the AA/AT group compared to the TT group in the studies with randomization (WMD = 1.17, 95% CI: 0.02, 2.33; $P = 0.046$), while in the studies without randomization lower serum insulin was observed in the AA/AT group (WMD = -1.71, 95% CI: -2.81, -0.62; $P = 0.002$). However, meta-regression did not find randomization, study duration, participants' age, and study quality as

Table 1: Characteristics of included studies investigating *FTO*-rs9939609 gene variant and hypocaloric diets on insulin resistance and glycemic control.

First author, publication year	Country	Sample size (male/female), n	Mean age (years)	Randomization	Duration	Diet type	Jaded score
Grau, 2009 ^[11]	Sweden, Denmark, United Kingdom, The Netherlands, Czech Republic, France, and Spain	733 (579/154)	NR	Yes	10 weeks	1. Low fat, high CHO, hypoenergetic diet 2. High fat, low CHO, hypoenergetic diet	3
de Luis, 2012 ^[12]	Spain	305 (80/225)	43.23	Yes	3 months	1. Hypocaloric low-CHO diet 2. Hypocaloric low-fat diet	2
Matsuo, 2012 ^[13]	Japan	204 (0/204)	51.89	No	14 weeks	Weight-loss diet	0
de Luis, 2013 ^[14]	Spain	106 (36/70)	49.62	No	3 months	Hypocaloric low-fat diet	1
Matsuo, 2014 ^[15]	Japan	47 (0/47)	52.60	No	14 weeks	Weight loss diet	1
de Luis, 2015 ^[16]	Spain	233 (56/177)	48.17	Yes	3 months	1. High MUFA hypocaloric diet 2. High PUFA hypocaloric diet	2
de Luis, 2015 ^[3]	Spain	195 (58/137)	50.40	No	9 months	1. High-protein/low-CHO diet 2. Standard hypocaloric diet	1
Zheng, 2015 ^[17]	USA	738 (285/453)	51.01	Yes	2 years	Weight loss diet	2
Loria-Kohen, 2016 ^[18]	Spain	159 (not reported)	42.80	No	12 weeks	Weight loss diet	0

NR: Not reported; CHO: Carbohydrate; MUFA: Mono-unsaturated fatty acid; PUFA: Poly-unsaturated fatty acid.

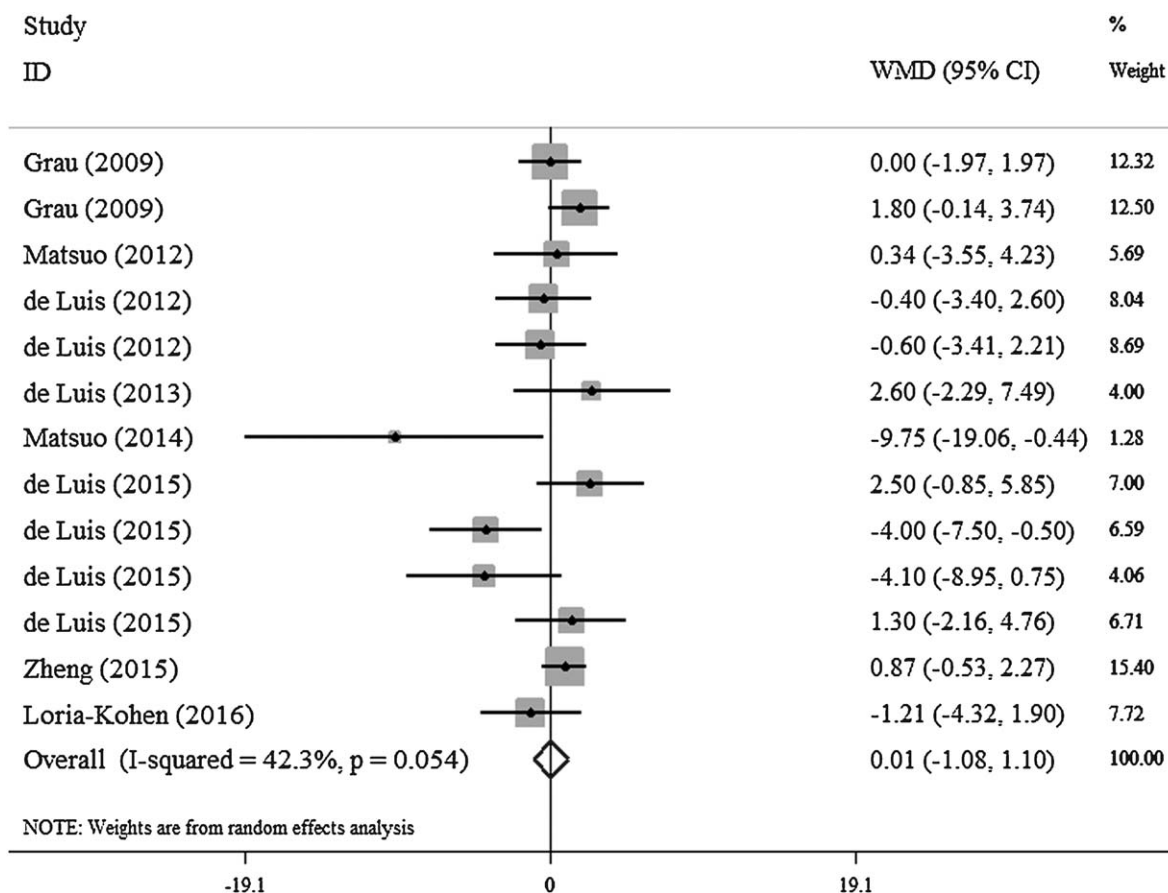


Figure 2: Forest plot of trials examining the effect of the rs9939609 genotype on the fasting blood sugar following a hypocaloric diet.

Table 2: Overall estimates of meta-analysis on the effect of rs9939609 genotype on the FBS, insulin, and insulin resistance.

Outcomes	Subgroups	Effect size, <i>n</i>	References	WMD (95% CI)	<i>P</i>	<i>I</i> ² (%)	<i>P</i> for heterogeneity
FBS		13	3–11	0.01 (–1.08, 1.10)	0.984	42.3	0.054
Randomization	Yes	7	3, 4, 8, 10	0.78 (–0.04, 1.61)	0.064	0.0	0.637
	No	6	5–7, 9, 11	–1.87 (–4.35, 0.60)	0.138	47.8	0.088
Study quality	Low	11	4–11	0.03 (–0.85, 0.92)	0.936	44.6	0.054
	High	2	3	0.91 (–0.46, 2.30)	0.194	38.5	0.202
Insulin		11	3, 4, 6, 8–11	0.20 (–0.86, 1.26)	0.707	71.7	<0.001
Randomization	Yes	7	3, 4, 8, 10	1.17 (0.02, 2.33)	0.046	67.8	0.005
	No	4	6, 9, 11	–1.71 (–2.81, –0.62)	0.002	0.0	0.826
Study quality	Low	9	4, 6, 8–11	0.09 (–1.25, 1.43)	0.895	72.2	<0.001
	High	2	3	0.62 (–1.22, 2.48)	0.506	78.7	0.030
HOMA-IR		11	3, 4, 6, 8–11	–0.39 (–0.94, 0.16)	0.167	91.8	<0.001
Randomization	Yes	7	3, 4, 8, 10	–0.48 (–1.37, 0.39)	0.279	94.7	<0.001
	No	4	6, 9, 11	–0.19 (–0.44, 0.05)	0.121	0.0	0.394
Study quality	Low	9	4, 6, 8–11	–0.18 (–0.59, 0.21)	0.361	72.2	<0.001
	High	2	3	–0.97 (–2.67, 0.73)	0.264	98.2	<0.001

FBS: Fasting blood sugar; WMD: Weighted mean difference; CI: Confidence interval; HOMA-IR: Homeostasis model assessment of insulin resistance.

Table 3: Meta-regression for the effect of rs9939609 genotype on the FBS, insulin, and insulin resistance.

Variables	Coefficient	95% CI	<i>P</i>
FBS			
Age	0.28	–0.33, 0.90	0.308
Study duration	–0.01	–0.06, 0.03	0.486
Randomization	–3.09	–8.54, 2.35	0.215
Study quality	–7.69	–16.90, 1.52	0.087
Insulin			
Age	–0.09	–1.08, 0.89	0.802
Study duration	–0.01	–0.09, 0.05	0.54
Randomization	–3.09	–15.15, 8.96	0.516
Study quality	0.25	–7.92, 8.42	0.936
HOMA-IR			
Age	0.26	–0.75, 1.28	0.505
Study duration	–0.01	–0.08, 0.06	0.742
Randomization	–2.67	–14.84, 9.50	0.575
Study quality	–1.83	–10.26, 6.59	0.577

FBS: Fasting blood sugar; CI: Confidence interval; HOMA-IR: Homeostasis model assessment of insulin resistance.

sources of heterogeneity [Table 3]. Sensitivity analysis suggests no significant change in the results following the exclusion of any study. The funnel plot [Figure 3B] demonstrated no publication bias of trials in evaluating the impact of rs9939609 genotype on serum insulin following hypocaloric diet intervention (Egger’s test, *P* = 0.952; Begg’s test, *P* = 0.755).

Meta-analysis of the HOMA-IR

In total, seven studies (11 effect sizes; *n* = 699 AA/AT and 299 TT) investigated the role of rs9939609 genotype in the effect of hypocaloric diet on insulin resistance, assessed by HOMA-IR. Although subjects in AA/AT group had lower insulin resistance compared to TT genotype following intervention, this association was not statistically significant (WMD = –0.39, 95% CI: –0.94, 0.16, *P* = 0.167) [Figure 5]. There was a high level of heterogeneity among the studies (*I*² = 91.8%, *P* < 0.001). According to the subgroup analysis, studies with randomization had a high heterogeneity level (*I*² = 94.7%, *P* < 0.001), while the heterogeneity was not evident among studies without

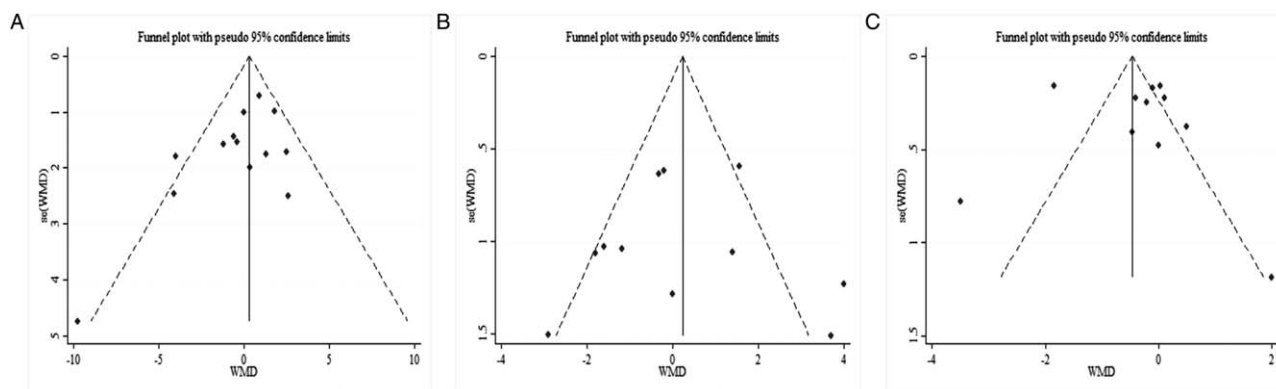


Figure 3: Funnel plots detailing publication bias in the studies selected for analysis. Visual inspection of funnel plots indicated that there is no publication bias among studies. (A) Fasting blood sugar. (B) Insulin. (C) Homeostasis model assessment of insulin resistance. WMD: Weighted mean difference.

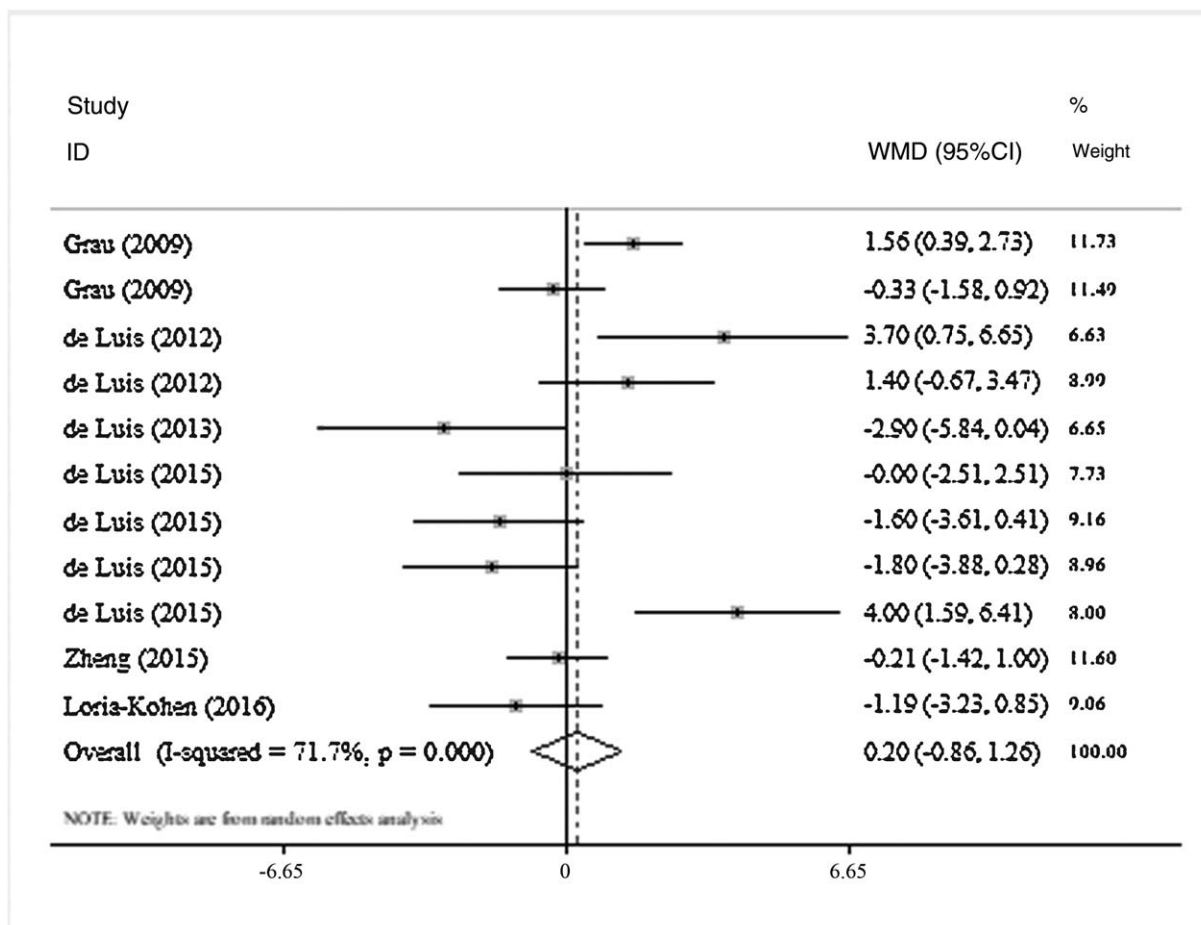


Figure 4: Forest plot of trials examining the effect of the rs9939609 genotype on the serum insulin following a hypo-caloric diet.

randomization ($I^2 = 0.0\%$, $P = 0.394$). Study quality was not identified as a source of heterogeneity in the subgroup analysis. One-by-one exclusion of the studies in the sensitivity analysis did not change the results. The heterogeneity among studies was not explained by randomization, study duration, participants' age, and study quality in the meta-regression [Table 3]. Publication bias was not obvious according to the funnel plot [Figure 3C], Begg's test ($P = 0.533$), and Egger's test ($P = 0.687$).

Discussion

In this systematic review and meta-analysis of trials, we found that overweight and obese individuals carrying the homozygous *FTO* obesity-predisposing allele (AA-AT genotype) did not have greater improvement of glycemic status than non-carriers (TT genotype) after adherence to hypocaloric diets.

The previous meta-analyses evaluated the role of *FTO*-rs9939609 gene variants in response to combine of weight loss intervention (diet/exercise) on anthropometric status. In this regard, the results of meta-analyses were not consistent. For example, a meta-analysis of ten studies reported that individuals with the *FTO* TA genotype and AA genotype may lose more weight through diet/lifestyle

interventions than TT genotype.^[7] Inconsistently, Livingstone *et al* indicated that carriage of the *FTO* (rs9939609 or a proxy) minor allele respond equally to weight loss interventions (dietary, physical activity, or drug) on anthropometric indexes such as body mass index, body weight, or waist circumference.^[19]

However, few meta-analyses have been conducted to investigate interaction of *FTO* diet on glycemic status, and previous trials have shown inconsistent results. There are several reasons for these contradictory results. There are several reasons for these contradictory results. First, the difference in macronutrients (fat, protein, and carbohydrates) ratio and the type of dietary fat in the hypocaloric diets are potential reasons for discrepant findings, which can affect glycemic responses. De Luis *et al*^[12] reported that in obese subjects with *FTO*-rs9939609 gene variant, glycemic improvement was better in A carriers with a low fat hypocaloric diet than low carbohydrate hypocaloric diet. Other study showed that A allele carriers have a greater response to high polyunsaturated fat hypocaloric diet on insulin levels and HOMA index, but similar results were not reported for high monounsaturated fat hypocaloric diet.^[16] Secondly, existence of polymorphism diversity in *FTO* gene can cause a difference in the results of studies. Zheng *et al*^[17] have demonstrated that in

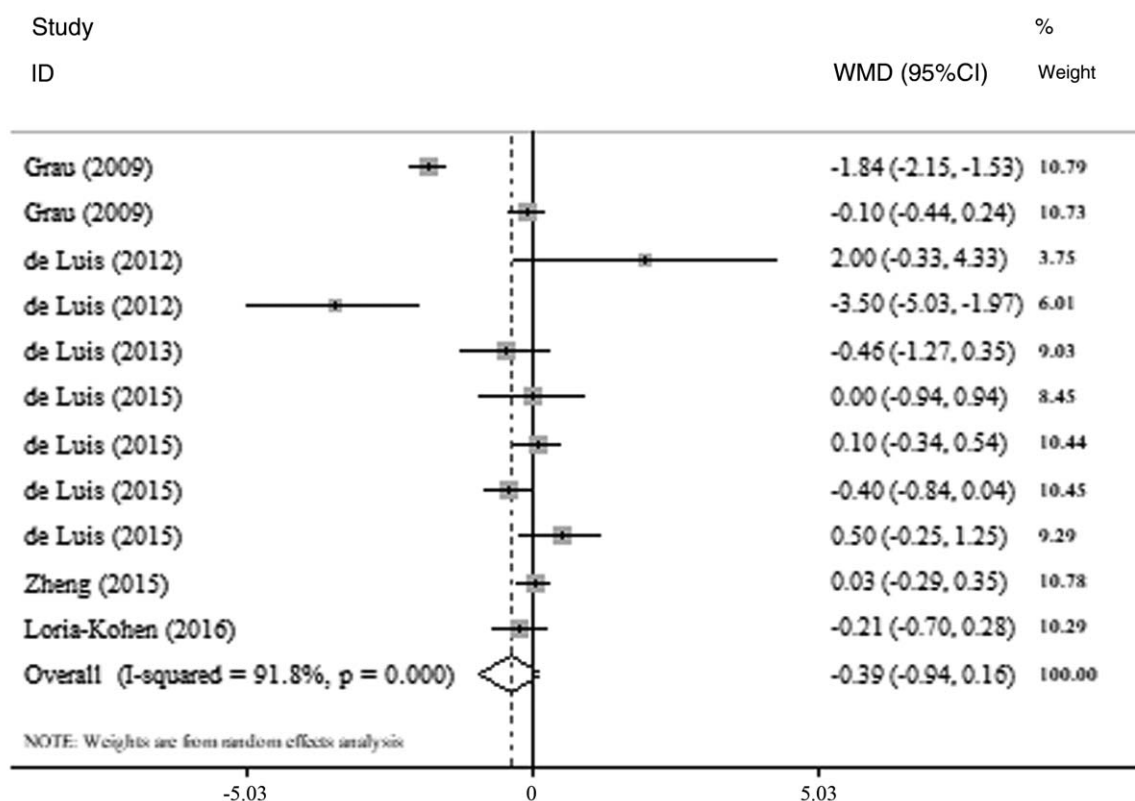


Figure 5: Forest plot of trials examining the effect of the rs9939609 genotype on the homeostasis model assessment of insulin resistance following a hypocaloric diet.

overweight or obese adults, *FTO* variants rs1558902 play a role in improving insulin sensitivity by consuming high-fat weight-loss diets; on the other hand their results showed that the association between *FTO*-rs9939609 and changes in insulin resistance was not affected by dietary fat modifies. In the present meta-analysis to remove this confounding factor, exclusively one of the *FTO* gene variants (rs9939609) was evaluated.

The present study showed that different randomization schemes caused contradict on the results of serum insulin. The randomization in clinical trials is useful for minimize selection and accidental bias, balance treatment assignment in order to maximize the power of the comparison and to obtain the basis for a correct statistical interpret.^[20] In present study, due to the nature of the intervention (diet therapy) in clinical trials, the design of more studies (55%) was without randomization.

There are several limitations in our study. First, studies included in the meta-analysis varied in intervention duration, race/ethnicity, sample size, and other individuals characteristics. Second, although in our meta-analysis, studies with combined weight loss interventions (diet plus exercise/lifestyle changes) were excluded. However, due to the limited number of published articles, studies related to

weight loss diets were included in the study regardless of calorie and the macronutrient ratio of diets. Thus, more studies are needed to examine gene-diet interaction of *FTO*-rs9939609 gene polymorphism and standard weight loss diets.

In conclusion, our results showed there was no significant difference between AA/AT and TT genotype of *FTO*-rs9939609 on FBS, serum insulin level and insulin resistance in response to hypocaloric diets for overweight and obese subjects. Nevertheless, Long-term randomized clinical trials with same distribution of macronutrients are highly recommended.

Conflicts of interest

None.

References

- Ashtary-Larky D, Daneghian S, Alipour M, Rafei H, Ghanavati M, Mohammadpour R, *et al.* Waist circumference to height ratio: better correlation with fat mass than other anthropometric indices during dietary weight loss in different rates. *Int J Endocrinol Metab* 2018;16: e55023. doi: 10.5812/ijem.55023.
- Ashtary-Larky D, Ghanavati M, Lamuchi-Deli N, Payami SA, Alavi-Rad S, Boustaninejad M, *et al.* Rapid weight loss vs. slow weight loss:

- which is more effective on body composition and metabolic risk factors? *Int J Endocrinol Metab* 2017;15:e13249. doi: 10.5812/ijem.13249.
3. de Luis DA, Izaola O, Aller R, de la Fuente B, Bachiller R, Romero E. Effects of a high-protein/low carbohydrate versus a standard hypocaloric diet on adipocytokine levels and insulin resistance in obese patients along 9 months. *J Diabetes Complications* 2015; 29:950–954. doi: 10.1016/j.jdiacomp.2015.06.002.
 4. San-Cristobal R, Navas-Carretero S, Livingstone KM, Celis-Morales C, Macready AL, Fallaize R, *et al.* Mediterranean diet adherence and genetic background roles within a web-based nutritional intervention: the food4me study. *Nutrients* 2017;9:E1107. doi: 10.3390/nu9101107.
 5. Caro-Gomez MA, Naranjo-González CA, Gallego-Lopera N, Parra-Marín MV, Valencia DM, Arcos EG, *et al.* Association of Native American ancestry and common variants in ACE, ADIPOR2, MTNR1B, GCK, TCF7L2 and FTO genes with glycemic traits in Colombian population. *Gene* 2018;677:198–210. doi: 10.1016/j.gene.2018.07.066.
 6. Haupt A, Thamer C, Machann J, Kirchhoff K, Stefan N, Tschritter O, *et al.* Impact of variation in the FTO gene on whole body fat distribution, ectopic fat, and weight loss. *Obesity (Silver Spring)* 2008;16:1969–1972. doi: 10.1038/oby.2008.283.
 7. Xiang L, Wu H, Pan A, Patel B, Xiang G, Qi L, *et al.* FTO genotype and weight loss in diet and lifestyle interventions: a systematic review and meta-analysis. *Am J Clin Nutr* 2016;103:1162–1170. doi: 10.3945/ajcn.115.123448.
 8. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, *et al.* Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1–12. doi: 10.1016/0197-2456(95)00134-4.
 9. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–188. doi: 10.1016/0197-2456(86)90046-2.
 10. Higgins JP, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. 2011; John Wiley & Sons, doi: 10.1002/9780470712184, Available from www.cochrane-handbook.org.
 11. Grau K, Hansen T, Holst C, Astrup A, Saris WH, Arner P, *et al.* Macronutrient-specific effect of FTO rs9939609 in response to a 10-week randomized hypo-energetic diet among obese Europeans. *Int J Obes (Lond)* 2009;33:1227–1234. doi: 10.1038/ijo.2009.159.
 12. de Luis DA, Aller R, Izaola O, de la Fuente B, Conde R, Sagrado MG, *et al.* Evaluation of weight loss and adipocytokines levels after two hypocaloric diets with different macronutrient distribution in obese subjects with rs9939609 gene variant. *Diabetes Metab Res Rev* 2012;28:663–668. doi: 10.1002/dmrr.2323.
 13. Matsuo T, Nakata Y, Murotake Y, Hotta K, Tanaka K. Effects of FTO genotype on weight loss and metabolic risk factors in response to calorie restriction among Japanese women. *Obesity (Silver Spring)* 2012;20:1122–1126. doi: 10.1038/oby.2011.322.
 14. de Luis DA, Aller R, Conde R, Izaola O, Gonzalez Sagrado M, Castrodeza Sanz J. The rs9939609 gene variant in FTO modified the metabolic response of weight loss after a 3-month intervention with a hypocaloric diet. *J Investig Med* 2013;61:22–26. doi: 10.2310/JIM.0b013e318276161d.
 15. Matsuo T, Nakata Y, Hotta K, Tanaka K. The FTO genotype as a useful predictor of body weight maintenance: initial data from a 5-year follow-up study. *Metabolism* 2014;63:912–917. doi: 10.1016/j.metabol.2014.03.013.
 16. de Luis DA, Aller R, Izaola O, Pacheco D. Role of rs9939609 fto gene variant in weight loss, insulin resistance and metabolic parameters after a high monounsaturated vs a high polyunsaturated fat hypocaloric diets. *Nutr Hosp* 2015;32:175–181. doi: 10.3305/nh.2015.32.1.9169.
 17. Zheng Y, Huang T, Zhang X, Rood J, Bray GA, Sacks FM, *et al.* Dietary fat modifies the effects of FTO genotype on changes in insulin sensitivity. *J Nutr* 2015;145:977–982. doi: 10.3945/jn.115.210005.
 18. Loria-Kohen V, Espinosa-Salinas I, Marcos-Pasero H, Lourenço-Nogueira T, Herranz J, Molina S, *et al.* Polymorphism in the CLOCK gene may influence the effect of fat intake reduction on weight loss. *Nutrition* 2016;32:453–460. doi: 10.1016/j.nut.2015.10.013.
 19. Livingstone KM, Celis-Morales C, Papandonatos GD, Erar B, Florez JC, Jablonski KA, *et al.* FTO genotype and weight loss: systematic review and meta-analysis of 9563 individual participant data from eight randomised controlled trials. *BMJ* 2016;354:i4707. doi: 10.1136/bmj.i4707.
 20. Rosenkranz GK. The impact of randomization on the analysis of clinical trials. *Stat Med* 2011;30:3475–3487. doi: 10.1002/sim.4376.

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