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Soy diet for nonalcoholic fatty liver disease
A meta-analysis of randomized controlled trials

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Abstract

Introduction: The efficacy of soy diet for nonalcoholic fatty liver disease remains controversial. We conduct a systematic review and meta-analysis to explore the influence of soy diet vs placebo on the treatment of non-alcoholic fatty liver disease.

Methods: We search PubMed, EMbase, Web of science, EBSCO, and Cochrane library databases through October 2020 for randomized controlled trials assessing the efficacy of soy diet vs placebo for nonalcoholic fatty liver disease. This meta-analysis is performed using the random-effect model.

Results: Five randomized controlled trials are included in the meta-analysis. Overall, compared with control group for nonalcoholic fatty liver disease, soy diet is associated with significantly reduced HOMA-IR (standard mean difference [SMD] $=-0.42$; 95% confidence interval [CI] $=-0.76$ to -0.08; $P=.01$), increased insulin (SMD $=-0.64$; 95% CI $=-0.98$ to -0.30; $P=.0002$) and decreased malondialdehyde (SMD $=-0.43$; 95% CI $=-0.74$ to -0.13; $P=.005$), but demonstrated no substantial impact on body mass index (SMD $=0.17$; 95% CI $=-0.20$ to 0.53; $P=.37$), alanine aminotransferase (SMD $=-0.01$; 95% CI $=-0.61$ to 0.60; $P=.98$), aspartate-aminotransferase (SMD $=0.01$; 95% CI $=-0.47$ to 0.49; $P=.97$), total cholesterol (SMD $=0.05$; 95% CI $=-0.25$ to 0.35; $P=.73$) or low density lipoprotein (SMD $=0$; 95% CI $=-0.30$ to 0.30; $P=.99$).

Conclusions: Soy diet may benefit to alleviate insulin resistance for nonalcoholic fatty liver disease.

Abbreviations: CI = confidence interval, RCTs = randomized controlled trials, SMD = standard mean difference.

Keywords: meta-analysis, nonalcoholic fatty liver disease, randomized controlled trials, soy diet

1. Introduction

Nonalcoholic fatty liver disease is known as the most common chronic liver disease with high lipid accumulation in the hepatocytes, usually greater than 5% of the liver weight.[1] Type 2 diabetes mellitus commonly occur in these patients and serves as a leading cause of chronic liver disease.[2,3] Progressive degeneration of liver tissue can result in hepatic fibrosis and cirrhosis.[4] Nonalcoholic fatty liver disease are commonly linked to insulin resistance, hypertension, elevated oxidative stress, and increased plasma fibrinogen.[5–7] Liver fat accumulation may also lead to triglyceride accumulation (steatosis), nonalcoholic steatohepatitis, cirrhosis, and even hepatocellular carcinoma.[8]

Current evidence revealed the significance of dietary modification particularly a restricted-calorie diet as the cornerstone treatment of non-alcoholic fatty liver disease.[5,7] Many studies have explored the efficacy of functional foods, as a complementary therapy. For instance, soybean-derived products such as soy milk is rich of isoflavones (e.g., genistein, daidzein, glycitein), bioactive peptides, unsaturated fatty acids and fiber. Several studies revealed the improvement in glycemic measures following supplementation with either soy-isoflavones or -protein in experimental models of fatty liver.[9–11]

However, the benefit of soy diet for nonalcoholic fatty liver disease has not been well established. Recently, several studies on the topic have been published, and the results have been conflicting.[12–15] With accumulating evidence, we therefore perform the meta-analysis of randomized controlled trials (RCTs) to explore the efficacy of soy diet for nonalcoholic fatty liver disease.

2. Materials and methods

Ethical approval and patient consent are not required because this is a systematic review and meta-analysis of previously published studies. The systematic review and meta-analysis are conducted and reported in adherence to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).[16]

2.1. Search strategy and study selection

Two investigators have independently searched the following databases (inception to October 2020): PubMed, EMbase, Web of science, EBSCO, and Cochrane library databases. The

electronic search strategy is conducted using the following keywords liver disease or steatohepatitis, and soy. We also check the reference lists of the screened full-text studies to identify other potentially eligible trials.

The inclusive selection criteria are as follows:

1. patients are diagnosed with non-alcoholic fatty liver disease;
2. intervention treatments are soy diet vs control intervention;
3. study design is RCT.

2.2. Data extraction and outcome measures

We have extracted the following information: author, number of patients, age, female, body mass index, weight, and detail methods in each group etc. Data have been extracted independently by 2 investigators, and discrepancies are resolved by consensus. We also contact the corresponding author to obtain the data when necessary.

The primary outcomes are homeostatic model assessment insulin resistance (HOMA IR) and insulin. Secondary outcomes include malondialdehyde (MDA), body mass index (BMI), alanine aminotransferase (ALT), aspartate-aminotransferase (AST), total cholesterol, and low density lipoprotein (LDL).

2.3. Quality assessment in individual studies

Methodological quality of the included studies is independently evaluated using the modified Jadad scale.[17] There are 3 items for
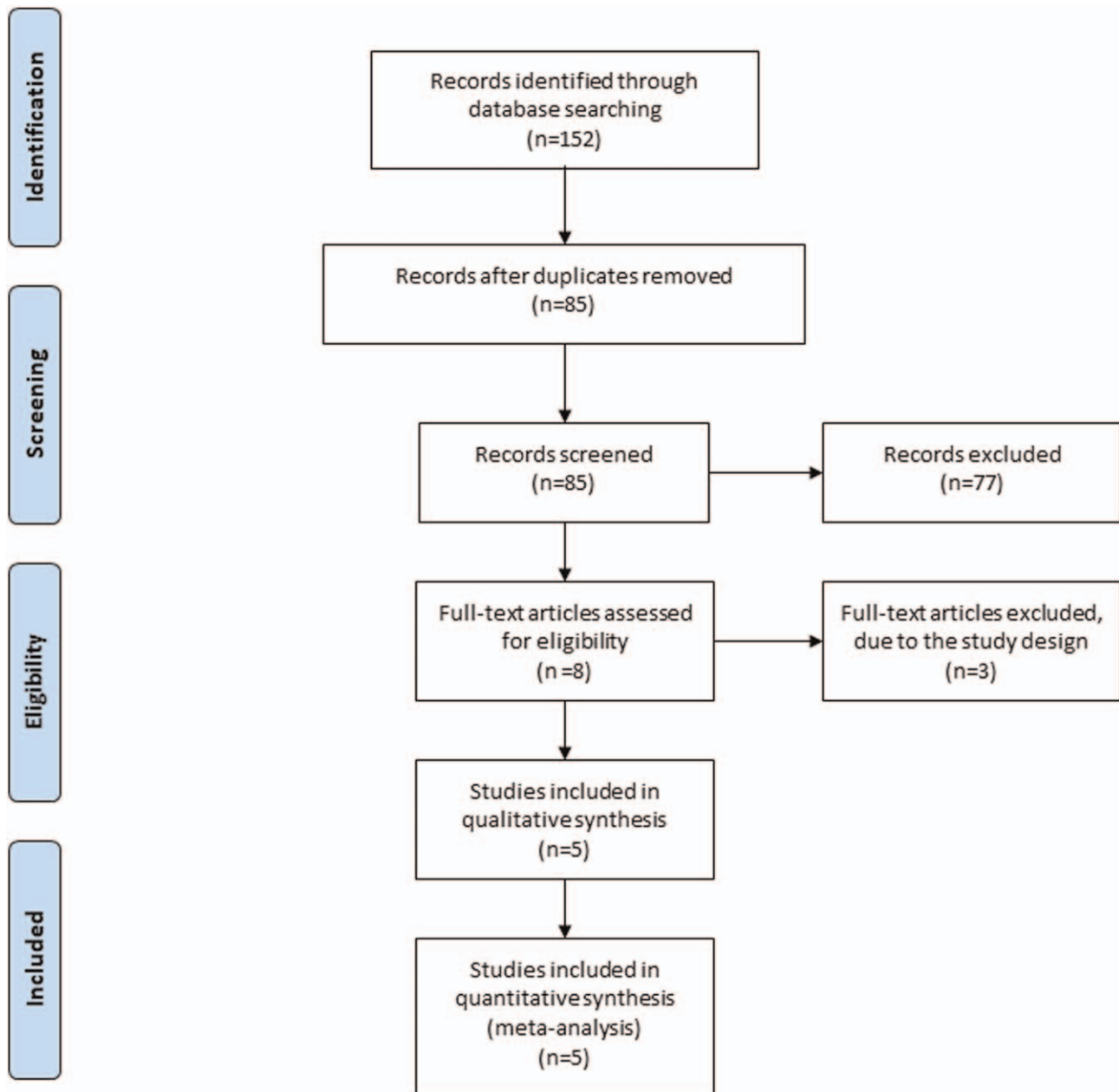

Figure 1. Flow diagram of study searching and selection process.

Table 1

Characteristics of included studies.

		Soy group					Control group						
No.	Author	Number	Age (yr)	Female (n)	Body mass index (kg/m^2)	Weight (kg)	Methods	Number	Age (yr)	Female (n)	Body mass index (kg/m^2)	Weight (kg)	Methods	Jada scores
1	Maleki 2019	31	46.16±10.53	21	30.85±3.53	83.03±9.98	240 mL/day soy milk plus 500-deficit calorie diet for 8 weeks	31	45.16±9.86	22	31.29±3.77	84.97±14.02	500-deficit calorie diet	4
2	Eslami 2019	32	46.25±10.51	22	–	–	240 mL of soy milk daily plus low-calorie diet for 8 weeks	32	45.16±9.86	23	–	–	low-calorie diet	4
3	Deibert 2019	11	57.0 (8.0), median (IQR)	3	32.2 (3.4),	101.1 (30.5)	soy-yogurt-honey preparation	11	54.0 (14.0), median (IQR)	6	32.4 (3.7)	99.5 (11.1)	guided lifestyle change	3
4	Amanat 2018	41	44.22±11.8	-	29.09±4.67	81.6±14.73	250 mg genistein for 8 weeks	41	42.94±9.55	-	27.83±4.51	74.92±11.51	placebo	5
5	Kani 2014	15	48.5±3.7	8	31.3±3.8	91.2±9.2	low calorie, low carbo-hydrate soy containing diet for 8 weeks	15	49.3±3.5	8	28±3.2	80.1±8.9	low calorie, low carbohydrate	4

IQR = interquartile range.

Jadad scale: randomization (0–2 points), blinding (0–2 points), dropouts, and withdrawals (0–1 points). The score of Jadad scale varies from 0 to 5 points. An article with Jadad score ≤2 is considered to be of low quality. If the Jadad score ≥3, the study is thought to be of high quality.[18]

2.4. Statistical analysis

We estimate the standard mean difference (SMD) with 95% confidence interval (CI) for all continuous outcomes. The random-effects model is used regardless of heterogeneity. Heterogeneity is reported using the I^2 statistic, and $I^2 > 50\%$ indicates significant heterogeneity.[19] Whenever significant heterogeneity is present, we search for potential sources of heterogeneity via omitting 1 study in turn for the meta-analysis or performing subgroup analysis. All statistical analyses are performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

3. Results

3.1. Literature search, study characteristics, and quality assessment

A detailed flowchart of the search and selection results is shown in Figure 1. One hundred fifty two potentially relevant articles are identified initially. Finally, 5 RCTs that meet our inclusion criteria are included in the meta-analysis.[10,12–15]

The baseline characteristics of the 5 eligible RCTs in the meta-analysis are summarized in Table 1. The 5 studies are published between 2014 and 2019, and the total sample size is 260. Among the 5 studies included here, 2 studies report HOMA IR and insulin,[12,15] 3 studies report MDA,[10,12,15] 4 studies report

BMI,[10,13–15] and 3 studies report ALT, AST, total cholesterol, and LDL.[10,13,15] Jadad scores of the 5 included studies vary from 3 to 5, and all 5 studies are considered to be high-quality ones according to quality assessment.

3.2. Primary outcomes: HOMA IR and insulin

These outcome data are analyzed with the random-effects model, and compared to control group for nonalcoholic fatty liver disease, soy diet is associated with significantly reduced HOMA-IR (SMD = −0.42; 95% CI = −0.76 to −0.08; P = .01) with no heterogeneity among the studies ($I^2 = 0\%$, heterogeneity P = .32; Fig. 2) and increased insulin (SMD = −0.64; 95% CI = −0.98 to −0.30; P = .0002) with no heterogeneity among the studies ($I^2 = 0\%$, heterogeneity P = .76; Fig. 3).

3.3. Sensitivity analysis

No heterogeneity is observed among the included studies for the primary outcomes, and thus we do not perform sensitivity analysis via omitting 1 study in turn to detect heterogeneity.

3.4. Secondary outcomes

In comparison with control group for non-alcoholic fatty liver disease, soy diet can substantially reduce MDA (SMD = −0.43; 95% CI = −0.74 to -0.13; P = .005; Fig. 4), but showed no obvious impact on BMI (SMD = 0.17; 95% CI = −0.20 to 0.53; P = .37; Fig. 5), ALT (SMD = −0.01; 95% CI = −0.61 to 0.60; P = .98; Fig. 6), AST (SMD = 0.01; 95% CI = −0.47 to 0.49; P = .97; Fig. 7), total cholesterol (SMD = 0.05; 95% CI = −0.25 to 0.35; P = .73; Fig. 8) or LDL (SMD = 0; 95% CI = −0.30 to 0.30; P = .99; Fig. 9).
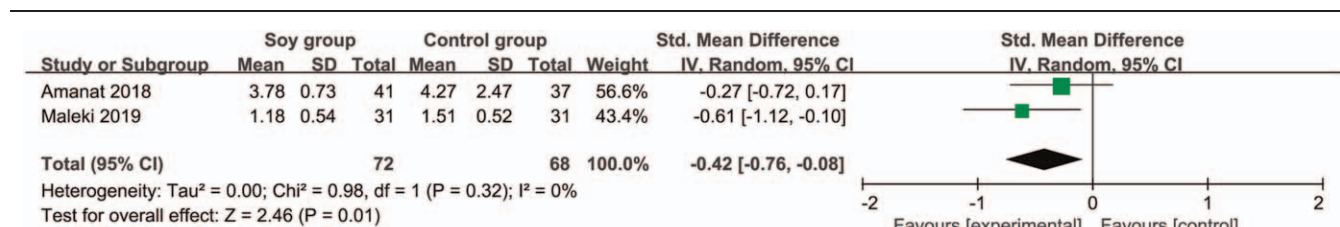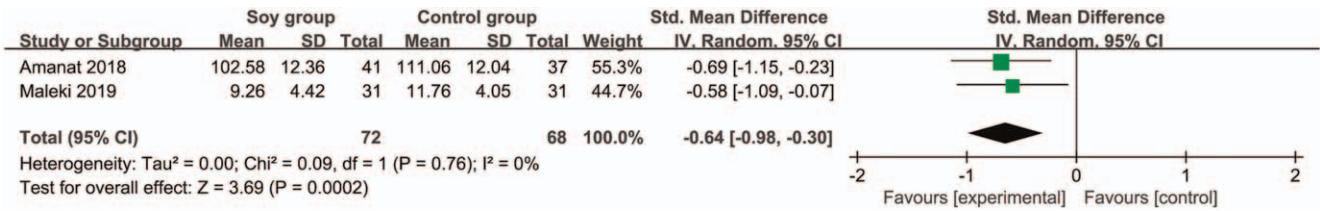

Figure 2. Forest plot for the meta-analysis of HOMA-IR.

Study or Subgroup	Soy group Mean	SD	Total	Control group Mean	SD	Total	Weight	Std. Mean Difference IV. Random. 95% CI
Amanat 2018	102.58	12.36	41	111.06	12.04	37	55.3%	-0.69 [-1.15, -0.23]
Maleki 2019	9.26	4.42	31	11.76	4.05	31	44.7%	-0.58 [-1.09, -0.07]
Total (95% CI)			72			68	100.0%	-0.64 [-0.98, -0.30]

Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.76); I² = 0%
Test for overall effect: Z = 3.69 (P = 0.0002)

Figure 3. Forest plot for the meta-analysis of insulin.

Study or Subgroup	Soy group Mean	SD	Total	Control group Mean	SD	Total	Weight	Std. Mean Difference IV. Random. 95% CI
Amanat 2018	1.76	0.29	41	1.96	0.4	37	45.2%	-0.57 [-1.03, -0.12]
Kani 2014	19.1	24.1	15	20.8	24.6	15	18.2%	-0.07 [-0.78, 0.65]
Maleki 2019	4.07	1.09	31	4.6	1.27	31	36.6%	-0.44 [-0.95, 0.06]
Total (95% CI)			87			83	100.0%	-0.43 [-0.74, -0.13]

Heterogeneity: Tau² = 0.00; Chi² = 1.36, df = 2 (P = 0.51); I² = 0%
Test for overall effect: Z = 2.78 (P = 0.005)
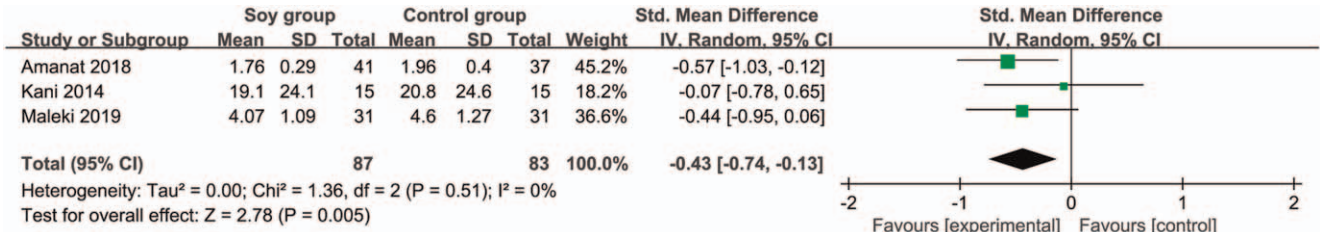
Figure 4. Forest plot for the meta-analysis of MDA. MDA = malondialdehyde.

Study or Subgroup	Soy group Mean	SD	Total	Control group Mean	SD	Total	Weight	Std. Mean Difference IV. Random. 95% CI
Amanat 2018	28.89	4.83	41	28.18	4.96	37	35.3%	0.14 [-0.30, 0.59]
Deibert 2019	29.6	3.3	11	29.3	4.5	11	15.1%	0.07 [-0.76, 0.91]
Eslami 2019	29.97	3.49	32	30.47	3.54	32	31.7%	-0.14 [-0.63, 0.35]
Kani 2014	29.8	3.6	15	26.9	3.2	15	17.9%	0.83 [0.08, 1.58]
Total (95% CI)			99			95	100.0%	0.17 [-0.20, 0.53]

Heterogeneity: Tau² = 0.05; Chi² = 4.52, df = 3 (P = 0.21); I² = 34%
Test for overall effect: Z = 0.89 (P = 0.37)

Figure 5. Forest plot for the meta-analysis of BMI. BMI = body mass index.

Study or Subgroup	Soy group Mean	SD	Total	Control group Mean	SD	Total	Weight	Std. Mean Difference IV. Random. 95% CI
Amanat 2018	41.83	31.85	41	36.51	27.44	37	37.0%	0.18 [-0.27, 0.62]
Eslami 2019	29.06	13.38	32	37.53	15.17	32	35.2%	-0.58 [-1.09, -0.08]
Kani 2014	30.9	8.7	15	26.8	7.8	15	27.8%	0.48 [-0.24, 1.21]
Total (95% CI)			88			84	100.0%	-0.01 [-0.61, 0.60]

Heterogeneity: Tau² = 0.21; Chi² = 7.43, df = 2 (P = 0.02); I² = 73%
Test for overall effect: Z = 0.02 (P = 0.98)

Figure 6. Forest plot for the meta-analysis of ALT. ALT = alanine aminotransferase.

Study or Subgroup	Soy group Mean	SD	Total	Control group Mean	SD	Total	Weight	Std. Mean Difference IV. Random. 95% CI
Amanat 2018	31.46	16.22	41	26.35	12.35	37	38.7%	0.35 [-0.10, 0.80]
Eslami 2019	24.5	20.32	32	32.5	20.47	32	36.0%	-0.39 [-0.88, 0.11]
Kani 2014	30.5	11.8	15	30	4.3	15	25.3%	0.05 [-0.66, 0.77]
Total (95% CI)			88			84	100.0%	0.01 [-0.47, 0.49]

Heterogeneity: Tau² = 0.10; Chi² = 4.68, df = 2 (P = 0.10); I² = 57%
Test for overall effect: Z = 0.04 (P = 0.97)

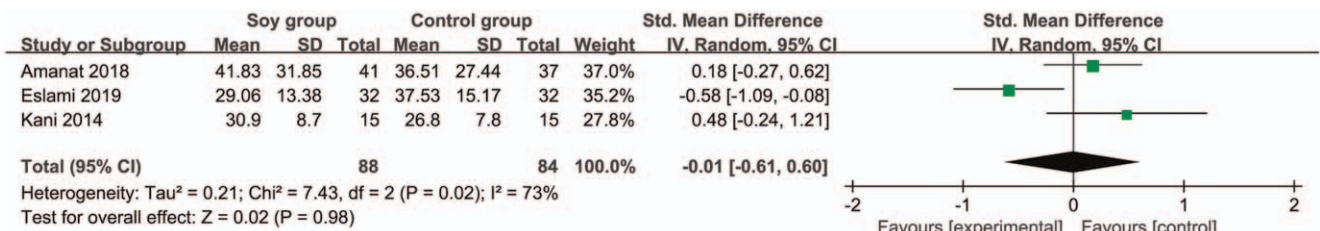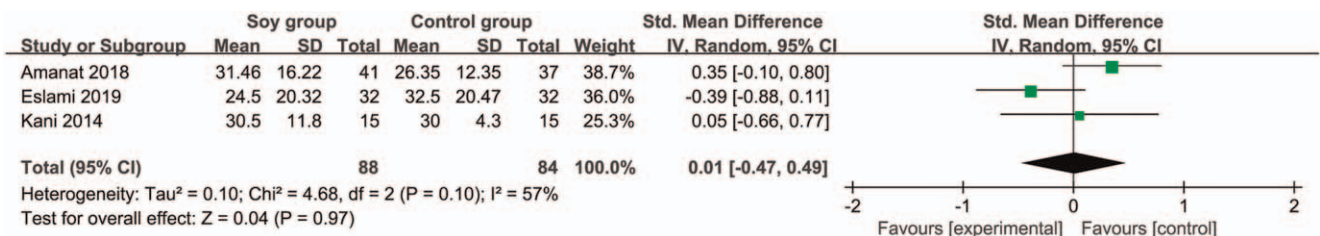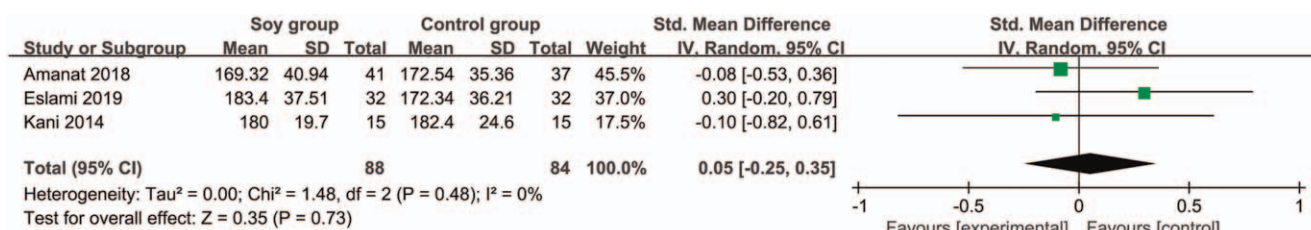**Figure 7.** Forest plot for the meta-analysis of AST. AST = aspartate-aminotransferase.

Figure 8. Forest plot for the meta-analysis of total cholesterol.
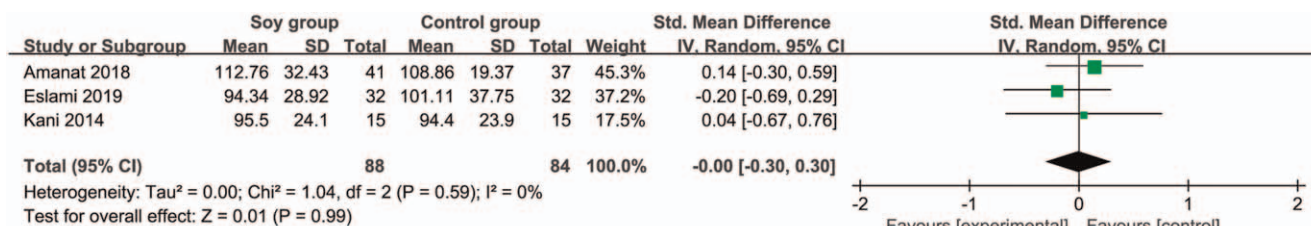

Figure 9. Forest plot for the meta-analysis of LDL. LDL = low density lipoprotein.

4. Discussion

The aggravation of nonalcoholic fatty liver disease may lead to nonalcoholic steatohepatitis which is characterized by hepatocellular damage, inflammation, and liver fibrosis that can progress to cirrhosis.[20–22] Type 2 diabetes mellitus can also increase the risk of developing cirrhosis, hepatocellular carcinoma, and double the death risk from liver cirrhosis.[23] It is crucial to control the metabolic index of diabetes mellitus. However, there is no approved pharmacologic agent for the treatment of nonalcoholic fatty liver disease. Several antidiabetic agents have showed some potential in alleviating insulin resistance for nonalcoholic fatty liver disease, but the results are variable.[24–26]

Our meta-analysis includes 5 RCTs and the results confirmed that soy diet could significantly reduce HOMA IR and increase insulin in patients with nonalcoholic fatty liver disease. Soy supplementation is recommended at the dose of 240 mL soy milk daily.[12,13] Regarding the potential mechanisms of reducing insulin resistance and improving glucose homeostasis in nonalcoholic fatty liver disease, soy isoflavones was reported to decrease the activity of intestinal alpha-glucosidase and protein tyrosine kinases.[27–29] In addition, soy diet may increase the uptake of glucose mediated by glucose transporter type,[30,31] and inhibit expression of lipogenesis transcription factors such as carbohydrate responsive element binding protein, sterol-regulatory element binding protein-1, liver X receptor, and retinoid-X-receptor.[9,32] In addition, the oxidative stress was substantially reduced after soy diet intervention for nonalcoholic fatty liver disease, as evidenced by the reduced MDA.

However, the results of this meta-analysis revealed no obvious impact on BMI, ALT, AST, total cholesterol or LDL after soy diet intervention for nonalcoholic fatty liver disease. The beneficial effect of reducing insulin resistance is not translated to liver function and fat accumulation. Only treatment for 8 weeks is used in the included RCTs, and this treatment duration may be short to assess the beneficial change of liver function and fat accumulation. Additionally, the bioactive peptides found in soy protein act as the inhibitors of angiotensin-converting enzyme, limit the effect of angiotensin II on vasoconstriction, stimulate the activity of Bradykinin vasodilator and consequently decrease blood pressure.[33] The high content of arginine in soy food is a precursor of nitric oxide, a known vasodilator.[34,35] Some types of soy isoflavones such as genistein are shown to have a diuretic activity and subsequently reduce blood pressure.[36]

Our meta-analysis also has some important limitations. Firstly, our analysis is based on 5 RCTs, and all of them have a relatively small sample size (n < 100). Overestimation of the treatment effect was more likely in smaller trials compared with larger samples. Although there is no heterogeneity, different methods and products of soy diet may produce some bias. Finally, treatment duration of 8 weeks may be not sufficient to produce the positive results of liver function.

5. Conclusions

Sitagliptin treatment may provide additional benefits to reduce insulin resistance in nonalcoholic fatty liver disease.

Author contributions

Conceptualization: Pian Xiong.
Data curation: Pian Xiong.
Formal analysis: Pian Xiong.
Supervision: Yong-fen Zhu.
Writing – original draft: Pian Xiong, Yong-fen Zhu.
Writing – review & editing: Pian Xiong.

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