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Betaine supplementation fails to improve body composition: a systematic review and meta-analysis

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Abstract

Previous studies evaluating the effects of betaine supplementation on body composition offer contradictory findings. This systematic review and meta-analysis assessed the effects of betaine supplementation on body composition indices (body mass (BM), BMI, body fat percentage (BFP), fat mass (FM), fat-free mass (FFM)), and dietary intakes. Studies examining the effects of betaine supplementation on body composition and dietary intakes published up to August 2021 were identified through PubMed, the Cochrane Library, Web of Science, Embase, SCOPUS and Ovid databases. Betaine supplementation failed to significantly affect BM ((weighted mean difference (WMD): −0·40 kg, 95 % CI −1·46, 0·64), $P = 0·447$), BMI ((WMD: −0·05 kg/m^2, 95 % CI −0·36, 0·25), $P = 0·719$), BFP ((WMD: 0·26 %, 95 % CI −0·82, 1·36), $P = 0·663$), FM ((WMD: −0·57 kg, 95 % CI −2·14, 0·99), $P = 0·473$) and FFM ((WMD: 0·61 kg, 95 % CI −1·27, 2·49), $P = 0·527$). Subgroup analyses based on participant's age (< 40 and > 40 years), sex, BMI, trial duration (< 8 and ≥ 8 weeks), betaine supplementation dosage (< 4 and ≥ 4 g) and health status (healthy or unhealthy) demonstrated similar results. Other than a potential negligible increase in protein intake (WMD: 3·56 g, 95 % CI 0·24, 6·88, $P = 0·035$), no changes in dietary intakes were observed following betaine supplementation compared with control. The present systematic review and meta-analysis does not show any beneficial effects of betaine supplementation on body composition indices (BM, BMI, FM and FFM).

Key words: **Betaine supplementation: Body composition: Fat mass: Fat-free mass: Meta-analysis**

Betaine is a non-toxic and chemically stable compound that is extensively distributed in nature[1]. It was initially identified in the juice of sugar beets (B. Vulgaris) and has subsequently been observed in other organisms[2]. Foods containing betaine include wheat products, spinach, beets and liver, among others[3]. However, the precise amount of dietary betaine depends both on the food source and cooking method[3]. Dietary betaine intake influences betaine content in kidneys, liver and brain which seem to be the primary destinations of ingested betaine[4]. Intakes of 9–15 g of betaine appear to be safe in humans[4]. Besides dietary intake, betaine can be made from choline in the human body[5]. Previous studies indicate that betaine supplementation may improve cardiovascular risk and inflammatory status[5,6].

While 'betaine' technically refers to a class of related molecules, the term is most commonly used to describe a glycine molecule with three additional methyl groups, termed trimethylglycine[4]. Reports have shown that both choline and betaine supplements can combat obesity in animals, including rats[7], pigs[8,9] and chickens[10]. Moreover, human studies have reported that higher betaine

Abbreviations: BFP, body fat percentage; BM, body mass; FFM, fat-free mass; FM, fat mass; RCT, randomised controlled trials; WMD, weighted mean difference.

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concentration is related to lower BMI, body fat percentage (BFP) and waist circumference[11–13]. Recently, a meta-analysis of six randomised controlled trials (RCT) by Gao *et al.* has shown that betaine supplementation significantly reduced fat mass (FM) and BFP without affecting body mass (BM) and BMI[14]. However, the previous meta-analysis[14] failed to include two RCT that did not show any significant changes in FM and/or BFP following betaine supplementation[15,16]. Moreover, a recently published study failed to show any beneficial effects of betaine supplementation on BFP[17]. Therefore, the previous meta-analytic findings did not fully reflect the documented effects of betaine supplementation on body composition. As a result, there is no clear consensus regarding the overall utility of betaine supplementation for body composition changes.

Dietary changes have typically been considered the primary component for improving body composition in obesity management[18]. Numerous studies have shown that alteration in dietary intake (carbohydrate, protein, fat and total energy) can result in body composition alterations[19–22]. Since the existing literature offers contradictory findings of the effects of betaine supplementation on body composition, it seems necessary to evaluate whether differences in dietary intake concurrent with betaine supplementation could have influenced these findings. Therefore, we aimed to conduct a systematic review and meta-analysis of the pooled data from RCT in adult humans to compare the efficacy of betaine supplementation for altering body composition indices (BM, BMI, FM, BFP and fat-free mass (FFM)) and influencing dietary intake (carbohydrate, protein, fat and total energy).

Experimental methods

The present systematic review and meta-analysis is reported in accordance with the Preferred Reporting Items of Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines[23].

Data sources and search strategies

A comprehensive literature search of five databases, including PubMed, the Cochrane Library, Web of Science, Embase and SCOPUS, was performed using the related terms 'betaine', 'betaine supplementation' and 'trimethylglycine', in combination with the keywords 'body composition', 'anthropometry', 'weight', 'body mass', 'fat mass', 'body fat percentage', 'waist circumference', 'hip circumference', 'fat-free mass', 'lean body mass', 'lean mass', 'body mass index', 'BMI', 'weight loss', 'fat loss', dietary intake', 'intake', 'diet', 'carbohydrate', 'fat', 'protein', 'calorie', 'energy', to identify studies published until 18 December 2020. The process of the search strategy is shown in the flow diagram (Fig. 1).

Study selection and eligibility criteria

Two investigators (DAL and SK) selected eligible studies separately by reading the full-text versions of them. All human RCT, either parallel or crossover designs, which reported the effect of betaine supplementation on body composition indices including BM, BMI, FM, BFP, FFM and dietary intake (carbohydrate, protein, fat and total energy) on adults (> 18 years) and published in the English language were considered. The following studies were excluded: (1) RCT with follow-up period < 10 d, (2) studies without a control/placebo arm. When resolution could not be obtained, a third author (RB) was involved by consensus. The participants, intervention, comparators, outcomes and study design criteria are listed in Table 1.

Data extraction

The following data were extracted from the full-text versions of eligible studies using a pre-designed abstraction form: first author, year of publication, country, number of participants, study design, the dose of interventions and study duration. In cases of lack of relevant data, the authors were contacted via email to obtain additional information. Two investigators (DAL and SS) carried out the process of data extraction from the original publications independently in order to minimise potential errors. When resolution could not be obtained, a third author (RB) was involved by consensus.

Quality assessment of studies

The quality of studies for assessing the risk of bias was assessed by the Cochrane Collaboration's tool as previously described[24]. Briefly, nine items were scored, and these items were divided into six domains of bias with three rating categories available for each item: (1) low risk of bias; (2) unclear risk of bias and (3) high risk of bias. The quality of each selected article was assessed by two authors (DAL and WK). When resolution could not be obtained, a third author (OA) was involved by consensus (Table 2).

Meta-analysis of data

To analyse the effect size for BM, BMI, FM, BFP, FFM, dietary carbohydrate, protein, fat and total energy, the mean change and its SD were extracted for intervention and control groups, the latter of which served as the comparison group. To calculate the effect size of each study, we used the mean change and SD of the outcome measures from baseline to the end of the intervention in the control and intervention groups[25]. When the outcome measure was reported as mean and 95 % CI or mean and SEM, values were estimated using Review Manager 5·3 software. If the outcome measures were reported in median, range, or 25th–75th percentiles, mean and SD values were estimated using the following formula:

$$SD = \sqrt{\begin{array}{l}((SD\ pretreatment)^2 + (SD\ posttreatment)^2 \\ -(2R \times SD\ pretreatment \times SD\ posttreatment))\end{array}}$$

published by Wan *et al.*, where R = 0.8 was assumed as a correlation coefficient[26]. If the outcome measures were only reported in figures, we used software (GetData Graph Digitizer) to estimate the value. When an SEM or SE was reported instead of SD, the SD was calculated based on the following formula: $SD = SEM \times \sqrt{n}$ (n = sample size in each group).

A random effects model was used to calculate weighted mean differences (WMD) with 95 %CI. Between-study heterogeneity was tested by Cochran's Q test and quantified by I^2 statistics.

British Journal of Nutrition

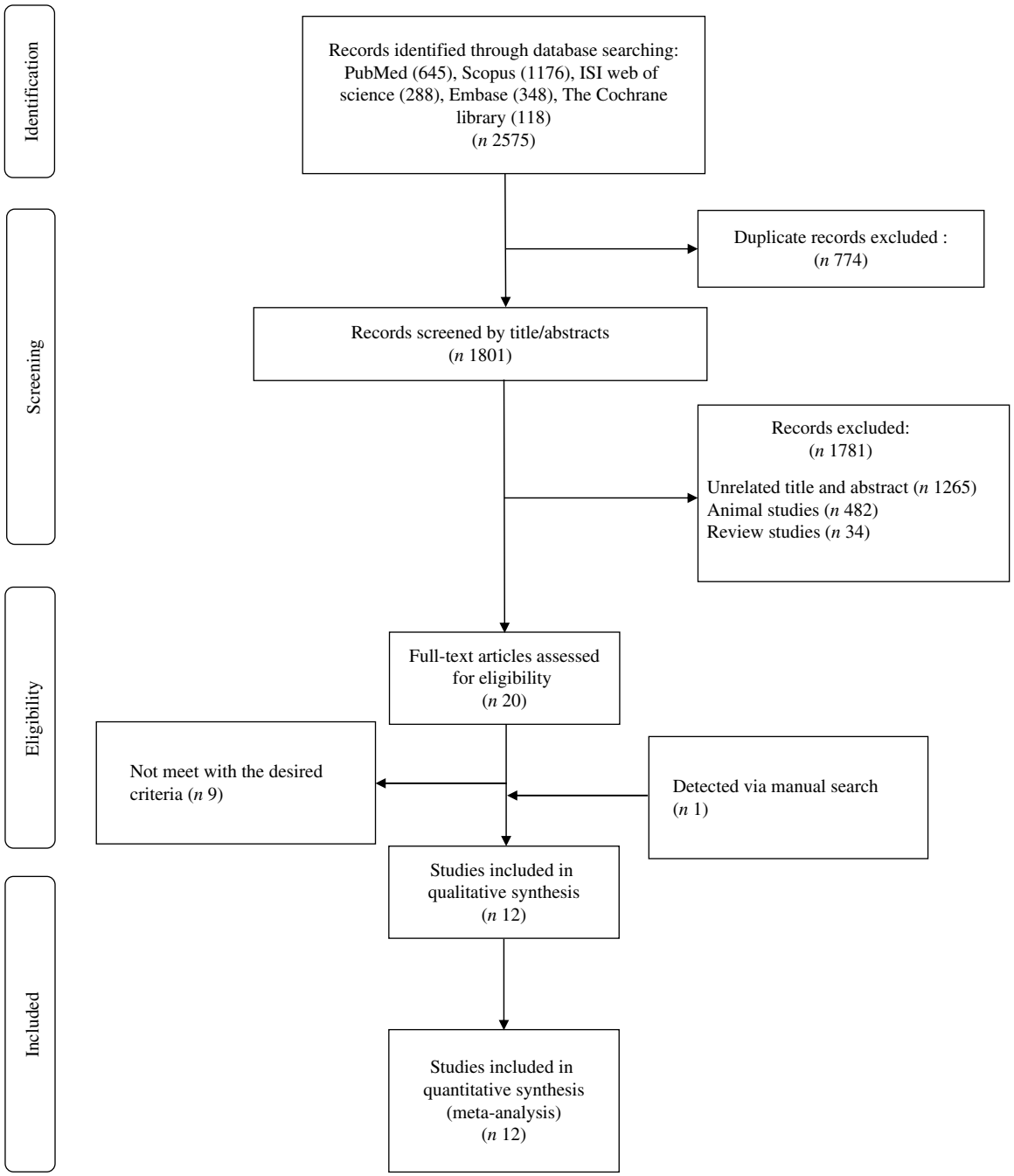

Fig. 1. Flow diagram of the literature search.

Table 1. Participants, intervention, comparators, outcomes, study design (PICOS) criteria for inclusion of studies

Population	Adult individuals
Intervention	Betaine supplementation
Comparison	Control group
Outcomes	Body mass, BMI, fat mass, body fat percentage, fat-free mass, dietary intakes of carbohydrate, protein, fat and total energy
Study design	Human RCT either parallel or crossover designs

RCT, randomised controlled trials.

A subgroup analysis based on BMI ((18·5; 24·9 kg/m^2), (25; 29·9 kg/m^2), or ≥ 30 kg/m^2), duration of the study (< 8 or ≥ 8 weeks), the intervention dose (> 4 g or ≤ 4 g/d) and health status (healthy or unhealthy) was conducted to detect potential sources of heterogeneity. Participants with any chronic disease such as diabetes and prediabetes, fatty liver disease, and obesity were considered as unhealthy in health status subgroup[27,28]. Moreover, studies which stated their participants as healthy and/or excluded the participants with any diseases were considered as healthy in the subgroup. Sensitivity analysis was conducted

Table 2. Quality assessment (method: Cochrane collaboration's tool for assessing risk of bias)

	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	Total
Article	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Anything else, ideally pre-specified	Low on risk of bias
Schwab *et al.* 2002	U	L	L	U	L	L	L	5/7
Abdelmalek *et al.* 2009	L	L	L	L	H	H	H	4/7
Lee *et al.* 2010	L	H	U	U	L	H	H	2/7
Schwab *et al.* 2011	U	L	L	U	L	L	L	5/7
Trepanowski *et al.* 2011	U	U	L	U	H	L	L	3/7
Favero *et al.* 2012	L	U	L	U	L	L	L	5/7
Cholewa *et al.* 2013	U	L	L	L	L	H	H	4/7
Tiihonen *et al.* 2016	U	L	L	U	L	L	H	4/7
Rajdi *et al.* 2016	U	L	H	H	L	L	H	3/7
Grizales *et al.* 2018	U	L	H	H	L	L	H	3/7
Cholewa *et al.* 2018	L	L	L	L	H	H	L	5/7
Moro *et al.* 2020	L	L	L	L	H	H	H	4/7

L, low; U, unclear; H, high.

by removing each study one by one and recalculating the pooled evaluations. Egger's regression asymmetry test and visual inspection of funnel plots were performed to detect potential publication bias. Statistical analysis was conducted using STATA, version 11·2 (Stata Corp). The statistically significant value was set at $P < 0{\cdot}05$.

Results

Selection and identification of studies

Out of the initial 2575 potentially relevant reports that were obtained by searching the databases, 774 were immediately excluded due to duplication. In addition, we further excluded 1781 studies since they were unrelated to the present meta-analysis (according to our inclusion criteria). From these, 1265 studies did not use betaine supplementation, 482 were conducted on animals, and 34 were review studies. After full-text analysis of the remaining twenty articles, nine studies[29–37] were excluded, since they did not evaluate body composition and/or dietary intake following betaine supplementation. Furthermore, one investigation was detected via manual search[38] (by searching the references of relevant studies). In total, twelve studies were included in the final analysis[15–17,38–46].

Characteristics of studies

According to Cochrane scores, eleven from twelve included studies were classified as high-quality studies (score ≥ 3), and one was classified as low quality (score < 3). The result of the quality assessment is reported in Table 2. Overall, 12 RCT with 13 treatment and 13 control arms were included in the analysis, with a total sample size of 369 participants, out of which 199 participants were in the betaine group/condition and 195 belonged to the control group/condition. The discrepancy between total participants and participants in each group/condition is due to the inclusion of two crossover studies[41,43].

The mean age of participants in these studies ranged from 21 to 59 years. These studies were published between the years 2002 and 2020. The studies were conducted in Finland[39,42], USA[40,41,43–46], Brazil[15], Japan[38], Czech Republic[16] and Italy[17]. A daily dose of betaine ranged from 1·5 to 20 g/d. The trial duration also varied from 2 to 52 weeks. Study participants included patients with prediabetes[46], fatty liver disease[38,40], obesity[39] and healthy individuals[15–17,41–45]. The characteristics of twelve studies eligible for inclusion in the present meta-analysis are shown in Table 3.

Meta-analysis of data

Effects of betaine supplementation on body mass and BMI. Pooled analysis of nine and five effect sizes indicated that the participants assigned to betaine supplementation did not change BM (WMD: −0·40 kg, 95 % CI −1·46, 0·64, $I^2 = 0{\cdot}0$ %, $P = 0{\cdot}447$) or BMI (WMD: −0·05 kg/m^2, 95 % CI −0·36, 0·25, $I^2 = 0{\cdot}0$ %, $P = 0{\cdot}719$) in comparison with placebo (Fig. 2(a): BM and Fig. 2(b): BMI). Subgroup analysis showed that betaine supplementation in different doses (≥ 4 or < 4 g), participant's age (< 40 and ≥ 40 years), sex (male, female and both sexes) and trial duration (≥ 8 or < 8 weeks) did not have significant effects on BM or BMI (Table 4).

Effects of betaine supplementation on body fat percentage and fat mass. Overall, seven arms indicated the effects of betaine supplementation on BFP. Our results showed that betaine supplementation did not affect BFP (WMD: 0·26 %, 95 % CI −0·82, 1·36, $I^2 = 0{\cdot}0$ %, $P = 0{\cdot}633$) in comparison with control (Fig. 3(a)). Moreover, from five arm assessed, betaine supplementation failed to change FM (WMD: −0·57 kg, 95 % CI −2·14, 0·99, $I^2 = 0{\cdot}0$ %, $P = 0{\cdot}473$) (Fig. 3(b)). Subgroup analysis showed that betaine supplementation in different doses (≥ 4 or < 4 g), participant's age (< 40 and ≥ 40 years), sex (male, female and both sexes), trial duration (≥ 8 or < 8 weeks) and

Table 3. The characteristics of the included trials

Study	Country	Study design	Participants	Baseline mean BMI	Baseline mean age	*n* (control/ intervention)		Sex (F/M)	Exercise training	Duration	Dose of betaine	Main findings
Schwab *et al.* 2002	Finland	Parallel	Healthy adults	33·5	44	42	20/ 22	28/14	No	12 weeks	6 g	↔ BM, BMI, FM, BFP, FFM, dietary intake
Abdelmalek *et al.* 2009	USA	Parallel	Patients with non-alcoholic steatohepatitis	33·5	47	35	18/ 17	22/13	No	52 weeks	20 g	↔ BM
Lee *et al.* 2010	USA	Crossover	Healthy, recreationally active adults	ND	21	12	12/ 12	0/12	Yes	2 weeks	2·5 g	↔ BM
Schwab *et al.* 2011	Finland	Parallel	Healthy adults	22·6	27	63	31/ 32	50/13	No	24 weeks	4 g	↔ BM, BMI, dietary intake
Trepanowski *et al.* 2011	USA	Crossover	Resistance-trained men	26	23	13	13/ 13	0/13	Yes	2 weeks	2·5 g	↔ dietary intake
Favero *et al.* 2012 (A)	Brazil	Parallel	Resistance-trained men	ND	18 to 35	17	8/9	0/17	Yes	10 d	2 g	↔ BM, FM, BFP, FFM, dietary intake
Favero *et al.* 2012 (B)	Brazil	Parallel	Resistance-trained men	ND	18 to 35	17	9/8	0/17	Yes	10 d	2 g	↔ BM, FM, BFP, FFM, dietary intake
Cholewa *et al.* 2013	USA	Parallel	Resistance-trained men	ND	18 to 35	23	12/ 11	0/23	Yes	6 weeks	2·5 g	↓FM, BFP ↑FFM
Tiihonen *et al.* 2016	Japan	Parallel	Men with mild fatty liver disease	24·9	44	20	10/ 10	0/20	No	12 weeks	3 g	↔ BM, BMI
Cholewa *et al.* 2018	USA	Parallel	Healthy, recreationally active women	24·9	21	23	12/ 11	23/0	Yes	8 weeks	2·5 g	↔ BM, FFM, dietary intake ↓FM, BFP
Rajdi *et al.* 2016	Czech Republic	Parallel	Healthy adults	26	ND	48	23/ 25	0/48	No	4 weeks	3 g	↔ BMI, BFP
Grizales *et al.* 2018	USA	Parallel	Prediabetic	31·5	59	27	13/ 14	8/19	No	12 weeks	9·9 g	↔ BM, BMI
Moro *et al.* 2020	Italy	Parallel	CrossFit athletes	24·1	35	29	14/ 15	14/15	Yes	6 weeks	2·5 g	↔ BFP

BM, body mass; BFP, body fat percentage; FM, fat mass; FFM, fat-free mass; ND, non-defined; ↔, unchanged, ↓, decreased; ↑, increased.

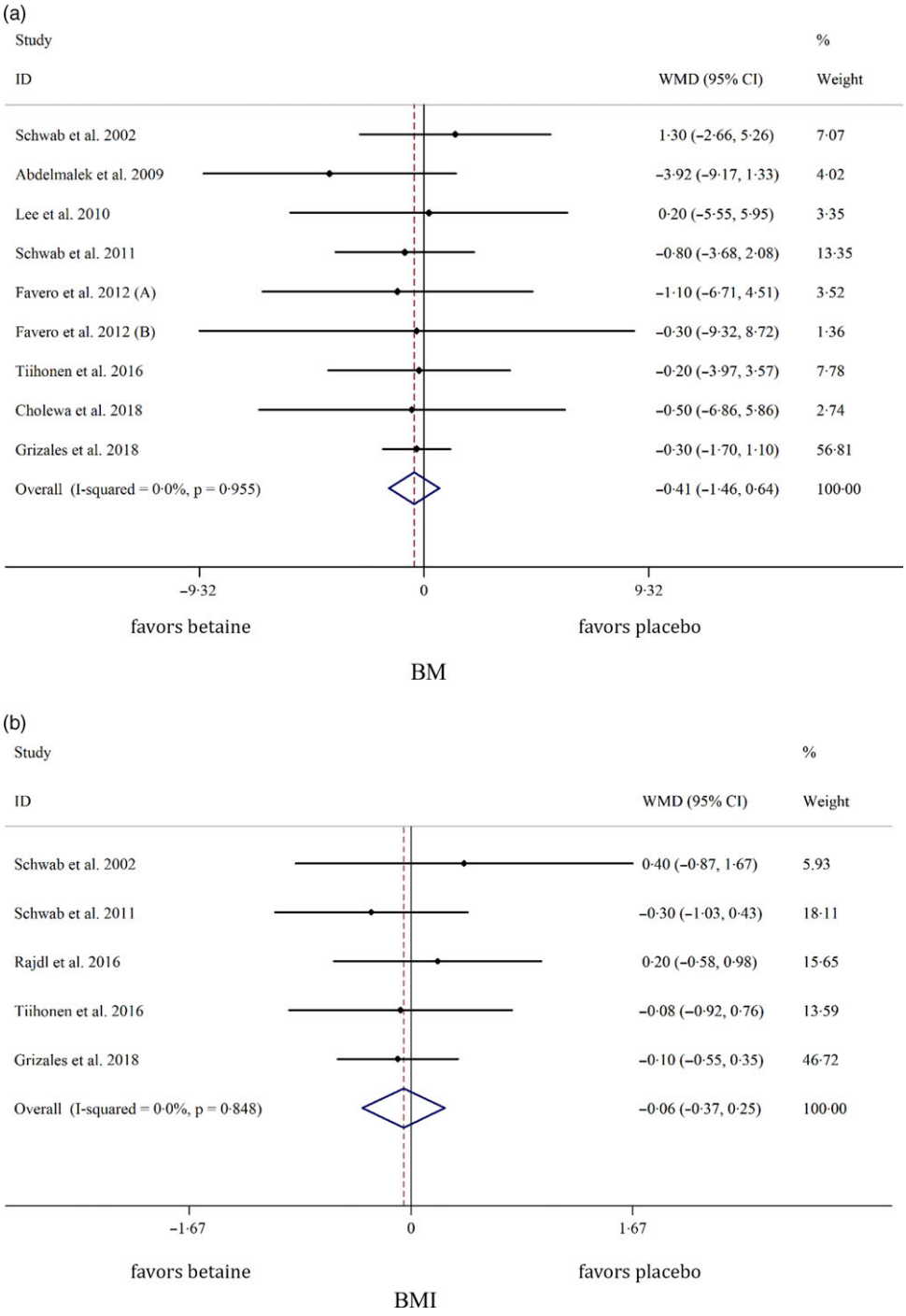

Fig. 2. Forest plot of the random effects meta-analysis of the effect of betaine supplementation on (a) BM and (b) BMI. BM, body mass. WMD, weighted mean difference.

health status (healthy or unhealthy) did not have significant effects on BFP or FM (Table 4).

Effects of betaine supplementation on fat-free mass. In total, five studies evaluated the effects of betaine supplementation on FMM. Forest plots summarising the efficacy of betaine supplementation on FFM are shown in Fig. 4. The individuals supplemented with betaine were shown insignificant changes of FFM ((WMD: 0·61 kg, 95 % CI −1·27, 2·49, $I^2 = 0·0$ %, $P = 0·527$), Fig. 4)). Subgroup analysis showed that betaine supplementation in different doses (≥ 4 or < 4 g), participant's age (< 40 and ≥ 40 years), sex (male, female and both sexes), trial duration (≥ 8 or < 8 weeks) and health status (healthy or unhealthy) did not significantly affect FFM (Table 4).

Effects of betaine supplementation on dietary intakes. In total, six studies evaluated dietary intakes following betaine supplementation. There was no significant difference in energy

Table 4. Subgroup analysis of betaine supplementation on body composition

	n	WMD	95 %CI	*P*	P heterogeneity	I^2
Subgroup analyses of betaine supplementation on BM						
Overall effect	9	−0·40	−1·46, 0·64	0·447	0·955	0·0 %
Baseline BMI (kg/m^2)						
(18·5; 24·9)	2	−0·57	−2·86, 1·70	0·620	0·804	0·0 %
>30	3	−0·34	−1·62, 0·92	0·593	0·294	18·4 %
Participant's age (years)						
<40	5	−0·64	−2·77, 1·48	0·554	0·998	0·0 %
≥40	4	−0·33	−1·54, 0·87	0·590	0·483	0·0 %
Participant's sex						
Both sexes	4	−0·42	−1·58, 0·74	0·478	0·470	0·0 %
Male	4	−0·32	−2·95, 2·30	0·810	0·991	0·0 %
Female	1	−0·50	−6·85, 5·85	0·877	–	–
Health status						
Healthy	5	−0·64	−2·77, 1·48	0·554	0·998	0·0 %
Unhealthy	4	−0·33	−1·54, 0·87	0·590	0·483	0·0 %
Dose (g)						
≥4	4	−0·42	−1·58, 0·74	0·478	0·470	0·0 %
<4	5	−0·34	−2·77, 2·08	0·779	0·998	0·0 %
Trial duration (weeks)						
≥8	6	−0·40	−1·50, 0·69	0·469	0·770	0·0 %
<8	3	−0·43	−4·10, 3·22	0·815	0·950	0·0 %
Subgroup analyses of betaine supplementation on BMI						
Overall effect	5	−0·05	−0·36, 0·25	0·719	0·848	0·0 %
Baseline BMI (kg/m^2)						
(18·5; 24·9)	2	−0·20	−0·75, 0·34	0·463	0·698	0·0 %
(25; 29·9)	1	0·20	−0·58, 0·98	0·616	–	–
>30	2	−0·04	−0·47, 0·38	0·841	0·468	0·0 %
Participant's age (years)						
<40	1	−0·30	−1·02, 0·42	0·419	–	–
≥40	3	−0·05	−0·43, 0·32	0·792	0·766	0·0 %
Participant's sex						
Both sexes	3	−0·10	−0·47, 0·25	0·561	0·643	0·0 %
Male	2	0·07	−0·50, 0·64	0·811	0·633	0·0 %
Health status						
Healthy	2	−0·06	−0·60, 0·46	0·802	0·359	0·0 %
Unhealthy	3	−0·05	−0·43, 0·32	0·792	0·766	0·0 %
Dose (g)						
≥4	3	−0·10	−0·47, 0·25	0·561	0·643	0·0 %
<4	2	0·07	−0·50, 0·64	0·811	0·633	0·0 %
Trial duration (weeks)						
≥8	4	−0·10	−0·44, 0·23	0·543	0·829	0·0 %
<8	1	0·20	−0·58, 0·98	0·616	–	–
Subgroup analyses of betaine supplementation on FM						
Overall effect	5	−0·57	−2·14, 0·99	0·473	0·650	0·0 %
Participant's age (years)						
<40	3	−0·55	−2·64, 1·53	0·604	0·917	0·0 %
≥40	1	0·70	−2·21, 3·61	0·638	–	–
Participant's sex						
Both sexes	1	0·70	−2·21, 3·61	0·638	–	–
Male	3	−1·06	−3·08, 0·96	0·303	0·490	0·0 %
Female	1	−1·30	−6·13, 3·53	0·598	–	–
Health status						
Healthy	4	−1·09	−2·96, 0·76	0·249	0·697	0·0 %
Unhealthy	1	0·70	−2·21, 3·61	0·638	–	–
Dose (g)						
≥4	1	0·70	−2·21, 3·61	0·638	–	–
<4	4	−1·09	−2·96, 0·76	0·249	0·697	0·0 %
Trial duration (weeks)						
≥8	2	0·16	−2·32, 2·66	0·896	0·487	0·0 %
<8	3	−1·06	−3·08, 0·96	0·303	0·490	0·0 %
Subgroup analyses of betaine supplementation on BFP						
Overall effect	7	0·26	−0·82, 1·36	0·633	0·426	0·0 %
Participant's age (years)						
<40	4	−0·56	−2·47, 1·35	0·565	0·936	0·0 %
≥40	1	0·30	−2·55, 3·15	0·837	–	–
Participant's sex						
Both sexes	2	0·02	−2·23, 2·28	0·983	0·757	0·0 %
Male	4	0·54	−0·76, 1·86	0·414	0·188	37·3 %

Table 4. (*Continued*)

	n	WMD	95 %CI	*P*	P heterogeneity	I^2
Female	1	−1·70	−5·82, 2·42	0·419	–	–
Health status						
Healthy	6	0·26	−0·92, 1·44	0·667	0·309	16·3 %
Unhealthy	1	0·30	−2·55, 3·15	0·837	–	–
Dose (g)						
≥4	1	0·30	−2·55, 3·15	0·837	–	–
<4	6	0·26	−0·92, 1·44	0·667	0·309	16·3 %
Trial duration (weeks)						
≥8	2	−0·34	−2·69, 2·00	0·771	0·435	0·0 %
<8	5	0·43	−0·80, 1·67	0·489	0·284	0·0 %
Subgroup analyses of betaine supplementation on FFM						
Overall effect	5	0·61	−1·27, 2·49	0·527	0·978	0·0 %
Participant's age (years)						
<40	3	0·42	−2·02, 2·87	0·733	0·856	0·0 %
>40	1	0·50	−3·37, 4·37	0·800	–	–
Participant's sex						
Both sexes	1	0·50	−3·37, 4·37	0·800	–	–
Male	3	0·33	−2·61, 3·28	0·823	0·837	0·0 %
Female	1	1·00	−2·17, 4·17	0·537	–	–
Health status						
Healthy	4	0·64	−1·51, 2·80	0·559	0·931	0·0 %
Unhealthy	1	0·50	−3·37, 4·37	0·800	–	–
Dose (g)						
≥4	1	0·50	−3·37, 4·37	0·800	–	–
<4	4	0·64	−1·51, 2·80	0·559	0·931	0·0 %
Trial duration (weeks)						
≥8	2	0·79	−1·65, 3·25	0·524	0·845	0·0 %
<8	3	0·33	−2·61, 3·28	0·823	0·837	0·0 %
Subgroup analyses of betaine supplementation on carbohydrate intake						
Overall effect	6	−1·85	−9·45, 5·75	0·633	0·603	0·0 %
Participant's age (years)						
<40	5	−4·24	−13·88, 5·39	0·388	0·557	0·0 %
>40	1	2·10	−10·28, 14·48	0·740	–	–
Participant's sex						
Both sexes	2	−1·67	−9·51, 6·15	0·675	0·440	0·0 %
Male	3	−9·72	−48·91, 29·46	0·627	0·244	29·1 %
Female	1	4·90	−49·28, 59·08	0·859	–	–
Health status						
Healthy	5	−4·24	−13·88, 5·39	0·388	0·557	0·0 %
Unhealthy	1	2·10	−10·28, 14·48	0·740	–	–
Dose (g)						
≥4	2	−1·67	−9·51, 6·15	0·675	0·440	0·0 %
<4	4	−4·70	−36·45, 27·05	0·772	0·391	0·2 %
Trial duration (weeks)						
≥8	3	−1·54	−9·29, 6·21	0·627	0·722	0·0 %
<8	3	−9·72	−48·91, 29·46	0·697	0·244	29·1 %
Subgroup analyses of betaine supplementation on fat intake						
Overall effect	6	2·71	−0·24, 5·66	0·072	0·206	30·5 %
Participant's age (years)						
<40	5	0·86	−2·99, 4·73	0·659	0·278	21·5 %
>40	1	5·30	0·71, 9·88	0·023	–	–
Participant's sex						
Both sexes	2	2·87	−0·27, 6·02	0·074	0·153	51·1 %
Male	3	7·04	−3·72, 17·81	0·200	0·306	15·6 %
Female	1	−7·70	−21·61, 6·21	0·278	–	–
Health status						
Healthy	5	0·86	−2·99, 4·73	0·659	0·278	21·5 %
Unhealthy	1	5·30	0·71, 9·88	0·023	–	–
Dose (g)						
≥4	2	2·87	−0·27, 6·02	0·074	0·153	51·1 %
<4	4	1·52	−6·99, 10·03	0·074	0·167	40·8 %
Trial duration (weeks)						
≥8	3	2·35	−0·71, 5·42	0·132	0·125	51·9 %
<8	3	7·04	−3·72, 17·81	0·200	0·306	15·6 %
Subgroup analyses of betaine supplementation on protein intake						
Overall effect	6	3·56	0·24, 6·88	0·035	0·375	6·5 %
Participant's age (years)						
<40	5	2·61	−1·25, 6·49	0·185	0·345	10·7 %
>40	1	6·20	−0·24, 12·64	0·059	–	–

Table 4. (*Continued*)

	n	WMD	95 %CI	*P*	P heterogeneity	I^2
Participant's sex						
Both sexes	2	2·90	−0·62, 6·42	0·106	0·231	30·2 %
Male	3	4·76	−9·36, 18·88	0·509	0·363	1·2 %
Female	1	13·00	−1·07, 27·07	0·070	–	–
Health status						
Healthy	5	2·61	−1·25, 6·49	0·185	0·345	10·7 %
Unhealthy	1	6·20	−0·24, 12·64	0·059	–	–
Dose (g)						
≥4	2	2·90	−0·62, 6·42	0·106	30·2 %	0·231
<4	4	8·89	−1·07, 18·86	0·080	0·0 %	0·443
Trial duration (weeks)						
≥8	3	3·49	0·08, 6·91	0·045	0·193	39·3 %
<8	3	4·76	−9·36, 18·88	0·509	0·363	1·2 %
Subgroup analyses of betaine supplementation on energy intake						
Overall effect	6	25·72	−72·12, 123·57	0·606	0·498	2·9 %
Participant's age (years)						
<40	5	12·58	−100·44, 125·61	0·827	0·293	19·1 %
>40	1	65·00	−130·45, 260·45	0·515	–	–
Participant's sex						
Both sexes	2	39·04	−77·05, 155·15	0·510	0·746	0·0 %
Male	3	−8·07	−277·33, 261·19	0·953	0·087	59·0 %
Female	1	−6·00	−252·41, 240·41	0·962		
Health status						
Healthy	5	12·58	−100·44, 125·61	0·827	0·293	19·1 %
Unhealthy	1	65·00	−130·45, 260·45	0·515	–	–
Dose (g)						
≥4	2	39·04	−77·05, 155·15	0·510	0·181	0·0 %
<4	4	−6·94	−188·72, 174·83	0·940	0·746	38·4 %
Trial duration (weeks)						
≥8	3	30·86	−74·16, 135·89	0·565	0·900	0·0 %
<8	3	−8·07	−277·33, 261·19	0·953	0·087	59·0 %

WMD, weighted mean differences; BM, body mass; BFP, body fat percentage; FM, fat mass; FFM, fat-free mass.

intake between the groups (WMD: 107·61 kJ, 95 % CI −72·12, 123·57, $I^2 = 2·9$ %, $P = 0·606$) (Fig. 5(d)). Moreover, pooled analysis of six effect sizes demonstrated that dietary protein intake may have marginally increased with betaine supplementation as compared with control ((WMD: 3·56 g, 95 % CI 0·24, 6·88, $I^2 = 6·5$ %, $P = 0·035$), Fig. 5(c))) without differences for dietary carbohydrate ((WMD: −1·85 g, 95 % CI −9·45, 5·75, $I^2 = 0·0$ %, $P = 0·633$), Fig. 5(a))) and fat intake ((WMD: 2·71 g, 95 % CI −0·24, 5·66, $I^2 = 30·5$ %, $P = 0·072$), Fig. 5(b))).

Sensitivity analysis

The sensitivity analysis showed that results for each variable were not substantially changed after excluding each study individually.

Publication bias

The results of Egger's test revealed that with the exception of BFP ($P = 0·009$), there was no publication bias for outcome variables (BM, $P = 0·809$; BMI, $P = 0·302$; FM, $P = 0·351$; FFM, $P = 0·161$; carbohydrate, $P = 0·733$; fat, $P = 0·400$; protein, $P = 0·657$; and energy, $P = 0·687$). Funnel plots for outcome variables are presented in Supplementary file 1. Due to significant publication bias for BFP, we conducted trim and fill analysis, and the results of the analysis showed that with the publication of seven new studies, the results of the publication bias would be non-significant. However, the estimated effects of betaine supplementation on BFP did not significantly change (WMD: 0·26 %, 95 %CI −0·82, 1·36, $P = 0·633$).

Discussion

In this meta-analysis, we evaluated the effects of betaine supplementation on body composition indices. According to the results derived from this study, betaine supplementation failed to affect body composition indices, including BM, BMI, FM, BFP and FFM. Moreover, our findings showed that those who supplemented with betaine potentially had a slightly increased dietary protein intake, although the magnitude of the difference is negligible. Furthermore, subgroup analyses based on the duration of interventions (≤ 8 and > 8 weeks), participant's age (< 40 and ≥ 40 years), sex (male, female and both sexes), betaine dose (< 4 and ≥ 4 g/d), baseline BMI ((18·5; 24·9 kg/m^2), (25; 29·9 kg/m^2) or ≥ 30 kg/m^2) and health status (healthy or unhealthy) did not reveal any significant differences.

Prior meta-analytic work of six RCT by Gao *et al.* evaluated the effects of betaine supplementation on body composition[14]. They have shown that betaine supplementation significantly reduced FM and BFP without affecting BM and BMI[14]. The present findings exhibit some discrepancies with the results of the study by Gao *et al.*, who provided new knowledge on several relevant topics. First, Gao *et al.* included only four studies for assessing the effects of betaine supplementation on FM and BFP while we included five

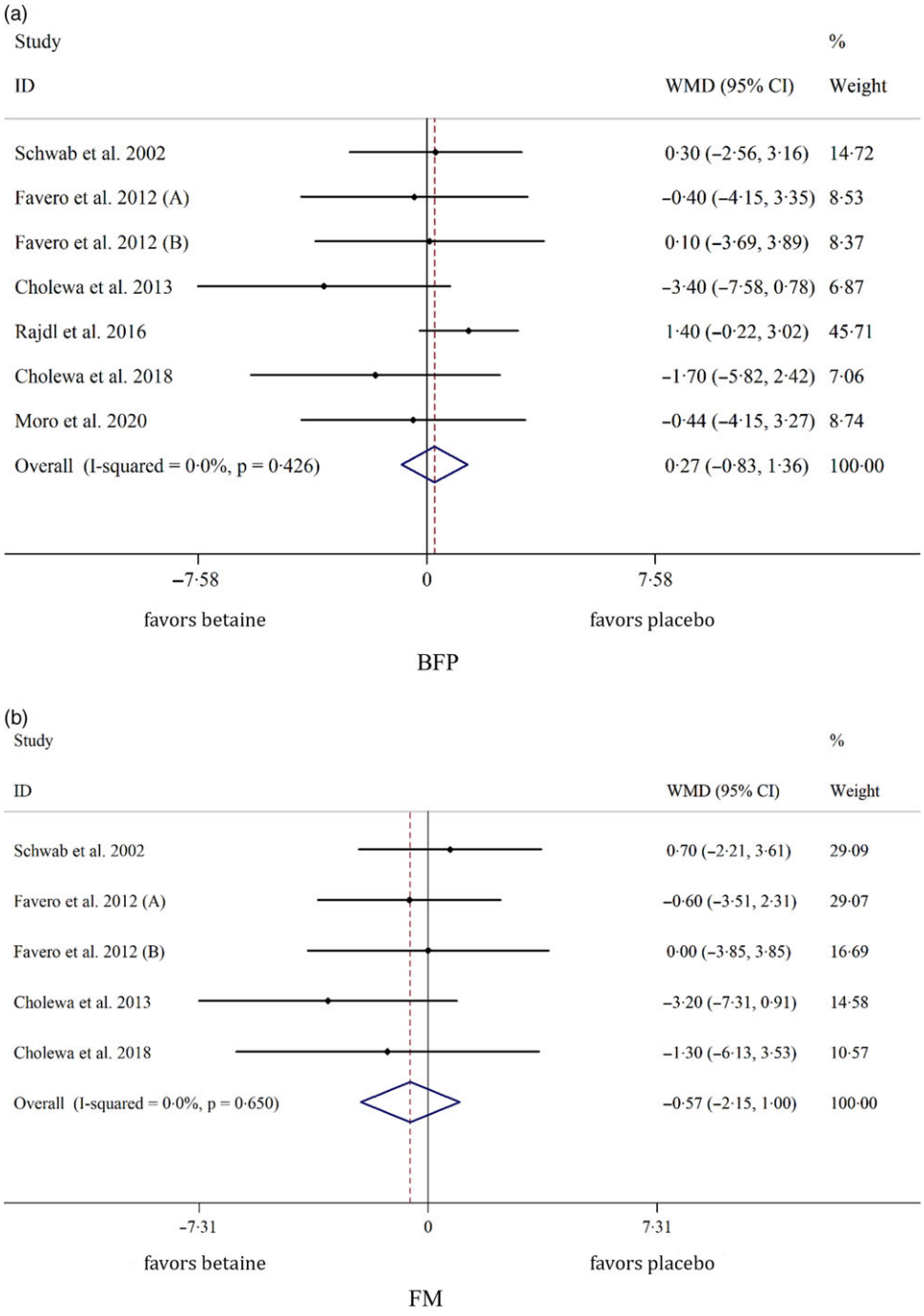

Fig. 3. Forest plot of the random effects meta-analysis of the effect of betaine supplementation on (a) BFP and (b) FM. BFP, body fat percentage; FM, fat mass. WMD, weighted mean difference.

and seven trials, respectively. The lower number of included studies in the previous meta-analysis resulted in one study[44] having relatively high weight in the analysis (68·83 % and 68·44 % for FM and BFP, respectively), which might have influenced the trend of the pooled effects of betaine supplementation on body fat. Second, some aspects of the meta-analytical methods may have differed between investigations. For example, Gao *et al.* reported a much narrower 95 % CI for the study of Cholewa *et al.*[44] in terms of FM reduction (–4·96 kg, –1·44 kg) as compared with the CI calculated in the present investigation (–7·31 kg, 0·91 kg). This is notable as this was the same investigation that had a very high weight (68·83 %) in the previous meta-analysis study. Third, Gao *et al.*[14] did not evaluate the influence of betaine supplementation on FFM, while we showed that betaine supplementation was unable to induce any significant changes in FFM. Fourth, due to the limited trials in the previous study, subgroup analysis was not performed. However, we showed the effects of betaine supplementation in different subgroups based on duration, dosage and

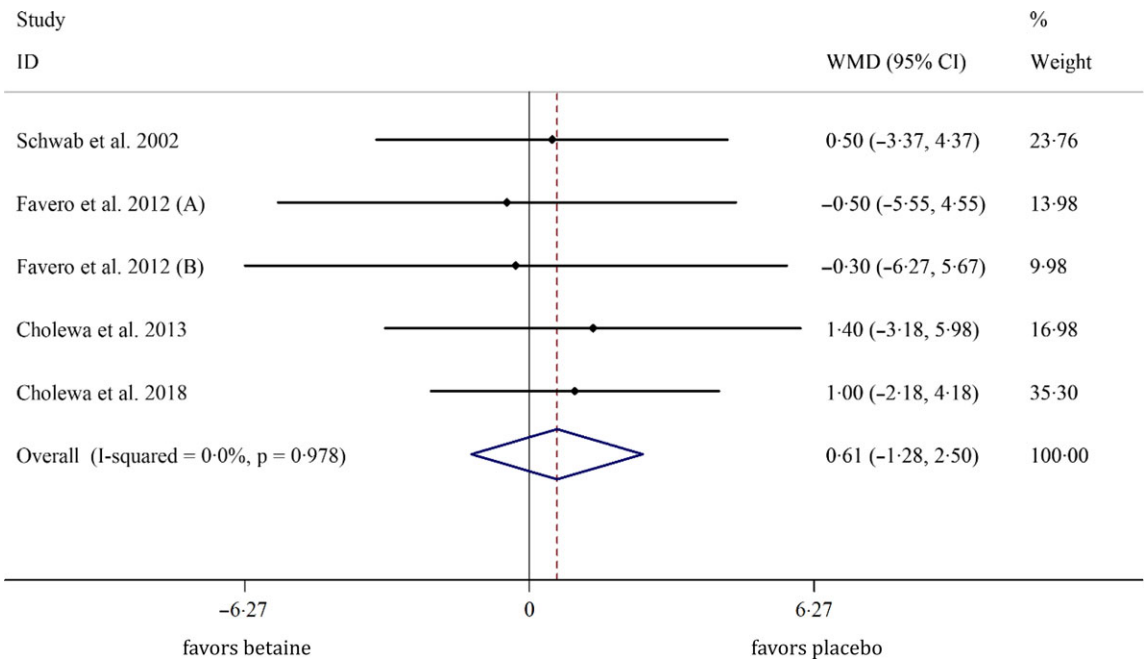

Fig. 4. Forest plot detailing weighted mean difference and 95 % CI for the effect of betaine supplementation on FFM. FFM, fat-free mass. WMD, weighted mean difference.

baseline BMI. Fifth, we analysed dietary intake to determine if there were any significant changes following betaine supplementation. Therefore, the inclusion of seven additional studies, increasing the sample size by 89 % in the current analysis, has a substantial influence on the available evidence. In contrast with the previous meta-analysis[14], our findings suggest that betaine supplementation does not improve body composition indices.

In healthy adults, serum betaine concentration is normally between 20 and 60 μmol/l[47]. From all included studies, the two studies by Cholewa *et al.*[44,45] reported significant body fat-lowering effects of betaine supplementation; however, betaine concentration was not measured in these investigations. Nevertheless, based on the other included studies reporting serum concentration of betaine[16,38,39,42,46], it seems that all participants had normal or nearly normal betaine concentration. Moreover, these investigations failed to show any significant difference in body composition indices[16,38,39,42,46]. These results suggest that at least when betaine concentration is normal or near-normal, betaine supplementation may not affect body composition indices. To reveal the extent to which the effects of betaine supplementation are dependent on baseline concentration, studies could be conducted in individuals with varying serum concentration of betaine.

Betaine is a commonly used additive in the animal's diet. Some studies showed that betaine is effective in increasing lean mass in pigs[48–50] and chickens[51]. The possible mechanism for increasing lean mass in animals is unclear. However, animal studies showed that betaine supplementation may act as a methyl donor in methionine-deficient diets and may result in growth rates comparable to animals fed diets with adequate methionine[52–54]. For example, a study by Saunderson *et al.* demonstrated reductions in FM and increased protein content of chicken breast following betaine supplementation[51]. However, there is no evidence that betaine supplementation can improve FFM in humans. All studies included in our analysis reported a non-significant change of FFM following betaine supplementation[15,39,44,45]. Therefore, betaine supplementation appears to reduce FM and increase FFM in animals, but the results from our analysis do not support the efficacy of betaine supplementation to alter these indices in humans.

Dietary intake changes are the most important factor affecting the rate of BM and FM alterations[55]. In agreement with the 'calories in, calories out' theory, the unchanged energy intake following betaine supplementation corresponded to no changes in BM and BMI. Although protein intake significantly increased following betaine supplementation, the magnitude was very small and not clinically significant. Overall, based on the current evidence, betaine supplementation is not an effective supplement for BM loss[39,40,46].

Only three of the included studies were conducted in individuals with overweight and obesity. Further long-term interventional studies, especially in populations with obesity, may be needed to allow for additional evaluation of the influence of betaine supplementation on body composition indices. As mentioned, examining the potential influence of betaine supplementation in those with suboptimal concentration may reveal differential effects as compared with those with normal concentrations.

Betaine supplementation may not be effective for improving BM, BMI, FM, FFM and BFP. Moreover, our findings showed that dietary intake did not meaningfully change following betaine supplementation. Additional longer-term and high-quality studies are needed to further evaluate and confirm these findings.

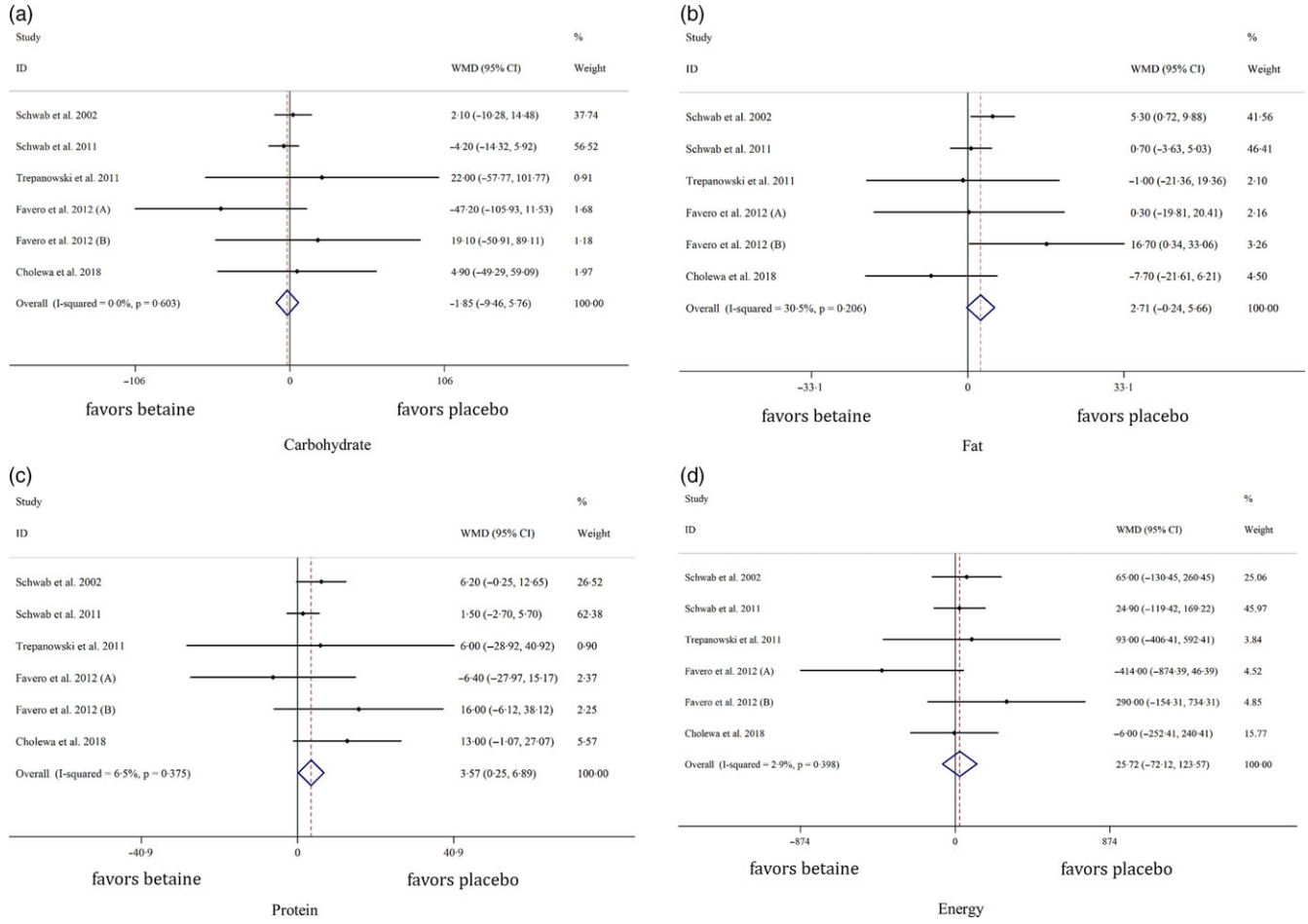

Fig. 5. Forest plot of the random effects meta-analysis of the effect of betaine supplementation on (a) dietary carbohydrate intake, (b) dietary fat intake, (c) dietary protein intake and (d) dietary energy intake. WMD, weighted mean difference.

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