Acta Diabetologica (2019) 56:187–195
https://doi.org/10.1007/s00592-018-1243-7

ORIGINAL ARTICLE

Dietary branched-chain amino acids intake exhibited a different relationship with type 2 diabetes and obesity risk: a meta-analysis

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Received: 14 May 2018 / Accepted: 9 October 2018 / Published online: 9 November 2018

Abstract

Aim To assess whether oral branched-chain amino acids (BCAA) supplementation exerts influence on circulating BCAA and the significance of dietary BCAA in type 2 diabetes and obesity risk.

Method We searched PUBMED, EMBASE and Cochrane library through June 2018 to retrieve and screen published reports for inclusion in the meta-analysis after methodological assessment. Heterogeneity of studies was evaluated using I^2 statistics, while sensitivity analysis and funnel plot were used to evaluate the potential effect of individual studies on the overall estimates and publication bias, respectively, using RevMan 5.3.

Result Eight articles on randomized clinical trial of oral BCAA supplementation, and seven articles on dietary BCAA intake and type 2 diabetes/obesity risks were eligible for inclusion in our meta-analyses. Mean difference and 95% confidence interval (CI) of circulating leucine was 39.65 (3.54, 75.76) µmol/L, $P=0.03$ post-BCAA supplementation. Also, OR and 95% CI for higher total BCAA intake and metabolic disorder risks were, 1.32 (1.14, 1.53), $P=0.0003$—type 2 diabetes and 0.62 (0.47, 0.82), $P=0.0008$—obesity.

Conclusion Oral BCAA supplementation exerts modest influence on circulating leucine profile and higher total BCAA intake is positively and contra-positively associated with type 2 diabetes and obesity risk, respectively.

Keywords Branched-chain amino acids · Obesity · Type 2 diabetes · Meta-analysis

Introduction

BCAA are essential amino acids (AA) with diverse importance in body metabolism [1, 2]. They account for up to 35% of essential AA in muscle protein, 40% of required AA and approximately 50% of essential AA in the food supply of mammals [3]. They are important substrates for proteins, essential for the maintenance of energy homeostasis and vital nutrient signals with direct and indirect effects [4, 5]. Many studies have investigated the profiles of circulating BCAA in obese and type 2 diabetes (T2DM) subjects [6–13] but with limited findings on the significance of dietary BCAA on circulating BCAA as it relates to metabolic disorders.

Circulating BCAA has been observed to upregulate negative feedback signaling (via activation of mammalian target rapamycin) to insulin receptor substrate 1 which promotes insulin resistance and impaired glucose metabolism [14]. Also, epidemiological reports from different population backgrounds [1, 15, 16] have reported higher dietary intake

Managed by Massimo Federici.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00592-018-1243-7) contains supplementary material, which is available to authorized users.

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of BCAA are inversely related to obesity risk. Contrariwise, other reports [17–19] have observed higher dietary BCAA intake promoted T2DM risk.

Whether dietary BCAA intake exert influence on the circulating BCAA is rarely reported in the literature. Also, if excess dietary BCAA intake are responsible for elevated circulating BCAA profiles and how both interact to be associated with obesity risk needs clarification. Though previous reviews [20–23] on this subject have documented the potential significance of elevated circulating BCAA profiles in metabolic disorders, evidence(s) appears unclear on the potential role of dietary BCAA in the circulating BCAA–metabolic disorder risk link. The goal of this meta-analysis is to explore whether oral BCAA supplementation exerts influence on circulating BCAA. Also, we sought to clarify the significance of dietary BCAA with respect to T2DM and/or obesity risk.

Methods

Literature search

We registered the meta-analysis in the International Prospective Register of Systematic Reviews (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=39142) and reported using MOOSE guidelines [24]. Two reviewers independently explored PUBMED, EMBASE and Cochrane catalogues through June 2018 to identify appropriate previously published studies (as well as references and supplementary data), using the following search terms: 'BCAA supplementation' OR 'isoleucine supplementation' OR 'leucine supplementation' OR 'valine supplementation' OR 'isoleucine' OR 'leucine' OR 'valine' OR 'branched chain amino acid' OR 'BCAA' AND 'obesity' OR 'type 2 diabetes'. Titles and abstracts of each citation were evaluated independently and any incongruity was resolved by consensus or recourse to a third reviewer. The meta-analyses were in three categories and studies were included in the meta-analyses upon meeting the inclusion criteria.

Inclusion criteria

The inclusion criteria for any study in each of the meta-analysis are as follows:

a. Meta-analysis of RCT on BCAA supplementation and effect on circulating BCAA profiles: A report is included in this meta-analysis if, (a) it was a pre-registered RCT in humans, (b) the intervention was BCAA/protein regimen high in BCAA and placebo applied as comparison for intervention in the same study and (c) the study reported the outcome of the intervention on at least one circulating BCAA alongside at least one biochemical and/or anthropometric parameter such as fasting glucose, insulin, body mass index (BMI), body fat, fat mass, and lipid profile.
b. Meta-analysis of dietary BCAA intake and T2DM risk: A report is included in this meta-analysis if, (a) it is a population study, (b) the primary exposure and outcome were dietary BCAA intake and T2DM, respectively, in the same population, (c) the study reported the proportion of population with exposure to higher and lower dietary isoleucine or leucine or valine or total BCAA intake as comparison in the same population (d) the study reported at least one of the following biochemical/anthropometric outcomes: circulating glucose, circulating insulin, BMI, body fat, HDL and lipid profile.
c. Meta-analysis of dietary BCAA intake and overweight/obesity risk: A report is included in this meta-analysis if, (a) it is a population study, (b) the primary exposure and outcome were dietary BCAA intake and obesity respectively, in the same population, (c) the study reported the proportion of population with exposure to higher and lower dietary isoleucine or leucine or valine or total BCAA intake as comparison in the same population (d) the study reported at least one of the following biochemical/anthropometric outcomes: circulating glucose, circulating insulin, BMI, body fat, HDL and lipid profile.

Studies were excluded in the meta-analyses if they were, infant/pregnancy related, review, abstracts, letter to the editor, case reports, etc (Fig. 1).

Critical assessment of included studies

Cochrane Collaboration guidelines [24] was applied for methodological quality assessment and risk of bias of the included studies. Furthermore, quality of evidence in the included studies was graded (independently by two reviewers and differences were resolved by consensus) using the Jadad scale for reporting randomized controlled trials [25] and the Newcastle–Ottawa scale for assessing the quality of non-randomized studies [26] in the meta-analyses.

Data extraction

Two reviewers extracted information such as, name and initials of the first author, year of publication, country, study population setting, main outcome of the study, sample sizes, oral BCAA intervention dosage(s), duration of intervention, type of placebo, influence of intervention on circulating BCAA profiles [reported mean and standard deviation (SD), standard error of the mean (SEM), and confidence intervals (CI)], etc. Also, methods of BCAA determination,

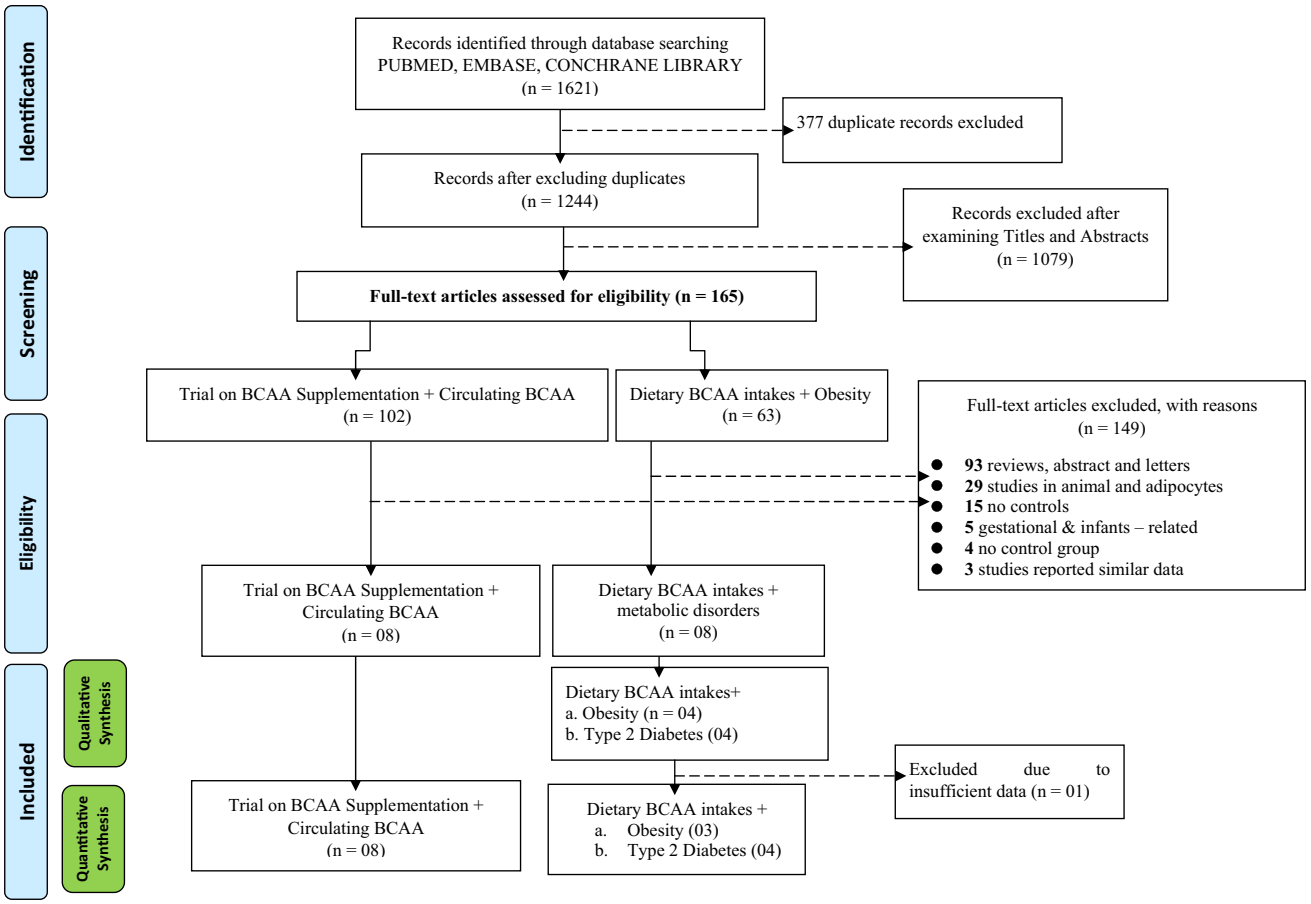


Fig. 1 PRISMA flowchart for inclusion and exclusion of studies in the meta-analyses

criteria for defining T2DM, obesity and control subjects, the proportion of cases and controls in the highest and lowest quintile of dietary BCAA intake in the population were also noted. Circulating BCAA statistics reported as SEM and CI were transformed to SD and units of BCAA concentrations were converted to μmol/L (where reported otherwise) for uniformity. All differences were resolved by consultation with a third reviewer.

Statistical analysis

Data from included studies in the meta-analyses were pooled in the following categories:

a. Meta-analysis of RCT on BCAA supplementation and effect on circulating BCAA profiles: Mean difference and 95% CI were computed for circulating BCAA concentration between oral BCAA supplemented group and placebo post-supplementation.
b. Meta-analysis of dietary BCAA intake and T2DM risk: Pooled OR and 95%CI for highest quintile of dietary BCAA intake (compared to the lowest quintile of dietary BCAA intake) were computed for T2DM risk using the Mantel–Haenszel test for dichotomous outcomes.
c. Meta-analysis of dietary BCAA intake and overweight/obesity risk: Pooled OR and 95%CI for highest quintile of dietary total BCAA intake (compared to the lowest quintile of dietary BCAA intake) was computed for overweight/obesity risk using the Mantel–Haenszel test for dichotomous outcomes.

All statistical analysis was carried out using Review Manager 5.3. Heterogeneity of the pooled effect estimates and the extent of variability across studies were estimated using I^2 test statistics. Where $I^2 > 50\%$ or $P < 0.05$, a random effects model was applied. Our random effect model was based on the postulation that effect estimates were not the same but followed a normal distribution. While the area of the black square in forest plots denotes the weighted contribution of each study, $P < 0.05$ (two-tailed) was considered statistically significant. Publication bias and stability of the

Table 1 Summary of mean difference, 95% CI and *P* value of circulating BCAA profiles

Amino acids (μmol/L)	Δ in serum BCAA profiles after oral BCAA supplementation			
	N	Mean difference	*P* value	DOR
Isoleucine	08	2.09 (−11.19, 15.38)	0.76	↔
Leucine	08	39.65 (3.54, 75.76)	0.03	↑
Valine	08	38.93 (−7.54, 85.40)	0.10	↔

N number of studies, *DOR* direction of relationship, ↔ no association or relationship, ↑ increasing

results were evaluated through funnel plots and leave-one-out technique [27] respectively.

Results

Search strategy of the meta-analyses

PRISMA flowchart describing the study selection strategy for our meta-analyses is presented in Fig. 1. Eight RCTs [28–35], four articles on dietary BCAA intake and T2DM risk [17, 19, 36, 18] and three articles on dietary BCAA intake and overweight/obesity risk [1, 15, 37] were

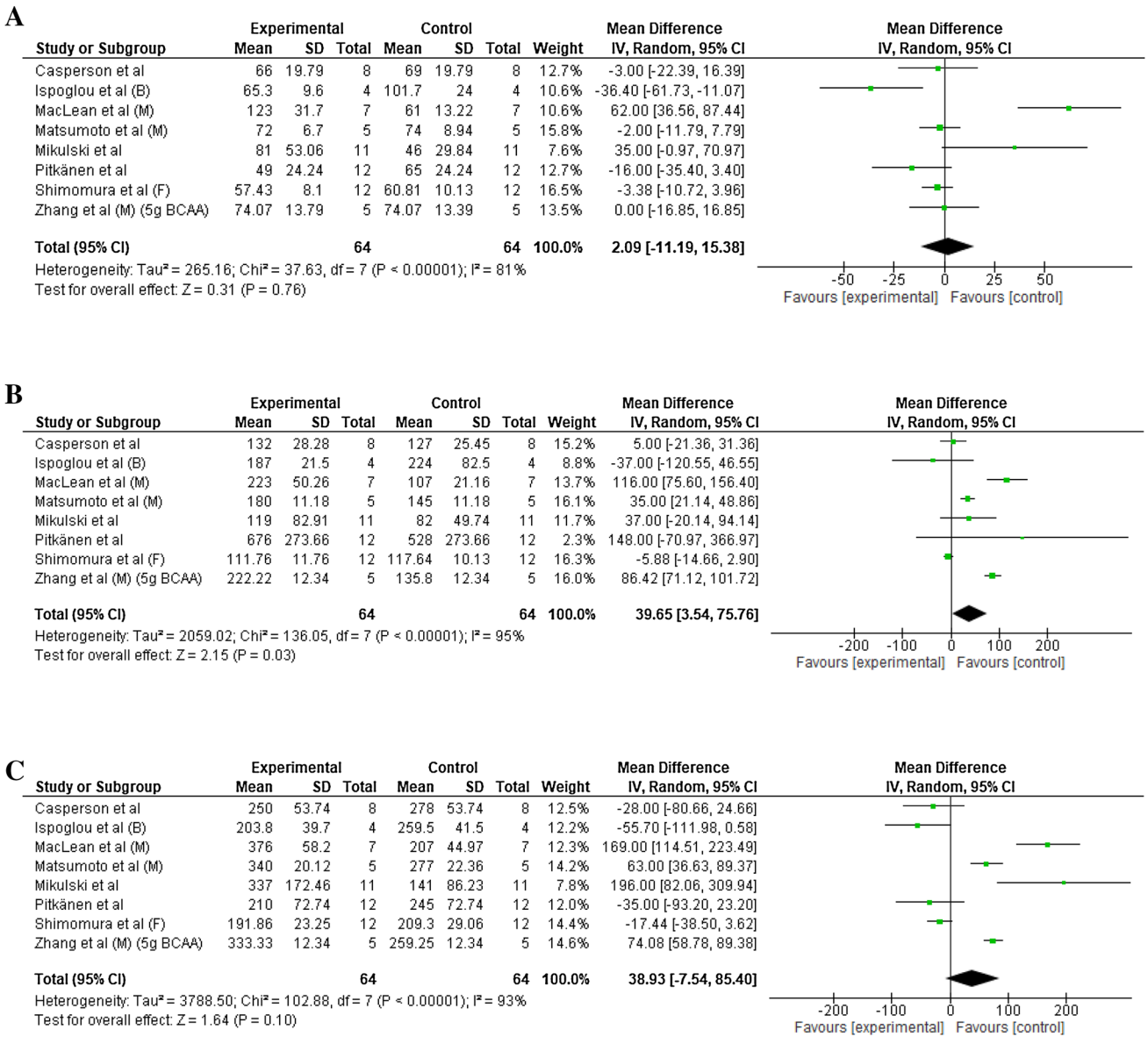


Fig. 2 Forest plots of mean difference in circulating isoleucine (**a**), leucine (**b**), valine (**c**) after RCT after BCAA supplementation

included in the meta-analyses. Detailed characteristics of the included studies are shown in Electronic supplementary materials (ESM) Tables 1 and 2.

Methodological assessment of included studies in the meta-analyses

Most of the studies included in the meta-analyses were with low risk of bias and details are provided in ESM (Tables S3 and S4, Figure S1).

Pooled mean difference of circulating BCAA between experimental and placebo groups

Mean differences of circulating BCAA profiles between oral BCAA-supplemented group and placebo are reported in Table 1 and Fig. 2a–c. The I^2 statistics range was 81–95%, the mean difference of circulating leucine profile [39.65 (3.54, 75.76) µmol/L, $P=0.03$] was significantly higher, but not Ile [2.09 (− 11.19, 15.38) µmol/L, $P=0.76$] and valine [38.93 (− 7.54, 85.40) µmol/L, $P=0.10$) profiles after oral BCAA supplementation.

OR of risk of T2DM or overweight/obesity between highest vs. lowest quintile of dietary BCAA intake

Higher dietary intake of isoleucine 1.58 (1.42, 1.76), $P<0.00001$, leucine 1.43 (1.21, 1.70), $P<0.0001$, valine 1.37 (1.16, 1.61) $P=0.0002$ and total BCAA 1.32 (1.14, 1.53), $P=0.0003$ was associated with increased T2DM risk (Table 2; Fig. 3a–d). Contrariwise, higher dietary intake of total dietary BCAA 0.62 (0.47, 0.82), P = 0.0008 was inversely related to the prevalence of overweight/obesity (Table 2; Fig. 3e).

Publication bias

Graphed funnel plots found no significant evidence of publication bias in the meta-analyses. Details are provided in ESM Figure S2.

Sensitivity analysis

Using a leave-one-out method, we tested the effect of excluding individual studies on the stability of the effect estimates. Generally, the exclusion of each study had no significant effect on the effect estimates, indicating that no individual study exerted a significant effect on the final results of our meta-analysis. Details of the sensitivity analysis are provided in ESM Tables S5&S6.

Discussion

To the best of our knowledge, our meta-analysis is the first to investigate the significance of dietary BCAA in the relationship between circulating BCAA profiles and T2DM or obesity risk. First, we found short-term oral BCAA administration significantly increased circulating leucine profile post-supplementation. Second, dietary BCAA intake were positively and inversely associated with T2DM and overweight/obesity risk, respectively.

Our observation that oral BCAA supplementation exerted short-term modest influence on circulating leucine is in tandem with an earlier postulation [21], but studies on the long-term influence of dietary BCAA on circulating BCAA are necessary to further understand this phenomenon. Similarly, several RCTs have reported the effectiveness of oral BCAA supplementation (particularly leucine) on immune function [38], glucose and cholesterol metabolism [39], reduced accumulation of triglycerides [40], alleviation of exercised

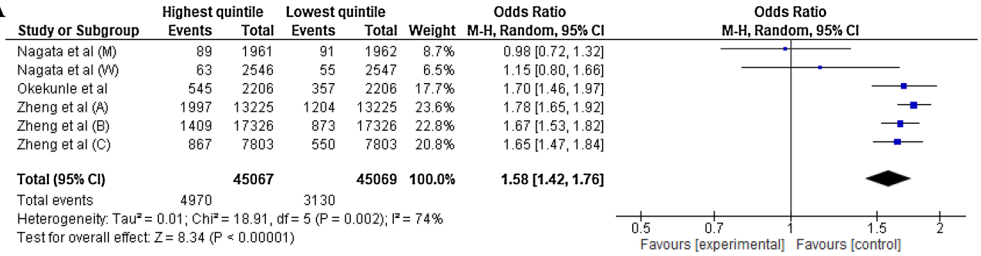
Table 2 Odds ratio (OR), 95% CI and *P* value of the significance of BCAA intake (highest vs. lowest quintile) and risk of metabolic disorders

Dietary amino acid intake	*N*	Subjects	Pooled OR (95% CI)	*P* value	DOR	I^2 (%)
Type 2 diabetes						
Isoleucine	06	90,136	1.58 (1.42, 1.76)	< 0.00001	↑	74
Leucine	06	90,136	1.43 (1.21, 1.70)	< 0.0001	↑	90
Valine	06	74,530	1.37 (1.16, 1.61)	0.01	↑	89
Total BCAA	09	204,541	1.32 (1.14, 1.53)	0.0003	↑	96
Obesity						
Total BCAA	11	8750	0.62 (0.47, 0.82)	0.0008	↓	85
Subgroup analysis higher dietary total BCAA intake and obesity risk stratified by population setting						
Brazil, US and UK	05	2898	0.57 (0.31, 1.04)	0.07	↓	92
Japan and China	04	2386	0.53 (0.41, 0.67)	< 0.00001	↓	0

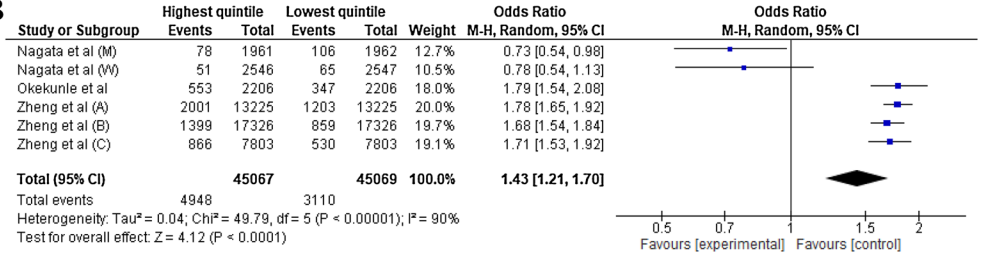
Dietary branched-chain amino acids intake exhibited a different relationship with type 2 diabetes and obesity risk: a meta-analysis

N number of studies, *DOR* direction of risk, ↑ increased risk, ↓ decreased risk

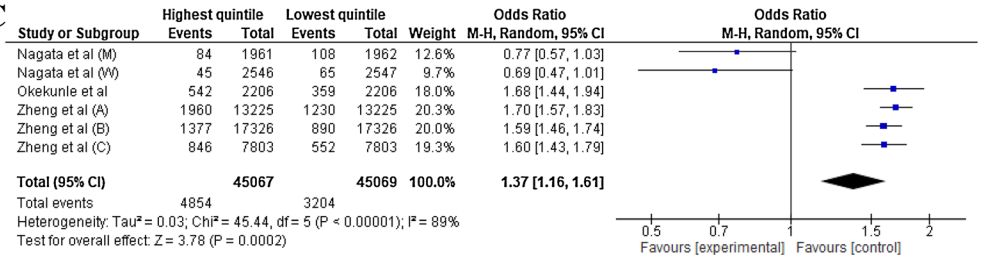
A


Highest quintile
Lowest quintile
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Nagata et al (M) 89 1961 91 1962 8.7% 0.98 [0.72, 1.32]
Nagata et al (W) 63 2546 55 2547 6.5% 1.15 [0.80, 1.66]
Okekunle et al 545 2206 357 2206 17.7% 1.70 [1.46, 1.97]
Zheng et al (A) 1997 13225 1204 13225 23.6% 1.78 [1.65, 1.92]
Zheng et al (B) 1409 17326 873 17326 22.8% 1.67 [1.53, 1.82]
Zheng et al (C) 867 7803 550 7803 20.8% 1.65 [1.47, 1.84]
Total (95% CI) 45067 45069 100.0% 1.58 [1.42, 1.76]
Total events 4970 3130
Heterogeneity: Tau² = 0.01; Chi² = 18.91, df = 5 (P = 0.002); I² = 74%
Test for overall effect: Z = 8.34 (P < 0.00001)
0.5 0.7 1 1.5 2
Favours [experimental] Favours [control]

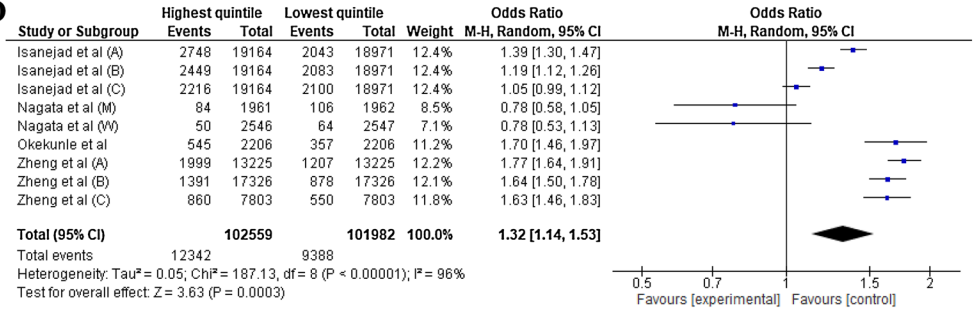
B


Highest quintile
Lowest quintile
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Nagata et al (M) 78 1961 106 1962 12.7% 0.73 [0.54, 0.98]
Nagata et al (W) 51 2546 65 2547 10.5% 0.78 [0.54, 1.13]
Okekunle et al 553 2206 347 2206 18.0% 1.79 [1.54, 2.08]
Zheng et al (A) 2001 13225 1203 13225 20.0% 1.78 [1.65, 1.92]
Zheng et al (B) 1399 17326 859 17326 19.7% 1.68 [1.54, 1.84]
Zheng et al (C) 866 7803 530 7803 19.1% 1.71 [1.53, 1.92]
Total (95% CI) 45067 45069 100.0% 1.43 [1.21, 1.70]
Total events 4948 3110
Heterogeneity: Tau² = 0.04; Chi² = 49.79, df = 5 (P < 0.00001); I² = 90%
Test for overall effect: Z = 4.12 (P < 0.0001)
0.5 0.7 1 1.5 2
Favours [experimental] Favours [control]

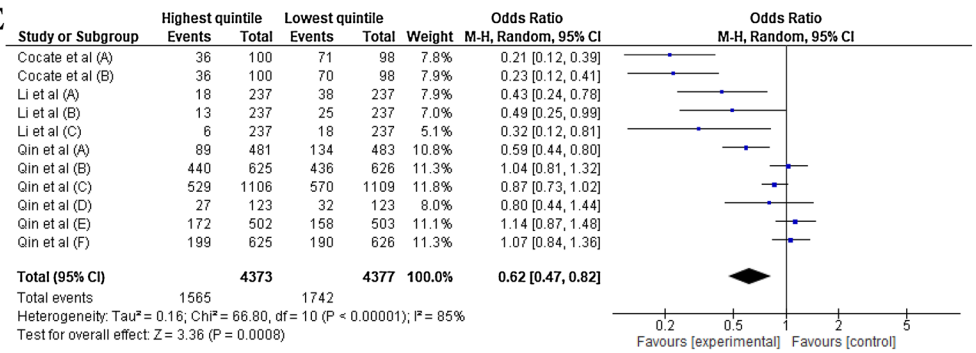
C


Highest quintile
Lowest quintile
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Nagata et al (M) 84 1961 108 1962 12.6% 0.77 [0.57, 1.03]
Nagata et al (W) 45 2546 65 2547 9.7% 0.69 [0.47, 1.01]
Okekunle et al 542 2206 359 2206 18.0% 1.68 [1.44, 1.94]
Zheng et al (A) 1960 13225 1230 13225 20.3% 1.70 [1.57, 1.83]
Zheng et al (B) 1377 17326 890 17326 20.0% 1.59 [1.46, 1.74]
Zheng et al (C) 846 7803 552 7803 19.3% 1.60 [1.43, 1.79]
Total (95% CI) 45067 45069 100.0% 1.37 [1.16, 1.61]
Total events 4854 3204
Heterogeneity: Tau² = 0.03; Chi² = 45.44, df = 5 (P < 0.00001); I² = 89%
Test for overall effect: Z = 3.78 (P = 0.0002)
0.5 0.7 1 1.5 2
Favours [experimental] Favours [control]

D


Highest quintile
Lowest quintile
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Isanejad et al (A) 2748 19164 2043 18971 12.4% 1.39 [1.30, 1.47]
Isanejad et al (B) 2449 19164 2083 18971 12.4% 1.19 [1.12, 1.26]
Isanejad et al (C) 2216 19164 2100 18971 12.4% 1.05 [0.99, 1.12]
Nagata et al (M) 84 1961 106 1962 8.5% 0.78 [0.58, 1.05]
Nagata et al (W) 50 2546 64 2547 7.1% 0.78 [0.53, 1.13]
Okekunle et al 545 2206 357 2206 11.2% 1.70 [1.46, 1.97]
Zheng et al (A) 1999 13225 1207 13225 12.2% 1.77 [1.64, 1.91]
Zheng et al (B) 1391 17326 878 17326 12.1% 1.64 [1.50, 1.78]
Zheng et al (C) 860 7803 550 7803 11.8% 1.63 [1.46, 1.83]
Total (95% CI) 102559 101982 100.0% 1.32 [1.14, 1.53]
Total events 12342 9388
Heterogeneity: Tau² = 0.05; Chi² = 187.13, df = 8 (P < 0.00001); I² = 96%
Test for overall effect: Z = 3.63 (P = 0.0003)
0.5 0.7 1 1.5 2
Favours [experimental] Favours [control]

E


Highest quintile
Lowest quintile
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Cocate et al (A) 36 100 71 98 7.8% 0.21 [0.12, 0.39]
Cocate et al (B) 36 100 70 98 7.9% 0.23 [0.12, 0.41]
Li et al (A) 18 237 38 237 7.9% 0.43 [0.24, 0.78]
Li et al (B) 13 237 25 237 7.0% 0.49 [0.25, 0.99]
Li et al (C) 6 237 18 237 5.1% 0.32 [0.12, 0.81]
Qin et al (A) 89 481 134 483 10.8% 0.59 [0.44, 0.80]
Qin et al (B) 440 625 436 626 11.3% 1.04 [0.81, 1.32]
Qin et al (C) 529 1106 570 1109 11.8% 0.87 [0.73, 1.02]
Qin et al (D) 27 123 32 123 8.0% 0.80 [0.44, 1.44]
Qin et al (E) 172 502 158 503 11.1% 1.14 [0.87, 1.48]
Qin et al (F) 199 625 190 626 11.3% 1.07 [0.84, 1.36]
Total (95% CI) 4373 4377 100.0% 0.62 [0.47, 0.82]
Total events 1565 1742
Heterogeneity: Tau² = 0.16; Chi² = 66.80, df = 10 (P < 0.00001); I² = 85%
Test for overall effect: Z = 3.36 (P = 0.0008)
0.2 0.5 1 2 5
Favours [experimental] Favours [control]

◂**Fig. 3** Forest plots of meta-analyses: highest vs. lowest quintile of isoleucine (**a**), leucine (**b**), valine (**c**) and total BCAA intake (**d**) and diabetes risk, highest vs. lowest quintile of total BCAA intake (**e**) and overweight/obesity risk

induced fatigue [41, 42], maintenance of lean body mass [43], attenuation of transcriptional coactivator peroxisome proliferator-activated receptor-γ coactivator (PGC-1α4) to prevent insulin resistance [44], enhancement of integrative myofibrillar protein synthesis [45], etc., among apparently healthy subjects.

While very limited studies [28–35, 46] have reported the potential modest short-term effects of oral BCAA supplementation on circulating BCAA profiles, a few related controlled trials [47–52] are worth citing. For example, a null post-intervention relationship between whey protein (a rich source of dietary BCAA) supplementation and circulating BCAA profiles was observed in an 8-week trial (combined with weight loss) among obese women. Though whey protein supplementation exerted modest influence on BCAA metabolism, calorie restriction and/or protein intake manipulations played a prominent role in the BCAA metabolism–insulin post-intervention interaction, because BCAA profile was unrelated to homeostasis model assessment [50]. In another trial, post-intervention circulating BCAA profiles were elevated, significantly correlated with down-regulation of lipolysis, lipogenic indices and improved insulin sensitivity but unrelated with alterations in body weight among subjects with non-alcoholic fatty liver disease and T2DM after 6 weeks on high animal or plant protein (without caloric restriction) [51].

It is plausible post-intervention circulating BCAA profiles differ by dietary exposure. For example, BCAA alongside other metabolites distinctively discriminated low-fat (highest carbohydrate composition) diet in a 12-week trial of isocaloric and hypocaloric experimental meal regimens with varying percentage composition of carbohydrate, protein and fats [low fat (60%:20%:20%), low glycemic index (40%:40%:20%) and very low carbohydrate (10%:60%:30%) diets] among obese adults [47]. Also, average-energy protein diets were effective in lowering circulating BCAA (even after adjusting for the effect of weight loss) and enhancing insulin sensitivity compared to high-energy protein diet [49]. Contrariwise, restricted BCAA and protein consumption were related to improved metabolic health under significant caloric restrictions with significant glucose control, weight and fat mass loss [48, 53].

Dietary manipulations responsible for these variations are largely unknown due to imprecision in evaluating diet-associated factors (such as protein intake, calorie restrictions, dietary pattern adherence, etc.) related to BCAA intake and metabolism, but we observed most RCTs with beneficial pathophysiological effects were particularly executed under significant energy and caloric intake restriction. Similarly, while it is quite largely impracticable to adequately differentiate between the effects of dietary BCAA and protein intake in the experimental diets, the vitality of diet quality to sturdy metabolic health cannot be underestimated.

Furthermore, we observed higher dietary BCAA intake are positively and contra-positively related to T2DM and overweight/obesity risk, respectively. Elevated and lowered T2DM risk attributable to higher dietary BCAA intake has been observed in the US [19] and Japanese [36] populations, respectively. Also, some reports have observed an inverse relationship between higher dietary BCAA intake and risk of metabolic disorders in animal models [39, 40, 54] and human population [1, 15, 16, 36, 37]. Most of these studies adjusted for energy intake of respondents, but did not consider the diet-related environment of the population under study.

Recent studies have emphasized the impact of dietary exposure to the dietary BCAA–disease link. For example, it has been observed that the overall pattern that contributes to raised circulating BCAA profiles appears to modulate chronic disease risk outcomes [55]. Similarly, the higher dietary BCAA–T2DM/obesity link contextually depends on dietary pattern adherence [18, 56]. Also, meat intake and T2DM risk [17] reported though BCAA and meat intake were independently associated with T2DM risk, and dietary BCAA in part is associated with T2DM risk after adjusting for meat intake. In addition, higher dietary and circulating BCAA were jointly associated with T2DM risk among women with history of gestational diabetes independent of BMI. However, the joint relationship was absent under lower circlating BCAA state, but higher circulating BCAA was associated with T2DM risk independent of the magnitude of dietary BCAA intake [57]. These observations suggest the dietary BCAA-metabolic disorder risk link might not be principally dependent on dietary BCAA. How BCAA intake modulate circulating BCAA profiles to promote metabolic disorder risk is likely influenced by the dietary environment exposure.

The number of studies on this topic is relatively scarce, making the interpretation of obtained results quite difficult. In addition, a certain amount of publication bias is likely as a result of registered but undisclosed or unpublished trials, but our search strategy was elaborate and not limited by time. Variations in the magnitude of BCAA supplementation and concentrations among studies existed in our meta-analysis, as a result of methodological and technical differences, but indifference of overall findings of our meta-analysis after subgroup stratification renders such variations insignificant. Heterogeneity was high and a random effects model was applied to the effect estimates in this study. It is essential to ascertain the legitimacy of any distribution in such an assumption, and sensitivity analysis showed that no single

study exerted a disproportionate effect on the effect estimates. It is difficult to differentiate between the effects of individual BCAA supplementation/intake vs. T2DM/obesity risk.

In our meta-analyses, oral BCAA supplementation modestly elevates circulating leucine and dietary BCAA intake were positively and inversely related to T2DM and overweight/obesity risk, respectively. Future studies of multi-ethnic longitudinal cohort on implications of long-term dietary BCAA intake (from conventional diets with accurate evaluation of the effect of other macro-nutrients) on circulating BCAA profiles and how it manipulates metabolic disorder risks are necessary.

Author contributions APO, RNF and CLL conceived and designed the meta-analysis. APO, MZ, ZW, XYW and JUO carried out the literature search, data acquisition and analysis. APO and RNF reviewed the literature search, data acquisition, and quality assessment. APO, RNF and CLL wrote the paper. APO, MZ, ZW, RNF and CLL revised the paper, and all authors approved the final version for publication.

Funding Funds from the Postdoctoral Science Foundation (2016M600264 and LBH—Z16253) were used in conducting this study. APO (2015BSZ778) and JUO (2017BSZ011594) were supported by the China Scholarship Council.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights This article does not contain any studies with human or animal subject performed by any of the authors.

Informed consent Not applicable.

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