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# Effects of collagen peptide supplementation on cardiovascular markers: a systematic review and meta-analysis of randomised, placebo-controlled trials

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## Abstract

Previous studies have advocated that collagen peptide supplementation (CPS) can positively affect cardiovascular health. However, the widespread impact of CPS on CVD-related markers is not fully resolved. Consequently, the current systematic review and meta-analysis aimed to assess the efficacy of CPS on CVD-related markers. A systematic search in the Scopus, PubMed and ISI Web of Science databases were completed to identify relevant randomised, placebo-controlled trials (RCT) published up to November 2021. Mean Differences were pooled using a random-effects model, while publication bias, sensitivity analyses and heterogeneity were assessed using previously validated methods. Twelve RCT, comprising of a total of eleven measured markers, were selected for the quantitative analysis. Pooled data revealed that CPS significantly decreased fat mass (−1·21 kg; 95 % CI: −2·13, −0·29; $I^2 = 0·0$ %; $P = 0·010$) and increased fat-free mass, based on body mass percentage (1·49 %; 95 % CI: 0·57, 2·42; $I^2 = 0·0$ %; $P = 0·002$). Moreover, collagen peptide supplementation led to a significant decrease in serum LDL (−4·09 mg/dl; 95 % CI: −8·13, −0·04; $I^2 = 93·4$ %; $P = 0·048$) and systolic blood pressure (SBP) (−5·04 mmHg; 95 % CI: −9·22, −0·85; $I^2 = 98·9$ %; $P = 0·018$). Our analysis also indicated that CPS did not affect glycemic markers. Our outcomes indicate that CPS reduces fat mass, LDL and SBP while increasing fat-free mass. Future investigations with longer CPS duration are needed to expand on our results.

**Keywords:** **Cardiovascular: Glycaemic markers: Body composition: Health**

According to the WHO's latest report, CVD claims the lives of 17·9 million people per year, representing the leading cause of mortality[1,2]. It is well known that major risk factors for CVD such as obesity, diabetes, dyslipidaemia, hypertension and poor nutrition lead to a rise of atherosclerosis[3–8], widely considered to be the chief component in cardiovascular pathologies. Consequently, prevention and treatment strategies targeting the above-mentioned risk factors are pivotal avenues to reduce costs and mortality associated with CVD.

A growing body of evidence has suggested that dietary interventions can effectively treat and prevent CVD[9]. One of these interventions is collagen, a type of extracellular protein that

**Abbreviations:** CPS, collagen peptide supplementation; DBP, diastolic blood pressure; SBP, systolic blood pressure.

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makes up 25–30 % of the total protein in the human body[10]. This compound is also highly available in fish and meat and thus is broadly used as a dietary supplement. However, given that collagen is not hydrolysed, its oral absorption is minimal, requiring hydroxylation before it becomes a physiologically accessible supplement[11,12]. In recent years, collagen peptide has been used in the food industry as a functional component. The physiological benefits of circulating dipeptides reflect the importance of consuming collagen peptides[13]. Collagen peptides play essential biological roles, which include inhibiting the activity of angiotensin I-converting enzyme[14], acting as signal messengers in anabolic cellular processes in cartilage, tendons and ligaments[15–17] and activating the mechanistic target of rapamycin signalling pathway[18]. In addition, collagen peptides may improve lipid metabolism and increase insulin sensitivity[19], reduce Cyp450, nitric oxide and prostaglandin $I^2$ while increasing bradykinin[20,21]. Over the last decade, evidence from various clinical investigations focused on the effects of CPS on CVD-related markers; however, this line of research produced conflicting findings. For instance, Zhu *et al.*[22] indicated that daily supplementation of 13 g of CPS for 12 weeks led to a significant reduction in LDL, HDL, TAG, total cholesterol, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting blood sugar and HbA1c in patients with Type 2 diabetes mellitus and primary hypertension. Zdzieblik *et al.*[23] also reported that 15 g/d of specific CPS for 12 weeks significantly increased fat-free mass and decreased fat mass in middle-aged men. Moreover, Kouguchi *et al.*[24] demonstrated that 2·9 g/d of chicken collagen hydrolysate supplementation for 12 weeks significantly decreased SBP and DBP in patients with mild hypertension. Conversely, another randomised controlled trial showed that collagen peptide supplementation (CPS) daily supplementation of 2 g of CPS for 12 weeks did not change body mass, fat mass, LDL, HDL, TAG, total cholesterol and fasting blood sugar in healthy volunteers[25]. Moreover, Jendricke *et al.*[26] indicated that 15 g/d of specific CPS for 12 weeks significantly increased fat-free mass but did not affect body mass and fat mass in active women. These discrepancies could be attributed to differences in study design, CPS dosage and/or participant characteristics (age, sex, health status, etc.), which highlights the importance of a comprehensive review on this topic.

There are currently no comprehensive reviews to systematically assess the effect of CPS on CVD-related markers (e.g. body mass, fat mass, fat-free mass, LDL, HDL, TAG, total cholesterol, blood pressure and fasting blood sugar), which denotes a gap in knowledge. Therefore, we completed the current systematic review and meta-analysis of randomized controlled trials to determine the effects of CPS on cardiovascular markers.

## Materials and methods

### Systematic search and study selection

This review followed the 2020 PRISMA guidelines[27]. Description of population, intervention, comparator and outcome is displayed in Supplementary Table 1. A systematic search was conducted using Scopus, PubMed and ISI Web of Science databases. The medical subject headings were used in the search strategy to find the relevant studies. A systematic search was carried out by applying the reported strategy and the key terms displayed in Supplementary Table 2. The search process was conducted with no date or language restrictions. The databases were searched up to 1 November 2021. Database searches were completed in conjunction with searches of reference lists derived from individual studies. Two researchers (SM and HM) independently carried out the search strategy and screening. Any discrepancies were resolved via discussion with another author (CJ).

### Eligibility criteria

Two authors (SM and HM) identified the eligible records by screening the titles, abstracts and full text of eligible studies. All randomised, placebo-controlled trials in humans (either parallel or cross-over designs) that assessed the efficacy of CPS on a range of CVD-related markers were included in the review. These markers included: anthropometric and body composition (body mass, fat mass, fat-free mass and BMI), lipid profile (LDL, HDL, TAG and total cholesterol), blood pressure (both SBP and DBP) and glycaemic indices including fasting blood sugar, HbA1c and insulin resistance. The exclusion of the studies was based on the following criteria: (1) clinical trials with an intervention duration of less than two weeks, (2) clinical trials without a placebo group, (3) animal studies and (4) those with insufficient data for the outcomes of interest.

### Data extraction

The extracted study characteristics are presented in Table 1. If there was no available relevant data, corresponding authors were contacted to obtain any missing data. The data extraction procedure was conducted separately by two researchers (SM and FJ) to ensure reliability. Any disagreements were resolved by consensus and discussion.

### Quality assessment of studies

The Cochrane Collaboration's tool[28] was used to evaluate the quality of studies. This tool involved judging the degree of bias (either high, low or unclear) for a series of items covering different domains of potential bias. Two authors (SM and HM) assessed the quality (risk of bias) of the eligible studies individually. The quality evaluation procedure has been presented in previous works[29,30].

### Meta-analysis of data

To evaluate the effect size of the anthropometric, lipid profile, blood pressure and glycaemic markers, the mean and standard deviation (SD) changes were extracted from the intervention and placebo groups. Sub-group analyses relating to the mean study participant age (less than 50 years or more), sex (women or men), body mass (normal, overweight or obese), dosage (less than 10 g or 10 g and over), type of intervention (with or without exercise), trial duration (6 or 12 weeks) and participant health status (healthy or unhealthy) were performed to establish possible sources of heterogeneity. For the random-effects model, the DerSimonian and Laird method was

**Table 1.** Main characteristics of included studies

| First author (publication year) | Country | Sample size (intervention/ control) sex | Target population | Mean age | Intervention/ Control | Mean BMI | Intervention/ Control | RCT design (blinding) | Duration (weeks) | Form and dose of intervention | Comparison | Results |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Han et al. (2008) | Korea | 30 (15/15) Female | Healthy participants | 46·25 | 3·28/ 50·67 ± 6·71 | NR | | Parallel (None) | 12 Weeks | Collagen peptide 6 g/d | Placebo (NR) | Collagen peptide supplementation did not change in LDL, HDL, TAG or TC compared with placebo. |
| Zhu et al. (2010) | China | 100 (50/50) Male and female | Patients with Type 2 diabetes mellitus | 67·64 | 0·95/ 63·66 ± 1·33 | 25·19 | 0·33/24·82 ± 0·46 | Parallel (double) | 6 and 12 Weeks | Collagen peptide 13 g/d | Placebo (boxymethylcellulose) | Collagen peptide supplementation significantly changed LDL, HDL, TAG, TC, SBP, DBP, FBS and HbA1c compared with placebo. |
| Kouguchi et al. (2013) | Japan | 58 (29/29) Male and female | Subjects with either mild hypertension | 54·3 | 9·2/51·2 ± 7·8 | 24·6 | 2·9/ 24·8 ± 3·0 | Parallel (double) | 6 and 12 Weeks | Collagen peptide 2·9 g/d | Placebo (NR) | Collagen peptide supplementation significantly changed SBP or DBP compared with placebo. |
| Kumar et al. (2014) | India | 30 (20/10) Male and female | Patients with osteoarthritis | NR | | 25·8 | 1·9 \26·1 ± 3·8 | Parallel (double) | 13 Weeks | Collagen peptide 5 g/d | Placebo (NR) | Collagen peptide supplementation did not change in FBS compared with placebo. |
| Zdzielik et al. (2015) | Germany | 53 (26/27) Male | Elderly sarcopenic | 72·2 | 4·68 | NR | | Parallel (double) | 12 Weeks | Collagen peptide 15 g/d plus training | Placebo (NR) | Collagen peptide supplementation significantly changed FM and FFM compared with placebo. |
| Ishii et al. (2016) | Japan | 56 (26/28) Female | Healthy participants | 51·5 | 0·80 | 21·5 | 0·6/ 21·6 ± 0·6 | Parallel (Double) | 12 Weeks | Active food contained 900 mg/d collagen peptide | Placebo (NR) | Collagen peptide supplementation significantly changed BM and FM compared with placebo. |
| Koizumi et al. (2017) | Korea | 71 (37/34) Female | Healthy participants | 46·49 | 5·74/ 47·37 ± 4·36 | NR | | Parallel (double) | 12 Weeks | Collagen peptide 3 g/d | Placebo (NR) | Collagen peptide supplementation did not change FBS or TC compared with placebo. |
| Tak et al. (2019) | Korea | 81 (40/41) Male and female | Overweight participants | 41·8 | 9·9/ 41·1 ± 11·2 | 25·4 | 2·0/ 25·8 ± 1·9 | Parallel (double) | 12 Weeks | Collagen peptide 2 g/d | Placebo (NR) | Collagen peptide supplementation did not change BM, FM, LDL, HDL, TAG, TC and FBS compared with placebo. |
| Igase et al. (2019) | Japan | 71 (44/46) Male and female | Healthy older individuals | NR | | NR | | Parallel (double) | 12 Weeks | Collagen peptide 2·5 g/d | Placebo (NR) | Collagen peptide supplementation did not change SBP or DBP compared with placebo. |
| Jendricke et al. (2019) | Germany | 78 (40/37) Female | Healthy participants | 38·3 | 8·7/41·6 ± 6·9 | 26·4 | 3·8/ 26·5 ± 3·4 | Parallel (double) | 12 Weeks | Collagen peptide 15 g/d plus training | Placebo (NR) | Collagen peptide supplementation did not change BM, FM or FFM compared with placebo. |
| Jendricke et al. (2020) | Germany | 59 (28/31) Female | Healthy participants | 25·4 | 4·2 1/26·8 ± 5·7 | 22·2 | 2·1/ 22·6 ± 1·6 | Parallel (double) | 12 Weeks | Collagen peptide 15 g/d plus training | Placebo (NR) | Collagen peptide supplementation did not change in in BM, FM or FFM compared with placebo. |
| Zdzieblik et al. (2021) | Germany | 61 (30/31) Male | Healthy participants | 51·8 | 4·56/47·4 ± 7·26 | 31·0 | 2·93/ 29·9 ± 2·56 | Parallel (double) | 12 Weeks | Collagen peptide 15 g/d | Placebo (NR) | Collagen peptide supplementation significantly changed FFM compared with placebo. |

BM, body mass; NR, not reported; FM, fat mass; FFM, fat-free mass; TC, total cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar.



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utilised[31]. Within-group changes were calculated by subtracting the baseline mean from the final mean value in each group. The SD of the mean difference was calculated using the following formula:

SD change = $\sqrt{[(\text{sd baseline})^2 + (\text{sd final})^2 - (2 \times 0 \cdot 8 \times \text{sd baseline} \times \text{sd final})]}$ [32].

For trials that reported only the standard error of the mean, SD was calculated using the following formula: $SD = SEM \times \sqrt{n}$, where '$n$' represented the number of participants in each group. Heterogeneity between studies was assessed by Cochrane's Q test (significance at $P < 0{\cdot}100$) and $I^2$ index. Publication bias was evaluated by the visual inspection of funnel plots and formal testing by Egger's regression asymmetry and Begg's rank correlation tests[33,34]. All statistical analyses were conducted using STATA software, version 16 (Stata Corp LP).

Outcomes were considered significant at $P < 0{\cdot}05$.

### Quality of evidence

The general certainty of evidence across randomised-controlled trials was rated using the Grading of Recommendations Assessment, Development, and Evaluation working group guidelines. Based on the related assessment criteria, the quality of evidence was categorised into four classes: high, moderate, low and very low[35].

## Results

### Selection and identification of studies

The study selection flow is displayed in Fig. 1. Our systematic database search yielded a total of 453 records, of which 239 were screened. Two hundred twenty-six studies failed to meet the inclusion criteria and were excluded from qualitative and quantitative analyses. One study was excluded from the quantitative assessment due to lacking a comparative placebo group[36]. Ultimately, twelve randomised-controlled trials, collectively comprising eleven outcome measures, were selected for the quantitative analysis[23,24,26,37–45].

### Characteristics of studies

In total, the twelve eligible studies included a total of 748 participants (359 individuals in the CPS and 389 in the placebo group) (Table 1). The mean age ranged from 25·4 ± 4·2 years to 72·2 ± 4·7 years. Studies were conducted in Germany[23,26,40,44], Korea[37,41,43], Japan[24,38,39], China[45] and India[42]. Included studies were performed in healthy[23,26,37–41] and overweight[43] participants, as well as in individuals with type 2 diabetes mellitus[45], mild hypertension[24], osteoarthritis[42] and age-related sarcopenia[44]. All of the trials used a parallel arms design. The twelve eligible trials were published between 2008 and 2021. The dose of CPS ranged from 900 mg/d to 15 g/d, while the duration of the clinical trials ranged from 6 to 12 weeks.

### Quality assessment of studies

According to the Cochrane risk of bias assessment, ten studies were ranked as high quality (demonstrating a low risk of bias on ≥ 3 domains)[23,24,26,39–45] and two as low quality (low risk of bias < 3 domains)[37,38] (Table 2).

### Meta-analysis of data

*Effects of collagen peptide supplementation on anthropometric and body composition parameters.* As illustrated in Fig. 2, pooled data from six studies revealed that the CPS did not significantly change body mass (–0·54 kg; 95 % CI: −2·13, 1·06; $I^2 = 65{\cdot}8$ %; $P = 0{\cdot}510$; $n$ 6) compared with the placebo group. Furthermore, results indicated that CPS significantly decreased fat mass (–1·21 kg; 95 % CI: −2·13, −0·29; $I^2 = 0{\cdot}0$ %; $P = 0{\cdot}010$; $n$ 4), but not body fat percentage (–0·65 %; 95 % CI: −1·76, 0·47; $I^2 = 75{\cdot}5$ %; $P = 0{\cdot}256$; $n$ 5) compared with the placebo group. Sub-group analyses suggested that body fat percentage significantly changed after CPS in men (–1·66 %; 95 % CI: −2·48, −0·47; $I^2 = 0{\cdot}0$ %; $P = 0{\cdot}006$; $n$ 2), obese or overweight participants (–1·22 %; 95 % CI: −2·39, −0·06; $I^2 = 0{\cdot}0$ %; $P = 0{\cdot}039$; $n$ 2) and in those supplementing in conjunction to exercise training (–1·36 %; 95 % CI: −2·60, −0·12; $I^2 = 0{\cdot}0$ %; $P = 0{\cdot}032$; $n$ 3) (Table 3). Further sub-group analyses involving age demonstrated that fat mass significantly decreased after CPS for participants only aged 50 years and over (–1·50 kg; 95 % CI: −3·07, −0·18; $I^2 = 0{\cdot}0$ %; $P = 0{\cdot}020$; $n$ 2) (Table 3). The observed between-study heterogeneity for anthropometric and body composition parameters was attenuated by all sub-group analysis (Table 3).

In addition, CPS significantly increased free fat mass based on body mass percentage (1·49 %; 95 % CI: 0·57, 2·42; $I^2 = 0{\cdot}0$ %; $P = 0{\cdot}002$; $n$ 3), but not based on kg (weighted mean differences: 0·67 kg; 95 % CI: −0·26, 1·59; $I^2 = 0{\cdot}0$ %; $P = 0{\cdot}441$; $n$ 4) compared with the placebo group (Fig. 2). Due to the lack of studies measuring fat-free mass, sub-group analyses were not feasible.

*Effects of collagen peptide supplementation on lipid profile.* Pooled data from studies assessing lipid profile demonstrated that CPS led to a significant decrease in LDL concentrations (–4·09 mg/dl; 95 % CI: −8·13, −0·04; $I^2 = 93{\cdot}4$ %; $P = 0{\cdot}048$; $n$ 5), unlike HDL (3·13 mg/dl 95 % CI: −0·18, 6·43; $I^2 = 64{\cdot}8$ %; $P = 0{\cdot}064$; $n$ 3), total cholesterol (–5·28 mg/dl; 95 % CI: −14·31, 3·75; $I^2 = 98{\cdot}1$ %; $P = 0{\cdot}252$; $n$ 7) and TAG (–6·51 mg/dl; 95 % CI: −13·71, 0·70; $I^2 = 92{\cdot}1$ %; $P = 0{\cdot}077$; $n$ 5), which remain unchanged compared with the placebo (Fig. 3). Sub-roup analyses according to dosage of intervention suggested that CPS significantly decreased LDL (–9·08 mg/dl; 95 % CI: −10·21, −7·94; $I^2 = 93{\cdot}4$ %; $P =< 0{\cdot}001$; $n$ 2), total cholesterol (–23·39, mg/dl; 95 % CI: −26·60, −19·98; $I^2 = 90{\cdot}7$ %; $P =< 0{\cdot}001$; $n$ 2), TAG (–12·84, mg/dl; 95 % CI: −15·45, −10·23; $I^2 = 95{\cdot}3$ %; $P =< 0{\cdot}001$; $n$ 2) and significantly increased HDL (6·76 mg/dl; 95 % CI: 2·63, 10·89; $I^2 = 0{\cdot}0$ %; $P =< 0{\cdot}001$; $n$ 2) following a 10 g and over CPS intervention, in contrast to a less than 10 g intervention (Table 3). The observed extreme between-study heterogeneity for lipid profile was attenuated by sub-group analysis based on the dosage of intervention (Table 3).

*Effects of collagen peptide supplementation on blood pressure.* CPS significantly decreased SBP (–5·04 mmHg; 95 % CI: −9·22, −0·85; $I^2 = 98{\cdot}9$ %; $P = 0{\cdot}018$; $n$ 6), but not DBP (0·71 mmHg; 95 % CI: −0·25, 1·68; $I^2 = 86{\cdot}7$ %; $P = 0{\cdot}148$; $n$ 6) compared with the placebo (Fig. 4). Sub-group analyses relating to the duration of intervention indicated that CPS

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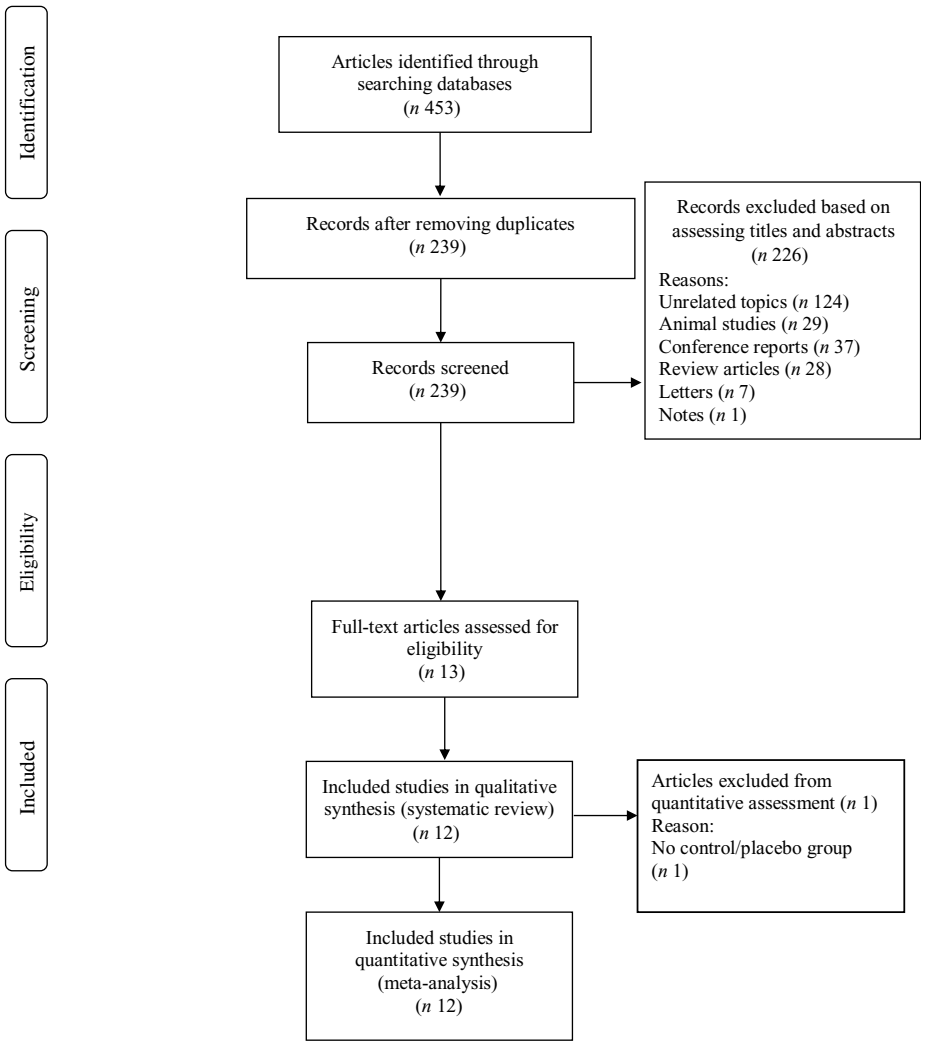


**Fig. 1.** Study selection flow chart

**Table 2.** Quality assessment

| Study | Random sequence generation | Allocation concealment | Blinding of participants' personnel | Blinding of outcome assessors | Incomplete outcome data | Selective outcome reporting | Other sources of bias |
|---|---|---|---|---|---|---|---|
| Han *et al.* (2008) | + | + | – | – | ? | ? | – |
| Zhu *et al.* (2010) | + | + | + | – | – | + | ? |
| Kouguchi *et al.* (2013) | + | + | + | + | + | ? | – |
| Kumar *et al.* (2014) | + | – | + | + | ? | + | – |
| Zdzielik *et al.* (2015) | + | + | + | + | ? | – | + |
| Ishii *et al.* (2016) | + | + | + | + | + | ? | – |
| Koizumi *et al.* (2017) | + | + | + | + | ? | + | – |
| Tak *et al.* (2019) | + | + | + | + | + | – | – |
| Igase *et al.* (2019) | + | – | + | – | – | – | ? |
| Jendricke *et al.* (2020) | + | + | + | + | – | ? | + |
| Zdzieblik *et al.* (2021) | + | + | + | + | + | ? | + |

+ shows low risk of bias; - shows high risk of bias; ? shows unclear risk of bias.

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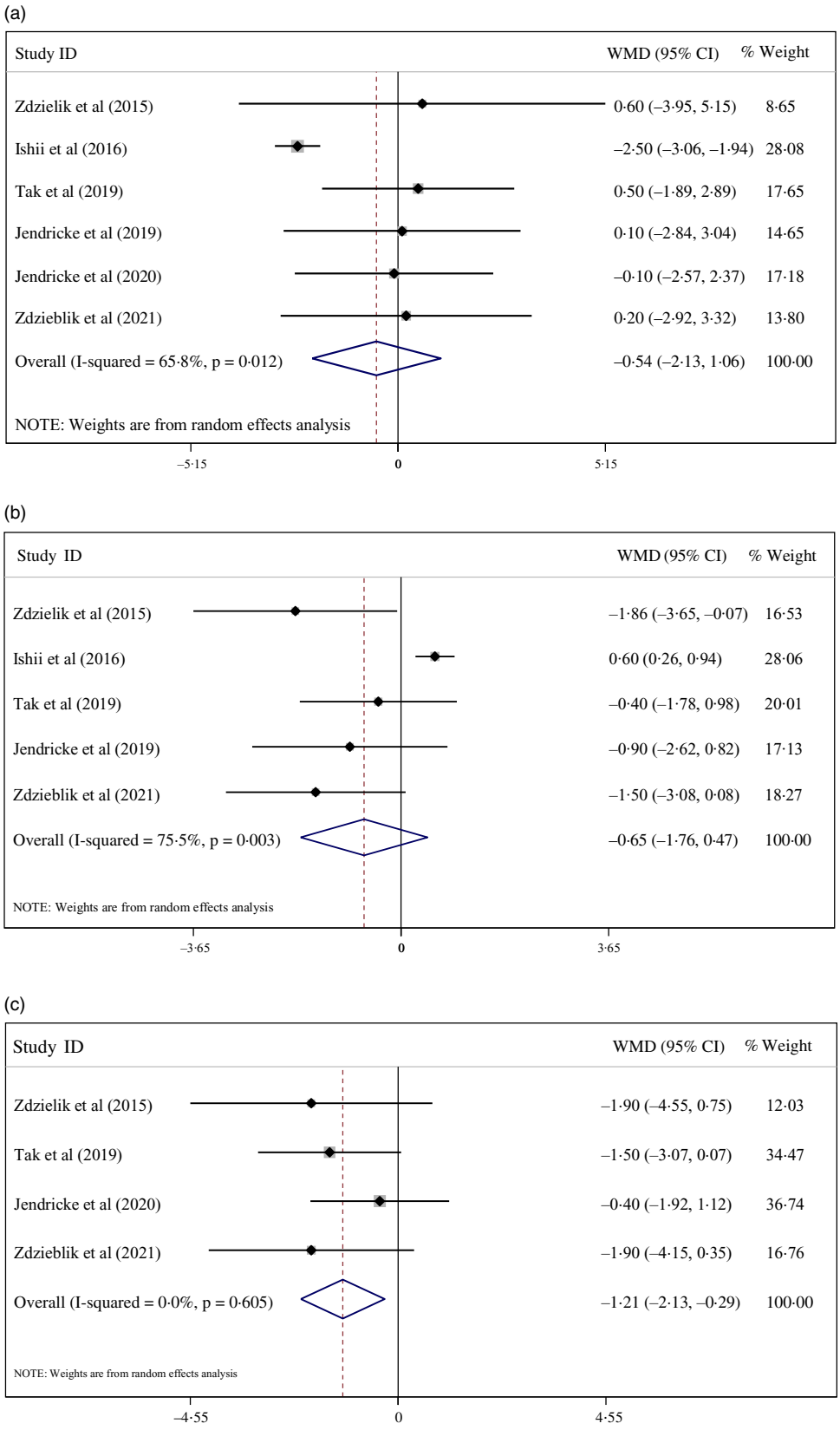


**Fig. 2.** (a) Forest plot displaying weighted mean difference and 95 % CI for the effects of collagen peptide supplementation *v.* placebo on body mass.

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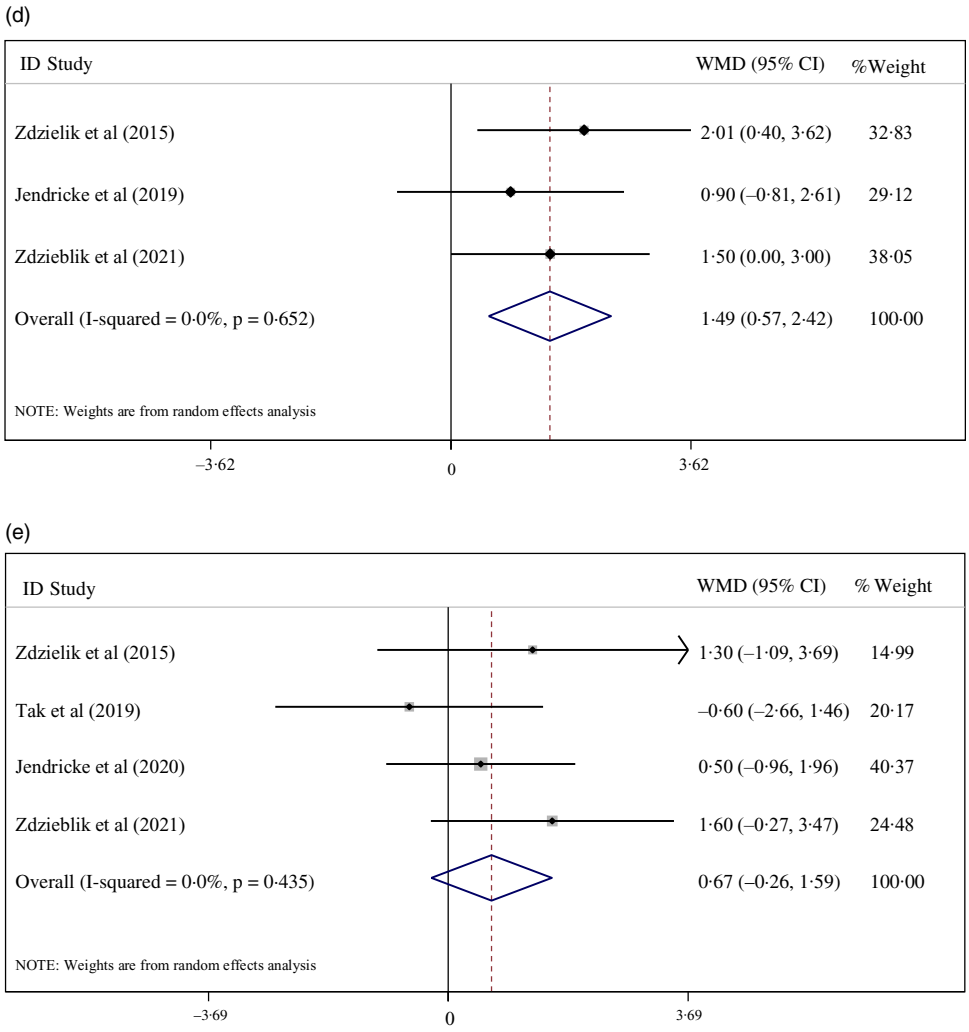


**Fig. 2.** (Continued).

significantly decreased SBP following a six-week intervention (–7·00 mmHg; 95 % CI: −13·80, −0·20; $I^2 = 0·0$ %; $P = 0·044$; $n$ 2), in contrast to a 12-week intervention duration, which failed to produce a significant results (Table 3). Sub-group analyses according to dosage of intervention suggested that CPS significantly decreased SBP (–9·35, mmHg; 95 % CI: −11·28, −7·43; $I^2 = 95·3$ %; $P =< 0·001$; $n$ 2) and significantly increased DBP (1·15 mmHg; 95 % CI: 0·25, 1·35; $I^2 = 55·1$ %; $P =< 0·001$; $n$ 2) following a 10 g and over CPS intervention, in contrast to a less than 10 g intervention (Table 3). The observed extreme between-study heterogeneity for DBP was attenuated by sub-group analysis based on the trial duration and dosage of intervention (Table 3).

*Effects of collagen peptide supplementation on glycaemic indices.* Our results failed to show a significant effect of CPS on glycaemic indices which included fasting blood sugar (–11·15, mg/dl; 95 % CI: –26·15, 3·84; $I^2 = 99·8$ %; $P = 0·145$; $n$ 6) and HbA1c (–0·26 %; 95 % CI: –0·58, 0·06; $I^2 = 98·3$ %; $P = 0·106$; $n$ 3) compared with the placebo group (Fig. 5). Sub-group analyses according to dosage of intervention suggested that CPS significantly decreased fasting blood sugar (–29·24, mg/dl; 95 % CI: –30·19, –28·28; $I^2 = 0·0$ %; $P =< 0·001$; $n$ 2) and HbA1c (–0·39 %; 95 % CI: –0·58, –0·20; $I^2 = 88·4$ %; $P =< 0·001$; $n$ 2) following a 10 g and over CPS intervention, in contrast to a less than 10 g intervention (Table 3). The observed extreme between-study heterogeneity for fasting blood sugar was attenuated by sub-group analysis based on the dosage of intervention (Table 3).

## Sensitivity analysis

Sensitivity analysis was performed by omitting each of the included studies. The results showed that the weighted mean differences was not changed significantly by omitting each of the studies. This indicated the meta-analysis results were stable and not sensitive to any one of the twelve studies (online Supplementary Fig. 1).

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**Table 3.** Sub-group meta-analyses for the effects of collagen peptide supplementation on metabolic parameters

| Sub-group analyses of collagen supplementation *v.* placebo on body mass | | | | | Heterogeneity | | |
|---|---|---|---|---|---|---|---|
| Sub-groups | NO | WMD | 95 % CI | *P* value | *P* values for within sub-groups | $I^2$ | *P* value for between sub-groups |
| Age | | | | | | | |
| Less than 50 year | 3 | −0·18 | −1·66, 1·30 | 0·810 | 0·941 | 0·0 % | 0·002 |
| 50 year and more | 3 | 1·25 | −0·96, 3·46 | 0·268 | 0·108 | 55 % | |
| Sex | | | | | | | |
| Women | 3 | 1·21 | −0·77, 3·18 | 0·231 | 0·047 | 67·2 % | 0·014 |
| Men | 2 | −0·33 | −2·90, 2·25 | 0·803 | 0·887 | 0·0 % | |
| Body mass status | | | | | | | |
| Normal | 3 | 0·96 | −1·22, 3·14 | 0·390 | 0·012 | 77·2 % | 0·054 |
| Overweight and obese | 2 | −0·15 | −2·29, 1·99 | 0·893 | 0·964 | 0·0 % | |
| Dosage | | | | | | | |
| Less than 10 g | 2 | 1·23 | −1·67,4·14 | 0·405 | 0·016 | 82·6 % | 0·003 |
| 10 g and over | 4 | −0·10 | −1·63,1·42 | 0·894 | 0·995 | 0·0 % | |
| Sub-group analyses of collagen supplementation *v.* placebo on fat mass (%) | | | | | | | |
| Age | | | | | | | |
| Less than 50 year | 2 | −0·60 | −1·67,0·48 | 0·278 | 0·657 | 0·0 % | 0·075 |
| 50 year and more | 3 | −0·77 | −2·58,1·05 | 0·409 | 0·002 | 84·5 % | |
| Sex | | | | | | | |
| Women | 2 | 0·10 | −1·48, 1·29 | 0·892 | 0·093 | 64·5 % | 0·001 |
| Men | 2 | −1·66 | −2·48, −0·47 | 0·006 | 0·768 | 0·0 % | |
| Body mass status | | | | | | | |
| Normal | 2 | 0·33 | −0·53, 1·20 | 0·452 | 0·168 | 47·3 % | 0·001 |
| Overweight and obese | 2 | −1·22 | −2·39, −0·06 | 0·039 | 0·61 | 0·0 % | |
| Dosage | | | | | | | |
| Less than 10 g | 2 | 0·33 | −0·53,1·20 | 0·452 | 0·168 | 47·3 % | < 0·001 |
| 10 g and over | 3 | −1·41 | −2·39, −0·44 | 0·005 | 0·744 | 0·0 % | |
| Kind of intervention | | | | | | | |
| With training | 3 | −1·36 | −2·60, −0·12 | 0·032 | 0·449 | 0·0 % | 0·006 |
| Without training | 3 | −0·25 | −1·52, 1·01 | 0·695 | 0·018 | 75·1 % | |
| Sub-group analyses of collagen supplementation *v.* placebo on fat mass (kg) | | | | | | | |
| Age | | | | | | | |
| Less than 50 year | 2 | −0·93 | −2·02, 0·16 | 0·094 | 0·323 | 0·0 % | 0·351 |
| 50 year and more | 2 | −1·50 | −3·07, −0·18 | 0·030 | 1·00 | 0·0 % | |
| Sub-group analyses of collagen supplementation *v.* placebo on LDL | | | | | | | |
| Dosage | | | | | | | |
| Less than 10 g | 3 | 1·03 | −1·46, 3·52 | 0·416 | 0·477 | 0·0 % | < 0·001 |
| 10 g and over | 2 | −9·08 | −10·21, −7·94 | < 0·001 | < 0·001 | 93·4 % | |
| Sub-group analyses of collagen supplementation *v.* placebo on LDL | | | | | | | |
| Dosage | | | | | | | |
| Less than 10 g | 3 | 1·12 | −3·38, 5·62 | 0·627 | 0·022 | 73·8 % | 0·067 |
| 10 g and over | 2 | 6·76 | 2·63, 10·89 | 0·001 | 0·522 | 0·0 % | |
| Sub-group analyses of collagen supplementation *v.* placebo on total cholesterol | | | | | | | |
| Dosage | | | | | | | |
| Less than 10 g | 5 | 2·09 | −1·73, 5·90 | 0·284 | 0·275 | 20·4 % | < 0·001 |
| 10 g and over | 2 | −23·39 | −26·60, −19·98 | < 0·001 | 0·001 | 90·7 % | |
| Sub-group analyses of collagen supplementation *v.* placebo on TAG | | | | | | | |
| Dosage | | | | | | | |
| Less than 10 g | 3 | −0·88 | −3·53, 1·17 | 0·514 | 0·763 | 0·0 % | < 0·001 |
| 10 g and over | 2 | −12·84 | −15·45, −10·23 | < 0·001 | 0·213 | 35·5 % | |
| Sub-group analyses of collagen supplementation *v.* placebo on systolic blood pressure | | | | | | | |
| Trial duration (week) | | | | | | | |
| 6 | 2 | −7·00 | −13·80, −0·20 | 0·044 | < 0·001 | 95·9 % | < 0·001 |
| 12 | 4 | −4·20 | −11·12, 3·02 | 0·261 | < 0·001 | 99·0 | |
| Health status | | | | | | | |
| Healthy | 2 | −0·43 | −7·16, 6·30 | 0·90 | 0·002 | 89·4 % | < 0·001 |
| Unhealthy | 4 | −7·62 | −9·59, −5·65 | < 0·001 | < 0·001 | 93·1 % | |
| Dosage | | | | | | | |
| Less than 10 g | 4 | −2·69 | −7·71, 2·33 | 0·294 | < 0·001 | 94·0 % | < 0·001 |
| 10 g and over | 2 | −9·35 | −11·28, −7·43 | < 0·001 | < 0·001 | 95·3 % | |

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**Table 3.** (*Continued*)

| Sub-group analyses of collagen supplementation *v.* placebo on body mass | | | | | Heterogeneity | | |
|---|---|---|---|---|---|---|---|
| Sub-groups | NO | WMD | 95 % CI | *P* value | *P* values for within sub-groups | $I^2$ | *P* value for between sub-groups |
| Sub-group analyses of collagen supplementation *v.* placebo on diastolic blood pressure | | | | | | | |
| Trial duration (week) | | | | | | | |
| 6 | 2 | 0·54 | −1·51, 2·60 | 0·605 | 0·050 | 73·9 % | < 0·001 |
| 12 | 4 | 0·31 | −1·47, 2·10 | 0·732 | < 0·001 | 91·1 | |
| Health status | | | | | | | |
| Healthy | 2 | 0·38 | −5·11, 5·87 | 0·892 | 0·023 | 80·6 % | < 0·001 |
| Unhealthy | 4 | 0·44 | −0·47, 1·35 | 0·343 | 0·001 | 81·8 % | |
| Dosage | | | | | | | |
| Less than 10 g | 4 | −0·66 | −3·91, 2·59 | 0·691 | < 0·001 | 90·4 % | 0·044 |
| 10 g and over | 2 | 1·15 | 0·25, 1·35 | < 0·001 | 0·136 | 55·1 % | |
| Sub-group analyses of collagen supplementation *v.* placebo on fasting blood sugar | | | | | | | |
| Dosage | | | | | | | |
| Less than 10 g | 4 | 0·45 | −1·13, 2·03 | 0·89 | 0·185 | 37·8 % | < 0·001 |
| 10 g and over | 2 | −29·24 | −30·19, −28·28 | < 0·001 | 0·356 | 0·0 % | |
| Sub-group analyses of collagen supplementation *v.* placebo on HbA1c | | | | | | | |
| Dosage | | | | | | | |
| Less than 10 g | 1 | 0·00 | −0·03, 0·03 | 0·99 | – | – | < 0·001 |
| 10 g and over | 2 | −0·39 | −0·58, −0·20 | < 0·001 | 0·004 | 88·4 % | |

WMD, weighted mean differences.

### *Publication bias*

Moreover, no evidence of publication bias was detected regarding the efficacy of CPS on fat mass ($P = 0·17$, Begg's test; $P = 0·30$, Egger's test), fat-free mass based on body mass percentage ($P = 0·69$, Begg's test; $P = 0·60$, Egger's test), kilograms ($P = 0·16$, Begg's test; $P = 0·33$, Egger's test), LDL (p = 0·62, Begg's test; $P = 0·14$, Egger's test), HDL ($P = 0·63$, Begg's test; $P = 0·95$, Egger's test), TAG ($P = 0·62$, Begg's test; $P = 0·77$, Egger's test), total cholesterol ($P = 0·65$, Begg's test; $P = 0·095$, Egger's test), SBP ($P = 0·57$, Begg's test; $P = 0·39$, Egger's test), DBP ($P = 0·57$, Begg's test; $P = 0·37$, Egger's test), fasting blood sugar ($P = 0·85$, Begg's test; $P = 0·82$, Egger's test) and HbA1c ($P = 0·12$, Begg's test; $P = 0·16$, Egger's test). However, the Egger's test results showed publication bias for body mass ($P = 0·04$) and body fat percentage ($P = 0·002$). These results were not confirmed by the Begg's test for body mass ($P = 0·34$) and body fat percentage ($P = 0·06$).

### *Quality of evidence*

To evaluate the quality of evidence for results, the GRADE guideline was utilised, which demonstrated the effect of fat mass (kg) to be of high quality. The evidence about fat-free mass (%), fat-free mass (kg) and SBP were downgraded to a moderate level. Based on the GRADE framework, body mass and LDL evidence were categorised as low quality. Finally, the fat mass (%), HDL, TAG, total cholesterol, DBP, fasting blood sugar and HbA1c were established as very low quality (Table 4).

## Discussion

The present review is the first to investigate the effects of CPS on cardiovascular disease-related markers, including blood pressure, anthropometric indices, lipid profile and glycaemic parameters. The pooled data that was derived from twelve randomised, controlled trials found that CPS (900 mg/d to 15 g/d), for a duration of 6 to 12 weeks, led to the significant reduction in fat mass, SBP, serum LDL concentrations and increased fat-free mass (measured by body mass percentage). Additional subgroup analyses demonstrated that CPS significantly decreased body fat percentage in men, obese or overweight participants, and when CPS was administered in combination with exercise.

A narrative review performed by Cicero *et al.*[46] revealed that bioactive peptides play potential roles in preventing and treating chronic diseases, including cancer and cardiovascular disorders. Indeed, several beneficial effects of ingesting collagen peptides are attributed to the physiological properties of circulating dipeptides, which are derived from collagen[47]. This includes the potential ability to alleviate a range of cardiovascular complications, including heart failure[48], a condition preceded by high blood pressure in 70 % of cases[49].

Our outcomes revealed that CPS significantly decreased SBP. Previous studies have documented that CPS can help improve blood pressure in various pathways[22,24,38]. Saiga *et al.*[50] reported that the hydrolysed collagen peptides extracted from the drumstick significantly suppressed high blood pressure by inhibiting angiotensin I-converting enzyme in spontaneously hypertensive rats. Moreover, Kouguchi *et al.*[24] suggested that CPS may have a beneficial effect on the vascular system by activating certain vasodilating agents such as nitric oxide, which decrease arterial stiffness. Zhu *et al.*[22] also showed that marine collagen peptides supplementation ameliorated hypertension by activating peroxisome proliferator-activated receptors, leading to down-regulation of nuclear factor-kB pathway and reduced production of cytochrome P450 and prostaglandin $I^2$. Their results also showed an upregulation of bradykinin, which confirmed the angiotensin I-converting enzyme-inhibitory effect

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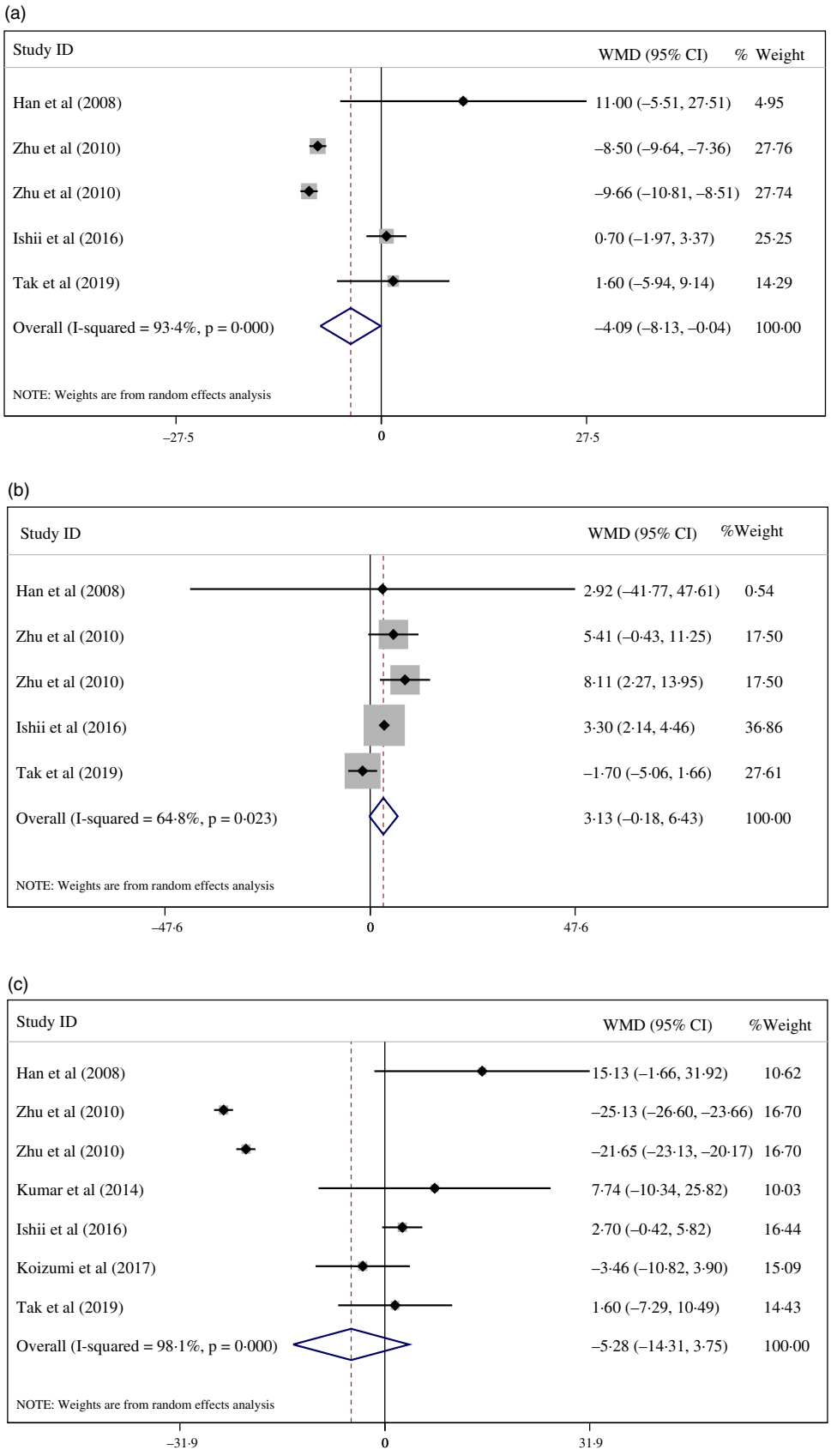


**Fig. 3.** (a)Forest plot displaying weighted mean difference and 95 % CI for the effects of collagen peptide supplementation *v.* placebo on low-density lipoprotein.

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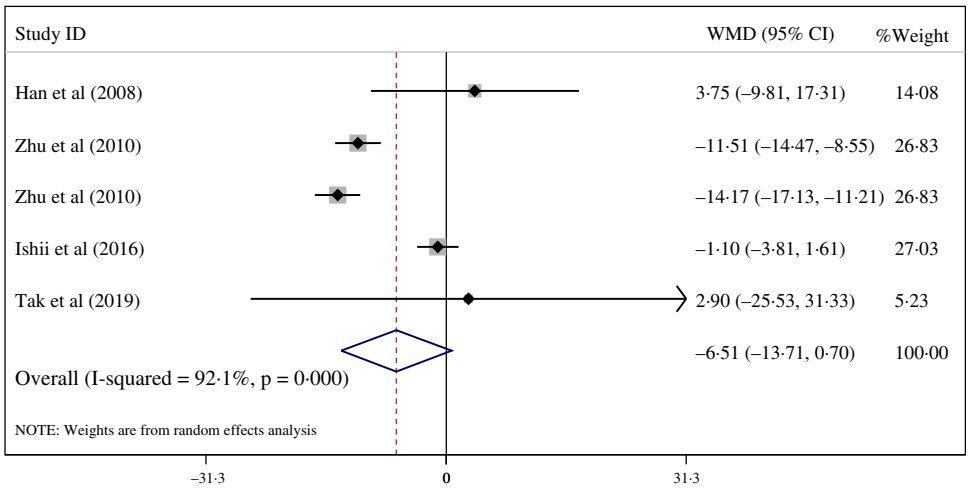
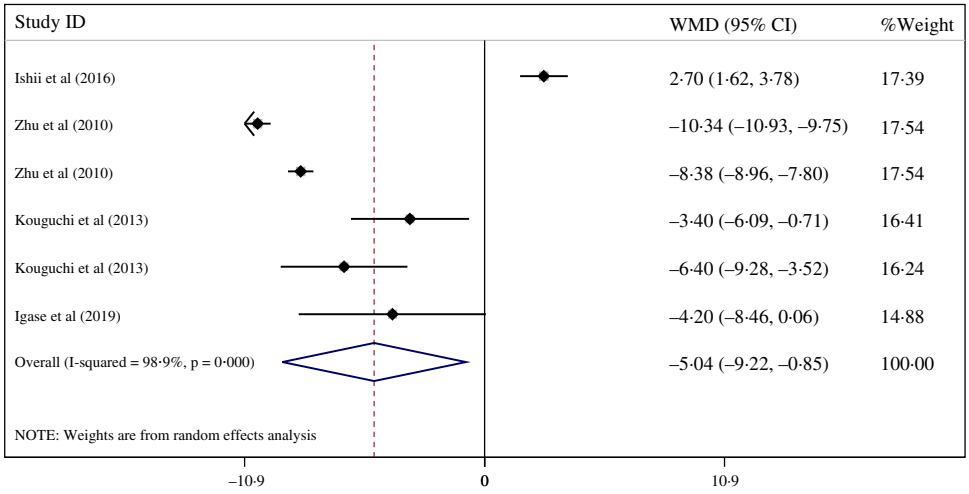



**Fig. 3.** (Continued).

(a)




(b)

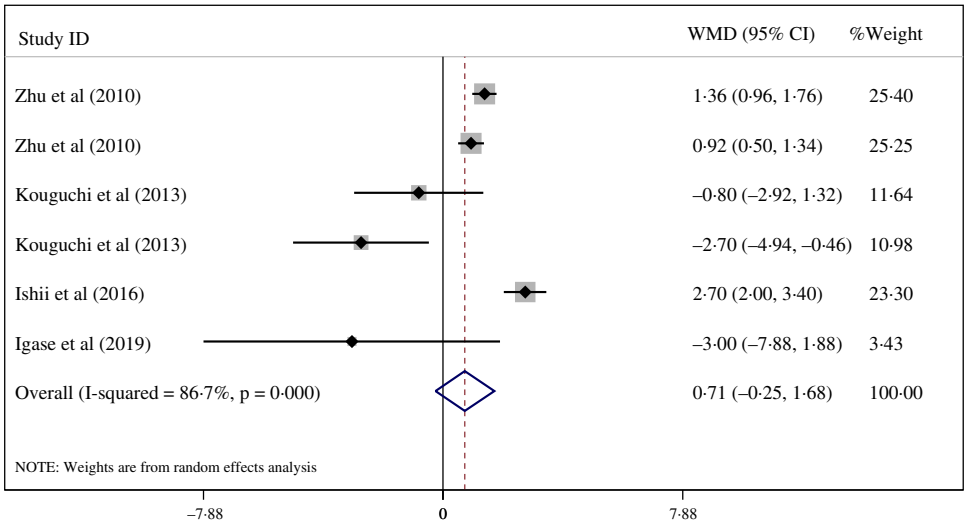



**Fig. 4.** (a) Forest plot displaying weighted mean difference and 95 % CI for the effects of collagen peptide supplementation *v.* placebo on systolic blood pressure.

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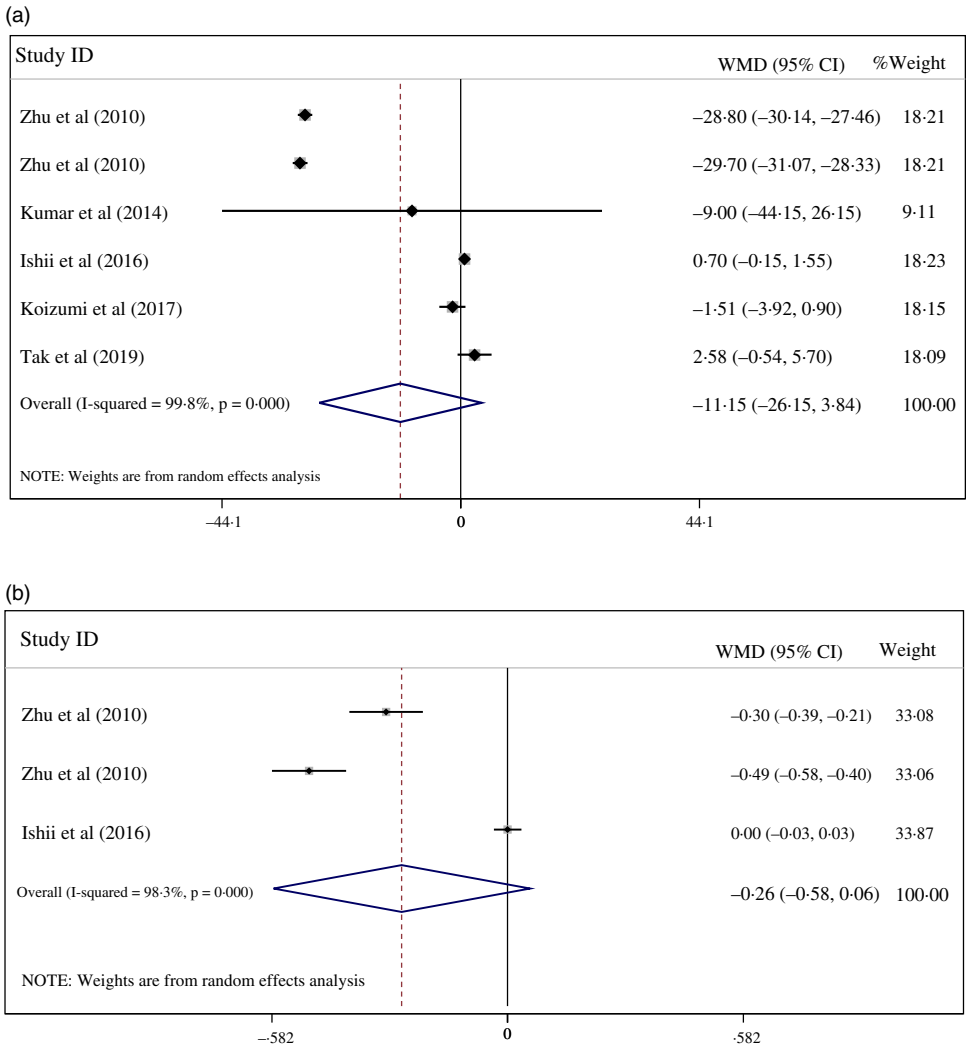


**Fig. 5.** (a) Forest plot displaying weighted mean difference and 95 % CI for the effects of collagen peptide supplementation *v.* placebo on fasting blood sugar.

of collagen on blood pressure regulation[22]. Importantly, it has been established that a reduction of 2 mmHg in SBP can lower coronary heart disease and stroke mortalities by 4 % and 6 %, respectively[51]. Hence, our findings indicating an SBP-lowering effect (~5 mmHg) of CPS support its clinical significance as a nutritional strategy for blood pressure improvement.

Elevated concentrations of blood lipids are well-established risk factors for cardiovascular diseases[52]. Our results revealed that CPS led to a significant decrease in LDL concentrations. Several investigations have assessed the potential blood lipid modulation by CPS therapy[22,25,37,39]. Lee *et al.*[53] indicated that fish-derived collagen peptide might improve lipid metabolism and accumulation by a reduction in genes expression of CCAAT enhancer-binding protein-$\alpha$ and peroxisome proliferator-activated receptor-$\gamma$ and adipocyte protein 2. Furthermore, Woo *et al.*[54] suggested that collagen peptide skate skin-derived with dose-dependent manner suppressed hepatic lipid accumulation and reduced the lipid droplet size in the adipose tissue. Prior investigations also reported that CPS could lower plasma and hepatic lipid concentrations by suppressing the hepatic protein expression for fatty acid cholesterol synthesis, including sterol regulatory element-binding protein-1, sterol regulatory element-binding protein-2, fatty acid synthase, acetyl-CoA carboxylase and 3-hydroxy-3-methylglutaryl-CoA reductase[54–56]. Recently, animal research by Vijayan *et al.*[57] showed that fish-derived collagen peptide has anti-lipidaemic properties that are mediated by a down-regulation of 3-hydroxy-3-methylglutaryl-CoA reductase expression and up-regulation Lecithin–cholesterol acyltransferase. On other hand, CPS may enhance lipid breakdown by upregulating gene expression of PPAR-$\alpha$, carnitine palmitoyltransferase 1 and synthesis of bile acid cytochrome P450 family 7 subfamily A member 1[54–56], which play a role in the process of $\beta$-oxidation.

Interestingly, the results of the current study revealed that CPS significantly increased free fat mass and decreased fat mass. A potential mechanism for the improvement of fat-free mass and decrease in fat mass is that hydroxyprolyl-glycine levels can be elevated in blood after CPS[58]. These dipeptides seem to have signalling effects and promote C2C12 myoblast differentiation and increase myotube hypertrophy by activating the mTOR signalling

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**Table 4.** Grade profile of collagen peptide supplementation for cardiovascular risk factors scores in adults

| | Quality assessment | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Outcomes | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Number of intervention/ control | WMD | 95 % CI | Heterogeneity ($I^2$) | Quality of evidence |
| Body mass | No serious limitations | Serious limitations | No serious limitations | Serious limitations | No serious limitations | 190/195 | –0·54 | –2·13, 1·06 | 65·8 % | ⊕⊕◯◯ Low |
| Fat mass (%) | No serious limitations | Serious limitations | No serious limitations | Serious limitations | No serious limitations | 162/164 | –0·65 | –1·76, 0·47 | 75·5 % | ⊕◯◯◯ Very low |
| Fat mass (kg) | No serious limitations | No serious limitations | No serious limitations | No serious limitations | No serious limitations | 136/136 | –1·21 | –2·13, –0·29 | 0·0 % | ⊕⊕⊕⊕ High |
| Free fat mass (%) | No serious limitations | No serious limitations | Serious limita-tions | No serious limitations | No serious limitations | 96/95 | 1·49 | 0·57, 2·42 | 0·0 % | ⊕⊕⊕◯ Moderate |
| Free fat mass (kg) | No serious limitations | No serious limitations | No serious limitations | Serious limitations | No serious limitations | 136/136 | 0·67 | –0·26, 1·59 | 0·0 % | ⊕⊕⊕◯ Moderate |
| LDL-C | No serious limitations | Very serious limitations | No serious limitations | No serious limitations | No serious limitations | 131/134 | –4·09 | –8·13, –0·04 | 93·4 % | ⊕⊕◯◯ Low |
| HDL-C | No serious limitations | Serious limitations | No serious limitations | Serious limitations | No serious limitations | 131/134 | 3·13 | –0·18, 6·43 | 64·8 % | ⊕◯◯◯ Very low |
| TG | No serious limitations | Very serious limitations | No serious limitations | Serious limitations | No serious limitations | 131/134 | –6·51 | –13·71, 0·70 | 92·1 % | ⊕◯◯◯ Very low |
| TC | No serious limitations | Very serious limitations | No serious limitations | Serious limitations | No serious limitations | 188/178 | –5·28 | –14·31, 3·75 | 98·1 % | ⊕◯◯◯ Very low |
| SBP | No serious limitations | Very serious limitations | No serious limitations | No serious limitations | No serious limitations | 149/153 | –5·04 | –9·22, –0·85 | 98·9 % | ⊕⊕⊕◯ Moderate |
| DBP | No serious limitations | Very serious limitations | No serious limitations | Serious limitations | No serious limitations | 149/153 | 0·71 | –0·25, 1·68 | 86·7 % | ⊕◯◯◯ Very low |
| FBG | No serious limitations | Very serious limitations | No serious limitations | Very serious limitations | No serious limitations | 173/163 | –11·15 | –26·15, 3·84 | 99·8 % | ⊕◯◯◯ Very low |
| HbA1c | No serious limitations | Very serious limitations | No serious limitations | Serious limitations | No serious limitations | 76/78 | –0·26 | 0·58, 0·06 | 98·3 % | ⊕◯◯◯ Very low |

TC, total cholestrol; FBG, fasting blood glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure.



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pathway[18]. The prolyl-hydroxyproline, as other collagen peptides, contain dipeptides[58,59], accelerates muscle regeneration by inducing several myogenically differentiated cells, including myogenin-positive myoblasts and myoglobin-positive myocytes[59]. Furthermore, it has been revealed that specific collagen peptides could act as signal messengers in anabolic cellular activities in ligaments, tendons and cartilage[15]. It also might be helpful to improve pain symptoms and performance in activity-related joint discomforts[23,44]. Hence, CPS could enhance body composition and increase functional performance by improving joint-related disorders and their symptoms. Other potential mechanisms for the effects of CPS on improving body composition are its anti-inflammatory and antioxidant effects. The collagen peptides' amino acids content, such as glycine, has been found to have powerful anti-inflammatory properties which can modulate muscle wasting in various models[60,61]. Additionally, Vijayan *et al.*[62] suggested that CPS can attenuate oxidative stress by improving enzymatic antioxidant defense catalase and superoxide dismutase, leading to decreased levels of membrane lipid peroxidation. Chen *et al.*[63] also indicated that CPS enhanced the anti-inflammatory process by decreasing lipoxygenase activity and nitric oxide radicals. Moreover, it is possible that the decrease in fat mass in our results might be associated with higher resting energy expenditure affected by the significant increase in fat-free mass.

Several strengths can be derived from the present review. Firstly, the reviewed studies considered a body of literature that measured several important markers associated with cardiovascular disease. A majority of the included studies appeared to be of high quality, as distinguished by a validated risk of bias assessment. In addition, there were no signs of publication bias according to Begg's and Egger's tests. Despite these strengths, the current review consisted of some potential limitations. Participants were supplemented with different collagen peptide doses between studies and undertook supplementation for varying timeframes. The cardiovascular markers were only considered as secondary outcomes in some of the included trials, potentially impacting the measurement of these markers. There was high heterogeneity between enrolled study participants, with studies comprising of participants displaying diverse health statuses and ages. Finally, lifestyle modifications throughout the study periods were not controlled in some of the included studies. Lifestyle modifications such as dietary intake and physical activity may be confounding factors by influencing the effects of CPS on the assessed markers.

## *Conclusion*

Taken together, this comprehensive review of collated data suggests that CPS may significantly decrease fat mass, fat-free mass (based on body mass percentage), SBP and serum LDL levels. Additional sub-group analyses revealed an important decline in fat mass among men, obese or overweight participants and those consuming collagen peptides while exercising. Additional long-term, well-designed randomised, placebo-controlled trials are recommended further to examine the impact of CPS on CVD-related markers and expand on our findings.

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SM and CJ designed this study. SM, MHK, and HM conducted the literature search. SM and FJ performed the statistical analysis and interpretation of the data. ZJ, FN, SPM, and SMG wrote the manuscript. RB, AW, and NT critically revised the manuscript. All authors approved the final version of the manuscript.

## Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114522001301

## References

1. Roth GA, Abate D, Abate KH, *et al.* (2018) Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* **392**, 1736–1788.
2. Kyu HH, Abate D, Abate KH, *et al.* (2018) Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* **392**, 1859–1922.
3. Timmis A, Townsend N, Gale CP, *et al.* (2020) European Society of Cardiology: cardiovascular disease statistics 2019. *Eur Heart J* **41**, 12–85.
4. Dwivedi AK, Dubey P, Cistola DP, *et al.* (2020) Association between obesity and cardiovascular outcomes: updated evidence from meta-analysis studies. *Curr Cardiol Rep* **22**, 1–19.
5. Kokubo Y & Matsumoto C (2016) Hypertension is a risk factor for several types of heart disease: review of prospective studies. *Hypertens: Basic Res Clin Pract* **956**, 419–426.
6. Sunkara A & Raizner A (2019) Supplemental vitamins and minerals for cardiovascular disease prevention and treatment. *Methodist Debakey Cardiovasc J* **15**, 179.
7. Kim J, Hoang T, Bu SY, *et al.* (2020) Associations of dietary intake with cardiovascular disease, blood pressure, and lipid profile in the Korean population: a systematic review and meta-analysis. *J Lipid Atheroscler* **9**, 205.
8. Aminde LN & Veerman L (2016) Interventions for the prevention of cardiovascular diseases: a protocol for a systematic review of economic evaluations in low-income and middle-income countries. *BMJ Open* **6**, e013668.
9. Mozaffarian D, Appel LJ & Van Horn L (2011) Components of a cardioprotective diet: new insights. *Circulation* **123**, 2870–2891.
10. Ohara H, Matsumoto H, Ito K, *et al.* (2007) Comparison of quantity and structures of hydroxyproline-containing peptides in human blood after oral ingestion of gelatin hydrolysates from different sources. *J Agric Food Chem* **55**, 1532–1535.
11. Oesser S, Adam M, Babel W, *et al.* (1999) Oral administration of 14C labeled gelatin hydrolysate leads to an accumulation of radioactivity in cartilage of mice (C57/BL). *J Nutr* **129**, 1891–1895.
12. Sibilla S, Godfrey M, Brewer S, *et al.* (2015) An overview of the beneficial effects of hydrolysed collagen as a nutraceutical on skin properties: scientific background and clinical studies. *Open Nutraceutical J* **8**, 29–42.

British Journal of Nutrition

https://doi.org/10.1017/S0007114522001301 Published online by Cambridge University Press

13. Shigemura Y, Kubomura D, Sato Y, *et al.* (2014) Dose-dependent changes in the levels of free and peptide forms of hydroxyproline in human plasma after collagen hydrolysate ingestion. *Food Chem* **159**, 328–332.
14. Qiu S, Li L, Weeber EJ, *et al.* (2007) Ascorbate transport by primary cultured neurons and its role in neuronal function and protection against excitotoxicity. *J Neurosci Res* **85**, 1046–1056.
15. Schunck M & Oesser S (2013) Specific collagen peptides benefit the biosynthesis of matrix molecules of tendons and ligaments. *J Int Soc Sports Nutr* **10**, 1–2.
16. Oesser S & Seifert J (2003) Stimulation of type II collagen biosynthesis and secretion in bovine chondrocytes cultured with degraded collagen. *Cell Tissue Res* **311**, 393–399.
17. McAlindon T, Nuite M, Krishnan N, *et al.* (2011) Change in knee osteoarthritis cartilage detected by delayed gadolinium enhanced magnetic resonance imaging following treatment with collagen hydrolysate: a pilot randomized controlled trial. *Osteoarthritis Cartilage* **19**, 399–405.
18. Kitakaze T, Sakamoto T, Kitano T, *et al.* (2016) The collagen derived dipeptide hydroxyprolyl-glycine promotes C2C12 myoblast differentiation and myotube hypertrophy. *Biochem Biophys Res Commun* **478**, 1292–1297.
19. Wang J, Xie Y, Pei X, *et al.* (2008) The lipid-lowering and antioxidative effects of marine collagen peptides. *Zhonghua yu fang yi xue za zhi (Chinese J Prev Med)* **42**, 226–230.
20. Koenig RJ, Peterson CM, Jones RL, *et al.* (1976) Correlation of glucose regulation and hemoglobin AIc in diabetes mellitus. *N Engl J Med* **295**, 417–420.
21. Marion-Letellier R, Dechelotte P, Iacucci M, *et al.* (2009) Dietary modulation of peroxisome proliferator-activated receptor gamma. *Gut* **58**, 586–593.
22. Zhu C-F, Li G-Z, Peng H-B, *et al.* (2010) Therapeutic effects of marine collagen peptides on Chinese patients with type 2 diabetes mellitus and primary hypertension. *Am J Med Sci* **340**, 360–366.
23. Zdzieblik D, Jendricke P, Oesser S, *et al.* (2021) The influence of specific bioactive collagen peptides on body composition and muscle strength in middle-aged, untrained men: a randomized controlled trial. *Int J Environ Res Public Health* **18**, 4837.
24. Kouguchi T, Ohmori T, Shimizu M, *et al.* (2013) Effects of a chicken collagen hydrolysate on the circulation system in subjects with mild hypertension or high-normal blood pressure. *Biosci Biotechnol, Biochem* **77**, 691–696.
25. Tak YJ, Kim YJ, Lee JG, *et al.* (2019) Effect of oral ingestion of low-molecular collagen peptides derived from skate (Raja Kenojei) skin on body fat in overweight adults: a randomized, double-blind, placebo-controlled trial. *Mar Drugs* **17**, 157.
26. Jendricke P, Kohl J, Centner C, *et al.* (2020) Influence of specific collagen peptides and concurrent training on cardiometabolic parameters and performance indices in women: a randomized controlled trial. *Front Nutr* **7**, 580918.
27. Page MJ, McKenzie JE, Bossuyt PM, *et al.* (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* **372**, n71.
28. Higgins JP, Altman DG, Gøtzsche PC, *et al.* (2011) The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* **343**, d5928.
29. Moradi S, Ziaei R, Foshati S, *et al.* (2019) Effects of spirulina supplementation on obesity: a systematic review and meta-analysis of randomized clinical trials. *Complementary Ther Med* **47**, 102211.
30. Hadi A, Ghaedi E, Moradi S, *et al.* (2019) Effects of melatonin supplementation on blood pressure: a systematic review and meta-analysis of randomized controlled trials. *Hormone Metab Res* **51**, 157–164.
31. DerSimonian R & Kacker R (2007) Random-effects model for meta-analysis of clinical trials: an update. *Contemp Clin Trials* **28**, 105–114.
32. Wan X, Wang W, Liu J, *et al.* (2014) Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Meth* **14**, 135.
33. Begg CB & Mazumdar M (1994) Operating characteristics of a rank correlation test for publication bias. *Biom* **50**, 1088–1101.
34. Egger M, Smith GD, Schneider M, *et al.* (1997) Bias in meta-analysis detected by a simple, graphical test. *BMJ* **315**, 629–634.
35. Guyatt GH, Oxman AD, Vist GE, *et al.* (2008) GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* **336**, 924–926.
36. Giglio BM, Schincaglia RM, da Silva AS, *et al.* (2019) Whey protein supplementation compared to collagen increases blood Nesfatin concentrations and decreases android fat in overweight women: a randomized double-blind study. *Nutrients* **11**, 2051.
37. Han C-J & Kang S-M (2008) The Effect of collagen supplementation from pork skin on serum collagen, serum sex steroid hormone, serum lipid and skin crack in Korean middle-aged women. *Korean J Community Nutr* **13**, 912–921.
38. Igase M, Kohara K, Okada Y, *et al.* (2018) A double-blind, placebo-controlled, randomised clinical study of the effect of pork collagen peptide supplementation on atherosclerosis in healthy older individuals. *Biosci Biotechnol, Biochem* **82**, 893–895.
39. Ishii Y, Okada Y, Matsuoka S, *et al.* (2016) Effect of supplement containing Silybum marianum extract, soy extract, collagen peptide, bifidobacteria and apple extract on skin: a randomized placebo-controlled, double-blind, parallel group comparative clinical study. *Glycative Stress Res* **3**, 156–171.
40. Jendricke P, Centner C, Zdzieblik D, *et al.* (2019) Specific collagen peptides in combination with resistance training improve body composition and regional muscle strength in premenopausal women: a randomized controlled trial. *Nutrients* **11**, 892.
41. Koizumi S, Inoue N, Shimizu M, *et al.* (2018) Effects of dietary supplementation with fish scales-derived collagen peptides on skin parameters and condition: a randomized, placebo-controlled, double-blind study. *Int J Pept Res Ther* **24**, 397–402.
42. Kumar S, Sugihara F, Suzuki K, *et al.* (2015) A double-blind, placebo-controlled, randomised, clinical study on the effectiveness of collagen peptide on osteoarthritis. *J Sci Food Agric* **95**, 702–707.
43. Tak YJ, Kim YJ, Lee JG, *et al.* (2019) Effect of oral ingestion of low-molecular collagen peptides derived from skate (Raja Kenojei) skin on body fat in overweight adults: a randomized, double-blind, placebo-controlled trial. *Mar Drugs* **17**, 157.
44. Zdzieblik D, Oesser S, Baumstark MW, *et al.* (2015) Collagen peptide supplementation in combination with resistance training improves body composition and increases muscle strength in elderly sarcopenic men: a randomised controlled trial. *Br J Nutr* **114**, 1237–1245.
45. Zhu CF, Li GZ, Peng HB, *et al.* (2010) Therapeutic effects of marine collagen peptides on chinese patients with type 2 diabetes mellitus and primary hypertension. *Am J Med Sci* **340**, 360–366.
46. Cicero AFG, Fogacci F & Colletti A (2017) Potential role of bioactive peptides in prevention and treatment of chronic diseases: a narrative review. *Br J Pharmacol* **174**, 1378–1394.
47. Shigemura Y, Kubomura D, Sato Y, *et al.* (2014) Dose-dependent changes in the levels of free and peptide forms of hydroxyproline in human plasma after collagen hydrolysate ingestion. *Food Chem* **159**, 328–332.


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48. Florea VG & Anand IS (2012) Troponin T and plasma collagen peptides in heart failure. *Circulation: Heart Failure* **5**, 394–397.
49. McKee PA, Castelli WP, McNamara PM, *et al.* (1971) The natural history of congestive heart failure: the Framingham study. *N Engl J Med* **285**, 1441–1446.
50. Saiga A, Iwai K, Hayakawa T, *et al.* (2008) Angiotensin I-Converting enzyme-inhibitory peptides obtained from chicken collagen hydrolysate. *J Agric Food Chem* **56**, 9586–9591.
51. Chobanian AV, Bakris GL, Black HR, *et al.* (2003) The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. *JAMA* **289**, 2560–2571.
52. Nelson RH (2013) Hyperlipidemia as a risk factor for cardiovascular disease. *Primary Care: Clin Offic Pract* **40**, 195–211.
53. Astre G, Deleruyelle S, Dortignac A, *et al.* (2018) Diet-induced obesity and associated disorders are prevented by natural bioactive type 1 fish collagen peptides (Naticol®) treatment. *J Physiol Biochem* **74**, 647–654.
54. Woo M, Song YO, Kang K-H, *et al.* (2018) Anti-obesity effects of collagen peptide derived from skate (Raja kenojei) skin through regulation of lipid metabolism. *Mar Drugs* **16**, 306.
55. Lammi C, Zanoni C, Scigliuolo GM, *et al.* (2014) Lupin peptides lower low-density lipoprotein (LDL) cholesterol through an up-regulation of the LDL receptor/sterol regulatory element binding protein 2 (SREBP2) pathway at HepG2 cell line. *J Agric Food Chem* **62**, 7151–7159.
56. Lammi C, Aiello G, Bollati C, *et al.* (2021) Trans-Epithelial transport, metabolism and biological activity assessment of the multi-target lupin peptide LILPKHSDAD (P5) and its metabolite LPKHSDAD (P5-Met). *Nutrients* **13**, 863.
57. Vijayan DK, Raman SP, Dara PK, *et al.* (2021) *In vivo* anti-lipidemic and antioxidant potential of collagen peptides obtained from great hammerhead shark skin waste. *J Food Sci Technol* **59**, 1140–1151.
58. Shigemura Y, Akaba S, Kawashima E, *et al.* (2011) Identification of a novel food-derived collagen peptide, hydroxyprolylglycine, in human peripheral blood by pre-column derivatisation with phenyl isothiocyanate. *Food Chem* **129**, 1019–1024.
59. Jimi S, Koizumi S, Center NGIR, *et al.* (2021) Collagen-derived dipeptide pro-hyp administration accelerates muscle regenerative healing accompanied by less scarring after wounding on the abdominal wall in mice. *Sci Rep* **11**, 1–12.
60. Koopman R, Caldow MK, Ham DJ, *et al.* (2017) Glycine metabolism in skeletal muscle: implications for metabolic homeostasis. *Curr Opin Clin Nutr Metab Care* **20**, 237–242.
61. Sun K, Wu Z, Ji Y, *et al.* (2016) Glycine regulates protein turnover by activating protein kinase B/mammalian target of rapamycin and by inhibiting MuRF1 and atrogin-1 gene expression in C2C12 myoblasts. *J Nutr* **146**, 2461–2467.
62. Vijayan DK, Sreerekha PR, Dara PK, *et al.* (2021) Antioxidant defense of fish collagen peptides attenuates oxidative stress in gastric mucosa of experimentally ulcer-induced rats. *Cell Stress Chaperones* **27**, 45–54.
63. Chen Y-P, Liang C-H, Wu H-T, *et al.* (2018) Antioxidant and anti-inflammatory capacities of collagen peptides from milkfish (Chanos chanos) scales. *J Food Sci Technol* **55**, 2310–2317.

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