Cinnamon supplementation improves Blood pressure in type 2 diabetic patients: a systematic review and meta-analysis of randomized controlled trials

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Cinnamon supplementation improves Blood pressure in type 2 diabetic patients: A systematic review and meta-analysis of randomized controlled trials

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Abstract:

Background: Some studies have suggested that consumption of some herbal medicines may improve blood pressure. The present systematic review and meta-analysis was conducted to assess the efficacy of cinnamon supplementation on blood pressure in type 2 diabetic patients.

Methods: The systematic search was undertaking using several online databases (PubMed, Embase, Scopus and Web of Sciences) to identify randomized controlled trials (RCTs) investigating the effect of cinnamon supplementation on systolic blood pressure (SBP) or diastolic blood pressure (DBP) in type 2 diabetic patients that were published up until 10 December 2019. Potential publication bias was assessed using the Egger regression test.

Results: Five full-text articles were included in this meta-analysis. Pooled results of the meta-analysis on 332 participants indicated a significant reduction in SBP and DBP following cinnamon administration. No publication bias was found.

Conclusion: The results of the present study suggested that cinnamon might be effective in improving blood pressure in type 2 diabetic patients.

Keywords: Cinnamon, Blood pressure, Cardiovascular, Nutrition, Meta-analysis

1 Introduction

Hypertension is one of the most common adult chronic disorders and affects approximately 25% of the adult population and 8.5% of diabetic patients globally. The complications of hypertension is also estimated to cause 7 million deaths annually (1, 2). There is an urgent need to improve the

control blood pressure in hypertensive patients, as guideline recommended targets are often not adequately attained using current drug treatment. It has been reported that only approximately 50% of people with HTN have controlled BP (less than 140/90 mmHg), whereas more than 13% of patients have systolic (SBP) >160 mmHg and/or diastolic blood pressure (DBP) >100 mmHg (3). Moreover, the complications and adverse effects of antihypertensive drugs as well as their high costs appear to reduce the adherence to treatment of hypertensive patients (4). Hence alternative, or complementary medicines, for hypertension are receiving some interest.

Recently, there has been more attention focused on using nutritional and bioactive compounds for prevention of chronic illnesses and enhancement of well-being (5). Cinnamomum (Cinnamon) is a genus from the Lauraceae family of plants and is considered to be a dietary herbal medicine (6). Cinnamon has been reported to have numerous properties, including antidiabetic, anti-inflammatory, lipid-lowering, antioxidant, antimicrobial, and anticancer properties (7). It has also been suggested that it could be used as an herbal remedy for the treatment of several disorders including cardiovascular diseases, type 2 diabetes, chronic digestive difficulties, and Alzheimer's disease (8). Some previous studies have reported that cinnamon supplementation can significantly reduce systolic and diastolic blood pressure in the subjects with type 2 diabetes mellitus (9-11). The results of some other studies have not been consistent (12, 13). Therefore, the effect of cinnamon intake on the systolic and diastolic blood pressure remains unclear. Disagreements among the findings of published trials might be due to the differences in dosage of cinnamon used, study design, characteristics of study populations, and duration of the trials.

The present meta-analysis aimed to assess the effect of cinnamon supplementation on the blood pressure and anthropometric parameters as known critical risk factors for hypertension.

2 Methods:

The present meta-analysis was conducted as recommended by the Preferred Reporting Items for Systematic reviews and Meta-Analyses (*PRISMA*) (14).

2.1 ***Systematic search***

Our systematic search was undertaken using several online databases: PubMed, Embase, Scopus and Web of Sciences, to identify randomized controlled trials (RCTs) investigating the effects of cinnamon supplementation on blood pressure in type 2 diabetic patients for all potential publication from the earliest available time up to 10th December 2019. The following search strategy was used without any time or language limitation: [Keywords for supplement] AND [Keywords for outcomes] AND [Keywords for disease] AND [Keywords for study design]. To complete search process, Google scholar, Cochrane Library and list of relevant references were then hand-searched to identify eligible papers that might have been missed.

2.2 ***Inclusion and exclusion Criteria***

Relevant articles were selected for meta-analysis that met the following inclusion criteria: (1) being a RCT, (2) using cinnamon as supplement in confirmed type 2 diabetic patients, (3) reporting sufficient data for baseline and final trials of SBP or/and DBP in both cinnamon and control groups, (4) human studies and (5) English languages publication. Unpublished data and gray literature, such as conference abstracts, book chapters, editorials and letters and the like,

studies conducted on other types of diabetes or related disorders, healthy and just glucose-intolerant subjects were excluded.

2.3 ***Data extraction***

Eligible articles were abstracted by two reviewers separately and following information were extracted using a pre-defined form: last name of first author, publication year, country, sample size, age of participants, target population, intervention duration, dose of cinnamon, type of the supplement and mean changes / standard deviation (SD) of the outcomes. Net changes were calculated by subtracting pre-test from post-test. Also, SD for changes was obtained using the following formula: $\sqrt{([(\text{SD pre})^2 + (\text{SD post})^2] - [2r \times \text{SD pre} \times \text{SD post}])}$ (15), with considering coefficient correlation (r) as 0.5. Furthermore, any doubts were clarified through a discussion with the third reviewer.

2.4 ***Risk of bias assessment***

The Cochrane Collaboration risk of bias Tool (16) was used to qualify the included RCTs based on following criteria: “randomization generation, allocation concealment, blinding of participants and outcome assessors, incomplete outcome data, selective outcome reporting and other sources of bias”. Any discrepancy was discussed between the two reviewers and resolved by corresponding author.

2.5 ***Statistical analysis***

STATA software (version 13) was used to analyze the data. Due to a high degree of heterogeneity among the included RCTs, random-effects model was used to calculate the mean

difference (MD) and its 95% confidence intervals (CI). To identify statistical heterogeneity, I^2 (high ≥ 50%, low < 50%) and *P*-value (significant < 0.05) were used. Random-effects meta-regression was applied by mean age of participants, duration of intervention and dose of cinnamon to seek the potential sources of statistical heterogeneity between studies. Furthermore, subgroup analyses by treatment duration (2 months, 3 months), baseline SBP (> 134 mmHg, < 134 mmHg) and dosage (>1.7 gram/day, <1.7 gram/day) were performed. Also, Sensitivity analysis was undertaken to evaluate the impact of each study on the pooled results. Egger's test was applied to detect potential publication bias (17). A $P < 0.05$ was considered as statistically significant.

3 Results:

3.1 ***Literature search***

As shown in Figure 1, 865 papers regarding the effect of cinnamon supplementation on blood pressure were identified from online databases. Of these, 430 duplicate papers were excluded; 435 articles remained for title/abstract screening and 420 records were removed. Then, at the final step, 15 articles were assessed for eligibility and full-text screening. After full-text assessment, 5 articles were included in the present meta-analysis.

3.2 ***Study characteristics***

Table 1 outlines the main characteristics of the included trials. Five trials were published from 2010 to 2016, which were conducted in Asia and Europe. Study sample sizes ranged from 19 to 49 participants in the intervention group and 18 to 50 subjects in the controls. A total number of participant that was included in this meta-analysis was 332. The minimum and maximum mean age of the subjects in the treatment group was 54.9 – 61.7 years, respectively.

The duration of the interventions was 2 months in three studies and 3 months in the two other studies. The minimum dose of cinnamon supplementation among the studies was 1.2 gram/day and the maximum was 3 grams/day. All of the included trials used oral cinnamon as the supplement. The methodological quality and risk of bias of the included RCTs based on authors' judgment is shown in Table 2.

3.3 *Effect of cinnamon supplementation on blood pressure*

Pooled effects of 5 datasets (Figure 2) revealed a significant reduction in SBP (MD = -0.53, 95% CI = [-1.03, -0.02], P = 0.04, I^2 = 79.8%) following cinnamon administration compared with the control participants. Furthermore, high heterogeneity was decreased following subgroup analysis (Table 3) by baseline SBP (> 134 mmHg), treatment duration (2 months) and doses less than 1.7 gram/day.

Moreover, from the current meta-analysis we found that DBP was significantly affected by cinnamon supplementation (MD = -0.70, 95% CI = [-1.30, -0.07], P = 0.03, I^2 = 86.0%) in type 2 diabetic patients as compared with the control group. Also, high statistical heterogeneity decreased following subgroup analyses (Table 3) by baseline SBP (> 134 mmHg), intervention duration (3 months) and doses less than 1.7 gram/day.

3.4 *Meta-regression:*

As shown in Table 4, meta-regression of SBP and DBP could not identify the potential source of heterogeneity by mean age, duration and dose of cinnamon.

3.5 *Publication bias and sensitivity analysis*

No significant publication bias was found for both SBP (P = 0.60) and DBP (P = 0.78). Also, impact of each trial on the pooled result was checked and showed that the results of the present study were not affected by removing one study at a time.

Discussion:

To the best of our knowledge, this is the first study to review the available literature and recent randomized clinical trials (RCTs) regarding the effects of cinnamon supplementation on blood pressure in diabetic patients as a meta-analysis. The results of this study demonstrated that cinnamon supplementation significantly reduced systolic blood pressure. But there was a high heterogeneity among studies regarding the effects of cinnamon on SBP and this was reduced by sub-group analysis and considering different features of the included studies such as duration, dose of supplementation, and baseline BP. Moreover, patients with type 2 diabetes receiving cinnamon supplement also showed significant improvements in DBP compared with the control group.

Many studies have evaluated and confirmed the hypotensive effects of cinnamon (9, 18, 19). Our results were also in line with the results of a study by Akilen et al. as they demonstrated that cinnamon supplementation could significantly decrease SBP in diabetic patients (10). Furthermore, our results also confirmed the results of a study by Sengsuk et al. regarding the blood pressure-lowering effects of cinnamon (20).

A possible explanation for the effects of cinnamon on BP might be related to its active components, including: cinamaldehyde, cinnomic acid, eugenol, and coumarin (19). Some of the flavonoids and phytochemicals in cinnamon might cause endothelial relaxation. Cinnamon has

been reported to increase the levels of cyclic guanosine monophosphate (cGMP) that can mediate the nitric oxide (NO) production and help the relaxation of vascular smooth muscle (21). In addition, active ingredients of cinnamon might exert an anti-hypertensive effects through their cholinergic and diuretic properties (22, 23). Another mechanism regarding the anti-hypertensive effects of cinnamon is related to its effects as an antioxidant and hypoglycemic agent that both are completely pertinent to the improvement of endothelial dysfunction (10, 24). In diabetic patients, these effects may be more pronounced. Normal vascular contraction through normal Ca^{2+} influx via insulinotropic effects of cinnamon is the main cause of hypotensive effect of cinnamon in diabetic patients (25).

Cinnamon may also have BP-lowering properties through peripheral vasodilation (26). Furthermore the potential beneficial effect of cinnamon may be explained by its effect on increasing eGFR. The damaging effects of hypertension may in part be due to its effects on the kidney which might be attenuated by cinnamon ingestion (27). In one study, the effects of cinnamon on reducing vascular cell-adhesion molecule-1 and SICAM-1 was reported that was mediated through inhibiting the expression of endothelial factors at the transcriptional level especially by decreasing mRNAs (28). Additionally, it seems that cinnamon might mediate antihypertensive effects by improving arterial wall compliance (29). It can also enhance NO production according to one previous study (30). Moreover, cinnamon can alleviate hyperuricemia (31, 32), resting tachycardia, nerve traffic, and high plasma norepinephrine (33), that may all be associated with better BP control.

Another important point in the current analysis is about the difference between studies regarding the cinnamon dose that was evaluated by sub-group analysis. It was shown that the hypotensive effects of cinnamon on SBP and DBP were significant at doses of <1.7 g/day and >1.7 g/day,

respectively. Finding an exact dose of cinnamon for improving cardio-metabolic factors may be challenging, especially because of the effects of cinnamon on inhibiting blood clotting due to its coumarin content and considering the fact that many diabetic or cardiovascular patients are receiving anticoagulants (34). Hence, interpreting the dose-effect of cinnamon is not easy and should be interpreted with caution. Further investigations are warranted to clarify the exact safe dose of cinnamon for controlling BP.

On the other hand, effects of cinnamon on reducing SBP was more pronounced in studies done for shorter durations (in 2 months compared with 3 months). This is in accordance with the results of the study done by Sengsuk et al. (20). It is unclear whether this is due to compliance, or tachyphylaxis.

Another point to mention is that the effect of cinnamon supplementation on SBP is more pronounced in those with higher baseline SBP, as reported by Azimi and her colleagues (18).

It is also important to mention that the results of the current meta-analysis was not determined by any single study as assessed by sensitivity analysis.

The results of the current meta-analysis pooled the available RCTs according to the effects of cinnamon on BP control. However, this study has several weakness and the results should be interpreted with caution. It only includes five studies, and, there was high degree of heterogeneity among studies. However, the sub-group analysis considered the differences among studies including dose, duration, and baseline BP values and their effects on changes in BP following cinnamon supplementation, and another strength of the current study, was the inclusion of trials that were not restricted to a specific country or region and our results could generalize to the different ethnic groups.

Conclusion:

To sum up, in this systematic review and meta-analysis, oral cinnamon supplementation could reduce BP. More RCTs with various doses are recommended to be able to draw a final conclusion. Additionally, more animal or human studies are warranted to elucidate the exact safe and effective dose of cinnamon supplement for controlling BP in cardio-metabolic or diabetic patients.

Funding and conflict of interest:

None to declare.

Author contribution:

RJ and ZS contributed to study concept and design. RJ, MM, SPM and ZS contributed to literature search, data collection and analysis. RJ, MM, GAF and ZS contributed to drafting and reviewing the final manuscript. All authors read and approved the final manuscript.

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Table 1. Demographic characteristics of the included RCTs

First author (year)	Publication year	Country	Sample size (intervention / control)	Intervention groups age, mean (SD)	Population	Duration	Dose (gram/day)	Type of supplement
Akilen et al.	2010	United Kingdom	30 / 28	54.9 (10.14)	T2DM	3 months	2	Capsule
Wainstein et al.	2011	Israel	29 / 30	61.7 (6.3)	T2DM	3 months	1.2	Capsule
Vafa et al.	2012	Iran	19 / 18	54.11 (10.37)	T2DM	2 months	3	Capsule
Sengsuk et al.	2016	Thailand	49 / 50	57.2 (1.1)	T2DM	2 months	1.5	Capsule
Azimi et al.	2016	Iran	40 / 39	54.15 (1)	T2DM	2 months	3	Powder

Abbreviations: T2DM: Type 2 diabetes mellitus

Table 2. Methodological quality assessment of the included studies

Study	Sequence generation	Allocation concealment	Blinding	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other biases
Sengsuk (2016)							
Azimi (2016)							
Vafa (2012)							
Wainstein (2011)							
Akilen (2010)							

 : Low risk,  : High risk and  : Unclear

Table 3. Subgroup analyses of SBP and DBP based on publication year, intervention duration and dose

Subgroup		**Effect size**	**MD**	**95% CI**	**Overall *P***	**Heterogeneity (I^2 / *P*)**
SBP						
Baseline SBP	> 134 mmHg	2	-0.463	-0.779, -0.147	0.004	0.0 % / 0.896
	< 134 mmHg	3	-0.575	-1.587, 0.437	0.265	89.9 % / < 0.0001
Intervention duration	3 months	2	-1.062	-2.201, 0.078	0.068	87.9 % / 0.004
	2 months	3	-0.239	-0.509, 0.030	0.082	0.20 % / 0.367
Dose	> 1.7 g/day	3	-0.575	-1.587, 0.437	0.265	89.9 % / < 0.0001
	< 1.7 g/day	2	-0.779	-0.779, -0.147	0.004	0.0 % / 0.896

DBP						
Baseline SBP	> 134 mmHg	2	-0.292	-0.606, -0.022	0.068	0.0 % / 0.373
	< 134 mmHg	3	-0.976	-1.940, -0.012	0.047	88.4 % / < 0.0001
Intervention duration	3 months	2	-0.400	-0.979, 0.179	0.176	59.6 % / 0.116
	2 months	3	-0.868	-1.886 0.151	0.095	91.3 % / < 0.0001
Dose	> 1.7 g/day	3	-0.976	-1.940, -0.012	0.047	88.4 % / < 0.0001
	< 1.7 g/day	2	-0.292	-0.606, 0.022	0.068	0.0 % / 0.373
MD: mean difference, CI: confidence intervals, SBP: systolic blood pressure, DBP: diastolic blood pressure						

Table 4. Meta-regression of SBP and DBP by mean age, duration and dose

Covariates	**Coefficient**	***P* value**	**95 % CI**	**Tau^2**
SBP, overall Tau^2 = 6.75				
Mean age	0.73	0.40	-6.04, 7.50	7.76
Duration	1.95	0.50	-23.46, 27.37	8.85
Dose	5.44	0.23	-21.71, 32.61	4.176
DBP, overall Tau^2 = 8.92				
Mean age	-0.24	0.66	-1.90, 1.40	11.06
Duration	-0.39	0.90	-10.42, 9.63	11.85
Dose	2.46	0.20	-2.32, 7.26	6.25
CI: confidence intervals, SBP: systolic blood pressure, DBP: diastolic blood pressure				

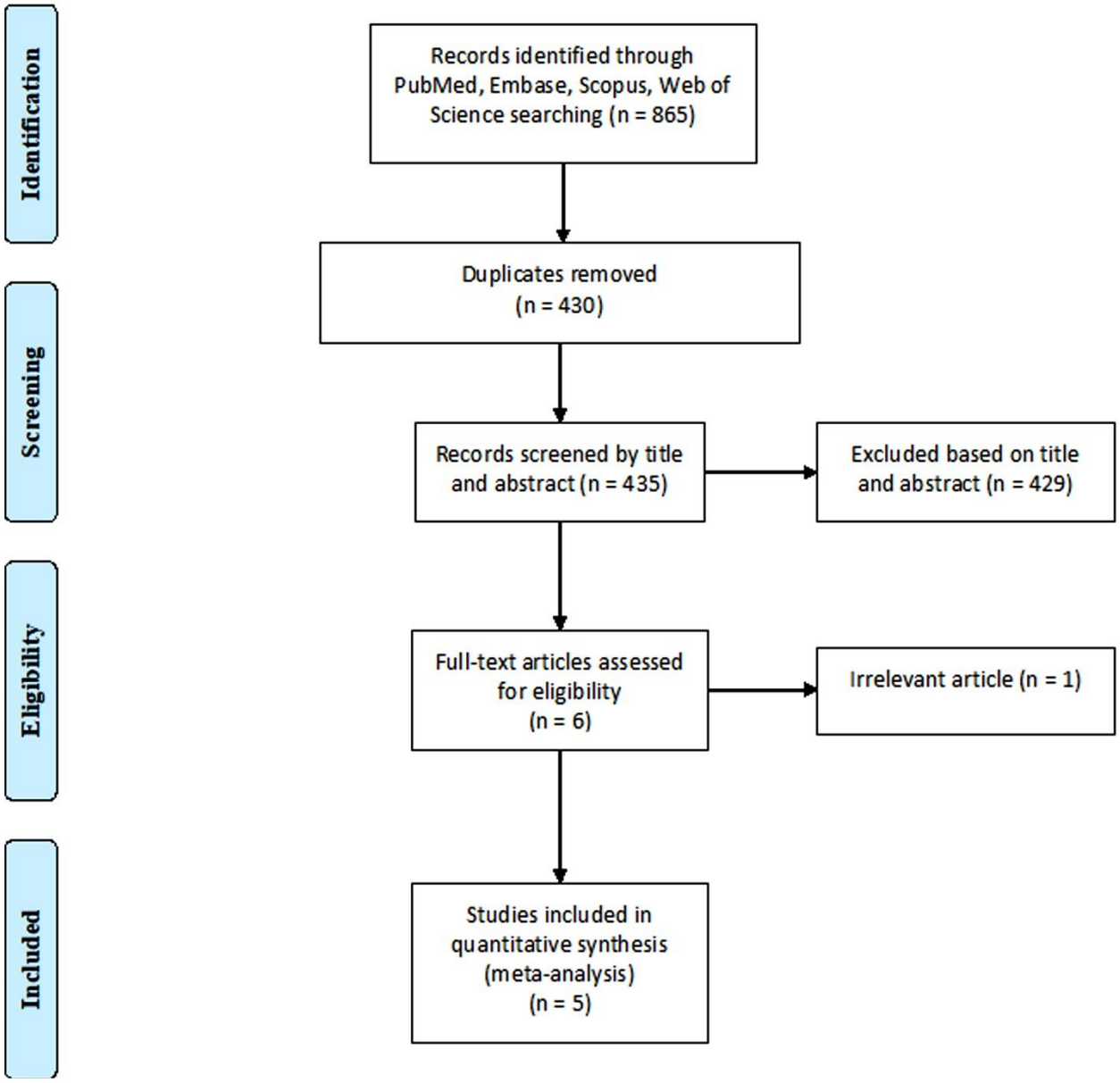
Identification
Screening
Eligibility
Included
Records identified through PubMed, Embase, Scopus, Web of Science searching (n = 865)
Duplicates removed (n = 430)
Records screened by title and abstract (n = 435)
Excluded based on title and abstract (n = 429)
Full-text articles assessed for eligibility (n = 6)
Irrelevant article (n = 1)
Studies included in quantitative synthesis (meta-analysis) (n = 5)

Figure 1. Flow diagram of data selection process

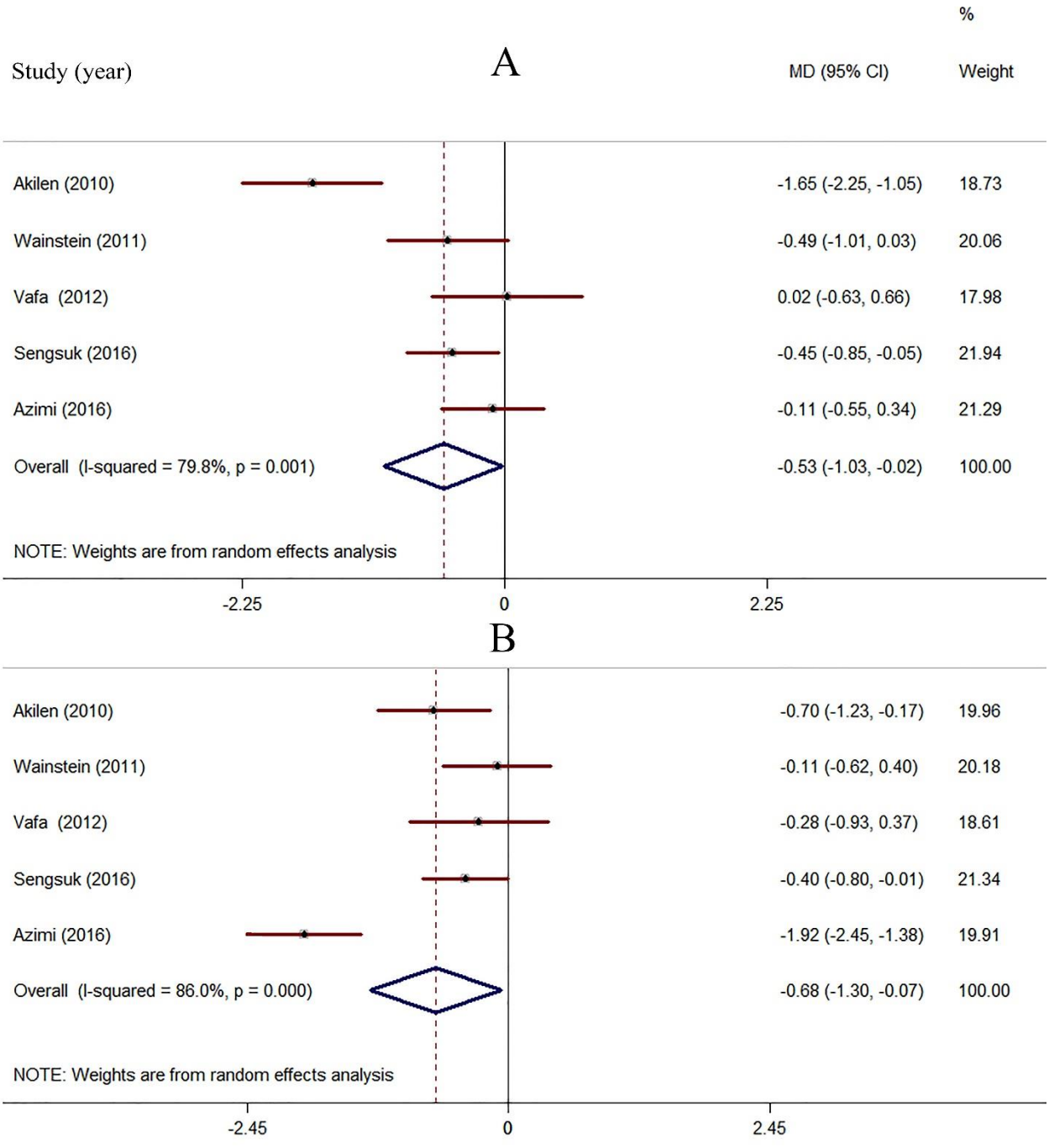

Figure 2. Forest plot detailing MDs and 95% CIs for the meta-analyses of SBP (A) and DBP (B)