

The correlation of blood pressure variability and cognitive function in hypertension patients: a meta-analysis

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Abstract

Background: Cognitive impairment is very common in patients with hypertension, it's necessary to conduct a meta-analysis to evaluate the association of cognitive function and blood pressure variability in patients with hypertension, to provide insights into the clinical management of hypertension and cognitive impairment. **Methods:** We searched PubMed et al databases for the case-control studies on the association between blood pressure variability and cognitive function up to July 15, 2021. Two researchers independently screened the literature and retrieved the data. RevMan 5.3 was used for data meta-analysis **Results:** A total of 13 studies involving 2754 patients were included. Meta-analysis indicated that 24-hour systolic [MD= 3.54, 95% CI (2.48, 4.60)] and diastolic [MD=2.43, 95%CI (1.55, 3.31)] blood pressure variation coefficient in the CI group were significantly higher than that of no CI group (all P<0.05). Standard deviation of systolic [MD=2.20, 95% CI (0.27, 4.13)] and diastolic [MD=1.79, 95% CI (0.80, 2.79)] blood pressure variation in the CI group were significantly higher than that of no CI group (all P<0.05). Mean systolic [MD=3.73, 95% CI (0.92, 6.53)]and diastolic [MD = 5.41, 95% CI (0.42, 10.40)] blood pressure variation in the CI group were significantly higher than that of no CI group (all P<0.05). There were no statistically significant differences in the morning peak systolic [MD=7.85,95% CI (-1.30,17.01)] and diastolic [MD=4.44,95% CI (-6.00, 14.89)] blood pressure drop between the CI group and no CI group(all P>0.05). **Conclusion:** Cognitive impairment in hypertensive patients is closely associated with increased blood pressure variability, and clinical medical staff should pay attention to the management of blood pressure variability in hypertensive patients to reduce the development of cognitive impairments.

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statistically significant differences in the morning peak systolic [MD=7.85,95% CI (-1.30,17.01)] and diastolic [MD=4.44,95% CI (-6.00, 14.89)] blood pressure drop between the CI group and no CI group(all P>0.05).

Conclusion: Cognitive impairment in hypertensive patients is closely associated with increased blood pressure variability, and clinical medical staff should pay attention to the management of blood pressure variability in hypertensive patients to reduce the development of cognitive impairments.

Keywords: hypertension; blood pressure; cognitive function; elder; treatment; care; meta-analysis

Review criteria: how did you gather the information you considered in your review?

We searched PubMed, Cochrane library, Web of Science, China National Knowledge Infrastructure(CNKI), Wanfang, China Biology Medicine disc (CBM), and Weipu database for the study on the association between blood pressure variability and cognitive function. Retrieval time limit was from the date of establishment of each database to July 15, 2021. Two researchers independently searched and screened relevant documents. The search results were imported into Endnote for double-checking, and then the initial screening was carried out based on the abstracts of the literature to eliminate irrelevant or unusable documents.

Message for the clinic: what is the ‘take-home’ message for the clinician?

The decline in cognitive function is related to the increase of blood pressure variability

Background

Hypertension is a syndrome with elevated blood pressure as the main clinical manifestation, with or without a variety of cardiovascular risk factors, which can cause a variety of cardiovascular and cerebrovascular diseases, and can even cause heart, brain, kidney and other organ failures¹. Elderly patients are the population with a high incidence of hypertension². The pathogenesis of hypertension is not clear. Related factors of hypertension include thickening of the arterial wall and decreased elasticity³. Studies^{4,5} have shown that blood pressure fluctuations and pulse pressure index changes in elderly hypertensive patients can cause cognitive impairment(CI), yet the potential mechanisms remain unclear.

CI refers to a series of pathological phenomena caused by abnormal brain functions related to learning, memory and thinking judgment⁶. It has significant physical, psychological, social and economic consequences for patients, caregivers and health care systems, and with the aging of the population, the burden of disease has increased exponentially^{7,8}. Studies^{9,10} have shown that the probability of CI turning into dementia is extremely high, and the progress is extremely fast. According to statistics^{11,12}, China currently has more than 10 million dementia patients, becoming one of the fastest growing countries in the world, resulting in high economic and social resource burdens. Studies¹³⁻¹⁵ have shown that persistent hypertension is an important risk factor for cognitive impairment. At the same time, more and more scholars have found that there is a certain correlation between blood pressure variability and cognitive function, but the results of the study are not consistent. Therefore, we aimed to conduct a meta-analysis to explore the association between blood pressure variability and cognitive function, and to provide reliable evidence support for the early intervention of hypertension and the prevention of CI.

Methods

We tried to conduct and report this meta-analysis in comply with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)¹⁶.

Literature search

We searched PubMed, Cochrane library, Web of Science, China National Knowledge Infrastructure(CNKI), Wanfang, China Biology Medicine disc (CBM), and Weipu database for the study on the association between blood pressure variability and cognitive function. The search terms included "blood pressure variability" OR "BPV" OR "ambulatory blood pressure" and "cognitive function" OR "cognitive functioning". The search was carried out by combining subject words and free words. Retrieval time limit was from the date of establishment of each database to July 15, 2021.

Inclusion and exclusion criteria

The inclusion criteria for this meta-analysis were: Study type: a publicly published case-control study on blood pressure variability and cognitive function; Research population: patients aged 18 to 80 years old and diagnosed with essential hypertension; Control: CI group and no CI group; The outcome indicators included blood pressure et al; Language: Chinese or English article. The exclusion criteria of this meta-analysis were: patients with severe cardiovascular diseases and other major diseases; articles that repeatedly publish or use the same data; studies with incomplete data.

Literature screening and data extraction

Two researchers independently searched and screened relevant documents. The search results were imported into Endnote for double-checking, and then the initial screening was carried out based on the abstracts of the literature to eliminate irrelevant or unusable documents. After completion, the researchers collected and recorded following information, including the author, publication year, country, age, sample size, outcome indicators, findings.

Quality Evaluation

The type of studies included in this meta-analysis was case-control study, so it was scored according to the Newcastle-Ottawa Scale (NOS) Literature Quality Evaluation Scale¹⁷. The full scale of the scale was 10 points. The evaluation items mainly included three items: population selection, comparability, and exposure. If the quality score was less than 5, it indicated a high risk of bias and needs to be excluded. Disagreements in the evaluation results were resolved through further discussion.

Statistical processing

We used RevMan 5.3 for data meta-analysis. Relevant indicators were visually displayed in forest plots, and funnel plots were used to detect the populations. Continuous variables were represented by the mean difference (MD) and its 95% confidence interval (CI). If $I^2 \leq 50\%$ or $P > 0.10$, the heterogeneity of the study was small, and the fixed-effects model was adopted; if $I^2 > 50\%$ or $P \leq 0.10$, the random-effects model was adopted. $P < 0.05$ indicated the differences between two groups were statistically different.

Results

Literature search results

172 documents were obtained by searching the database through the computer. After eliminating duplicates and irrelevant documents, 40 articles were included for further intensive reading of the full text, and finally 13 articles¹⁸⁻³⁰ were included in this meta-analysis. The study selection process was indicated in Figure 1.

Figure 1 PRISMA flow diagram of study selection

The basic characteristics of the included literature and the methodological quality evaluation

In the included 13 case-control studies, there were a total of 2754 patients with hypertension, including 1444 patients in the CI group and 1310 patients in the no CI group. The basic characteristics of the included literature were shown in Table 1. We conducted methodological quality evaluation based on the NOS evaluation scale, and the scores of each literature were all above 5 points, and the quality of the articles were good, see Table 2 for details.

Table 1 The characteristics of included studies

Table 2 The NOS quality score of included studies

Synthesized outcomes

24-hour blood pressure variation coefficient A total of 10 studies^{18,21-28,30} analyzed the coefficient of variation of 24-hour systolic and diastolic blood pressure, a total of 2163 cases were reported, including 1127 cases in the CI group and 1036 cases in the no CI group. The heterogeneity analysis of the coefficient of variation of

systolic blood pressure showed that there was heterogeneity among the studies ($I^2 = 99\%$, $P < 0.001$), so the random effects model was selected. The results of meta analysis showed that the differences between the two groups had statistical significance [MD= 3.54, 95% CI (2.48, 4.60), $P < 0.001$], indicating that the coefficient of variation of systolic blood pressure increased significantly in the CI group(Figure 2A). The results of the analysis of the coefficient of variation of diastolic blood pressure showed that there was heterogeneity among the studies ($I^2 = 98\%$, $P < 0.001$), and the random effects model was used. The results of meta-analysis showed that the difference between the two groups was statistically significant [MD=2.43, 95%CI (1.55, 3.31), $P < 0.001$], indicating the coefficient of variation of diastolic blood pressure in the CI group was significantly increased(Figure 2B).

Standard deviation of blood pressure A total of four studies^{18,23,24,29} included in this meta-analysis analyzed the associations between blood pressure standard deviation and cognitive function, with a total of 396 cases, including 185 cases in the CI group and 211 cases in the no CI group. The meta-analysis of systolic blood pressure standards showed that there was heterogeneity among the studies ($I^2 = 81\%$, $P = 0.001$), so the random effects model was chosen. Meta-analysis indicated the difference between the two groups was statistically significant [MD=2.20, 95% CI (0.27, 4.13), $P = 0.03$], indicating that the standard deviation of systolic blood pressure increased in the CI group(Figure 2C). The qualitative analysis of diastolic blood pressure standard deviations showed that there was heterogeneity among the studies ($I^2 = 61\%$, $P = 0.05$), so the random effects model was used. The results of meta-analysis showed that the difference between the two groups was statistically significant [MD=1.79, 95% CI (0.80, 2.79), $P < 0.001$], and the standard deviation of diastolic blood pressure of patients in the cognitive impairment group was increased(Figure 2D)

Figure 2 The forest plots of synthesized outcomes

Mean blood pressure A total of 11 studies^{18-20,22-26,28-30} reported the mean blood pressure with involvement of 1874 patients, including 821 cases in the CI group and 1053 cases in the no CI group. There was heterogeneity between the studies in the mean systolic blood pressure ($I^2 = 74\%$, $P < 0.001$), so the random effect model was selected. The combined results showed that the difference between the two groups was statistically significant [MD=3.73, 95% CI (0.92, 6.53), $P = 0.009$], indicating that the average systolic blood pressure of the CI group was higher than that of the no CI group(Figure 3A). There was heterogeneity among the studies in the mean diastolic blood pressure ($I^2 = 97\%$, $P < 0.001$). Therefore, the random effects model was selected. The meta-analysis results showed that the difference between the two groups was statistically significant [MD = 5.41, 95% CI (0.42, 10.40), $P = 0.03$], indicating that the mean diastolic blood pressure of the CI group was higher than that of the no CI group(Figure 3B).

Morning peak blood pressure drop A total of two studies^{25,26} reported that morning peak blood pressure with involvement of 357 patients, including 155 cases in the CI group and 202 cases in the no CI group. There was significant heterogeneity in the morning peak systolic($I^2 = 86\%$, $P = 0.008$) and diastolic($I^2 = 93\%$, $P < 0.001$) blood pressure drop, so random effects models were applied. The meta-analyses indicated that there were no statistically significant differences in the morning peak systolic [MD=7.85,95% CI(-1.30,17.01), Figure 3C] and diastolic[MD=4.44,95% CI(-6.00, 14.89), Figure 3D] blood pressure drop between the CI group and no CI group(all $P > 0.05$).

Figure 3 The forest plots of synthesized outcomes

Sensitivity analysis and publication bias

The sensitivity analysis of the included studies was carried out, each included study was removed one by one to see the changes in overall results. And we have found that no results were changed by removing any single study. The funnel plots and Egger's tests were performed for the synthesized outcomes of the included study to detect publication bias, and the results showed that there were no publication bias (all $P > 0.05$, Figure 4).

Figure 4 The funnel plots of synthesized outcomes

Discussions

Long-term hypertension can cause cerebral arteriosclerosis and cerebral blood circulation disorders, cause brain tissue function damage, and is related to cognitive dysfunction³¹. This meta-analysis has included thirteen case-control studies on the correlation between blood pressure variability and cognitive function, and the quality of the included literature is high. The synthesized outcomes have showed that the increase in blood pressure coefficient of variation is correlated with cognitive dysfunction, and cognitive function is also correlated with 24-hour blood pressure standard deviation and average blood pressure, but there is no correlation with the morning peak of blood pressure. The increase of blood pressure variability will increase the risk of cognitive dysfunction and adversely affect the prognosis of hypertensive patients³². It is worth noting that the large heterogeneity of the analysis indicators in this study may be related to the sample size and age or the inconsistent follow-up time of each study. Therefore, the results of this meta-analysis should be treated with cautions.

Short-term and long-term blood pressure variability are independently related to the development, progression, and severity of heart, blood vessel, and kidney damage, and are associated with an increased risk of cardiovascular events and death^{33,34}. Blood pressure variability has been considered that it has a better predictive effect on cardiovascular events than the average blood pressure [20]. Cognitive dysfunction covers the entire progression from mild cognitive impairment to dementia, and it is also a major problem in the prevention and treatment of hypertension complications. There has been a large amount of evidence in the past that hypertension is the most common risk factor for cognitive impairment, and recent studies^{35,36} has shown that blood pressure variability has a close clinical relationship with cognitive function. At present, the mechanism between blood pressure variability and cognitive function is not clear, but some scholars believe that it may be related to the white matter. Blood pressure variability is related to target organ damage, including white matter that has nothing to do with the 24-hour average blood pressure value, leading to the occurrence of white matter hyperintensity, and white matter lesions are the inducing conditions for cognitive impairment³⁷. The presence of high-strength lesions and cavities around the ventricles of the elderly with asymptomatic hypertension suggests the relationship between diurnal blood pressure changes and cerebrovascular injury, and cerebrovascular injury will further accelerate the progress of cognitive dysfunction, which is also a common predictor of stroke⁸.

Previous study³⁸ has showed that increased systolic blood pressure and increased sleep systolic pressure variability were related to the aggravation of brain atrophy. The aggravation of cerebral arteriosclerosis and cerebral arterial remodeling caused by long-term systolic hypertension may be related to the disorder of brain autoregulation³⁹. It leads to a decrease in cerebral blood flow and aggravation of brain atrophy, which leads to a decline in cognitive function⁴⁰. Recent studies^{41,42} have shown that increased blood pressure variability is associated with stroke and advanced carotid artery remodeling, and carotid artery remodeling can lead to cognitive impairment. The absolute dynamic systolic blood pressure level especially during sleep and the decrease in night systolic blood pressure are important indicators of brain volume and cognitive function. Based on the above results, it is believed that chronic ischemia caused by hypertension may cause the interruption of the day and night changes in blood pressure through the damage of the brain's self-regulatory function, and then the blood pressure does not drop during sleep⁴³. Previous studies^{44,45} have found that systolic blood pressure variability is more predictive of cognitive dysfunction than systolic blood pressure. It's been reported that through community experiments that higher blood pressure variability is related to the decline in cognitive function of patients assessed by simple mental status examination⁴⁶. Although the systolic blood pressure variability cannot predict whether the risk of dementia in the overall population increases, it is not found in the subgroup of individuals without a history of cardiovascular disease⁴⁷. The systolic blood pressure variability is positively correlated with the risk of dementia⁴⁸. Previous studies^{49,50} have reported that high or low blood pressure will lead to cognitive dysfunction. The above conclusions are consistent with the analysis results of this research. Therefore, it is speculated that blood pressure variability reflects the degree of cognitive decline to a certain extent, and can be used as an important clinical reference index in the prognosis of middle-aged and elderly hypertensive patients^{51,52}.

Several limitations in this present meta-analysis should be concerned. Firstly, most included studies were reported from China, therefore population and region biases may be existed, future studies from different

region and populations should be conducted. Secondly, studies have reported that cognitive impairment is related to factors such as pulse pressure index and ankle brachial index. Due to the limitations of the included research data, we cannot further analyze and discuss the correlation of these indicators. Future research should be further conducted to elucidate the correlation between blood pressure related indicators and CI.

Conclusions

In summary, the cognitive function of hypertensive patients is closely related to blood pressure variability. The decline in cognitive function is related to the increase of blood pressure variability, but whether it is related to morning peak blood pressure requires further clinical exploration. This provides certain prevention and treatment significance and prognostic value for clinical hypertension patients, but its specific physiological mechanism and reasons are still unclear, and it needs to be further explored in the future studies.

List of abbreviations

CI: cognitive impairment

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

CNKI: China National Knowledge Infrastructure

CBM: China Biology Medicine disc

MD: mean difference

95% CI: 95% confidence interval

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Figure legends

Figure 1 PRISMA flow diagram of study selection

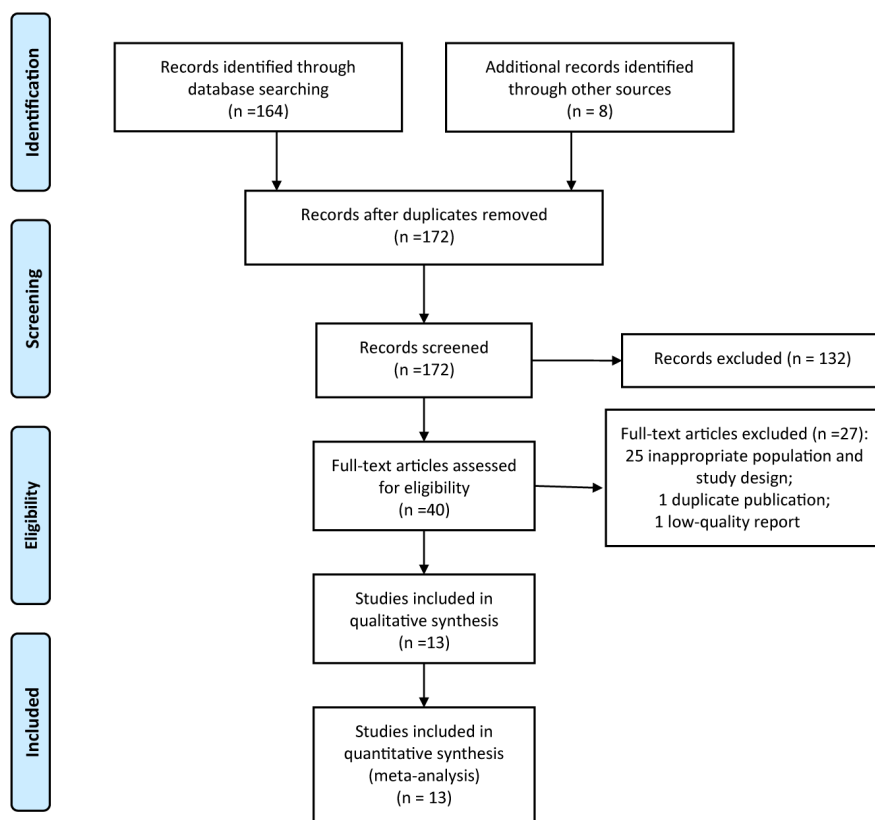
Figure 2 the forest plots of synthesized outcomes

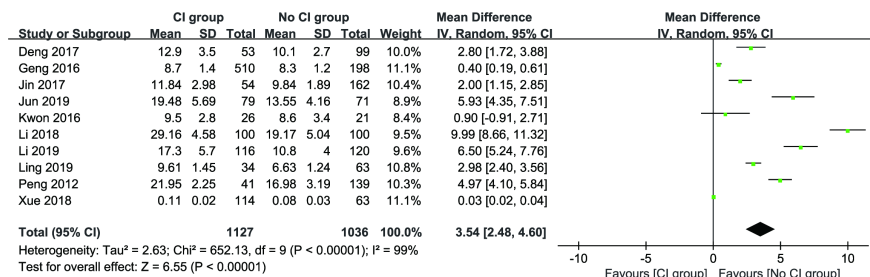
Figure 3 the forest plots of synthesized outcomes

Figure 4 the funnel plots of synthesized outcomes

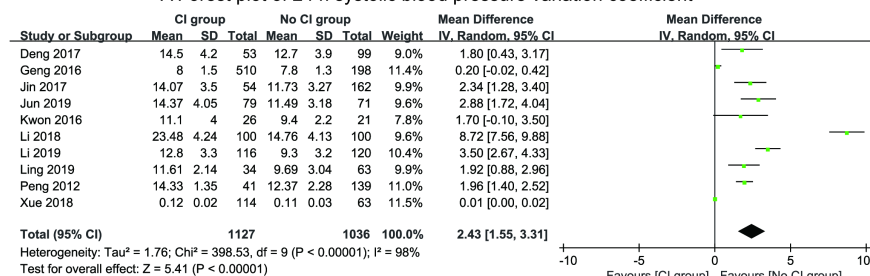
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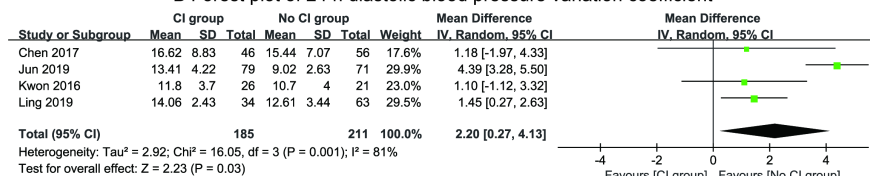




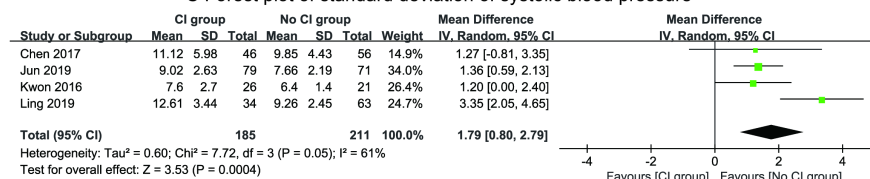
A Forest plot of 24 h systolic blood pressure variation coefficient



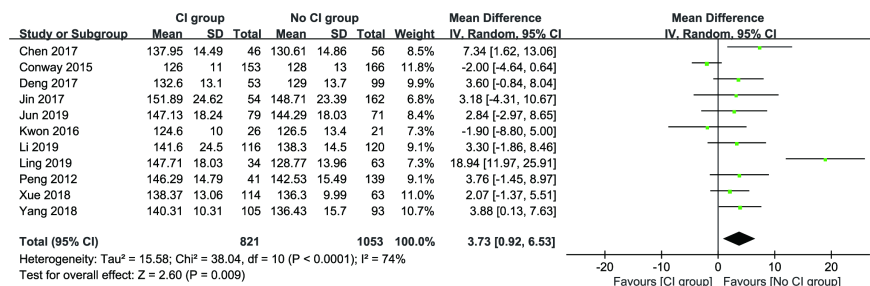
B Forest plot of 24 h diastolic blood pressure variation coefficient



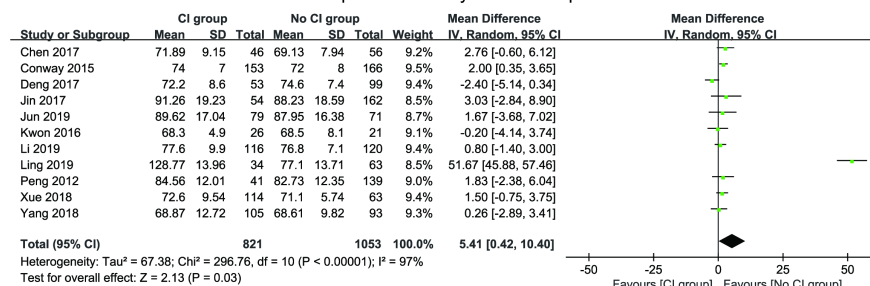
C Forest plot of standard deviation of systolic blood pressure



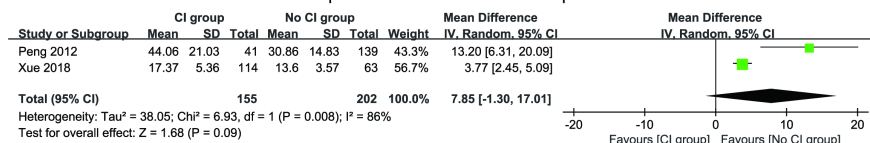
D Forest plot of standard deviation of diastolic blood pressure



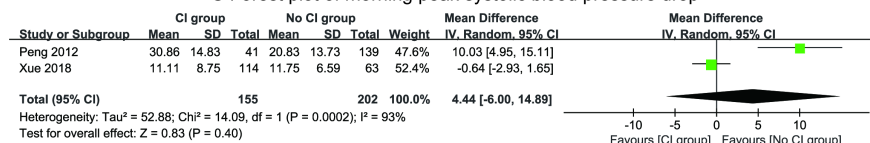
A Forest plot of mean systolic blood pressure



B Forest plot of mean diastolic blood pressure



C Forest plot of morning peak systolic blood pressure drop



D Forest plot of morning peak diastolic blood pressure drop

