Effect of mycophenolate mofetil on blood pressure: a meta-analysis

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Research article

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Abstract

Background: Long-term treatment of immunosuppressive agent have been proved to induce hypertension. The relative efficacy of mycophenolate mofetil (MMF) on blood pressure (BP) is not well known. Identifying the performance of this drug will help to reduce the incidence of the adverse reactions.

Methods: We systematically searched PubMed, MEDLINE, EMBASE, and the Cochrane Library for relevant studies published up to December, 2017. We compared blood pressure levels before and after the MMF treatment including systolic blood pressure and diastolic blood pressure. We used the Newcastle Ottawa scale for the assessment of the quality of studies. Analysis was performed using the statistical software Review Manager Version 5.0 and STATA 14.0.

Result: We retrieved 6 studies with 208 patients. The data extracted were systolic BP (SBP) and diastolic BP (DBP). Study quality was assessed using the method of Jadad, and data were synthesized using a random-effects model and weight mean difference. MMF caused a small reduce in DBP (0.79mmHg, 95% CI, 0.03 to 1.55, P=0.043), with no obvious effect on SBP (0.12mmHg, 95%CI -0.41 to 0.64). In meta-regression, country (china vs. other country), duration of follow-up, percentage of men, and mean age of study participants were proved to be not the contributing factors.

Conclusion: The MMF treatment can slightly reduce DBP, but not affect the SBP, which indicated the cardiovascular safety of this immunosuppressive agent.

Background

As a strong immunosuppressor, Mycophenolate mofetil (MMF) was wildly used in clinical practices. MMF could inhibit proliferation of lymphocyte, promote activated T lymphocyte apoptosis and decreases antibody synthesis, thus resulting in inhibition of inflammatory response [1]. It is proved to be efficient for inflammatory conditions such as IgA nephropathy or systemic lupus erthematodes[1]. It is also recognized as an anti-rejection drug, which is wildly used in preventing solid organ rejection and in vascularized composite allotransplantation.

MMF has become the most common used calcineurin inhibitor after kidney transplantation in the many countries. Many studies have revealed that this long-term treatment of immunosuppressive agent could induce hypertension, therefore increase the risk of cardiovascular diseases [2]. There were many reasons for immunosuppressive agent induced hypertension, including direct cytotoxic effects induced endothelial impairment and dysfunction, and direct contractile effects on vascular smooth muscle cells[3–5]. The clinical trials with most centres also proved that, immunosuppressive agent decreases in effective blood pressure control and subsequent increases in antihypertensive treatments in patients on immunosuppressive regimens.

However, the relationship between MMF and blood pressure is not well studied. Therefore, we preformed this meta-analysis to clarify this question.

Methods

Standard of systematic reviews.

This study is designed and performed according to the “Transparent reporting of systematic reviews and meta-analyses” (PRISMA) guidelines.

Systematic search and study selection.

The systematic literature searches of PubMed, Embase, and Cochrane Library database was conducted from inception to December, 2017 with no language restrictions. We use the following search strategy: (mycophenolate mofetil or mycophenolate sodium or mycophenolic acid or cellcept or myfortic or MMF) AND (hypertension or hypertensive or blood pressure or high blood pressure). All searched articles were carefully examined for additional article to avoid search missing. Articles identified as randomized controlled trials will be read throughout to further screen.

Data extraction and quality assessment.

Two reviewer (Guilan Cao and Qianqian Fan) extracted data from included trials independently. Disagreements were resolved by a third reviewer (Xiaoguang Li). The following data were extracted: first author’s names, years of publication, country, study population, sample size, mean age, year, patient male%, patient BMI and follow-up. Methodological quality of included studies was assessed by the Newcastle-Ottawa Scale (NOS).

Statistical analysis.

The information including study year, country, treatment characteristics (dose, duration, type of formulation), gender ratio, number of participants enrolled, follower-up and outcomes were collected. Besides, the level of SBP and DBP pretherapy and post-treatment were also abstracted. Differences of SBP between before and after MMF treatment were calculated as: $SBP_{\Delta} = SBP_{post\text{-}treatment} - SBP_{pre\text{-}treatment}$; Differences of DBP between before and after MMF treatment were calculated as: $DBP_{\Delta} = DBP_{post\text{-}treatment} - DBP_{pre\text{-}treatment}$; Standard deviations (SDs) of $SBP_{\Delta}$and DBP_{Δ} were calculated using the following formula: SD = square root $[(SD_{pre\text{-}treatment})^2+(SD_{post\text{-}treatment})^2-(2R\times SD_{pre\text{-}treatment}\times SD_{post\text{-}treatmen})$, assuming a correlation coefficient ($R_{SBP} = 0.399$,$R_{DBP} = 0.337$). If SD was not showed directly, SD was estimated using the following formula: SD = SEM×sqrt(n). Heterogeneity among the included studies was assessed by Cochran’s Q statisticc and by calculating the heterogeneity (I^2). Using reported cut-off values (>50% mild, 51% to 75% moderate, and >75% significant), the random-effects model is used when significant heterogeneity was obtained on analysis.

The effect sizes were expressed as weighted mean difference (WMD) and 95% confidence interval (CI). The sensitivity analysis was performed by leave-one-out method to assess the influence of each study on the overall effect size.

Statistical software.

All analyses were conducted using Review Manager 5.3 (Cochrane Editorial Unit, London, UK) software or STATA 14.0 (Stata Corporation, College Station, TX, USA) software.

Results

Study Selection

Based on an initial search with the review of articles and abstracts, a total of 1702 studies were enrolled. After selection of potentially relevant articles, articles were evaluated in detail. Of these studies, only 25 were clinical trials to evaluate the effect of MMF. Furthermore, 19 studies were excluded for: the values of blood pressure pre- and posttreatment were not applicable. After final assessment, 6 studies were included in this meta-analysis (Figure 1, Table S1) [6–11].

Study Characteristics

The characteristics of the included studies were presented in Table S1. Our meta-analysis finally identified 6 articles that included a total of 208 patients from 4 different countries (USA, Belgium, Spain, and China). Mean patient age was 48 years old, and 60% of patients were men.

Quality Evaluation

All selected studies were assessed quality evaluation according to the NOS. The minimum score of them was eight, while the maximum was nine. For selection, all the studies could obtain four stars (100%). In relation to comparability, two stars were also awarded for all studies (100%). For exhibition, more than half of the studies (65.0%) got more than two stars. All the studies got more than 7 stars, showing high scientific quality (Table S2).

Effect of MMF on SBP and DBP, Sensitivity analysis, Publication bias and Heterogeneity

Among 6 studies, MMF caused slightly decrease in DBP (0.79mmHg, 95% CI, 0.03 to 1.55, P = 0.043) (Figure 2), while no significant effect on SBP (0.12mmHg, 95%CI –0.41 to 0.64, P = 0.656) (Figure 3).

For sensitivity analysis, eliminating any study could not resulted in the significantly reduce in heterogeneity of the pooled SMDs on correlations between MMP treatment and SBP or DBP. For risk assessment, the funnel plots and Egger's regression test were used to help detect publication bias in this meta-analyses, all these revealed the existence of significant publication bias between all collected studies (Figure 4 and Figure 5, P = 0.456 for SBP, P = 0.096 for DBP), which may be related to the limited number of small enrolled trials. In addition, there were also exist significant heterogeneity when all studies were pooled (data not shown). When remove any study, no significant change was observed in heterogeneity. Besides, the meta-regression analyses for all two endpoints were then preformed (6 studies). The following variable factors were then detected: country (china vs. other country), duration of

follow-up, sex ratio, and mean age of enrolled subjects. The results showed no obvious effect of all above factors (Table S3 and Table S4).

Discussion

In the present meta-analysis, we included available data on the relationship between blood pressure and MMF treatment. As we know, there are lots of researches have studied the possible benefits of MMF therapy in cardiovascular risks [2], the effect of MMF treatment on blood pressure still unclear. This review demonstrates that MMF cause slightly decrease in DBP, with no significant effects on SBP. As far as we know, this study is the first systematic review and meta-analysis about the effect of MMF on blood pressure. The present review suggested that MMF therapy could help to slightly reduce DBP and not affect the SBP.

Immunosuppressive agent in cardiovascular risks

More than half of patients who received solid organ transplantation may develop hypertension[2]. Hypertension should be taken seriously, because it is a risk factor for decreased allograft survival, cardiovascular disease and stroke[12, 13]. In the 1970s, Svendsen proved that immune was involved in the progression of hypertension [14]. Hypertension is considered as an autoimmune disease. It usually associated with inflammatory immune cells infiltration of blood vessel walls and perivascular adipose tissue, and the abnormalities of innate immune cells include T cells and b cells, could help explicit the inflammation level of hypertension patients. Excessive excitement of the renin-angiotensin system (RAS), which could cause over-production of angiotensin II (Ang-II), vasoconstriction sodium and water retention, is one of the important mechanism of hypertension. Furthermore, activated immune system are involved in the regulation of RAS by stimulating its receptors and other ways [15]. As the pharmacological inhibiter of B and T cells, MMF could attenuate salt-sensitive hypertension in rat model through inhibiting the AT2 receptor [15]. Previous study also proved that MMF prevents high-fat diet–induced hypertension via inhibiting infiltration of $CD3^{+}$cells in the glomerulus and glomerular injury [16]. In consistent, our results also showed that MMF cause slightly decrease in DBP.

This study had several limitations. First, the enrolled subjects of all studies was 208 participants, which may be too few to detect complications of hypertension and other cardiac events, we only evaluated the effect of MMF on BP. Second, not all the author offered the initial blood pressure before and after the MMF treatment, our results should consider these problems. Furthermore, the conclusion of our study on the effect of MMF therapy on blood pressure is not very powerful, due to the limited enrolled RCT trails, more high-quality RCTs with larger sample sizes were needed. In spite of this, we are sure that we study is meaningful to side effects of MMF treatment.

Conclusions

this meta-analysis suggests that MMF treatment could only slightly reduce DBP and not affect the SBP. We believed that these could provide some evidence for the effect of MMF therapy on blood pressure. The MMF treatment not increases the risk of hypertension, show the favorable cardiac safety for transplant patients.

Abbreviations

Angiotensin II (Ang-II), blood pressure (BP), confidence interval (CI), blood pressure (BP); systolic BP(SBP); mycophenolate mofetil (MMF), Newcastle-Ottawa Scale (NOS), renin-angiotensin system (RAS), Standard deviations (SDs), systolic BP (SBP), weighted mean difference (WMD).

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Guilan Cao and Qianqian Fan extracted data from included trials, Disagreement was resolved by discussion with the third person (Xiaoguang Li). Kun Liu analyzed the data. Fengxiao Zhang and Guilan Cao designed the experiment and wrote the manuscript.

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Conflict of Interest Statement:

None.

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Tables

Due to technical limitations, the tables have been placed in the Supplementary Files section.

Figures

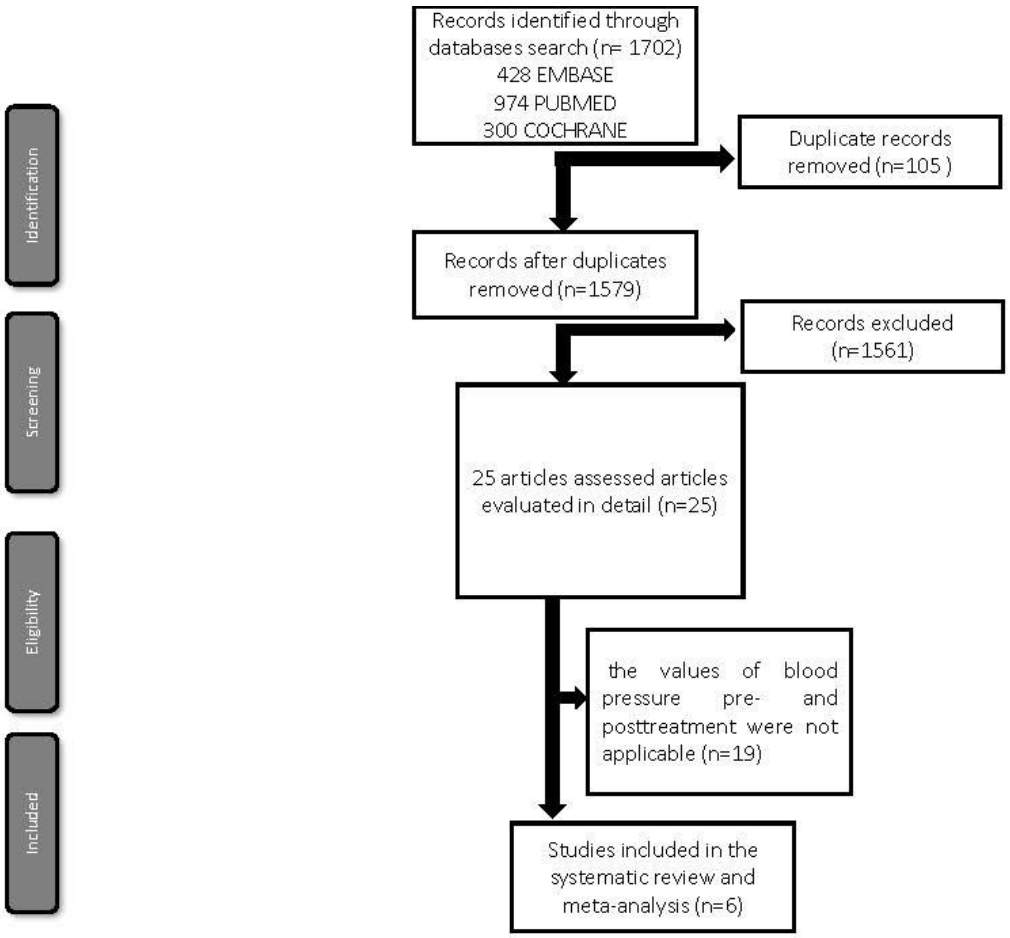

Figure 1

PRISMA flow diagram.

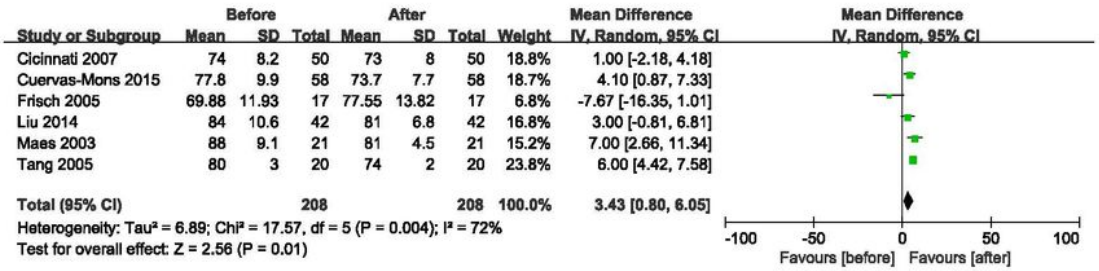

Figure 2

Effect of MMF on diastolic blood pressure (DBP). Data are given as mean (95% confidence interval CI).

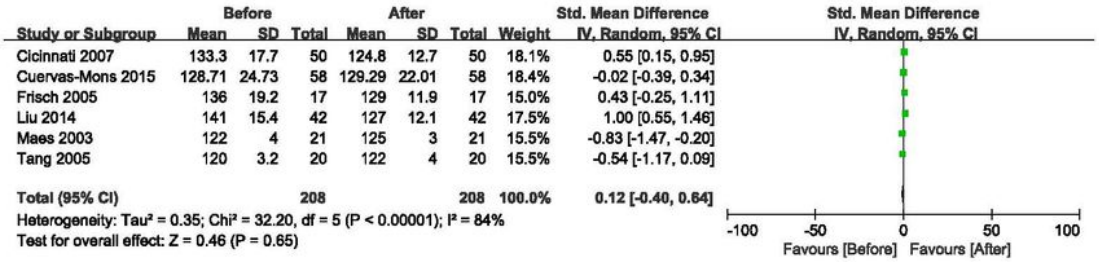

Figure 3

Effect of MMF on systolic blood pressure (SBP). Data are given as mean (95% confidence interval CI).

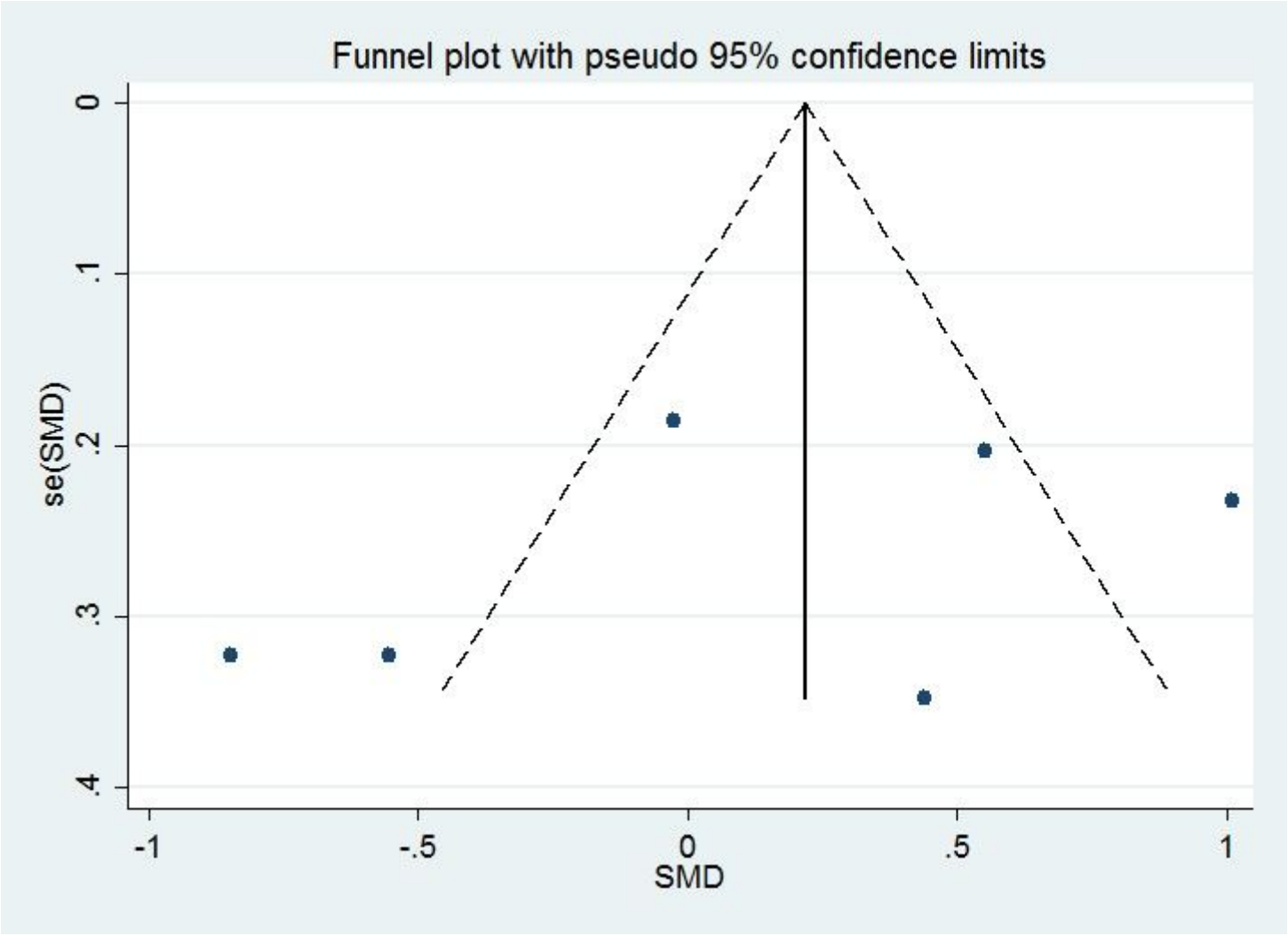

Figure 4

Funnel plot for studies of systolic blood pressure.

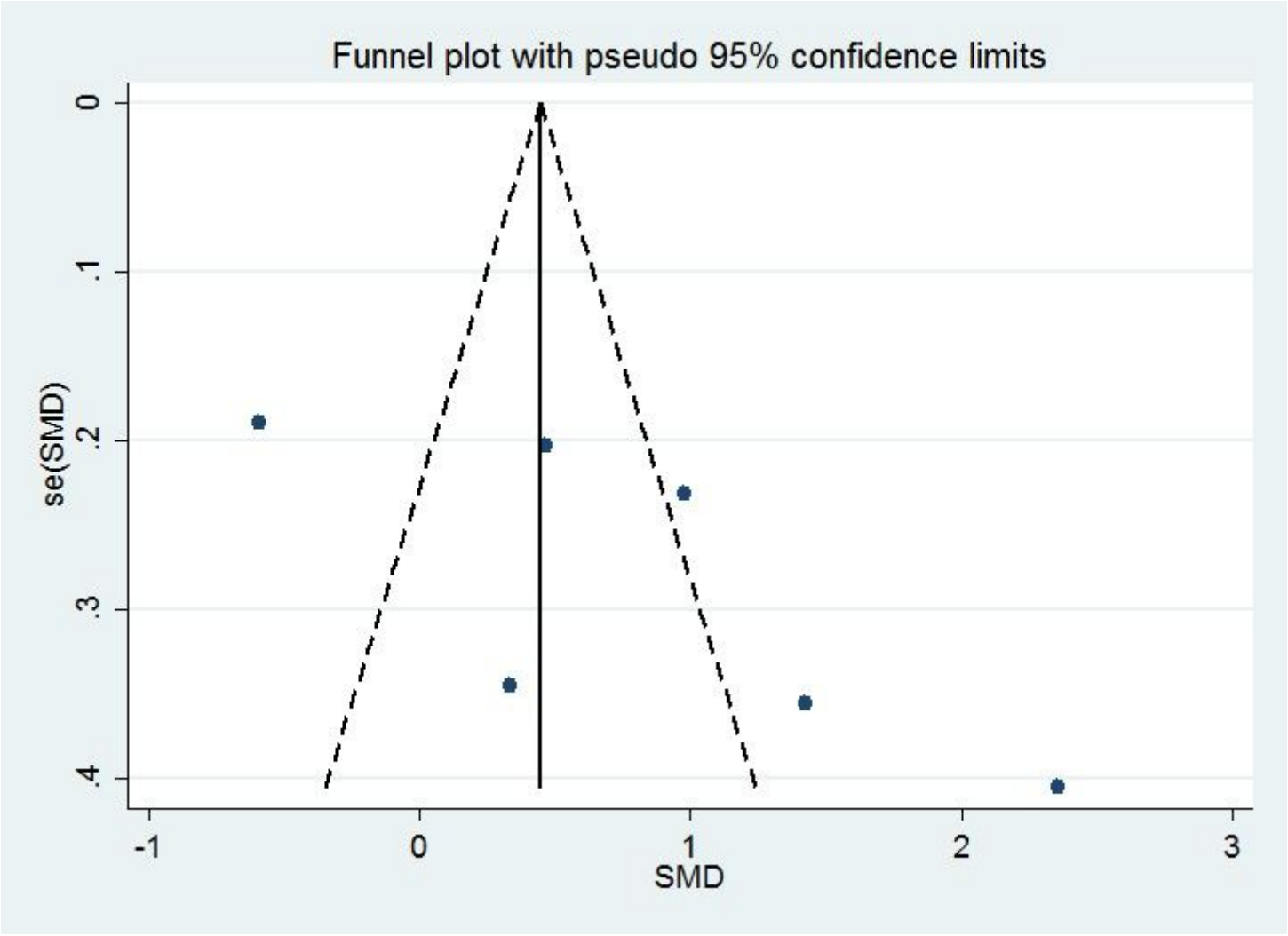

Figure 5

Funnel plot for studies of diastolic blood pressure.

Supplementary Files

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- Tables.docx