Meta-analysis on the risk of all-cause mortality and cardiovascular death in the early stage of hypertension

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A**bstract**: To evaluate the relationship among the early stage of hypertension, cardiovascular death, the mortality of coronary heart disease and stroke. Two researchers searched online data of PubMed, Embase and Cochrane library databases and other related papers and manual retrieval conference papers. A prospective cohort study of relative risks and 95% CIs about the comparison with ideal blood pressure, the pre-hypertension and the all-cause mortality or the death of cardiovascular that corrected a variety of risk factors. Compared with ideal blood pressure, the corrected risk factors, the pre-hypertension couldn't increase the RR of the all caused mortality; but it could increase remarkably the mortality of cardiovascular, coronary heart disease and stroke, and there was a significant differ ence between the two later (P<0.001). Compared with the ideal blood pressure, the pre-hypertension still increased the risk of death of cardiovascular disease and the death rate of the stroke was higher than coronary heart disease.

K**eywords**: All-cause mortality; the death of cardiovascular; meta-analysis.

INTRODUCTION

Cardiovascular disease is the leading cause to death in the world, and the death rate of it accounts for about 30% of all death worldwide(Murray and Lopez, 1997).While the abnormal blood pressure is an important cause of cardiovascular death (Chobanian *et al*., 2003), it is important to prevent and control the abnormal blood pressure in the public health. In addition to hypertension, the transition state between hypertension and ideal blood pressure, in other words that the early stage of hypertension, may be closely related to death and cardiovascular death. In an early meta-analysis showed that blood pressure levels were a log linear relationship with ischemic heart disease and stroke mortality in the age of 40~89 years old from the beginning of 115/75 mmHg (Lewington *et al*., 2002). However, due to the existence of multiple cardiovascular risk factors in the early stage of hypertension, which may affect the correlation between the early hypertension and all-cause mortality, cardiovascular death. In many prospective cohort studies, the results were not consistent with the correlation between the early stage of hypertension and the all-cause death, the death of cardiovascular after correction of cardiovascular risk factors (Mainous *et al*., 2004; Pednekar *et al*., 2009). It is helpful to further resolve the dispute through the prospective cohort study system and a comprehensive meta-analysis. Therefore, this study was designed to evaluate the relationship between pre-hypertension and the all-cause mortality, the death of cardiovascular, as well as the mortality of coronary heart disease and the stroke.

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MATERIAL AND METHOD

Information retrieval

This retrieve strategy is drafted and implemented according to "Meta-analysis of Observational Studies in Epidemiology" (Stroup *et al*., 2000). The two researchers researched independently. The online data research included Pubmed, Embase, Cochrane library and other data and the deadline of it was December 12th in 2012. The index words included: (1) related with exposure factors: "pre-hypertension" or "pre-hypertension" or "pre-hypertensive" or "pre-hypertensive" or "borderline pre-hypertension" of "blood pressure" or "arterial pressure" and (2) related with observe events: "mortality" or "death" or "deaths" or "fatal" and (3) related to research design: "Epidemiologic Studies" or "epidemiologic study" or "epidemiology" or "cohort study" or "longitudinal study" or "follow up" or "followed up" or "observational study" or "prospective". And the research didn't set up to limit the language and the form of the publications. Two researchers also searched the references and guidelines of relevant articles by hand in order to obtain more related references.

The criteria of inclusion and exclusion

The criteria of inclusion was: (1) the participants of prospective cohort study ≥ 18 years; (2) measured the baseline blood pressure and other vascular risk factors; (3) follow up time ≥2 h; (4) Exposure factors for the early stage of hypertension; (5) the control group was ideal blood pressure (<120/80 mmHg); (6): after correcting for a variety of other risk factors, the relative risks (RRs) and 95% confidence intervals were reported.

(1) The criteria exclusion included: Participants were selected for a specific risk factor or clinical feature, such as diabetes, chronic kidney disease, coronary heart disease and so on; (2) age and sex were corrected only, and other cardiovascular risk factors were not corrected; (3) data were derived from the twice analysis of the same cohort study, other cohort studies and clinical trials.

If there were several reports on the same event data from the same cohort study, the newly published data was selected only.

Data extraction and quality assessment

The mentioned search strategies above were adopted by researchers for data retrieval according to the inclusion criteria. After determining the inclusion of the study, the following information was extracted using a specially fabricated form: research name; public time; the ratio of pre-hypertension; sample size; sex ratio of male and female; the average age at the time of selection; the mean follow up time; whether to exclude the baseline CVD; correction of confounding factors and end events, etc. If there was disagreement, it was solved by the group discussion. If the main data in the original was not reported or unclear, we contacted with the corresponding author to get further information.

The quality of each study was assessed by according to the US Preventive Services Task Force guidelines (Harris *et al*., 2001; Lee *et al*., 2010; Lee *et al*., 2011). And the scale included: (1) design type for prospective study; (2) the control group was not changed in all the research; (3) fully corrected confounding factors (at least including the five in the following six items: age, sex, diabetes, body mass index or other index to inflect the overweight or obesity; cholesterol and smoking); (4) report the loss ratio; (5) Blind method to evaluate the correlation between the end events and the baseline state; (6) clearly defined exposure factors (pre-hypertension) and observation events; (7) temporality (the measure was the baseline state not the evaluated results); (8) at least 2 follow up time. It was quality when research and evaluation compliance with more than 7 to 8 standard, it was general when conformed to 4~6 standards, and it was worse less 4 standards.

STATISTICAL ANALYSIS

The primary endpoint of this study was all-cause mortality and cardiovascular mortality risk. The secondary endpoint was the risk of death from coronary heart disease and stroke. To analyze according to the level of blood pressure, age (<50 *vs.* ≥55), sex (male *vs.* female), race (Asian *vs.* not Asian), follow up time (>10 *vs.* ≥10), the sample size (<10000 *vs* .≥10000), whether include baseline CVD (yes *vs.* no) and the adequacy of the correction of other risk factors (yes *vs.* no).

We extracted the RRs and 95% CIs of the all-cause mortality and cardiovascular mortality after multiple corrections of each study. And then their post digital converter (log RRs) was used to calculate the corresponding standard errors. The inverse variance method, the log RRs and SEs were used to calculate the combined RRs and 95% Cis (Lee *et al*., 2010; Lee *et al*., 2011). Some studies did not provide the overall relative risks of pre-hypertension for selected people directly, but rather to provide the relative risks of male and female, different ages or different blood pressure ranges between pre-hytension and ideal blood pressure.

W e used the x^2 and I^2 to evaluate the heterogeneity between the studies. $I^2 \geq 50\%$, it was believed that there was significant heterogeneity between studies using random effects models combined analysis, otherwise, the fixed effects model analysis (Higgins *et al*., 2003was used. A funnel plot was used to detect bias. In addition, by comparing the value RR of the random effects model with fixed effects model, a single one study was excluded and the RR value was recombined to analyze the sensitivity. All statistical analyses were performed on Revman software in version 5.2 (Cochrane Collaboration, Copenhagen, Denmark). All analysis were adopted two-sided test and the significance level was 0.05.

There was statistical significance when the exposure factors (pre-hypertension) were for the relative risk of the events (all-cause mortality or cardiovascular death). And the population-attributable risk (PAR) was calculated according to the combined RR value and the percent of pre-hypertension to. PAR% referred to the occurrence of events in the study population attributable proportion of certain specific risk factors, namely if the risk factors could be eliminated, the percentage of the occurrence of the events could be reduced in the population. And the formula was: PAR%=(Pe)(RR-1)/[Pe(RR-1)+1] ×100 Qureshi *et al*., 2005). Among these represented proportion of exposure factors (pre-hypertension) in the population and the RR value was the relative risk value of the combined correction multiple factors.

RESULTS

Results of retrieve

Firstly, we obtained 6318 documents through PubMed, Embase and Cohrane and other database and manual retrievals, then excluded 421 repeated documents, eliminated 5847 documents through reading the abstracts carefully that the main causes were not relative to the blood pressure and death or cardiovascular. By reading the rest of the 50 in full text, 30 documents were further excluded which included 13 ones that were not compared with the relative risk of pre-hypertension and ideal blood pressure, 11 ones did not report the RRs and 95% CIs. And the other 6 documents only defined the pre-

hypertension with systolic blood pressure (n=1), none of documents defined multiple correction RRs (n=1). A secondary analysis of other cohort studies or meta-analysis (n=2), selected populations which contained less than 18 years old (n=1). The final inclusion included 20 meta-analysis of prospective cohort studies (Mainous *et al*., 2004; Bowman *et al*., 2005; Sairenchi *et al*., 2005; Pednekar *et al*., 2009). There were no differences in the final inclusion in the literature review. The included and excluded specific literatures were shown in fig. 1.

Research characteristics

(1) Eventually the included 20 studies were from the general population and were 1129098 participants in total.

(2) This research reported the risks of pre-hypertension

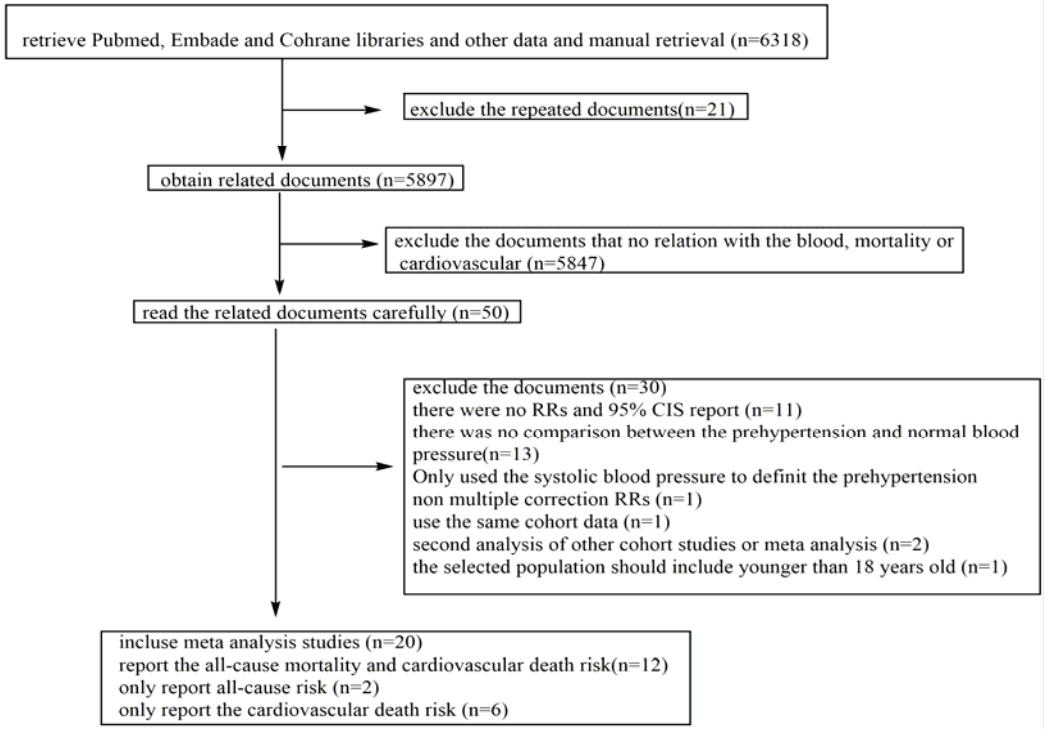

Fig. 1: The flow chart of including and excluding the documents

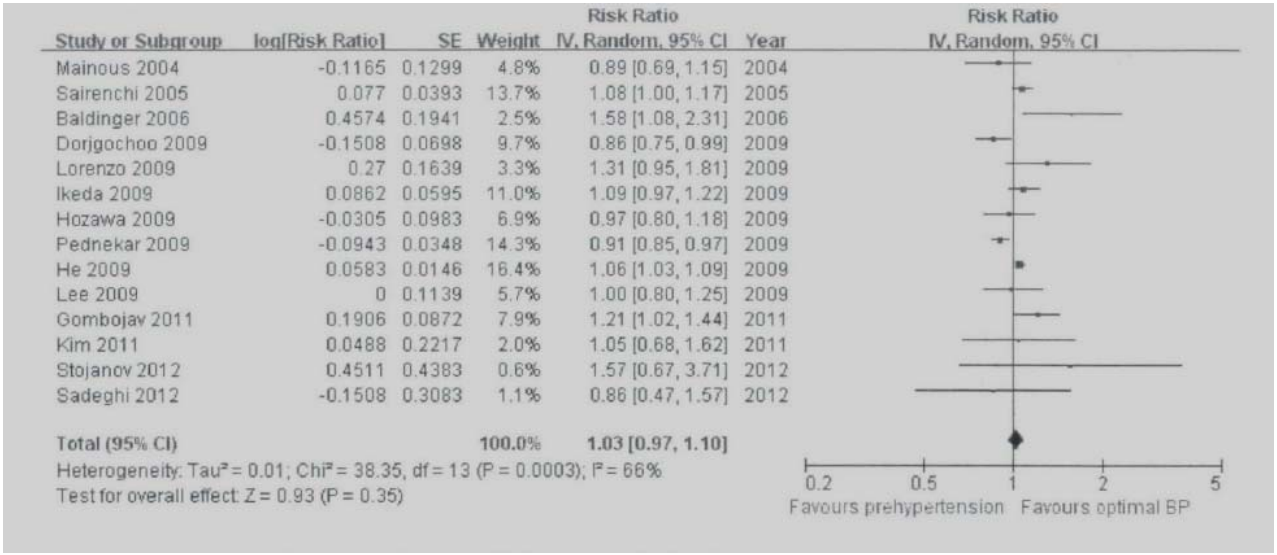

Fig. 2: The meta-analysis of relative risk between the pre-hypertension and all-cause mortality

Note: Figure adopted the random effect model to combine the relative risk. Size box showed the number of weights, the horizontal line represented the 95% confidence interval of each study and the bottom of the diamond represents represented the combined effect of multiple studies.

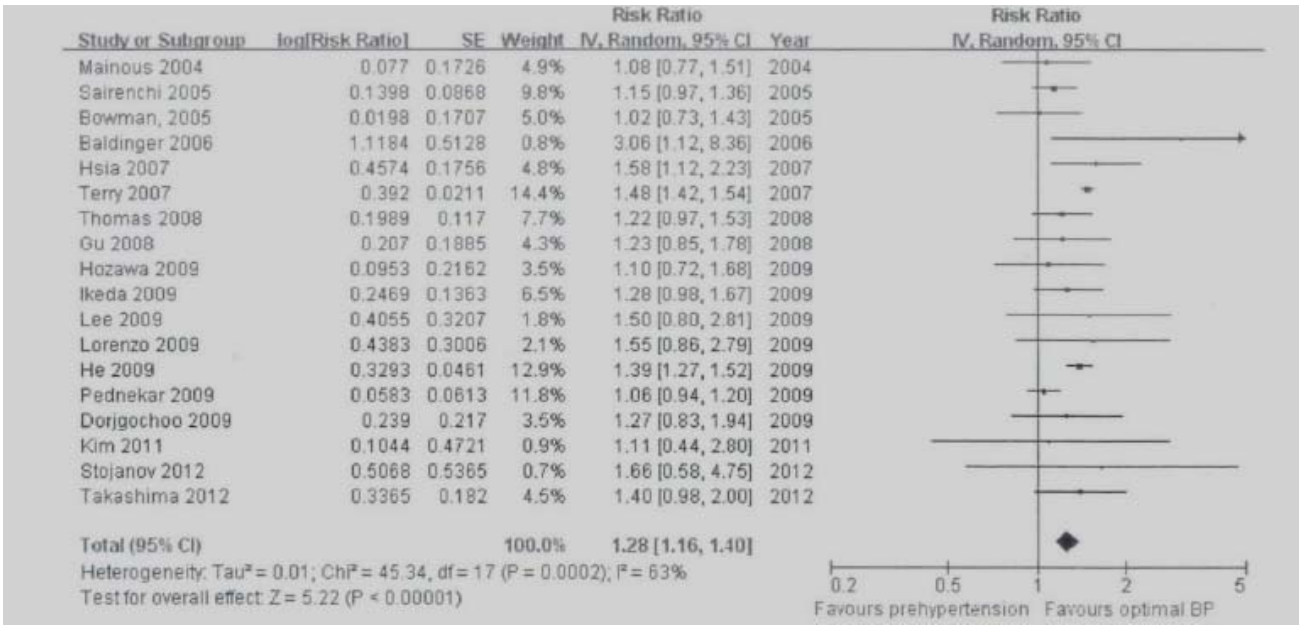

Fig. 3: The meta-analysis on relative of prehypertension and cardiovascular death.
Note: Figure adopted the random effect model to combine the relative risk. Size box showed the number of weights, the horizontal line represented the 95% confidence interval of each study and the bottom of the diamond represents represented the combined effect of multiple studies.

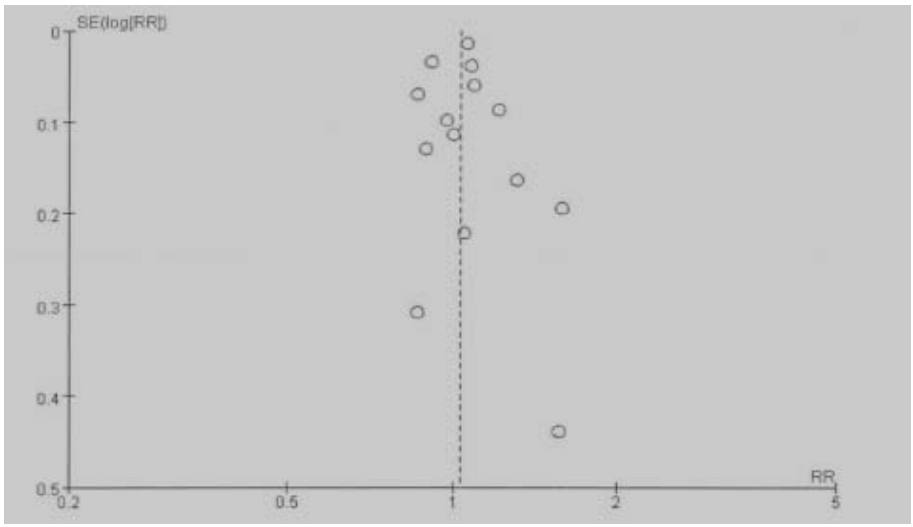

Fig. 4: A funnel plot analysis of the relative risk of prehypertension and all-cause mortality.
Note: Horizontal axis: the relative risk of hypertension dead of all-cause mortality; vertical axis: the standard error of relative risk value after conversion.

related with the all-cause mortality and cardiovascular mortality (Mainous *et al*., 2004; Bowman *et al*., 2005; Pednekar *et al*., 2009), 6 studies of them reported the only the risk of cardiovascular mortality (Bowman *et al*., 2005), two studies reported only the risk of all-cause mortality (Gombojav *et al*., 2011; Aghababaei *et al*., 2012). Therefore, there were 14 and 18 studies that analyzed all-cause mortality and cardiovascular mortality risk.

(3) There were 11 cohort studies from Asia (Sairenchi *et al*., 2005; Pednekar *et al*., 2009), and 9 ones from America (Mainous *et al*., 2004; Bowman *et al*., 2005) and Europe (Baldinger *et al*., 2006). The Asian studies occupied 48.2% of all the selected population

(4) The occurrence of the pre-hypertension was 28.5% and 77.1% (Baldinger *et al*., 2006).

(5) The shortest follow-up time was 5.1 years and the longest was 36 years.

(6) According to the predetermined quality score, the quality of 15 studies was good (Mainous *et al*., 2004; Sairenchi *et al*., 2005) and 5 were general (Bowman *et al*., 2005; Pednekar *et al*., 2009).

(7) 16 studies adequately adjusted for other risk factors, while the other 4 did not (Pednekar *et al*., 2009).

Table 1: The main characteristic of cohort research of inclusion of meta analysis

Research	Countries	The occurrence of pre-hyper-tension (%)	Sample size (% female)	Mean ages (scope or standard deviation)	The follow up time (years)	Whether excluded the baseline cardiovascular	The end events
Mainous, 2004	American	28.7	9087 (52.4)	NA (30-74)	12	no	all-cause mortality or cardiovascular mortality
Bowman, 2005	American	66.2	53163 (0)	53.0 (39-85)	5.7	yes	cardiovascular mortality
Sairenchi, 2005	Japan	39.8	89024 (66.0)	NA (40-79)	8.8	yes	all-cause mortality or cardiovascular mortality
Baldinger, 2006	Switzerland	77.1	22927 (0)	39(8)	8.2	no	all-cause mortality or cardiovascular mortality
Hsia, 2007	American	38.8	60785 (100)	62.8±7.0	7.7	yes	cardiovascular morality
Terry, 2007	American	NA	347978 (0)	45.9 (35-57)	2.5	yes	cardiovascular morality
Gu, 2008	American	30.8	16917 (47.8)	45.6 (≥18)	8.5	no	cardiovascular morality
Thomas, 2008	French	54.2	69989 (40.7)	56.5 (>50)	15.3	no	all-cause mortality or cardiovascular mortality
Lorenzo, 2009	American	31.6	3632 (56.9)	41.0 (25-64)	15.2	yes	all-cause mortality or cardiovascular mortality
Lee, 2009	Singapore	28.5	5830 (50.6)	39.7 (NA)	14.0	no	all-cause mortality or cardiovascular mortality
Dorjgochoo, 2009	China	33.2	68438 (100)	55.1 (9.1)	5.1	no	all-cause mortality or cardiovascular mortality
Hozava, 2009	Japan	41.8	12928 (57.3)	61.2 (9.4)	11.7	yes	all-cause mortality or cardiovascular mortality
He, 2009	China	34.5	169871 (50.8)	55.8 (≥40)	9	no	all-cause mortality or cardiovascular mortality
Ikeda, 2009	Japan	43	33372 (65.0)	50.5 (40-69)	11.0	yes	all-cause mortality or cardiovascular mortality
Pedmekar, 2009	India	38.8	148173 (40.2)	50 (≥35)	5.5	no	all-cause mortality or cardiovascular mortality
Kim, 2011	Korea	28.7	2376 (77.9)	69.8 (60-92)	7.6	yes	all-cause mortality or cardiovascular mortality
Gombojav, 2011	Korea	50.8	2496 (57.7)	73.6 (5.9)	11.8	no	all-cause morality
Aghababaei, 2013	Iran	36	3255 (100)	49.7 (≥35)	6.7	yes	all-cause mortality
Stokanov, 2012	Serbia	40.8	265 (48.7)	43.6 (30-60)	36	yes	all-cause mortality or cardiovascular mortality
Takashima, 2012	Japan	41.2	8592 (56.0)	49.4 (30-92)	21.3	yes	cardiovascular mortality

NA: loss the original data

The detailed characteristics of each study were shown in table 1 and the corrected cardiovascular risk factors and quality assessment were shown in table 2.

The relativity between pre-hypertension and all-cause mortality and cardiovascular mortality

There were 14 studies (n=571674) and 18 studies (n=1123347) including all-cause mortality and cardiovascular mortality analysis of meta. Due to the inclusion of a significant heterogeneity among the studies (all-cause mortality I^2=66%, the cardiovascular mortality I^2equaled 63%), therefore, random effects model was adopted to carry out the combined effect.

After correcting for multiple cardiovascular risk factors, the relative risk of total mortality did not increase in the pre-hypertension. (*RR*=1.03; 95%*CI*=0.97~1.10, *P*=0.35, fig. 2); the relative risk of cardiovascular death significantly increased (*RR*=1.28; 95% *CI*=1.16~1.40, *P*<0.001, fig. 3). Funnel plot analysis was used to find out the obvious bias (all-cause mortality: fig.4; cardiovascular mortality: fig. 5).

The correlation between pre-hypertension and coronary heart disease and stroke death.

There were 7 cohort studies (n=498700) reporting the relative risk of death in coronary and heart disease that related with pre-hypertension. There was no significant heterogeneity among the studies (the death of coronary I^2=12%; the death of stroke I^2=19%). Therefore, the fixed effect model was used to carry out the combined effect. After correcting the multiple risk factors, pre-hypertension increased 12% relative risk of death of

Table 2: The corrected of cardiovascular risk factors and quality assessment of each study

Study	Corrected of cardiovascular of risk factors	Quality of study
Mainous, 2004[4]	age, race, sex, smoking, BMI, sport, CHOL, DM, heart failure, history of heart disease and stroke	excellent
Bowman, 2005 [12]	age, BMI, sport, DM, smoking and drinking, the history of using aspirin and a variety of vitamins	general
Sairenchi, 2005[17]	age, sex, CHOLHDL-C, DM, BMI, atrial fibrillantion, proteinuria, smoking and drinking, use of lowering blood pressure drug	excellent
Baldinger, 2006[18]	age, BMI, smoking, abnormal glucose metabolism, history of other diseases	general
Hsia, 2007[19]	age, BMI, DM, CHOL and smoking	excellent
Terry, 2007[20]	age, race, income, CHOL, smoking and use of diabetes drugs	excellent
Gu, 2008[21]	age, sex, race, sport, smoking, obesity, hypercholesterolemia, DM, chronic kidney disease and heart failure, history of heart disease and stroke	excelletn
Thomas, 2008[22]	age, sex, CHOL, DM, sport, smoking, drinking and lowering blood pressure drugs	excellent
Lorenzo, 2009[23]	age, sex, race, degree of education, BMI, CHOL and smoking	excellent
Lee, 2009[24]	age, sex, race, BMI, CHOL, HDL-C, history of diabetes and CVD, smoking, drinking	excellent
Dorjgochoo, 2009[25]	age, degree of education, proportion of waist and hipline, smoking, history of diabetes and CVD	excellent
Hozava, 2009[26]	age, sex, smoking, abnormal glucose metabolism, CHOL and BMI	excellent
He, 2009[27]	age, sex, degree of education, smoking and drinking, BMI, sport, antihypertensive drug, history of diabetes and CVD, geographical region	excellent
Ikeda, 2009[28]	age, sex, BMI, smoking, drinking, antihypertensive drug, CHOL, DM and geographical region	excellent
Pedmekar, 2009[5]	age, degree of education, geographical region, mother tongue, smoking and BMI	general
Kim, 2011[29]	age, sex, BMI, fasting blood glucose, CHOL, HDL-C and smoking	excellent
Gombojav, 2011[30]	age, degree of education, sport, smoking, dringking, chronic disease and antihypertensive therapy	general
Aghababaei, 2013[31]	age, DM, CHOL, BMI, smoking and menopause	excellent
Stokanov, 2012[32]	age, sex and BMI	general
Takashima, 2012[33]	age, sex, BMI, CHOL, abnormal glucose metabolism, smoking and drinking	excellent

BMI: body mass index; CHOL: serum cholesterol; DM: diabete; HDL-C: High density lipoprotein cholesterol; CVD: cardiovascular

coronary heart disease (*RR*=1.12, 95%*CI*=1.02~1.23, P=0.02) and 41% of relative risk of stroke respectively (*RR*=1.41, 95%*CI*=1.28~1.56, P<0.001) (fig. 6). There was significant difference of relative risk death between the coronary and stroke (P<0.001).

The population attributable reason score on pre-hypertension to the cardiovascular death.

In the inclusion 20 studies, there were 19 studies reporting the occurrence of pre-hypertension, but one study was lack of data. Our team tried to contact the members of this research team, but we got no response. Therefore, we adopted the mean of other 19 studies of the occurrence of pre-hypertension to calculate the PARS. And pre-hypertension on the cardiovascular death, coronary and stroke death of PARS were respectively 10.5%, 4.8% and 14.6%.

DISCUSSION

Meta-analysis showed that after correcting the multiple risk factors, pre-hypertension still increased the risk of cardiovascular death, and the mortality risk of stroke was significantly higher than the death of coronary heart disease. According to the occurrence of pre-hypertension and the value of relative risk of meta-analysis, furthermore, we found that pre-hypertension on the cardiovascular death, coronary and stroke death, the PARS were 10.5%, 4.8% and 14.6%. It means that if pre-hypertension could be eliminated pre-hypertension, and the 10% cardiovascular death, 5% coronary death and 15 stroke death could be prevented. While, at the same time pre-hypertension did not increase the all-cause mortality risk in this study.

SENSITIVITY ANALYSIS

In the sensitivity analysis, there was non significant change of the conversion in the pre-hypertension on the all-cause mortality, cardiovascular death, coronary or stroke death no matter how the random effects model was conversed and the fixed effect model, or the single research was excluded to calculate the combined effect renew.

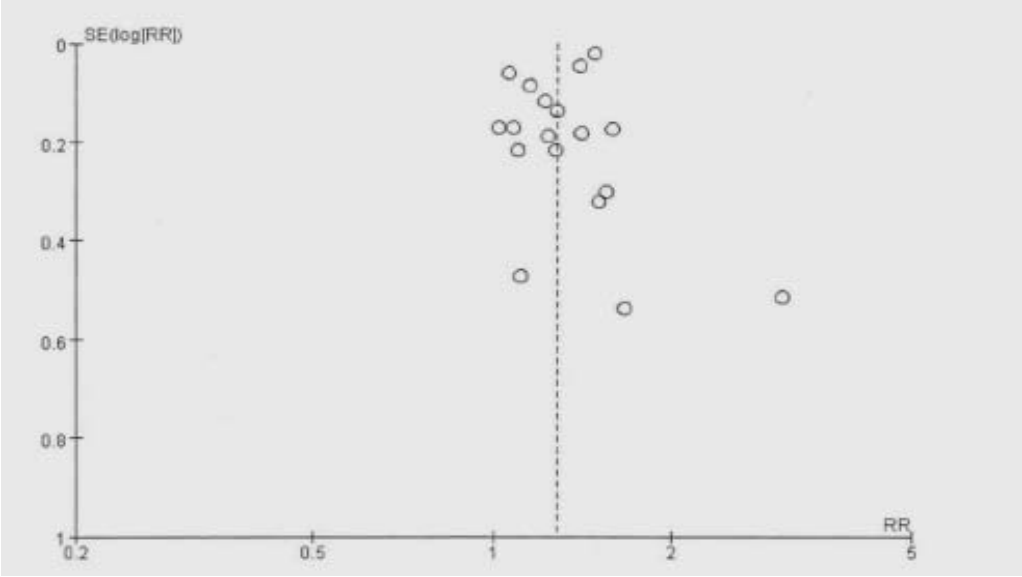

Fig. 5: A funnel plot analysis of the relative risk of pre-hypertension and cardiovascular death.
Note: Horizontal axis: the relative risk of pre-hypertension dead of cardiovascular mortality; vertical axis: the standard error of relative risk value after conversion.

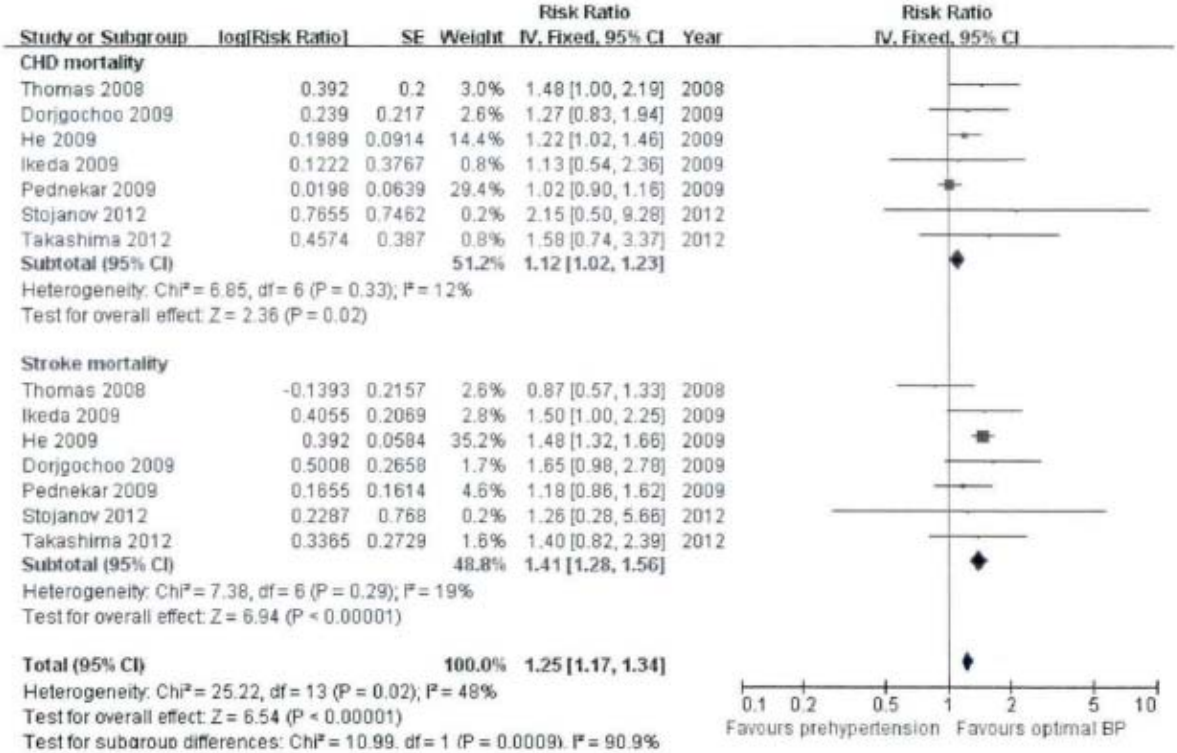

Fig. 6: The meta-analysis of relative risk of prehypertension and coronary death and stroke death
Note: Adopted the fixed model to combine the relative risk. Size box showed the number of weights, the horizontal line represented the 95% confidence interval of each study and the bottom of the diamond represents represented the combined effect of multiple studies.

CONCLUSION

Compared with the ideal blood pressure, the pre-hypertension still increased the risk death of cardiovascular disease and the death rate of the stroke was higher than the coronary heart disease.

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