Review

OPEN

White-coat hypertension is a risk factor for cardiovascular diseases and total mortality

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Background: Whether white-coat hypertension (WCH) is an innocent phenomenon is controversial.

Method: In this study, we evaluated the association of WCH and the risk of cardiovascular diseases (CVDs) and mortality, stratified by baseline antihypertensive treatment status. Databases (PubMed, EMBASE, CINAHL Plus, Scopus, and Google Scholar) were searched for prospective studies with data on CVD and total mortality associated with WCH. The primary outcomes were the risk of CVD and total mortality associated with WCH stratified by antihypertensive treatment status. The relative risks of events compared with normotension were calculated.

Results: A total of 23 cohorts (20 445 individuals), 11 cohorts (8656 individuals), and 12 cohorts (21 336 individuals) were included for analysis of cardiovascular risk associated with WCH in patients without baseline antihypertensive treatment (untreated), or under antihypertensive treatment (treated) or mixed population (including both untreated and treated patients), respectively. In untreated cohorts, WCH was associated with a 38 and 20% increased risk of CVD and total mortality compared with normotension, respectively. In the mixed population, WCH was associated with a 19 and 50% increased risk of CVD and total mortality. However, in the treated patients, neither the risk of CVD, nor total mortality was increased in WCH. Meta-regression analyses indicated that neither differences of clinic blood pressure, nor out-of-office blood pressure variables were correlated with risk of CVD in WCH.

Conclusion: We concluded that WCH is associated with long-term risk of CVD and total mortality in patients without antihypertensive treatment. Close follow-up should be performed in WCH patients.

Keywords: cardiovascular diseases, mortality, white-coat hypertension

Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CIs, confidence intervals; CVD, cardiovascular disease; HBPM, home blood pressure monitoring; HRs, hazard ratios; IDACO, International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes Population; MOOSE, Meta-analysis of Observational Studies in Epidemiology; RRs, relative risks; SEs, standard errors; WCH, white-coat hypertension

INTRODUCTION

'White-coat hypertension' (WCH), also referred to as isolated office or isolated clinic hypertension, is used to defined patients with elevated clinic blood pressure (BP) at repeated visits, whereas with normal BP outside the doctor's office (out-of-office BP), detected either on ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) [1]. Although it is recommended that WCH should be reserved to define patients without antihypertensive treatment (untreated) [1,2], some studies also included patients under antihypertensive treatment (treated) [3,4] or mixed population with treated and untreated patients [5–7] for analysis.

It is known that the overall prevalence of WCH in the general population is 10–15%, and it amounts to about 30% in patients with increased clinic BP readings [1,2]. However, whether WCH is a benign phenomenon is still under debate. Prospective longitudinal studies examined the relationship between WCH and cardiovascular risks that were with marked inconsistent results [6,8–12]. Two individual patient-level data meta-analyses from the International Database on ABPM in Relation to Cardiovascular Outcomes Population (IDACO) also showed conflicting conclusions [13,14]. Franklin *et al.* [13] found that in untreated patients, those with WCH defined by daytime ABPM and patients with normal BP were at similar risk of cardiovascular disease (CVD). However, Asayama *et al.* [14]

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reported that the risks of CVD were increased in patients with WCH considering daytime or night-time mean BP only, but not in those with considering 24-h mean BP. The inconsistency across studies may be caused by: different populations of inclusion (untreated, treated, or mixed) at baseline; difference in out-of-office BP monitoring protocol and cutoff values; and difference in study characteristics, endpoint assessment, sample size, and duration of follow-up.

Given these inconsistent results, we performed a systematic review and meta-analysis of prospective studies to examine the association of WCH and the risks of CVD and all-cause mortality, stratified by baseline antihypertensive treatment status.

METHODS

Search strategy and selection criteria

We performed the search in accordance with the recommendations of the Meta-analysis of Observational Studies in Epidemiology group [15]. Electronic databases (PubMed, EMBASE, CINAHL Plus, Scopus, and Google Scholar) were searched for prospective cohort studies to 31 August 2016 using a combined text and MeSH heading search strategy with the terms: 'white-coat hypertension', 'white-coat syndrome', 'white-coat effect', 'isolated clinic hypertension', 'isolated office hypertension', 'ambulatory blood pressure', 'ABPM', 'home blood pressure', 'pseudo-resistant hypertension', or 'false resistant hypertension' and 'cardiovascular disease', 'coronary artery disease', 'heart disease', 'atrial fibrillation', 'peripheral vascular disease', 'cardiovascular risk', 'cardiovascular event', 'stroke', 'cerebrovascular disease', 'mortality', or 'death'. There were no restrictions on language and publication forms. The reference lists of published articles and reviews on the topic were also checked to identify other eligible studies. The detailed strategy for the PubMed search is presented in online Supplementary Table S1, http://links.lww.com/HJH/A716. The strategy for other databases was similar but was adapted where necessary.

We screened titles and abstracts of the articles and reviewed full copies of potentially eligible studies for further assessment. The inclusion criteria of studies were as follows: prospective studies with adult participants (aged $\geq$18 years); with assessment of WCH on the risks of CVD or all-cause mortality; and with multivariate-adjusted relative risks (RRs) or hazard ratios and 95% confidence intervals (CIs) for events associated with WCH compared with normotension individuals. WCH was defined as high-clinic BP but normal out-of-office BP [ambulatory BP (ABP) or home BP (HBP)]. Normotension was defined as normal BP in both clinic and out-of-office settings.

Studies were excluded if enrollment depended on having a particular condition or risk factor (e.g. chronic kidney disease and diabetes mellitus); the reported RRs were unadjusted; or data were derived from the same cohort.

Only the most recent report was used for analysis, if duplicate publications reported the same outcome derived from the same cohort. However, if the duplicate publication offered additional messages for subgroup analysis that could not be derived from the primary included one, they were included in the subgroup analysis.

Data extraction and quality assessment

Two reviewers (Y.H. and W.H.) independently conducted the literature searches, reviewed and selected the studies according to the predefined criteria. Informations such as participant characteristics, follow-up duration, adjustment of risk factors, and outcome assessment were recorded in specially designed forms.

The quality assessment was evaluated on the basis of the Newcastle–Ottawa Quality Assessment Scale (NOS) for cohort studies [16], in which a study was judged on three broad perspectives as follows: selection (four items, one star each), comparability (one item, up to two stars), and exposure/outcome (three items, one star each). A star represents a high-quality choice of individual study. In this analysis, studies were graded as good quality, fair, and poor when they had at least seven, four to six and less than four awarded stars, respectively. We also evaluated whether the studies were adequately adjusted for potential confounders (at least six of seven factors: age; sex; previous CVD or exclusion of CVD at baseline; diabetes mellitus or fasting plasma glucose; BMI; cholesterol or hypercholesterolemia; and smoking) with reference to the United States. Preventive Task Force guidelines and used in previous studies [17,18].

Data synthesis and analysis

The primary outcome was the risk of CVD, secondary outcome was the risk of all-cause mortality associated with WCH. Three stratification comparisons were performed. First, the risks of CVD and all-cause mortality in population of WCH without antihypertensive treatment at baseline (we name it as 'untreated') in comparison with normotensive individuals; second, the risks were compared in population with WCH who were on antihypertensive therapy (we name it as 'treated') vs. patients whose BP was normalized (both in or out-off clinic) after medication; and third, the risks were compared in mixed population with WCH who were either on or without pharmacologic therapy vs. patients with normal BP, who were either normotensive or hypertension patients whose BP was normalized after medication treatment.

Subgroup analyses of the primary outcomes were conducted on the basis of way of measurement of out-of-office BP (ABPM vs. HBPM); times of visit (clinic BP obtained $\geq$2 visits vs. <2 visits); different thresholds for diagnosing WCH on ABPM (daytime ABP < 135/85 mmHg vs. 24-h ABP < 130/80 mmHg vs. others); follow-up duration (<8 vs. $\geq$8 years); participant's age (mean age <55 vs. $\geq$55 years); CVD endpoint (fatal vs. fatal and nonfatal CVD); adjustment of confounders (adequate vs. inadequate); and study quality (good vs. fair) if appropriate.

Multivariate-adjusted outcome data were used for analysis, by the inverse variance approach, combined log RRs, and corresponding standard errors (SEs) [19,20]. We used I^2 statistics to test heterogeneity. Values of I^2 value more than 50% were considered to be significant heterogeneity. A random effects model was used if there was significant heterogeneity in the pooled estimation.

Otherwise, a fixed effects model would be used. Publication bias was assessed by inspecting funnel plots for primary outcomes in which the ln(RR) was plotted against SE, as well as Egger's test (linear regression method) and Begg's test (rank correlation method). To assess the effect of individual studies on the pooled RR, we performed an influence analysis, in which the pooled RR was recalculated by omitting one study at a time. We also compared the differences between clinic BP and out-of-office BP in WCH and normotension individuals, and meta-regression analysis was used to determine the impact of differences of BP variables in WCH and normotension groups upon the primary outcome.

All analyses were performed with RevMan software version 5.3 for Windows (The Cochrane Collaboration, Copenhagen, Denmark) and Stata version 12.0 (Stata Corp LP, College Station, Texas, USA). All P values are two-tailed, and the statistical significance was set at 0.05.

RESULTS

Studies retrieved and characteristics

A total of 26 158 manuscripts were retrieved in the Emabse and PubMed databases. After screening of the titles and abstracts, 62 qualified for full review (Fig. 1). Finally, 14 articles were included in this study [3–12,14,21–23]. When stratified by baseline antihypertensive treatment, for cardiovascular risk associated with WCH, eight studies (23 cohorts, including 20 445 individuals with mean follow-up duration of 9.6 years) [6,8–12,14,21], four studies (11 cohorts, including 8656 individuals with mean follow-up duration of 5.3 years) [3,4,7,21], and six studies (12 cohorts, including 21 336 individuals with mean follow-up duration of 8.2 years) [5–7,10,22,23] were included in untreated, treated, and mixed populations comparisons, respectively. One study reported the CVD risk in untreated, treated, and mixed population from the IDACO database in 2007 [7]. However, we only included the treated and mixed population data for analysis, as data of untreated populations from IDACO were updated in another included record [14].

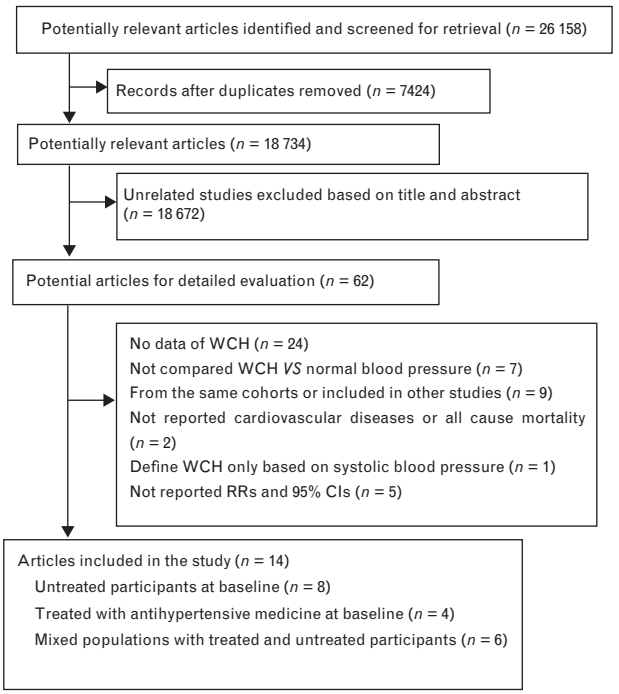

FIGURE 1 Flow of articles through review. CIs, confidence intervals; RRs, relative risks; WCH, white-coat hypertension.

For all-cause mortality, there were four [6,12,14,21] (15 793 participants with mean follow-up duration of 10.9 years) included for meta-analysis in untreated population. However, only one study [21] is with data of treated patients and another study [6] with data of mixed population, respectively. As no additional synthesis of data for all-cause mortality in treated or mixed patients, we just discussed results of these studies in the discussion.

Key characteristics of all the included studies were summarized in Table 1. According to the NOS quality assessment, 10 [4–7,9,10,12,14,21,22] and four [3,8,11,23] studies were graded as good and fair. The details of the quality assessment are presented in Supplemental Table 2, http://links.lww.com/HJH/A716. Two studies [9,23] were not adequately adjusted for potential confounders according to our predefined criteria, whereas all the others were adequately adjusted.

Stratified by baseline treatment status, the WCH patients in untreated, treated, and mixed population were with 27.6, 21.9, and 27.3 mmHg higher clinic SBP (Fig. 2), and 12.6, 9.8, and 12.1 mmHg higher clinic DBP than their corresponding normotension comparators, respectively (Fig. 3) (all $P < 0.001$). However, the out-of-office SBPs were only mildly increased in untreated (4.4 mmHg), mixed (3.8 mmHg), and treated (3.9 mmHg) in WCH population than in their corresponding normotension comparators, respectively (all $P < 0.01$); and the difference of out-of-office DBP between WCH patients and normotension comparators was no significant in the mixed population ($P > 0.05$) (Figs. 4 and 5).

Association between white-coat hypertension and risk of cardiovascular disease

All the datasets regarding the risk of CVD in untreated, treated, and mixed population did not show significant heterogeneity (all $I^2 < 50\%$). Therefore, the fixed-effects models were used for the analyses. After multivariate adjustment, WCH was associated with significantly increased risk of CVD in untreated patients (RR 1.38, 95% CI 1.15–1.65) and mixed populations (RR 1.19, 95% CI 1.01–1.41). However, the risk did not reach statistical significance in treated patients with WCH compared with patients whose BP been normalized by medication (RR 1.16, 95% CI 0.91–1.49) (Fig. 6). No bias of publication has been found on the basis of visual inspection of the funnel plot (Supplemental Fig. 1, http://links.lww.com/HJH/A716), nor on Begg's test and Egger's test (both $P > 0.05$).

The results of subgroup analyses for the risk of WCH on CVD were presented on Table 2. In untreated participants, WCH was significantly associated with higher risk of CVD in both subgroups of ABPM or HBPM for out-of-office BP measurement, either participant's age less than 55 or at least 55 years, studies with fatal CVD or fatal and nonfatal CVD.

TABLE 1. Study characteristics

Reference	Cohort	Definition of normal out-of-office BP and prevalence of WCH (%)[a]	Sample size (% women)	Age (year) (range or SD)	Follow-up (year)	Baseline CVD excluded	Events for analysis	Risk factors adjusted
Untreated participants								
Verdecchia *et al.*[b] [8]	Italy	Daytime ABP < 131/86 mmHg (women)/ <136/87 mmHg (men) (19.2%)	1392 (49.7)	51.3 (13)	3.2	No	Fatal and nonfatal CVD	Sex, age, BMI, smoking, TC, DM, clinic BP, clinic pulse pressure, and previous CVD
Kario *et al.* [9]	Japan	24-h ABP < 130/80 mmHg (24.6%)	958 (61.8)	72.0 (9.8)	3.5	Yes	Fatal and nonfatal stroke	Sex, age, BMI, and antihypertensive treatment during follow-up
Fagard *et al.* [10]	Belgium	Daytime ABP < 135/85 mmHg (NA)	265 (52)	70 (9)	10.9	Yes	Fatal and nonfatal CVD	Sex, age, BMI, smoking, TC, and DM
Pierdomenico *et al.* [11]	Italy	Daytime ABP < 135/85 mmHg (19.6%)	2037 (46.3)	48.8 (12)	6.4	Yes	Fatal and nonfatal CVD	Sex, age, BMI, smoking, FHCVD, clinical BP, LDL-C, creatinine, left ventricular hypertrophy, aspirin, statin, and antihypertensive drug at follow-up
Mancia *et al.* [6]	Italy	24-h ABP <125/79 mmHg or HBP < 132/83 mmHg (24.6%)	1292 (NA)	NA	16.0	No	Fatal CVD All-cause mortality	Sex, age, BMI, smoking, FPG, TC, and previous CVD
Sung *et al.* [12]	Taiwan, China	Daytime ABP < 135/85 mmHg (12.2%)	1257 (47)	53 (13)	15.0	Yes	Fatal CVD All-cause mortality	Sex, age, BMI, smoking, FPG, and TC/HDL-C ratio
Asayama *et al.*[c] [14]	International (12 cohorts)	Daytime ABP < 135/85 mmHg (9.1%)/24-h ABP < 130/80 mmHg (10.7%)/ night-time ABP < 120/70 mmHg (12.5%)	8237 (48.4)	50.7 (15.8)	11.1	No	Fatal and nonfatal CVD All-cause mortality	Sex, age, BMI, smoking, drinking, TC, DM, previous CVD, and cohort
Stergiou *et al.*[d] [21]	International (5 cohorts)	HBP < 135/85 mmHg (13.9%)	5007 (56.7)	57.1 (12)	8.3	No	Fatal and nonfatal CVD All-cause mortality	Sex, age, BMI, smoking, TC, DM, history of CVD, and cohort
Total	23 cohorts		20 445		9.6 (mean)			
Treated participants								
Bobrie *et al.* [4]	France	HBP < 135/85 mmHg (13.3%)	4939 (51.1)	70 (6.5)	3.2	No	Fatal and nonfatal CVD	Sex, age, smoking, hypercholesterolemia, DM, heart rate, and history CVD
Pierdomenico *et al.* [3]	Italy	Daytime ABP < 135/85 mmHg (19.7%)	746 (54.7)	59 (12)	5.0	No	Fatal and nonfatal CVD	Sex, age, BMI, smoking, FHCVD, previous CVD, clinic BP, LDL-C, creatinine, DM, and left ventricular hypertrophy
Hansen *et al.*[e] [7]	International (4 cohorts)	Daytime ABP < 135/85 mmHg (NA)	1520 (NA)	NA	9.5	No	Fatal and nonfatal CVD	Sex, age, BMI, smoking, drinking, TC, DM, previous CVD, antihypertensive treatment, and cohort
Stergiou *et al.*[d] [21]	International (5 cohorts)	HBP < 135/85 mmHg (15.9%)	1451 (57.7)	66.6 (10)	8.3	No	Fatal and nonfatal CVD All-cause mortality	Sex, age, BMI, smoking, TC, DM, history of CVD, and cohort
Total	11 cohorts		8656		5.3 (mean)			
Untreated and treated participants								
Fagard *et al.* [10]	Belgium	Daytime ABP < 135/85 mmHg (24%)	391 (60)	71 (9)	10.9	Yes	Fatal and nonfatal CVD	Sex, age, BMI, smoking, TC, DM, and antihypertensive treatment
Verdecchia *et al.*[f] [22]	International (4 cohorts)	Daytime ABP < 130/80 mmHg (9%)	5955 (50)	56 (14)	5.4	Yes	Fatal and nonfatal stroke	Sex, age, BMI, smoking, TC, and antihypertensive treatment
Hansen *et al.*[e] [7]	International (4 cohorts)	Daytime ABP < 135/85 mmHg (10.6%)	7030 (44.8)	56.2 (14.4)	9.5	No	Fatal and nonfatal CVD	Sex, age, BMI, smoking, drinking, TC, DM, previous CVD, antihypertensive treatment, and cohort

TABLE 1 (*Continued*)

Reference	Cohort	Definition of normal out-of-office BP and prevalence of WCH (%)[a]	Sample size (% women)	Age (year) (range or SD)	Follow-up (year)	Baseline CVD excluded	Events for analysis	Risk factors adjusted
Hermida *et al.* [23]	Spain	Daytime ABP < 135/85 mmHg (27.9%)	3344 (48.6)	52.6 (14.5)	5.6	Yes	Fatal and nonfatal CVD	Sex, age, DM, Chronic kidney disease, sleep duration, and hypertension treatment-time
Mancia *et al.* [6]	Italy	24-h ABP < 125/79 mmHg or HBP < 132/83 mmHg (24.6%)	1589 (52.1)	50.3 (11)	16.0	No	CVD Mortality All-cause mortality	Sex, age, BMI, smoking, FPG, TC, previous CVD, and antihypertensive treatment
Tientcheu *et al.* [5]	USA	HBP < 135/85 mmHg (3.3%)	3027 (55.2)	43.4 (18-65)	9.4	No	Fatal and nonfatal CVD	Sex, age, BMI, race, diabetes, smoking, TC, hypertension, and antihypertensive treatment
Total	12 cohorts		21 336		8.2 (mean)			

ABP, ambulatory blood pressure; BP, blood pressure; CVD, cardiovascular disease; DM, diabetes mellitus; FHPCVD, family history of premature CVD; FPG, fasting plasma glucose; HBP, home blood pressure; HDL-C, HDL cholesterol; IDACO, International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes; IDHOCO, The International Database of HOme blood pressure in relation to Cardiovascular Outcome; LDL-C, LDL cholesterol; NA, not available; SD, standardized differences; TC, total cholesterol; WCH, white-coat hypertension.

[a]WCH was defined as with normal out-of-office BP and high clinic BP (≥140/90 mmHg).

[b]Patients with any previous antihypertensive drugs withdrawn for at least 4 weeks.

[c]Including data from Copenhagen, Denmark; Ohasama, Japan; Noorderkempen, Belgium; Uppsala, Sweden; Montevideo, Uruguay; Jingning County, China; Irish Allied Bank, Dublin, Ireland; Novosibirsk, Russia; Pilsen, Czech Republic; Padova, Italy; Kraków, Poland; and Maracaibo, Venezuela.

[d]Data including from five population studies of home BP monitoring performed in Ohasama, Japan, Finland, Tsurugaya, Japan, Didima, Greece, and Montevideo.

[e]Including data from Copenhagen, Denmark; Ohasama, Japan; Noorderkempen, Belgium; and Uppsala, Sweden.

[f]International Collaborative Study, including the New York Prognostic Effects of ABPM study (NYPEAP) from the United States, Progetto Ipertensione Umbria Monitoraggio Ambulatoriale from Italy (PIUMA), Ohasama study and the Jichi Medical School (JMS)-ABPM Study from Japan.

The increased risks of CVD were also founded in subgroups with WCH defined as daytime ABP less than 135/85 mmHg, follow-up duration at least 8 years, adequate adjustment of confounders or good study quality. In the mixed populations, the risk of CVD was significantly increased in subgroups with WCH defined as HBP less than 135/85 mmHg, follow-up duration at least 8 years, adequate adjustment of confounders or good study quality. In treated participants, all subgroups analysis showed that WCH was not associated with the risk of CVD.

Association between white-coat hypertension and risk of all-cause mortality

Four studies presented data of all-cause mortality in untreated WCH patients. There was no significant heterogeneity among these studies. Analysis with fixed-effects models showed that the risk of all-cause mortality was increased in the untreated WCH (RR 1.20, 95% CI 1.03–1.40) compared with normotension (Fig. 7). We did not perform subgroup analyses in all-cause mortality because of the limited number of studies.

Sensitivity analyses and meta-regression analyses

Sensitivity analyses were conducted by using several methods, and these analyses confirmed that the primary results were not influenced by the use of fixed-effects models compared with random-effects models, or recalculating the RRs by omitting one study at a time. In untreated patients, when data of the 2007 IADCO study [7] were included for analysis instead of the 2014 publication [14], the CVD risk associated with WCH was not changed (RR 1.40, 95% CI 1.16–1.70). Significantly, when data only from studies with traditional definition of WCH (clinic BP ≥ 140/90 mmHg, and daytime ABP < 135/85 mmHg) were included for analysis, the risk of CVD was still significantly higher in untreated WCH population compared with normotension (RR 1.30 95% CI 1.02–1.66). Furthermore, in the primary analysis, we used the hazard ratios obtained by defining WCH as daytime ABP less than 135/85 mmHg and elevated clinic BP in the 2014 IADCO study [14] for analysis; however, when the hazard ratios obtained by defining WCH as 24-h ABP less than 130/80 mmHg were used for analysis, the risks of CVD (RR 1.35 95% CI 1.14–1.61), and all-cause mortality (RR 1.15 95% CI 1.00–1.32) were still significantly increased in untreated WCH population.

Meta-regression analyses showed that there was no significant correlation among all BP variables (differences of clinic SBP and DBP, out-of-office SBP and DBP) and risk of CVD (all $P > 0.05$).

DISCUSSION

To our knowledge, this is the most comprehensive meta-analysis examining the risk of target organ damage associated with WCH, stratified by antihypertensive therapies at baseline. We found that, after controlling for multiple cardiovascular risk factors, WCH was associated with higher risks of CVD and total mortality in people without antihypertensive treatment at baseline and in the mixed

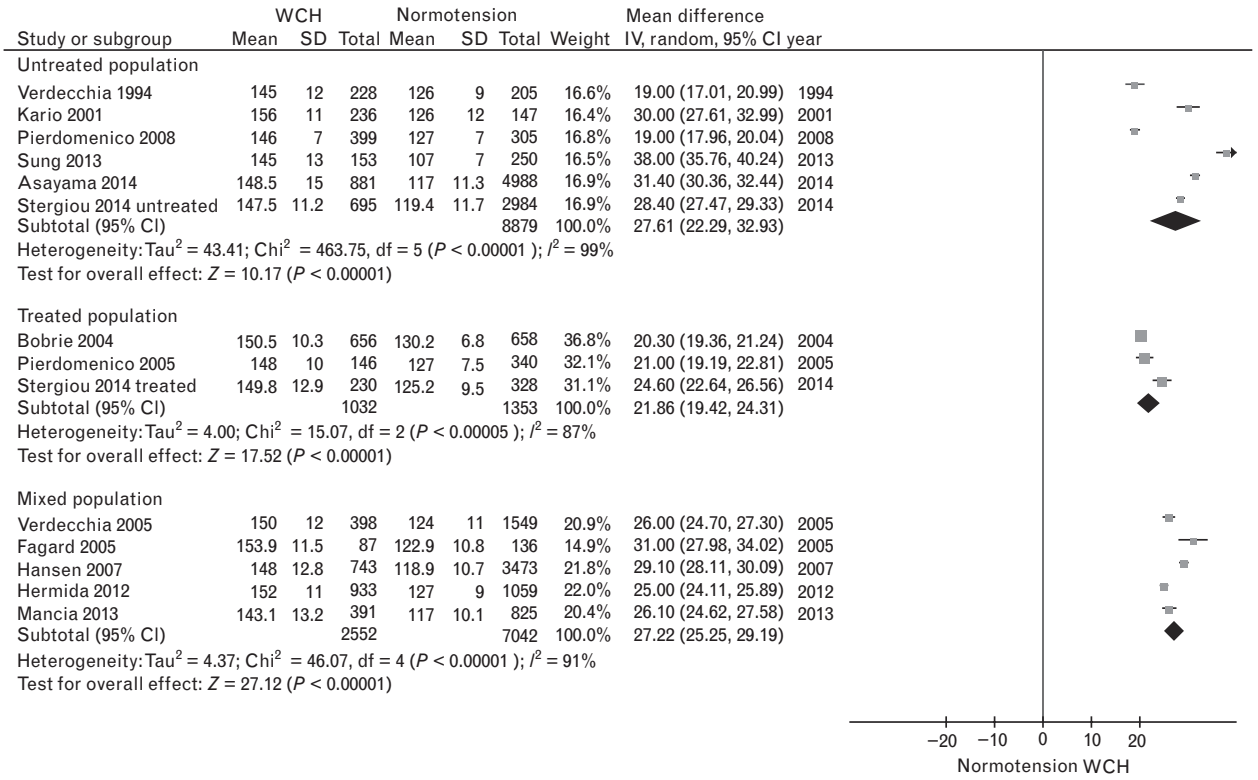

FIGURE 2 Forest plot of the comparison: white-coat hypertension vs. normotension, outcome: clinic SBP.

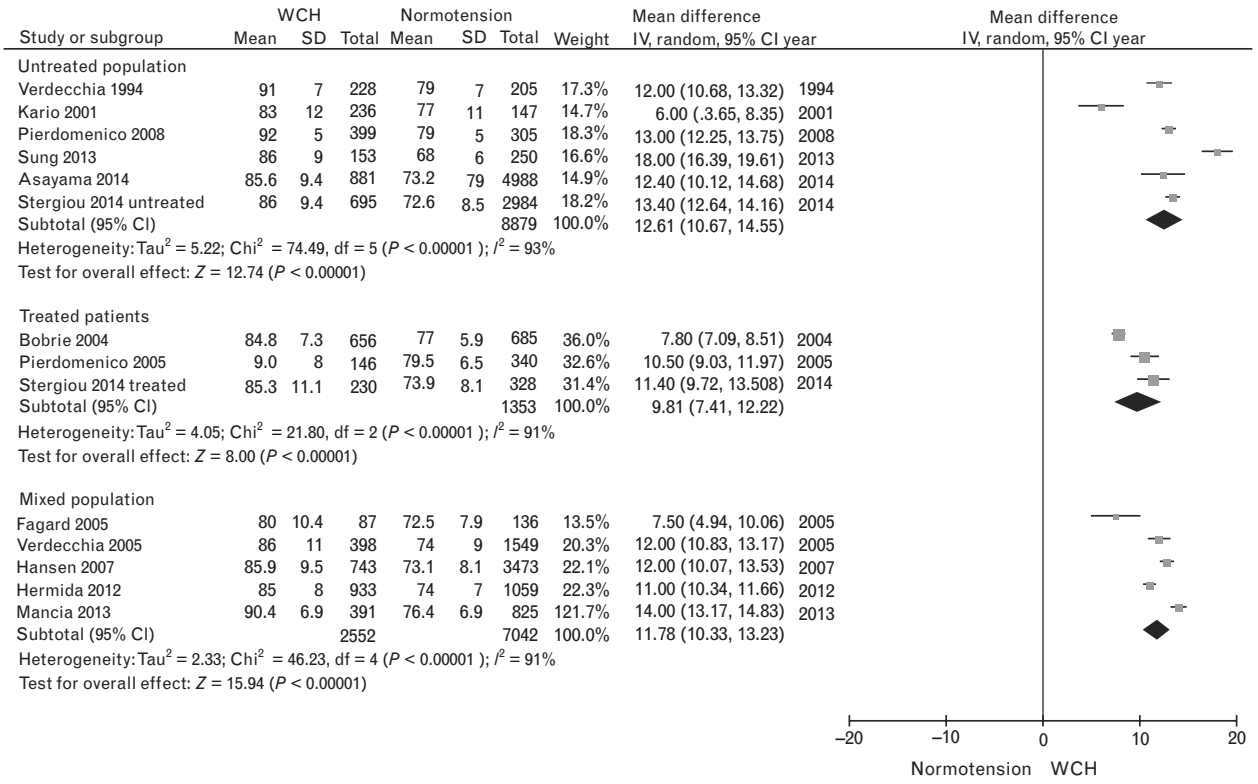

FIGURE 3 Forest plot of the comparison: white-coat hypertension vs. normotension, outcome: clinic DBP.

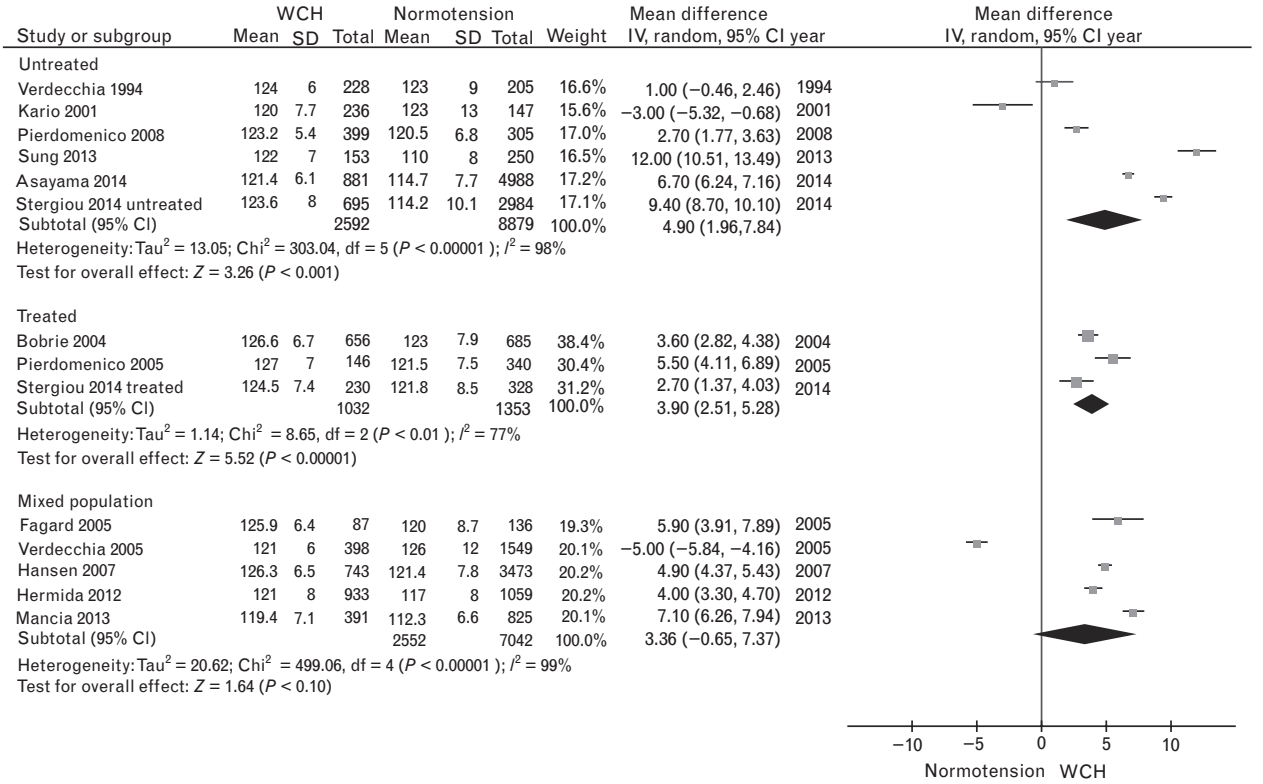

FIGURE 4 Forest plot of the comparison: white-coat hypertension vs. normotension, outcome: out-of-office SBP.

population (including both untreated and treated patients), whereas the risks of CVD and total mortality were similar in treated WCH compared with treated normotension.

Remarkably, our main findings are different from previously published meta-analyses [24,25]. One of them showed that WCH was not associated with cardiovascular

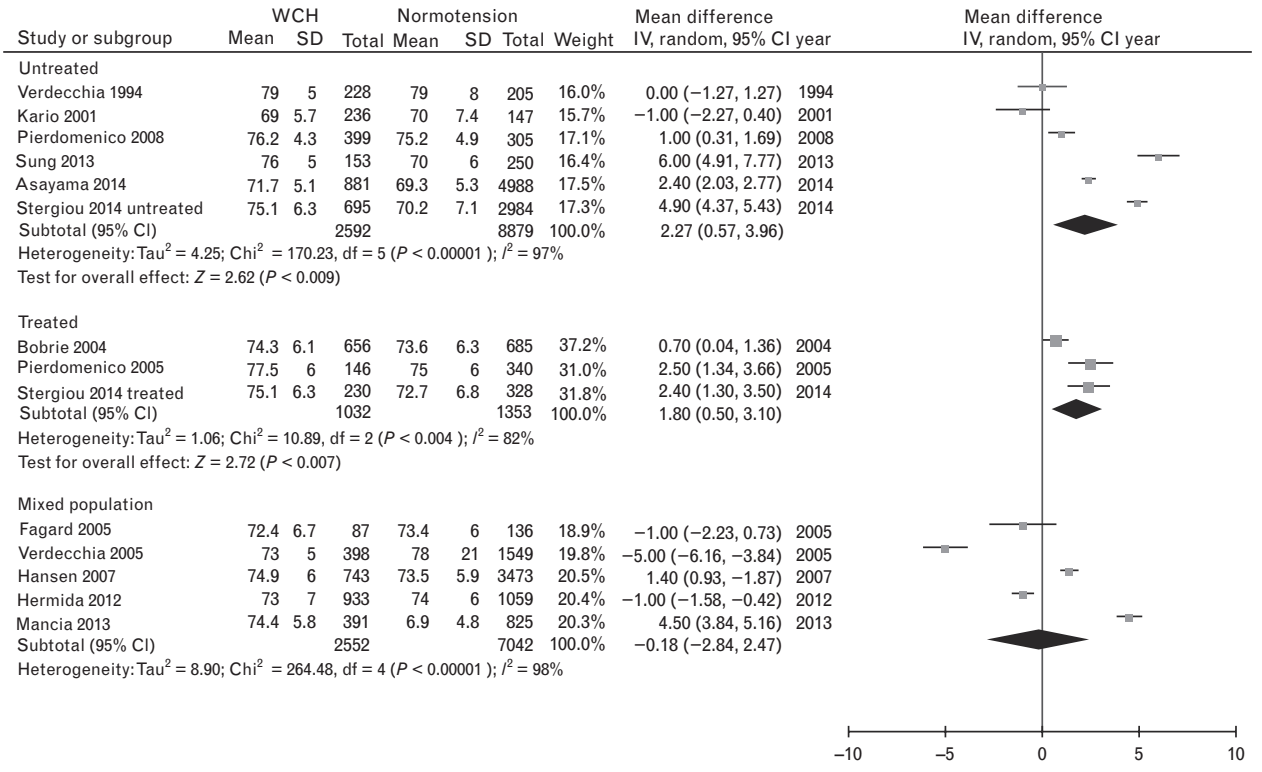

FIGURE 5 Forest plot of the comparison: white-coat hypertension vs. normotension, outcome: out-of-office DBP.

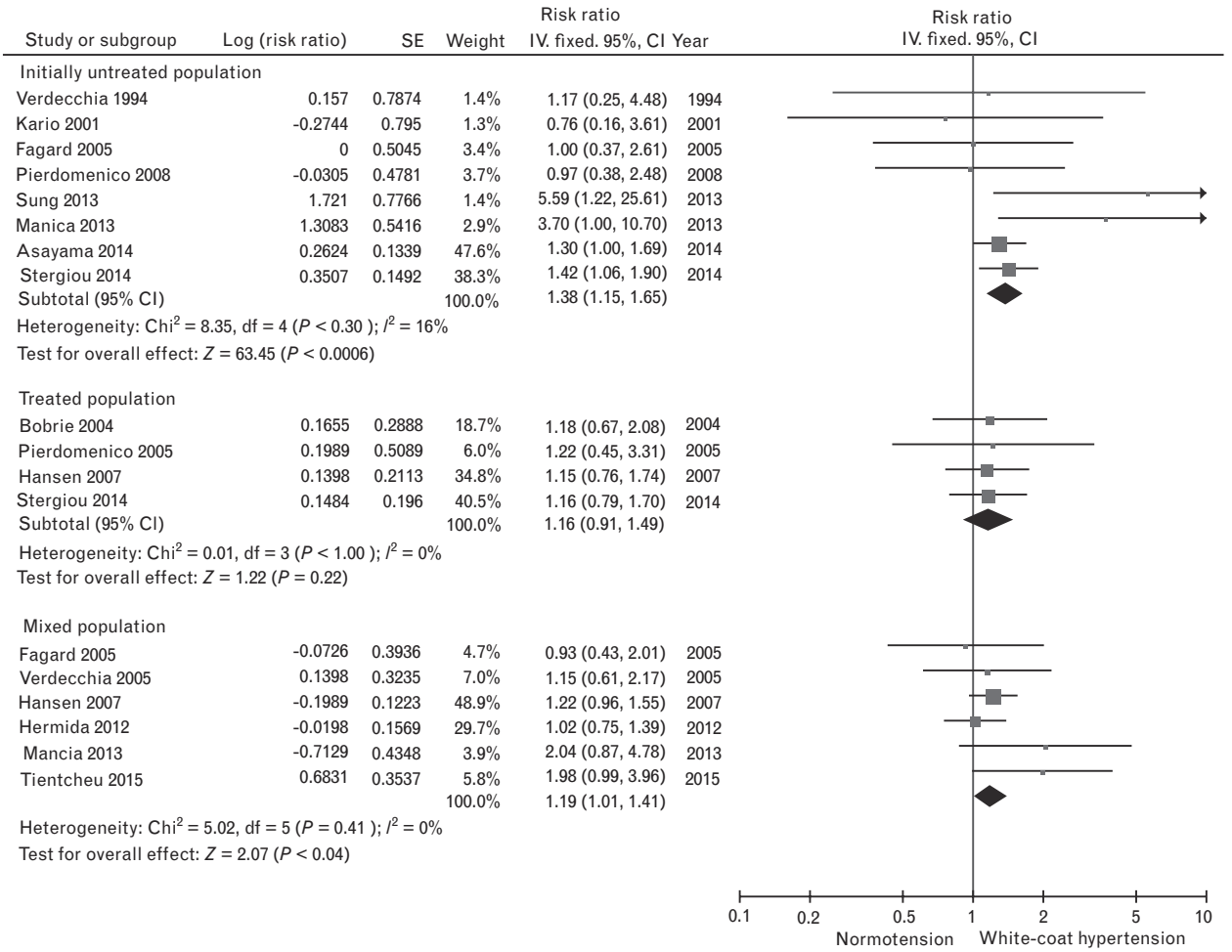

FIGURE 6 Forest plot of the comparison: white-coat hypertension vs. normotension and outcome: cardiovascular disease.

risk in initially untreated patients [24]. However, only five studies with 3670 participants were included in that meta-analysis. Recently, another meta-analysis showed that WCH was associated with increased risk of CVD, but the risk of all-cause mortality was NS [25]. The major limitation of that analysis was combining data from untreated and treated patients together. Compared with prior studies, the strengths of our current analysis include (first) the stratification of studies by baseline treatment status rather than lumping them together; (second) larger sample size and longer follow-up duration. In our study, 23 cohorts (20 445 individuals with mean follow-up duration of 9.6 years), 11 cohorts (8656 individuals with mean follow-up duration of 5.3 years), and 12 cohorts (21 336 individuals with mean follow-up duration of 8.2 years) were included in untreated, treated, and mixed populations comparisons, respectively. (Third) Consistent results were found in comprehensive subgroup analyses and sensitivity analyses; (fourth) being the first study to demonstrate increased total mortality in WCH.

Our results provide robust evidence that WCH is not 'innocent', on the contrary, it impacts on adverse long-term prognostics. It had been proposed that WCH patients had higher clinic and out-of-office BP values compared with normotensive patients, and this maybe accounts for the risk of CVD in WCH, as the association between BP levels and cardiovascular risk is linear [26,27]. A meta-analysis including 9299 participants who were followed up to 11.1 years showed that a 10-mmHg increase of daytime SBP would result in 21 and 6% increase of combined CVD and total mortality, respectively [28]. However, in our study, we found that although there was significant higher clinic BP in WCH group (≥20/10 mmHg) than normotension, the difference of out-of-office BP was very mild. The mildly increased out-of-office BP could not completely account for the significant increase of CVD (38%) and total mortality (20%) in initially untreated WCH population. This interpretation was further supported by our meta-regression analyses, which showed that there was no significant correlation between BP variables and the risk of CVD.

It was reported that WCH was accompanied by a greater proportion of other cardiovascular risk factors, such as impaired glucose metabolism, high BMI, and dyslipidemia [27,29,30], which were also known as risk factors for CVD. In our study, most of the included studies were adequately adjusted for these risk factors. These adjustments reduced the possibility that confounding factors would influent the association between WCH and the risk of CVD. Several mechanisms may be accounted for why WCH is associated with greater risk beyond average BP levels. First, WCH

TABLE 2. Subgroup analyses of the association between white-coat hypertension and risk of cardiovascular disease

Subgroups	Untreated population			Treated population			Mixed population		
	Number of studies	RR (95% CI)	P/I^2 value[a]	Number of studies	RR (95% CI)	P/I^2 value[a]	Number of studies	RR (95% CI)	P/I^2 value[a]
Measurement of out-of-office BP									
ABPM	6	1.34 (1.07, 1.69)	0.76/0%	2	1.16 (0.79, 1.70)	0.98/0%	5	1.15 (0.96, 1.37)	0.02/80.8%
HBPM	1	1.42 (1.06, 1.90)		2	1.17 (0.85, 1.60)		2	2.25 (1.30, 3.92)	
Thresholds for ABPM									
Daytime ABP < 135/85 mmHg	4	1.36 (1.08, 1.72)	0.73/0%	2	1.16 (0.79, 1.70)	–	3	1.13 (0.94, 1.35)	0.53/0%
24-h ABP < 130/80 mmHg	2	1.19 (0.92, 1.52)		–	–		–	–	
Others	1	1.17 (0.25, 5.48)		–	–		2	1.37 (0.78, 2.40)	
Measurement of clinic BP									
≥2 visits	3	0.96 (0.47, 1.96)	0.27/16.4%	2	1.16 (0.87, 1.53)	0.92/0%	1	1.98 (0.99, 3.96)	0.14/54%
<2 visits	5	1.45 (1.20, 1.74)		2	1.19 (0.73, 1.95)		5	1.16 (0.97, 1.37)	
Follow-up duration									
<8 years	3	0.96 (0.47, 1.96)	0.27/16.4%	2	1.19 (0.73, 1.95)	0.89/0%	2	1.04 (0.79, 1.38)	0.23/30%
≥8 years	5	1.45 (1.20, 1.74)		2	1.16 (0.87, 1.53)		4	1.29 (1.05, 1.59)	
Participant's average age									
<55 years	5	1.45 (1.15, 1.83)	0.71/0%	0	–	–	3	1.20 (0.92, 1.57)	0.93/0%
≥55 years	3	1.35 (1.03, 1.79)		3	1.17 (0.87, 1.59)		3	1.19 (0.96, 1.47)	
CVD endpoint									
Fatal CVD	2	3.61 (1.88, 6.95)	0.003/88.3%	0	–	–	1	2.04 (0.87, 4.78)	0.21/36.7%
Fatal and nonfatal CVD	6	1.31 (1.09, 1.57)		4	1.16 (0.91, 1.49)		5	1.17 (0.98, 1.39)	
Adjustment of confounders									
Adequate[b]	7	1.42 (1.19, 1.70)	0.43/0%	4	1.16 (0.91, 1.49)	–	5	1.28 (1.04, 1.56)	0.23/29.9%
Not adequate	1	0.76 (0.16, 3.61)		0	–		1	1.02 (0.75, 1.39)	
Study quality									
Good	6	1.43 (1.19, 1.72)	0.42/0%	3	1.16 (0.90, 1.49)	0.92/0%	5	1.28 (1.04, 1.56)	0.23/29.9%
Fair	2	1.02 (0.46, 2.27)		1	1.22 (0.45, 3.31)		1	1.02 (0.75, 1.39)	

ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; RR, relative risk.
[a]For heterogeneity among subgroups.
[b]Adequate adjustment denoted adjustment of at least: age; sex; previous CVD or exclusion of CVD at baseline; diabetes mellitus or fasting plasma glucose; BMI; cholesterol or hypercholesterolemia; and smoking.

represents greater BP reactivity to stressful events or situations. Individuals who have more reactive BP would also most likely have more variable BP, which is also a risk factor of CVD and mortality [31]. Second, WCH may be related with personality. A recent study showed that anxiety and conscientious personality related to pseudo-resistant and masked hypertension [32]. It had been reported that anxiety and conscientious personality are associated with all-cause mortality [33]. Third, although individuals may have normal HBP, but if their BP is raised every time when they encounter stressful events in daily life, such physiological reactivity may take a toll on their BP regulatory systems, increasing the likelihood of progressing to hypertension and CVD. Other plausible mechanisms, including inflammatory activation [34], neurogenic abnormality [35], endothelial dysfunction caused by circulating asymmetric dimethylarginine [36], and oxidized LDL [37], may be involved in the association between WCH and the risk of CVD.

Our data showed that the risk of CVD was increased in untreated and mixed population. However, the CVD risk was similar in treated patients with WCH compared with patients whose BP been normalized by medication. Similarly, the risk of all-cause mortality was increased in the untreated population as shown in our analysis, and in a mixed population in Mancia's study (RR 1.50, 95% CI 1.03–2.18) [6], whereas data from the International Database of HOme blood pressure in relation to Cardiovascular Outcome study showed that in treated patients, WCH was not associated with risk of all-cause mortality (RR 1.19, 95% CI 0.82–1.73) [21]. These results should not be interpreted as

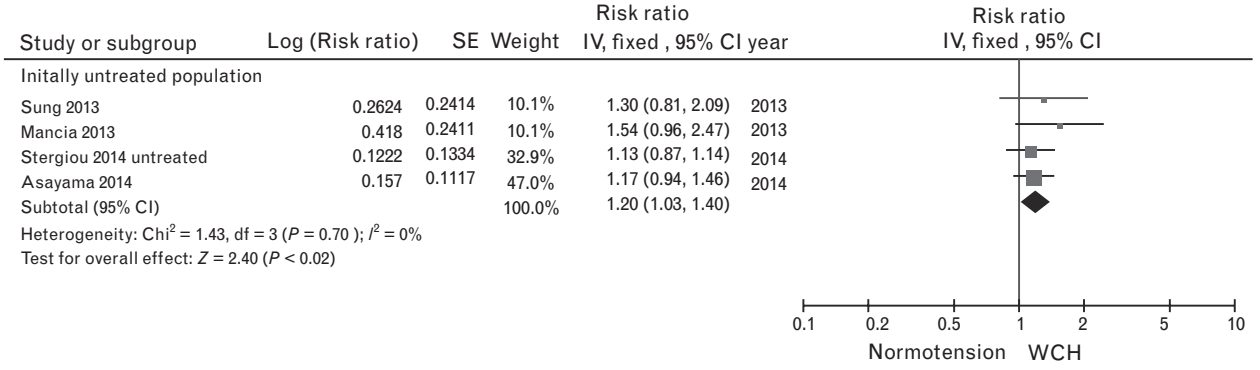

FIGURE 7 Forest plot of the comparison: white-coat hypertension vs. normotension and outcome: all-cause mortality.

WCH being benign in treated patients. First, in the treated populations, normotensive comparators were individuals with normal BP under antihypertensive treatment (treated normotension), who were not real normotensive (untreated normotension) patients. Although restoring BP to normal levels with treatment could decrease lifetime CVD burden associated with hypertension to some extent, it could not eliminate that completely. A study from the IDACO database, which defined WCH by isolated SBP (clinic BP $\geq$ 140/<90 mmHg and ABP < 135/85 mmHg), showed that compared with untreated normotensive individuals, patients with either WCH (adjusted hazard ratio 2.00; 95% CI 1.43–2.79) or normal BP after antihypertensive treatment (adjusted hazard ratio 1.98; 95% CI 1.49–2.62) were both at higher risk of CVD during a median follow-up of 10.6 years, whereas the latter two were with similar risk [13]. Based on these results, some scholars proposed caution in applying the term 'WCH' to persons receiving antihypertensive treatment. In sustained hypertensive patients whose out-of-office BP been normalized on antihypertensive therapy, whereas with high clinic BP caused by white-coat effect, terms of 'treated normalized hypertension with white-coat effect' [2,13] or 'pseudo-resistant hypertension due to white-coat effect' [38] may be more appropriate. Furthermore, treated patients with white-coat effect may be given more aggressively antihypertensive treatment, because of the high clinic BP readings. This might partly explain their more favorable prognosis [2]. Considering these results, we suggest that future studies about WCH should be stratified by baseline antihypertensive treatment status rather than to lump together.

HBPM used to be proposed as an alternative to ABPM in the diagnosis of hypertension and the detection of WCH [39]. However, it should be noted that the diagnostic agreement between ABPM and HBPM was moderate [40]. In our study, the risk of CVD was consistently increased in untreated WCH detected by ABPM or HBPM. These data suggest a complementary rather than competitive role of the two methods in management of hypertension [41,42].

Considering the high incidence of WCH [1,40], reasonable intervention in such a large population could have an important public health impact. Current guidelines recommend a close follow-up of WCH patients to identify those who develop sustained hypertension and/or have metabolic abnormalities [1]. However, whether patients with WCH would be benefited from antihypertensive treatment remains unknown. It has been shown that antihypertensive treatment might lower clinic BP, rather than ABP [40,43]. A post-hoc analysis of a subgroup of patients from the Systolic Hypertension in Europe trial also showed that in WCH, antihypertensive treatment did not lower cardiovascular events [44]. However, post-hoc analysis of the Hypertension in the Very Elderly Trial showed that patients with WCH got benefit from treatment in the very elderly [45]. Post-hoc design and limited number of patient in these studies do not allow firm conclusions to be drawn. Therefore, randomized, controlled trials aiming at BP control both in clinic and out-of-office in patients with WCH are urgently needed.

Some limitations of this study have to be noted. First, we had no access to individual patients' data. However, we only included studies with multivariate-adjusted data for analysis, and multiple sensitivity analyses also showed consistent results in our study. These characteristics may mitigate the possibility of influencing the association between WCH and risk of CVD by other confounding factors. Second, it has been suggested that WCH is associated with a greater risk for progression to sustained hypertension compared with normotension [1]. However, periodic data of ABPM and HBPM were not available, and only two studies included in our analysis were with adjustment of antihypertensive drug at follow-up. So at least in part, the risk of CVD in WCH may be caused by future sustained hypertension. Nevertheless, our results indicate that baseline WCH is associated with increased risks of CVD and total mortality. Third, the cutoff values of ABPM for defining WCH were different in the included studies. However, in sensitivity analysis, only studies with traditional definition of WCH (clinic BP $\geq$ 140/90 mmHg and daytime ABP < 135/85 mmHg) were included, the risk of CVD in untreated WCH was still significantly increased.

In conclusion, WCH, defined as high clinic BP but normal out-of-office BP (either by ABPM or HBPM) in untreated and mixed patients, is associated with long-term risks of CVD and total mortality compared with normotension. A close follow-up should be recommended in WCH patients. Randomized, controlled trials are necessary to clarify whether pharmacological treatment is beneficial in patients with WCH.

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Conflicts of interest

There are no conflicts of interest.

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Reviewers' Summary Evaluations

Reviewer 1

The article explores the important questions as to whether white-coat hypertension is innocuous. White-coat hypertension patients on no treatment are compared with those on treatment, and the results show that those on no treatment fared worse regarding mortality than those on treatment. The weakness of the study is that it relies on meta-analysis of nonrandomized studies. It may inspire others to do a carefully designed prospective study.

Reviewer 2

This study provides an up-to-date systematic review and meta-analysis of studies on white-coat hypertension and incidence of cardiovascular disease and all-cause mortality. A novel feature of the review is sub analyses by treatment status, demonstrating that compared to nonhypertensives, adults with white-coat hypertension without baseline antihypertensive treatment had significantly greater risk or cardiovascular disease and mortality, but this relation was not observed in adults with white-coat hypertension who were receiving antihypertensive treatment at baseline. As this review is based on longitudinal, observational studies, it remains for RCTs to demonstrate whether treating white-coat hypertension will reduce incidence of cardiovascular disease and premature mortality, but these data provide preliminary evidence to that effect.