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 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]...
Huang et al.

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’, ‘ABP’, ‘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 (ABPM > 135/85 mmHg vs. other); different thresholds for diagnosing WCH (both in or out-of-clinic) after medication treatment; and third, the risks were compared in mixed population with WCH who were on antihypertensive therapy (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-of-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 < 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 \( F \) statistics to test heterogeneity. Values of \( F \) 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.
Potentially relevant articles identified and screened for retrieval (n = 26 158)

Records after duplicates removed (n = 7424)

Potentially relevant articles (n = 18 734)

Unrelated studies excluded based on title and abstract (n = 18 672)

Potential articles for detailed evaluation (n = 62)

No data of WCH (n = 24)
Not compared WCH VS normal blood pressure (n = 7)
From the same cohorts or included in other studies (n = 9)
Not reported cardiovascular diseases or all cause mortality (n = 2)
Define WCH only based on systolic blood pressure (n = 1)
Not reported RRs and 95% CIs (n = 5)

Articles included in the study (n = 14)
Untreated participants at baseline (n = 8)
Treated with antihypertensive medicine at baseline (n = 4)
Mixed populations with treated and untreated participants (n = 6)

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

RESULTS

Studies retrieved and characteristics

A total of 26 158 manuscripts were retrieved in the Embase 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 (25 cohorts, including 20 445 individuals with mean follow-up duration of 9.6 years) [6, 8–12, 14, 21], four studies (11 cohorts, including 8 656 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]. 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 (Figs 2) (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) 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 I² < 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.
| Reference | Cohort | Definition of normal out-of-office BP and prevalence of WCH (%)<sup>a</sup> | 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.**[8]** | Italy  | Daytime ABP < 131/86 mmHg (women) or 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 < 133/85 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 < 133/85 mmHg (19.6%)                                    | 2037 (46.3)           | 48.8 (12)               | 6.4              | Yes                    | Fatal and nonfatal CVD  | Sex, age, BMI, smoking, FHCD, 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.**[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             | Yes                    | Fatal and nonfatal CVD All-cause mortality | Sex, age, BMI, smoking, drinking, TC, DM, previous CVD, and cohort |
| Stergiou et al.**[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** |        |                                                                     | 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, FHCD, clinical BP, LDL-C, creatinine, DM, and left ventricular hypertrophy |
| Hansen et al.**[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.**[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** |        |                                                                     | 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.**[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.**[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 | Definition of normal out-of-office BP and prevalence of WCH (%) | Sample size | Age (year) | Sample size (range of SD) | Baseline BP and prevalence | Follow-up (year) | CVD excluded | Events for analysis | Risk factors adjusted | Outcome |
|-----------|---------------------------------------------------------------|-------------|------------|--------------------------|-----------------------------|------------------|-------------|-------------------|---------------------|---------|
| Hermona et al. [23] | Ambulatory blood pressure (ABP) defined as 24-h ABP less than 130/80 mmHg | 3,444 (48.6) | 53.6 (14.5) | Yes | 5.6 | CVD | Yes | Fatal and non-fatal CVD | Sex, age, BMI, smoking, FG, TC, treatment-time, antihypertensive treatment, diabetes, chronic kidney disease, and hypertension | Risk of CVD, total mortality |
| Tientcheu et al. [125] | Daytime ABP less than 135/85 mmHg | 1,325/83 mmHg (24.6%) | 50.3 (11.1) | 16.0 | No | No | Fatal and non-fatal CVD | Sex, age, BMI, smoking, FPG, TC, previous CVD, and antihypertensive treatment | Risk of CVD, total mortality |

**Definition of white-coat hypertension (WCH)**
- 24-h ABP < 135/85 mmHg

**Risk factors adjusted**
- Sex, age, BMI, smoking, fasting plasma glucose (FPG), total cholesterol (TC), hypertension, and antihypertensive treatment

**Outcome**
- Risk of CVD, total mortality

**DISCUSSION**

The increased risks of CVD were also found 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 populations.
### 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.
White-coat hypertension and the risk of cardiovascular diseases

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 4 Forest plot of the comparison: white-coat hypertension vs. normotension, outcome: out-of-office SBP.](image_url)

![FIGURE 5 Forest plot of the comparison: white-coat hypertension vs. normotension, outcome: out-of-office DBP.](image_url)
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 influence 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
White-coat hypertension and the risk of cardiovascular diseases

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) | $P$ \(^2\) value | Number of studies | RR (95% CI) | $P$ \(^2\) value | Number of studies | RR (95% CI) | $P$ \(^2\) value |
| 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) | 3 | 1.13 (0.94, 1.35) | 0.53/0% | 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% | 5 | 1.16 (0.97, 1.37) | 1.98 (0.99, 3.96) | 32.9% |
| <2 visits | 5 | 1.45 (1.20, 1.74) | 0.76/0% | 2 | 1.19 (0.73, 1.95) | 0.95/0% | 5 | 1.16 (0.97, 1.37) | 1.98 (0.99, 3.96) | 32.9% |
| 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) | 0.76/0% | 2 | 1.16 (0.87, 1.53) | 0.95/0% | 4 | 1.29 (1.05, 1.59) | 1.98 (0.99, 3.96) | 32.9% |
| 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) | 0.71/0% | 4 | 1.16 (0.91, 1.49) | 0.95/0% | 5 | 1.17 (0.96, 1.39) |
| Adjustment of confounders | | | | | | | | |
| Adequate* | 7 | 1.42 (1.19, 1.70) | 0.43/0% | 4 | 1.16 (0.91, 1.49) | 0.95/0% | 5 | 1.28 (1.04, 1.56) | 0.23/29.9% |
| Not adequate | 1 | 0.76 (0.16, 3.61) | 0.27/16.4% | 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) | 0.27/16.4% | 1 | 1.22 (0.45, 3.31) | 0.95/0% | 1 | 1.02 (0.75, 1.39) |

ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; RR, relative risk.

* 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.

This 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 to 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, 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...
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 ≥ 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 1.49–2.62) 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 ≥ 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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White-coat hypertension and the risk of cardiovascular diseases

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www.jhypertension.com 687
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 of 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.